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The Effect of a Connexin43-Based Peptide on the Healing of Chronic Venous Leg Ulcers: A Multicenter, Randomized Trial

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The gap junction protein, connexin43 (Cx43), has critical roles in the inflammatory, edematous, and fibrotic processes following dermal injury and during wound healing, and is abnormally upregulated at the epidermal wound margins of venous leg ulcers (VLUs). Targeting Cx43 with ACT1, a peptide mimetic of the carboxyl-terminus of Cx43, accelerates fibroblast migration and proliferation, and wound reepithelialization. In a prospective, multicenter clinical trial conducted in India, adults with chronic VLUs were randomized to treatment with an ACT1 gel formulation plus conventional standard-of-care (SOC) protocols, involving maintaining wound moisture and four-layer compression bandage therapy, or SOC protocols alone. The primary end point was mean percent ulcer reepithelialization from baseline to 12 weeks. A significantly greater reduction in mean percent ulcer area from baseline to 12 weeks was associated with the incorporation of ACT1 therapy (79% (SD 50.4)) as compared with compression bandage therapy alone (36% (SD 179.8); $P = 0.02$). Evaluation of secondary efficacy end points indicated a reduced median time to 50 and 100% ulcer reepithelialization for ACT1-treated ulcers. Incorporation of ACT1 in SOC protocols may represent a well-tolerated, highly effective therapeutic strategy that expedites chronic venous ulcer healing by treating the underlying ulcer pathophysiology through Cx43-mediated pathways.

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INTRODUCTION

Venous leg ulcers (VLUs) develop as a result of chronic venous insufficiency, leading to venous hypertension and small vessel damage. Persistent inflammation within the extracellular matrix of the wound bed and the detrimental upregulation of connexins contribute to dysfunction of wound fibroblasts and keratinocytes and the underlying pathophysiology associated with an impaired wound-healing response in chronic VLUs (Brandner *et al.*, 2004; Charles *et al.*, 2008; Mendoza-Naranjo *et al.*, 2012; Kim *et al.*, 2014). In industrialized countries, VLUs affect ~3% of people over 65 years of age (Fletcher *et al.*, 1997; Bergan *et al.*, 2006). Given that therapeutic intervention extending beyond 1 year is common, and recurrence rates are ~60–70%, VLUs present a substantial economic and societal burden on the individual, family, and health-care system (de Araujo *et al.*, 2003; Abbade and Lastoria, 2005; O'Meara *et al.*, 2012).

Conventional treatment protocols involving infection control, nonadherent wound dressing, and limb compression remain the cornerstone of conservative treatment, healing between 30 and 75% of VLUs (O'Meara *et al.*, 2009). The Wound Healing Society suggests incorporation of adjunctive therapies in the treatment of VLUs that remain unresponsive to standard-of-care (SOC) treatment beyond 4 weeks (Tang *et al.*, 2012). Randomized controlled trials demonstrate the potential of advanced wound care matrices, such as Apligraf (Organogenesis Inc., Canton, MA). However, such living skin equivalents remain cumbersome, time-consuming and expensive, offer modest improvement over SOC, and may not address the underlying pathophysiology of chronic ulcers (Falanga *et al.*, 1998; Hankin *et al.*, 2012).

Gap junction (GJ) proteins have critical roles in the pathogenesis of chronic wounds, and targeting GJ signaling offers therapeutic opportunity (Qiu *et al.*, 2003; Gourdie *et al.*, 2006; Ghatnekar *et al.*, 2009; Churko *et al.*, 2012; Marquez-Rosado *et al.*, 2012; Mendoza-Naranjo *et al.*, 2012; Wright *et al.*, 2013; Grek *et al.*, 2014). Connexins are the channel-forming component of GJs that directly couple the cytoplasm between cells, permitting the exchange of small molecules (<1000 Da) and facilitating electrical propagation in excitable

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Abbreviations: AE, adverse event; Cx43, connexin43; GJ, gap junction; ITT, intent-to-treat; PP, per protocol; SOC, standard of care; VLU, venous leg ulcer

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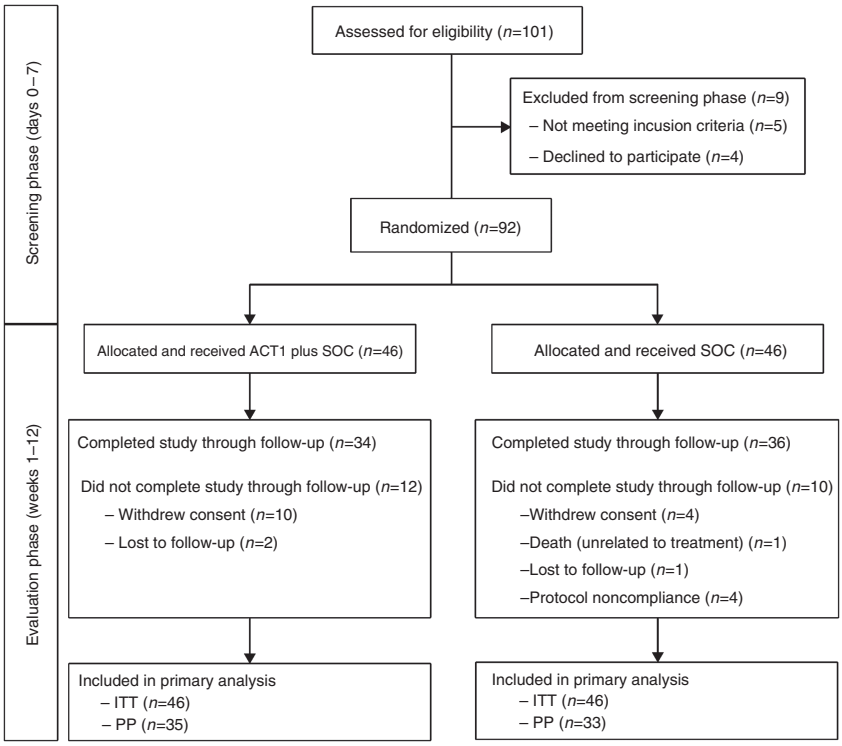

Figure 1. CONSORT flow diagram of participants. ITT, intent-to-treat; PP, per protocol; SOC, standard of care.

tissues. Connexin43 (Cx43) has critical roles in the regulation of inflammatory, edematous, and fibrotic processes following tissue injury and during healing, and is abnormally upregulated at the epidermal wound margins of chronic VLUs (Brandner *et al.*, 2004; Mendoza-Naranjo *et al.*, 2012).

ACT1 is a 25 amino acid synthetic peptide containing the carboxy-terminal PDZ binding domain of Cx43 that directly interacts with Cx43 binding partners, thus offering specific and reversible modulation of GJ communication. When applied topically on rodent and porcine skin wounds, ACT1 accelerates the wound closure rate, reduces inflammatory neutrophil infiltration, and reduces scar tissue formation (Gourdie *et al.*, 2006; Rhett *et al.*, 2008; Ghatnekar *et al.*, 2009). ACT1's mechanism of action with regard to tissue regeneration and the dampening of inflammatory responses is independent of Cx43 expression and is linked to mediated increases in the size of GJ channel aggregates and the sequestration of hemichannels from the perinexal region surrounding GJs (Hunter *et al.*, 2005; Rhett *et al.*, 2011). This study evaluated the efficacy and safety of ACT1 in accelerating the healing of chronic VLUs when incorporated into conventional treatment protocols.

RESULTS

Between 5 October 2011 and 10 May 2012, 101 patients were screened and a total of 92 patients were randomly assigned 1:1 to a treatment protocol involving ACT1 and conventional SOC protocols involving the maintenance of a moist wound environment and the application of compression bandage therapy or a control treatment of conventional therapy alone (Figure 1). Randomized groups showed similar baseline patient demographics in terms of mean age, race, mean weight, mean body mass index, ankle blood pressure, baseline mean ulcer area, and ulcer location (Table 1). At study outset, the participant population had an average ulcer size of 3.5 cm^2 lasting about 17 months.

Of the 92 participants who were assigned to randomization, 14 withdrew consent during the course of the study, 3 were lost to follow-up, 4 were determined to be in noncompliance post-facto, and 1 participant died as a result of myocardial infarction unrelated to intervention, resulting in a total of 70 participants who completed the study. The final analysis sample sizes consisted of an intent-to-treat (ITT) participant population ($n=92$) and a per protocol (PP) participant population ($n=68$) made up of participants lacking any major protocol deviation and present for all ulcer evaluations (Figure 1). ITT analyses avoid bias associated with the nonrandom loss of participants and included all participants with a baseline visit. The PP population excluded participants who had died, had withdrawn consent, were noncompliant to the protocol, or had major protocol violations such as missed visits/treatments and lack of wound evaluation data. Of note, the number of missing observations was relatively high but was similar in the control and treatment groups. Selection of the PP population was made according to the ICH-GCP guidelines, with complete information on post-randomization exclusion provided to avoid bias.

Primary and secondary ulcer healing outcomes

Preliminary assessment for normality confirmed a non-normal distribution of data ($P<0.001$), supporting the application of

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