

# A Comprehensive Approach to Treating Venous Leg Ulcers and Improving Patient Outcomes

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# Disclosures

- Janice Smiell, MD
  - Major
    - Chief Medical Officer, Alliqua BioMedical
  - Mild
    - Previously employed by Celgene Corporation and Johnson & Johnson

# Agenda

- Introduction
- Understanding the Pathology of Venous Ulcers and Standard Treatments
- Using MIST® Noncontact Low-Frequency Ultrasound to Accelerate Healing of VLUs
- Summary

# Natural History of Venous Pathology

## Venous return impairment from any cause

- Leads to **peripheral venous reflux or insufficiency**
- Involves deep veins, superficial veins or both
- Etiology of impaired venous system:
  - Primary **muscle pump failure** from venous obstruction (thrombotic or nonthrombotic)
  - Or from **venous valvular incompetence**, which may be segmental or involve whole leg



## Skin damage

- **RBCs & WBCs** stick to vessel walls and migrate out into tissues
- RBCs break down leaving **iron deposits** in tissues evidenced by brown discoloration
- Activated WBCs (in tissues) release **biochemicals** causing damage leading to tissue breakdown or build up of products (eg, **fibrin**) that impede diffusion of oxygen and other nutrients
- End Result: **Tissue necrosis** around veins leading to a venous ulcer (also called stasis ulcers, venous stasis ulcers, venous leg ulcers [VLUs])



# Addressing a Hostile Wound Environment

## Uncontrolled Sustained Inflammation

**NO TWO  
WOUND  
BEDS  
ARE THE  
SAME**

### Noncycling (senescent) CELLS

Impaired  
migration and  
proliferation

Decreased response to  
signaling molecules

**SHARP (Mechanical/Surgical)  
Debridement**

### MATRIX

Impaired  
ECM production and  
maintenance

Deficiency of  
TIMPs creates  
MMP imbalance

### BIOCHEMICALS

Abnormal levels/  
imbalance  
of cytokines and  
growth factors

Removes:  
Devitalized  
tissue, bone,  
bacteria  
proteolytic  
enzymes,  
senescent  
cells

Dependently  
drains pus

Changes  
chronic wound  
to acute

↓ EGF, FGF-2, TGF-β, PDGF, VEGF

↑ IL-1, IL-2, TGF-α

**INFECTION**  
Biofilm

**PRESSURE**

**ISCHEMIA**  
**VENOUS**  
**EDEMA**



# Key Factors Leading to Failure to Heal

- Underlying pathophysiology
  - Venous and/or arterial insufficiency
  - Infection/microbial imbalance
  - Sustained inflammation
  - Pressure or recurrent injury
- Diabetes/associated disorders/systemic disease/comorbid conditions
- Immunosuppression/impaired host
- Edema
- Nutritional deficits
- Concomitant medications
- Aging
- Smoking
- Abnormal wound microenvironment
- Pain
- Noncompliance: Not adhering to prescribed plan
- **Iatrogenic: Little wound healing guided by evidence**

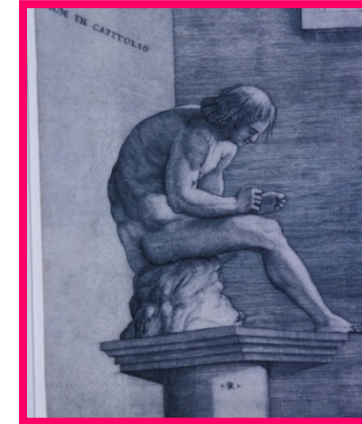



Photo courtesy of Gary W. Gibbons, MD

# Systemic Support: Treating Underlying Conditions

***Remember: it is a patient with a wound***

- **Address underlying pathology**
  - Revascularize patients with peripheral arterial disease
  - Evaluate and treat venous disease
  - For combined: treat arterial first then venous
  - Protect high risk areas
  - Control peripheral edema
- **Correct systemic factors interfering with wound healing**
  - Ensure adequate nutrition
  - Normalize blood glucose
  - Encourage smoking cessation
  - Adjust necessary systemic medication to promote wound healing
  - Physical and emotional therapy
  - Treat comorbid conditions



30-35 cal/Kg/day,  
1.5 g protein/Kg/day,  
vitamin C, multivitamin, trace  
minerals  
Blood Glucose: optimal control

# Conservative Therapy for Venous Disease

## ***Compression is essential for prevention of occurrence & recidivism***

- Reduces vein diameter & balances osmotic pressure, increasing flow velocity & restoring hemodynamics --improves calf muscle pump functioning, decreasing the chance of thrombosis; activates fibrinolytic activity in blood
- Reduces filtering of fluid out of the intravascular space & improves lymphatic flow, thereby reducing edema
- Graduated compression reduces reflux & improves venous outflow, thus decreasing venous pressure at rest & with ambulation
- Anti-inflammatory, yielding improvement in pain and swelling
- ***Three main types of compression***
  - elastic compression stockings or bandages
  - inelastic compression garments or bandages
  - pneumatic compression pumps

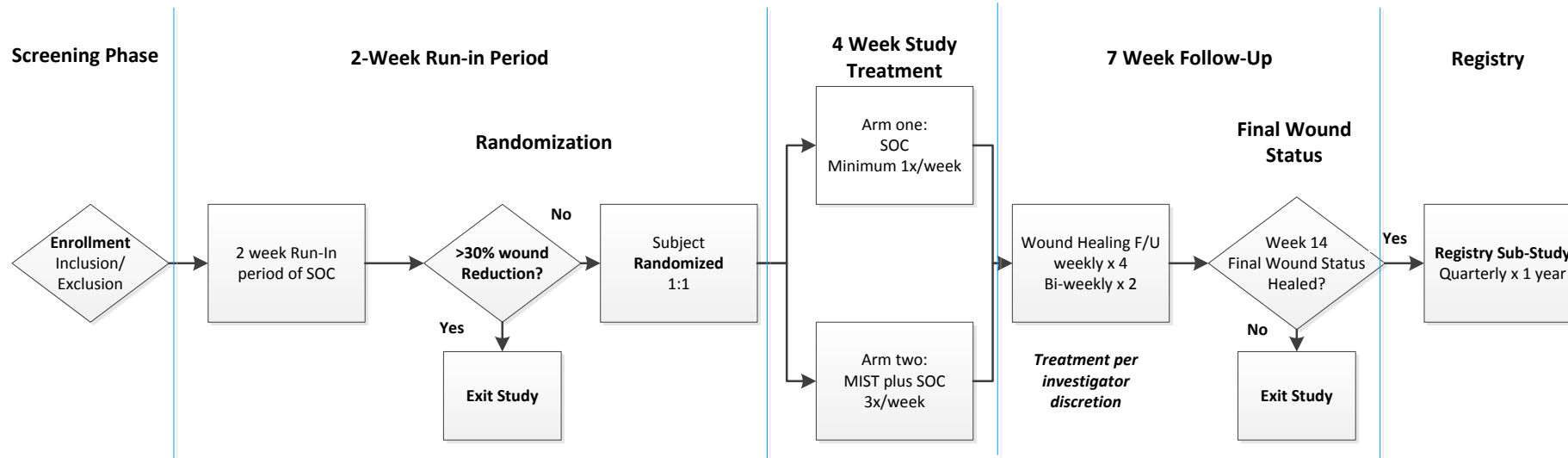
## ***Skin health and maintenance***

Moisturizers and anti-inflammatory creams

# *IN BALANCE* VLU RCT – Significant evidence of the value of MIST Therapy in the wound prep / treatment algorithm of VLUs

- Purpose:
  - Evaluate the healing outcomes Noncontact, Low-frequency Ultrasound (NLFU: MIST Therapy) plus Standard Care (SOC) compared to SOC alone in the treatment of lower extremity Venous Leg Ulcers (VLU)
- Design & Methods
  - Prospective, parallel, randomized, controlled, trial (PRCT)
  - Treatments = MIST+SOC vs. SOC alone
    - 2-week run in to standardize care
  - Multi-center (22 US sites, geographically spread)
    - Blinded adjudication of all subject eligibility
  - Primary Endpoint - % wound area reduction at 4 weeks
    - 80% power to detect a 15% difference ( $p < .05$  deemed significant)
    - Digital wound measurements (weekly)
    - Blinded third-party adjudication of wound measurements / healing

# *In Balance* Study Design Flowchart



## Study Phases:

- 2 wk run-in of standard of care (exited if reduced > 30%)
- 4 wk treatment phase (min. 1 x per week SOC; 3x/week MIST)
- 7 wk follow-up phase (SOC could use NLFU in follow-up phase)

# Standard Care

- All subjects
- Excisional or sharp debridement at enrollment
- Sharp debridement, as needed, at each visit
- Dressings to promote a moist wound environment
  - Wound veil primary contact dressing
  - Secondary dressing based on level of drainage (Telfa, Sorbsan, Mepilex)
- Compression wrap 30 to 40 mmHg (Profore 4-layer provided)
- Minimum frequency of dressing change/compression application once per week (and up to 3 times/week per investigator discretion)

# Primary Inclusion/Exclusion Criteria

## **Inclusion**

- Documented venous stasis with reflux (venous duplex/clinical assessment)
- Adequate arterial flow (ABI 0.8-1.2)
- Chronic VLU > 30 days duration
- Ulcer Area 4 cm<sup>2</sup> to 50 cm<sup>2</sup>

## **Exclusion**

- Ulcers of non-venous primary etiology
- Ulcer depth to muscles/tendon/bone
- Greater than 5 ulcers on index limb
- Biopsy required if ulcer > 6 months duration
- Comorbid conditions that (per investigator) would convolute study results
- Prior treatment / study participation required 14 - 30 day “wash out” period
- No planned corrective surgical procedures during trial

# Subject Eligibility

Interdisciplinary blinded adjudication of *all* subjects was performed using DSMB-approved procedures (based on FDA/ICH Guidelines):

- 156 subjects were consented for screening
  - 7 failed diagnostic criteria
  - 35 failed major inclusion exclusion criteria (20 per adjudication)
  - 2 withdrew in screening
- 112 eligible (study cohort)
  - 27 failed randomization criteria ( reduced > 30% in run-in)
  - 4 withdrawn prior to randomization
- 81 eligible subjects who were randomized

ITT analysis per FDA & ICH E9-Statistical Principles for Clinical Trials

# Demographics / Ulcer Characteristics

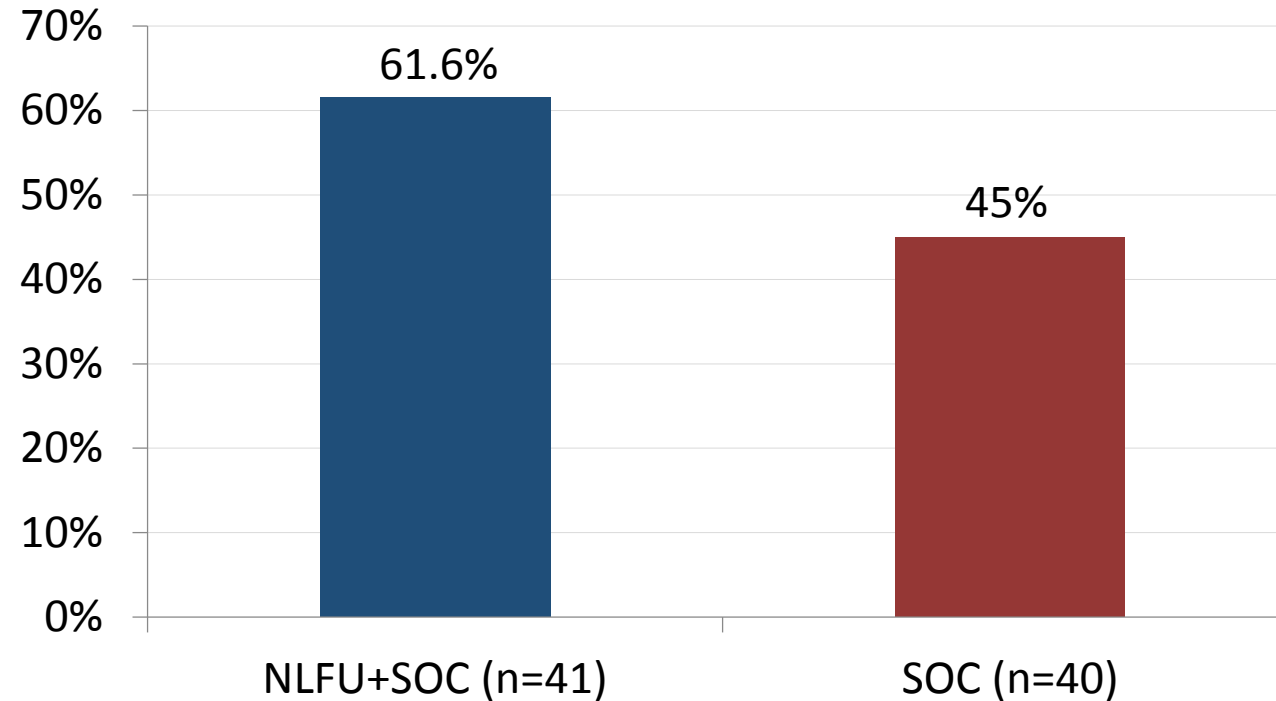
	Mean $\pm$ SD (N), Median [Interquartile Range], Range or % (n/N)		SOC vs MIST+SOC
Characteristic	SOC (N=40)	MIST+SOC (N=41)	p-value
Median Age (years)	60.0 [52.0, 67.5]	58.0 [51.0, 68.0]	0.9211
Male	72.5% (29/40)	68.3% (28/41)	0.8086
Median BMI (kg/m <sup>2</sup> )	33.2 [28.2, 42.2]	37.4 [29.3, 45.2]	(0.4414)
Recurrent ulcer (%)	60.0% (24/40)	51.2% (21/41)	0.5768
Median ulcer size at randomization (cm <sup>2</sup> )	9.8 [4.6, 16.8] 2.5 - 36.9	12.4 [6.5, 19.2] 3.1 - 53.3	(0.1470)
Median ulcer age at randomization (mos)	8.9 [3.6, 29.3] 1.7 - 204.5	10.3 [3.9, 24.1] 1.5 - 114.0	0.5332 (0.8464)

# Associated Comorbidities within Study Inclusion / Exclusion Criteria

	Mean ± SD (N), Median [Interquartile Range], Range or % (n/N)		SOC vs MIST
Characteristic	SOC	MIST	p-value*
BMI ≥40	27.5% (11/40)	36.6% (15/41)	0.4769
CAD	10.0% (4/40)	4.9% (2/41)	0.4321
Diabetes	27.5% (11/40)	41.5% (17/41)	0.2441
Hypertension	65.0% (26/40)	68.3% (28/41)	0.8161
Anemia	7.5% (3/40)	19.5% (8/41)	0.1935
Prior Ulcers	85.0% (34/40)	78.0% (32/41)	0.569
Edema (moderate or severe)	40.0% (16/40)	53.7% (22/41)	0.2681
ABI ≤ 0.9	2.5% (1/40)	9.8% (4/41)	0.3593
# Subjects and # comorbidities			0.5858
4 comorbidities	20.0% (8/40)	29.3% (12/41)	
5 comorbidities	7.5% (3/40)	9.8% (4/41)	
6 comorbidities	0	4.9% (2/41)	
7 comorbidities	0	2.4% (1/41)	
% Subjects with 4 or more associated comorbidities	27.5% (11/40)	46.3% (19/41)	0.1078

# Primary Endpoint: % Area Reduction at 4 weeks

**Mean % Wound Area Reduction at 4 weeks (p=0.02)\***

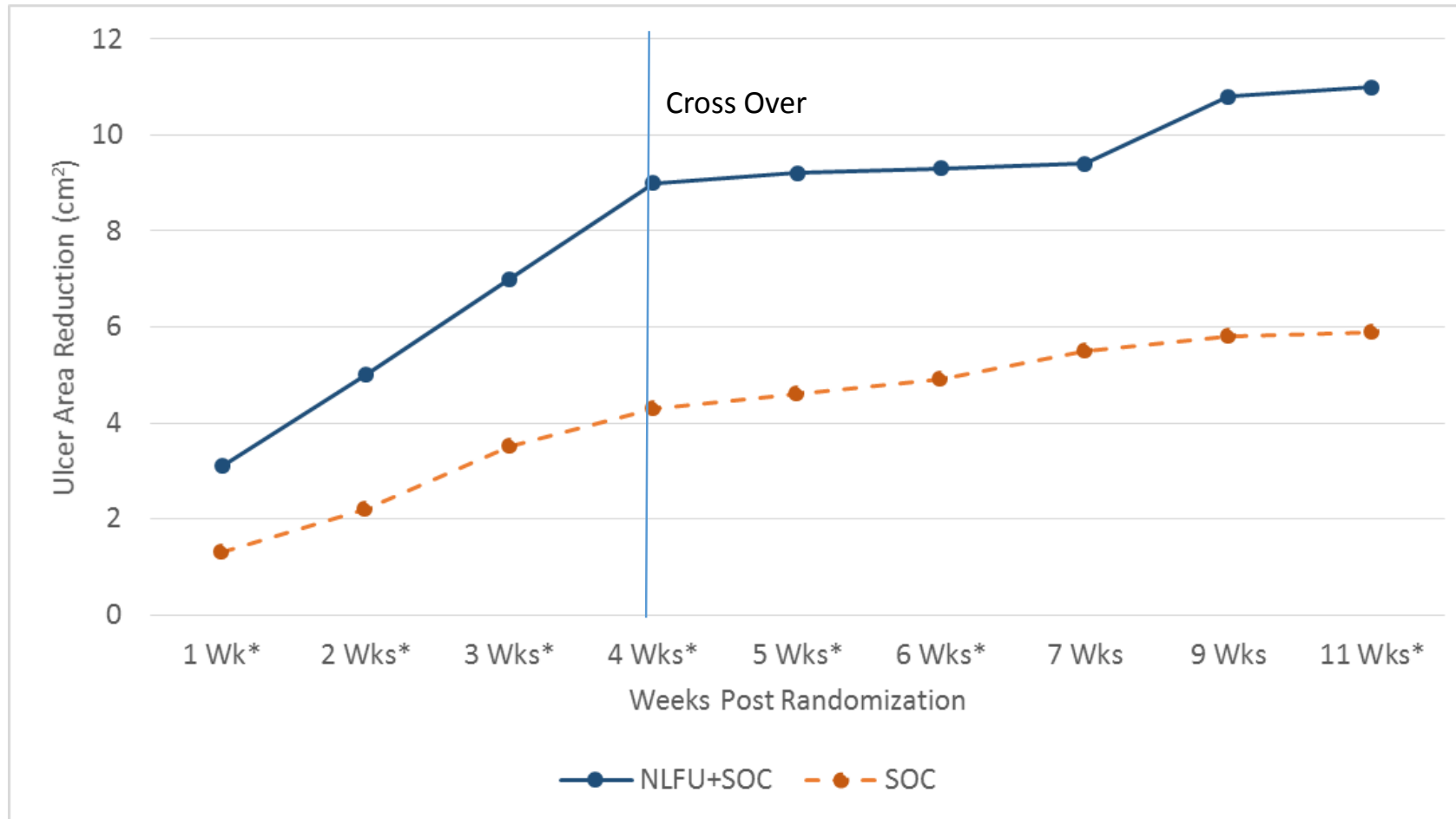


- Significance continues after adjusting for wound size and wound area
- *Median and absolute area reductions were also statistically significant*

The primary endpoint is a comparison of the treatments arm average % reduction (average of individual subjects % reductions)

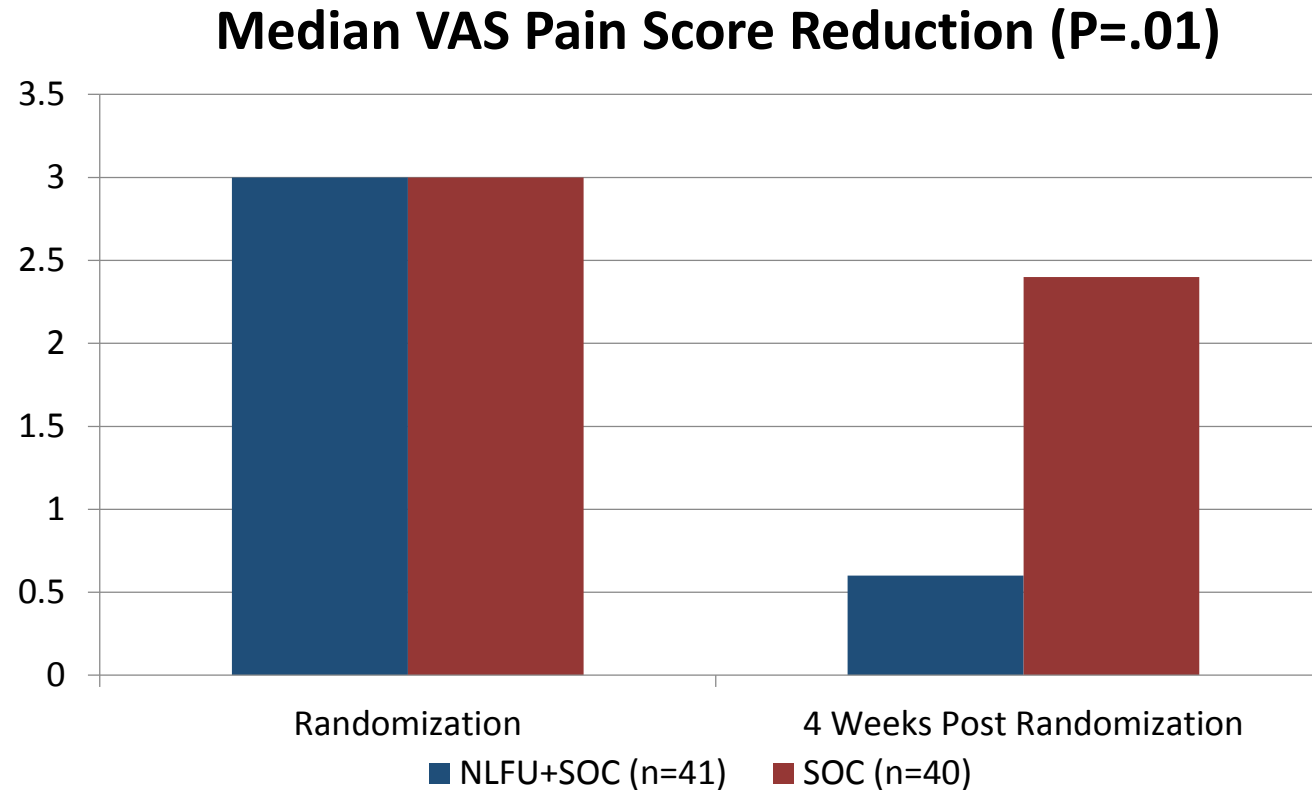
# Secondary Objective – Weekly Area Reduction

Weekly Mean Absolute Reduction in Wound Area (cm<sup>2</sup>)



\* Statistically significant differences demonstrated

# Secondary Endpoint – Bodily Pain Levels



- Significant differences noted in the reduction in pain scores (VAS 0-10 scale) from randomization to 4 weeks post treatment
- MIST+SC subjects reported an 80% reduction where SOC group reported a 20% reduction

# Wound Closure

- Primary Endpoint: Wound Area Reduction at 4 weeks: 61.6% MIST + SOC vs 45% SC alone ( $p=0.02$ )
- MIST+SOC had twice the number of complete closures by 7 weeks post randomization
- 41% of subjects experienced complete wound closure during the trial compared to
- In total, 23 subjects that received MIST during the trial healed compared to 10 SOC alone subjects

# Summary of Optimum VLU Treatment

- Pre-treatment
  - Evaluation to confirm Venous Disease and any comorbidities that require management
- Treatment:
  - Wound Preparation Weeks 0-4
    - Standard of Care (SOC) Control of Venous Disease with Compression Therapy and dressing to maintain healing environment
    - Aggressive and adequate initial debridement of VLU
    - Control of inflammation and bioburden with non-contact low frequency ultrasound therapy (NLFU)
  - Wound Closure Options
    1. Application of a CTP with maintenance SOC
    2. Continued NLFU with maintenance SOC
    3. Maintenance SOC alone (may not be an option; if non-healing, must add one of the above)

# Questions