A Phase II Randomized Double-Blind, Placebo Controlled Study in Patients with Critical Limb Ischemia to Evaluate the Safety and Efficacy of hSDF-1 plasmid (JVS-100) Post Open or Endovascular Revascularization (STOP-PAD Trial)

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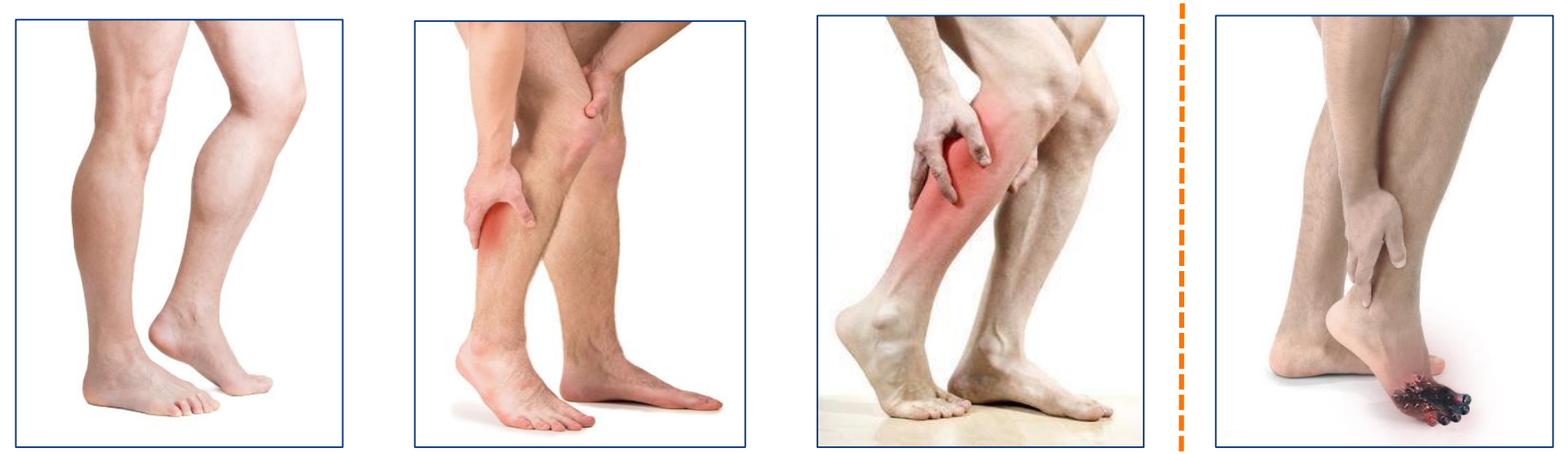
Michael Fitzgerald, Joseph Pastore, Vikram Kashyap, MD
for the STOP-PAD Investigators

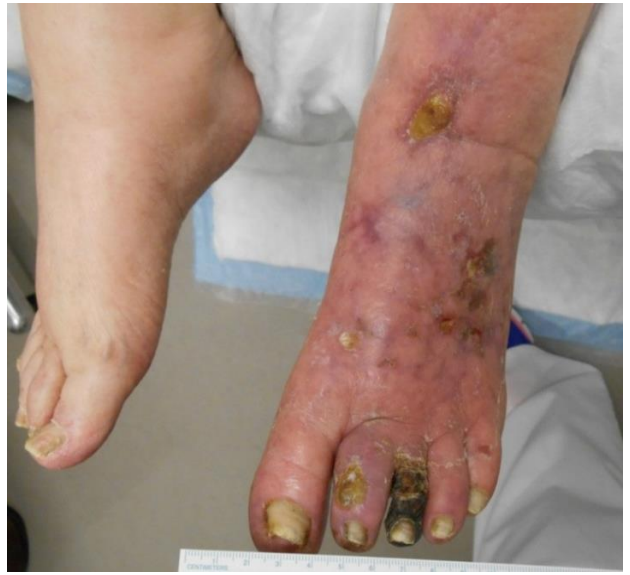
Background:
Clinical Spectrum of Peripheral Artery Disease

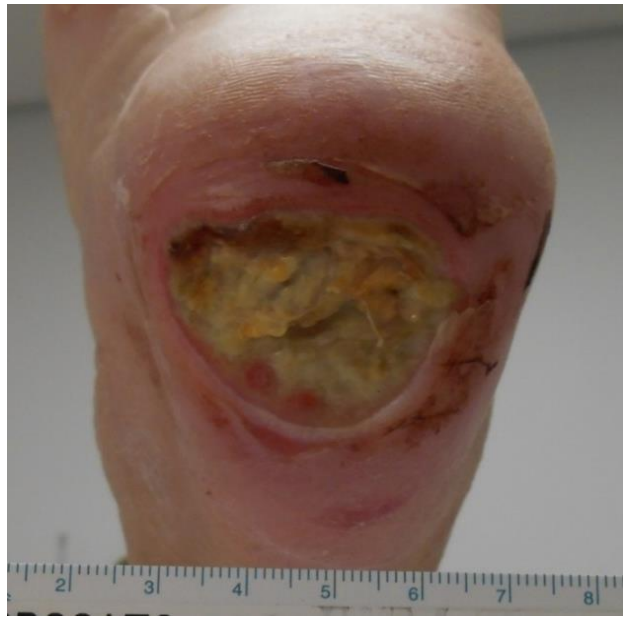


Asymptomatic PAD	Non-life style limiting claudication	Life style limiting claudication	Critical limb ischemia
Rutherford Category 0	**Rutherford Category 1-2**	**Rutherford Category 3**	**Rutherford Category 4-6**

Background – Critical Limb Ischemia

- After over 20 yrs of research we are left with bypass and angioplasty alone to treat this disease.
- However:
  - Only 20-30% of wounds heal within 3 months
  - Wounds are associated with:
    - Low quality of life
    - Depression
    - Amputations
    - Death
    - Increased health care cost

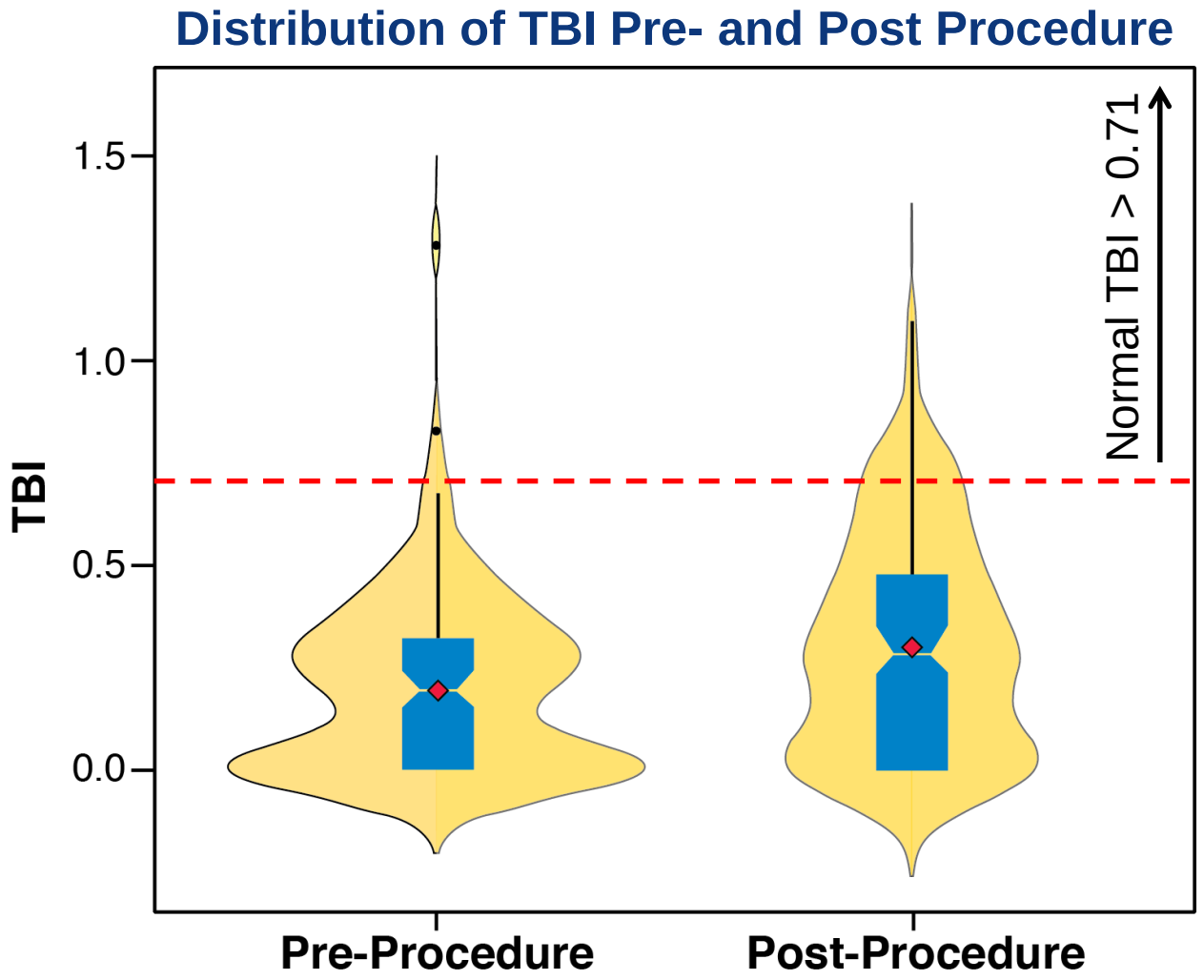




Shishehbor et al. J Am Coll Cardiol 2016;68:2002-15

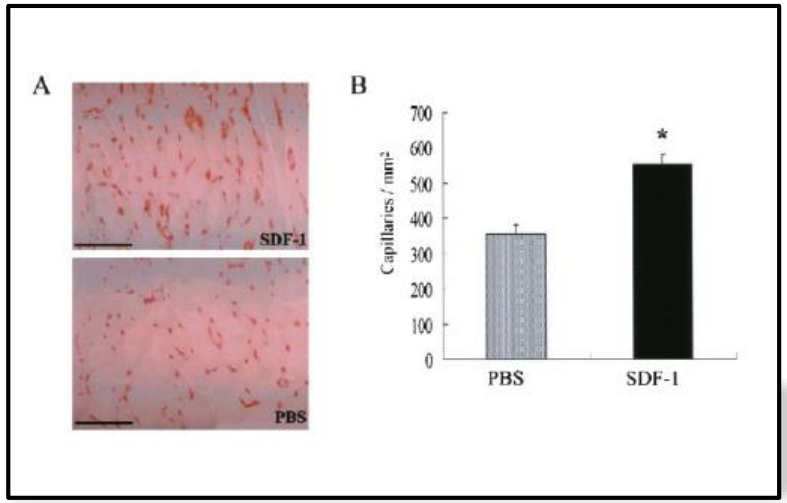
The Fundamental Problem in CLI is Perfusion

- Revascularization improves macrovascular perfusion
- But, there is seldom, if ever, a normalization of microvascular perfusion
- How can we improve both?



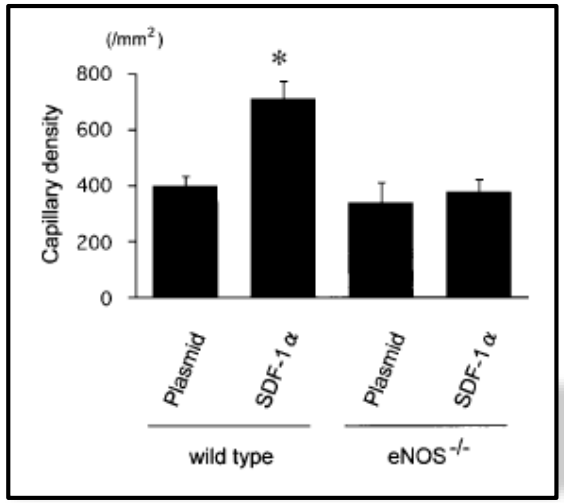
Reed and Shishehbor, JACC Cardiovasc Interv 2017;10:2451-7

- **JVS-100** is a non-viral DNA plasmid based therapy that encodes stromal cell-derived factor-1(SDF-1)



Yamaguchi, J. Circulation 2003;107:1322

- **SDF-1** through binding of the CXCR-4 receptor activates:
  - Endogenous regenerative repair pathways
  - Promotes new blood vessel growth
  - Prevents cell death
  - Causes remodeling of scar tissue



Hiasa, K. Circulation 2004;109:2454

Askari AT et al, Lancet 2003;362:697-703

Trial Objectives

- STOP-PAD is the first prospective, multicenter, randomized, double blinded, placebo controlled study to evaluate the safety and efficacy of biologic therapy (JVS-100) as an adjunct to revascularization in patients with Rutherford class V and VI CLI.

- The trial included 109 patients enrolled from 21 centers across United States.

Participating Sites	City, State	Principal Investigator	Number of patients enrolled
Holy Name Medical Center	Teaneck, NJ	John Rundback, MD	17
Morton Plant Mease Health Care	Clearwater, FL	Leslie Miller, MD	10
University Hospitals	Cleveland, OH	Vikram Kashyap, MD	11
St. Joseph's Hospital	Tampa, FL	Saihari Sadanandan, MD	9
St. Luke's MAHI	Kansas City,	Mathew Bunte, MD	8
NC Heart and Vascular	Raleigh, NC	Matt Hook, MD	6
Lifespan Health System	Providence, RI	Peter Soukas, MD	5
Cleveland Clinic	Cleveland, OH	Michael Maier, DPM	5
St. John Hospital & Medical Center	Detroit, MI	Tom Davis, MD	5
Cedars Sinai Heart Institute	Los Angeles, CA	Timothy Henry, MD	5
Northwestern University	Chicago, IL	Karen Ho, MD	5
Metro Health	Cleveland, OH	Sanjay Gandhi, MD	5
Cardiology Associates Research	Tupelo, MS	J. Murray Estess, MD	4
UC Davis	Davis, CA	Nasim Hedayati, MD	4
CV Institute of the South	Houma, LA	Craig Walker, MD	2
Mt. Sinai Medical Center	Miami, FL	Nirat Beohar, MD	2
Summa Health	Akron, OH	Justin Dunn, MD	2
Medical College of Wisconsin	Milwaukee, WI	James Gosset, MD	2
VCU Health System	Richmond, VA	Luis Guzman, MD	1
Mayo Clinic	Rochester, MN	Sanjay Misra, MD	1

STOP-PAD Committees

- **Steering Committee:**
  - **National PI:** Mehdi H. Shishehbor, DO, MPH, PhD
  - **Members:** Vikram Kashyap, MD; Jeffery Halpert, DPM; Michael Maier, DPM
- **Independent Data & Safety Monitoring Board:**
  - **Chair:** Richard P. Schwarz, PhD
  - **Members:** Corey K. Goldman, MD, PhD; Jeff Halpert, DPM; Jay Traverse, MD; Timothy O'Brien, MD
- **Independent Data and Statistical Analysis:**
  - Integrium, LLC (Tustin, CA)
- **Independent Wound Core Laboratory:**
  - Canfield Scientific (Parsippany, NJ)

Study Sponsor:
Juventus Therapeutics

Key Inclusion Criteria

- Presence of a **chronic wound** **AND** **met one of the following criteria**
  - ABI≤0.9, TBI≤0.51, toe systolic pressure ≤ 50 mmHg, no infrapopliteal runoff with dampened pulse volume recordings

- Successful below knee revascularization with straight in-line flow to the foot

- Post procedure evidence of **microvascular hypoperfusion**:
  - TBI≤0.51 or Toe pressure ≤50 mmHg or SPP≤40 mmHg or TcPO2 ≤40 mmHg

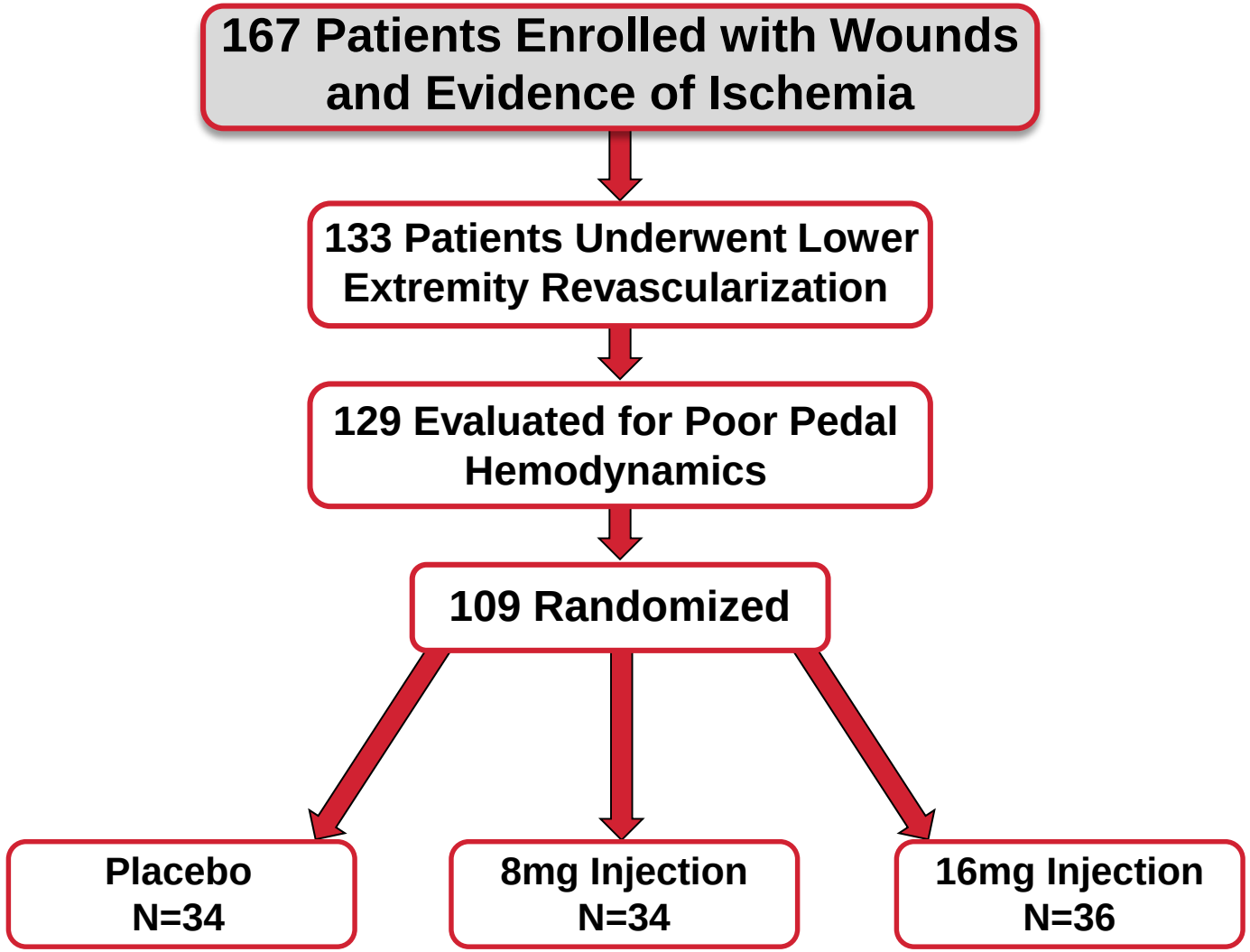
Unique Inclusion Criteria

- End stage renal disease
- Osteomyelitis
- Heel ulcer
- Presence of multiple wounds

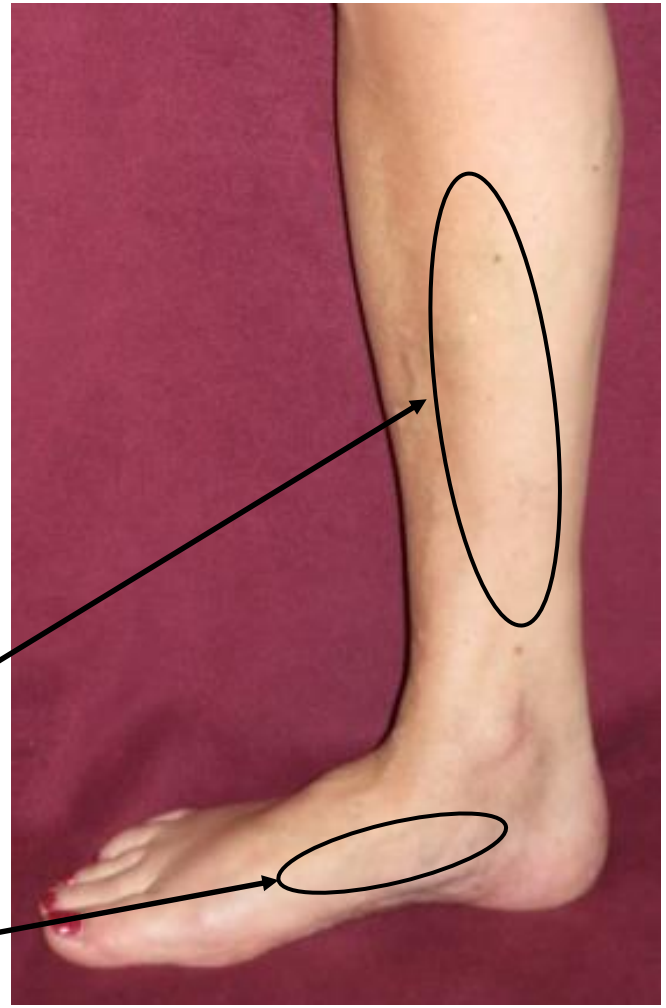
Key Exclusion Criteria

- Immunosuppressive therapy
- Minor amputation that were closed
- Wound > 25cm^2
- Significant improvement in perfusion post revascularization

STOP-PAD Trial Design and Patient Disposition

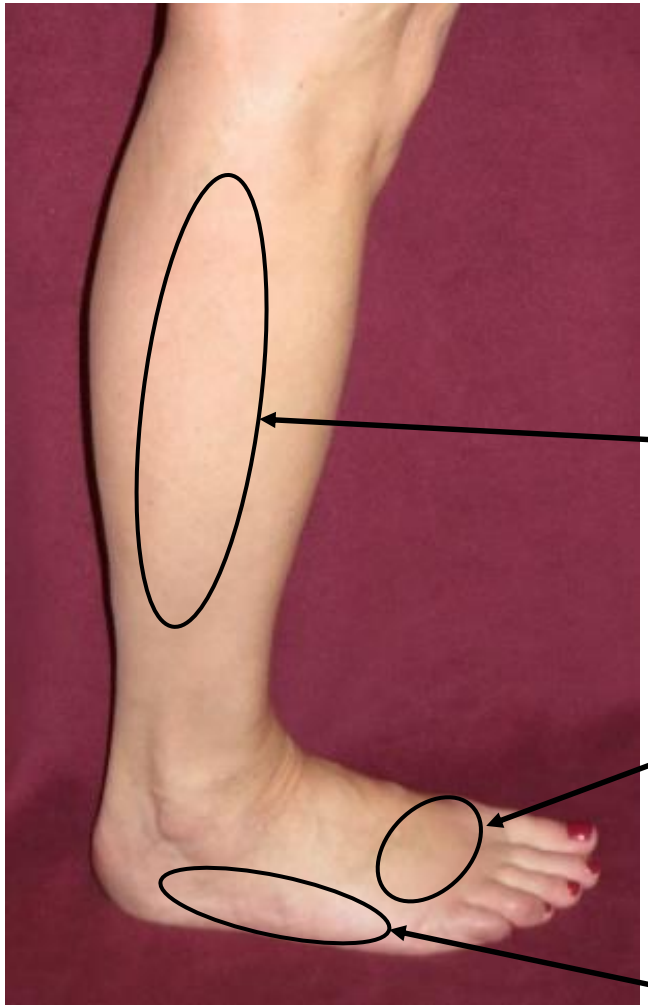


JVS-100 Injection



Injection area
(leg)

Injection area
(medial foot)



Injection area
(leg)

Injection area
(dorsal foot)

Injection area
(lateral foot)

Endpoints
Primary Efficacy

Wound Healing Score	Definition
5	Complete wound healing of index wound
3	>50% reduction in index wound surface area without evidence of necrosis
0	<50% reduction in index wound area or <25% increase in index wound area and no evidence of necrosis
-3	Evidence of necrosis within index wound area regardless of wound size.
-5	Wound progression defined as >25% increase in index wound area or, on the index leg: Amputation involving at least one metatarsal or amputation due to the index wound regardless of location

Endpoints

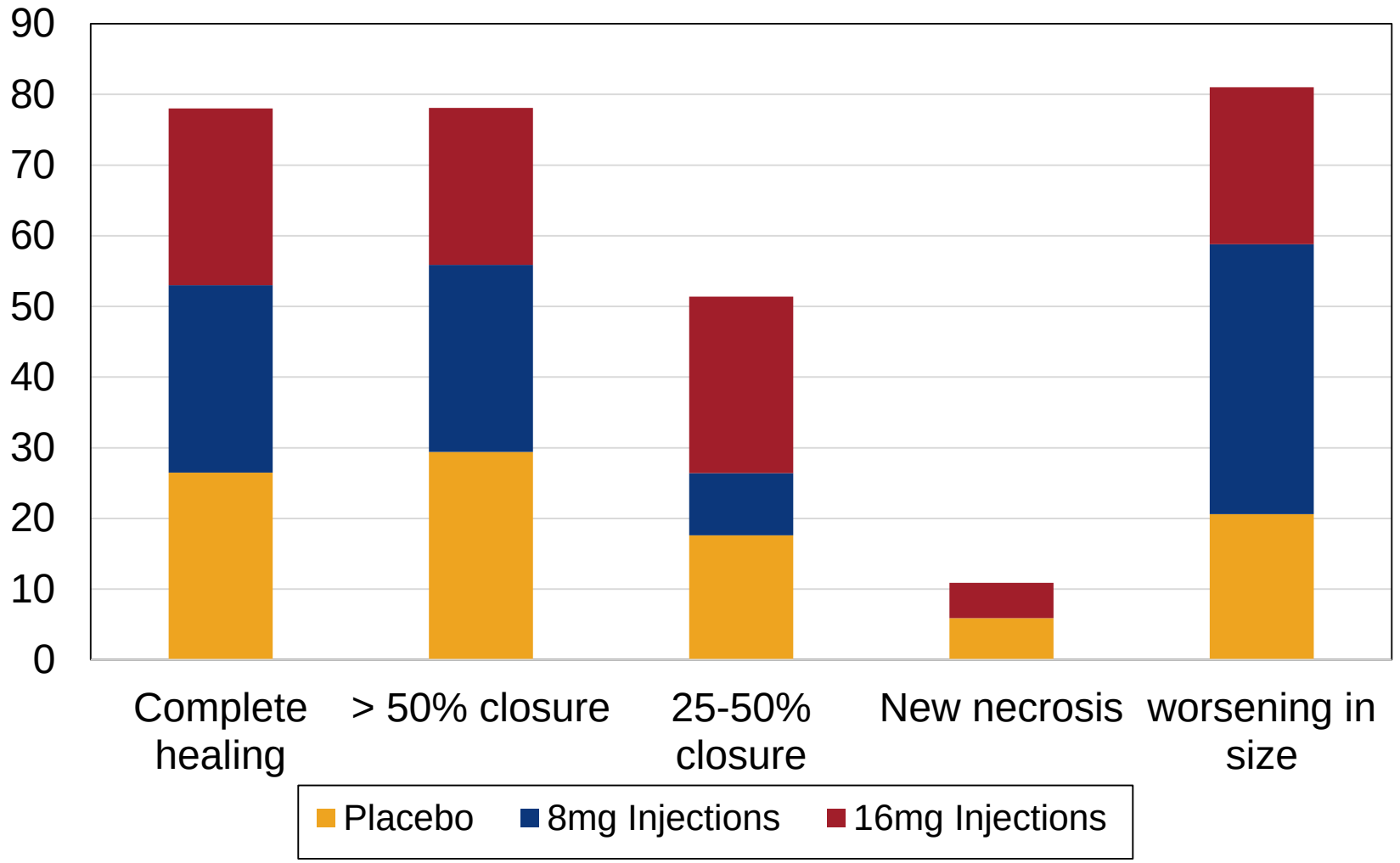
- **Safety:**
  - MALE (composite of major amputation plus clinically driven target lesion revascularization).

- **Secondary Endpoints:**
  - Changes from baseline wound measures, incidence of complete wound healing, wound size, development of wound necrosis, major amputation, all amputations, and all-cause mortality.

Baseline Characteristic mean ± SD or %	Placebo N=34	8mg Injection N=34	16mg Injection N=36
Demographics			
Age (years ± SD)	71± 12	68 ± 12	72 ± 9.8
Male gender	23 (68)	20 (59)	25 (69)
Diabetes	**28 (82)**	**26 (76)**	**29 (80)**
End stage renal disease, ESRD	**3 (8.8)**	**3 (8.8)**	**3 (8.3)**
Wound Characteristics			
Area	2.69 ± 2.04	3.542 ± 4.40	3.746 ± 5.78
Location of index wound			
Heel	**4 (11.8)**	**3 (8.8)**	**5 (14)**
Metatarsal	28 (82)	27 (79)	26 (72)
Plantar surface of the foot	2 (5.9)	3 (8.8)	4 (11)
Dorsal surface of the foot	0	1 (2.9)	1 (2.8)

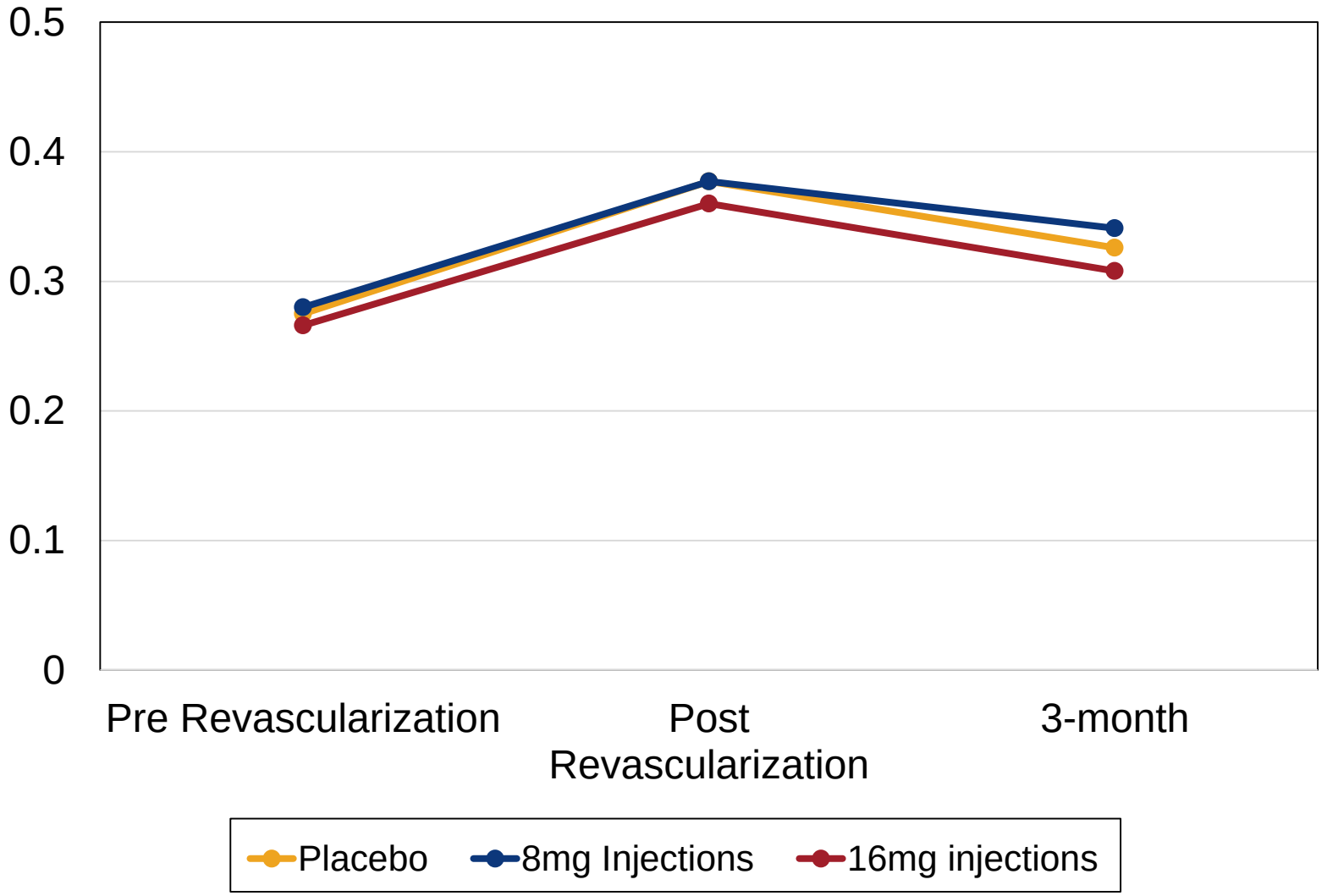
Baseline Hemodynamics and Angiographic Characteristics mean ± SD or N	Placebo N=34	8mg Injection N=34	16mg Injection N=36
Post Revascularization Hemodynamics			
Ankle brachial index, ABI	**N=28** **0.88 ± 0.40**	**N=28** **0.95 ± 0.40**	**N=32** **1.01 ± 0.50**
Toe brachial index, TBI	**N=27** **0.26 ± 0.16**	**N=26** **0.27 ± 0.16**	**N=31** **0.26 ± 0.17**
Angiographic			
Revascularized lesion location			
Popliteal	9	8	10
Posterior tibial	14	14	15
Anterior tibial	20	17	15
Peroneal	10	7	8
Foot and arch	8	7	8

Primary Efficacy (P = 0.93)



Component of Primary and Secondary Endpoints	Placebo N=34	8mg Injection N=34	16mg Injection N=36
Wound Healing			
Complete	**9 (26.5)**	**9 (26.5)**	**9 (25.0)**
>50%	10 (29.4)	9 (26.5)	8 (22.2)
25-50%	6 (17.6)	3 (8.8)	9 (25.0)
Evidence of necrosis	2 (5.9)	0	2 (5.6)
Progression of > 25%	**7 (20.6)**	**13 (38.2)**	**8 (22.2)**
Amputation as Endpoint	**5 (14.7)**	**7 (20.6)**	**7 (19.4)**
Major amputations	**0**	**1(2.9)**	**1 (2.8)**
Major adverse limb events (MALE)	**3 (8.8)**	**7 (20)**	**3 (8.3)**
Death	**1(2.9)**	**2 (5.9)**	**0**

Microcirculatory Hemodynamic Changes



Study Limitations

- Short duration
- Angiosome based approach was not mandated
- The optimal route and location to deliver JVS-100 may not be ideal
- Wound care was not standardized
- TBI may not be sensitive enough to assess microcirculation

Conclusions

- Adjunctive injection of JVS-100 failed to impact wound healing or rates of MALE in patients with Rutherford class V and VI CLI
- Only 25% of wounds healed within 3 months despite advanced revascularization and rigorous follow-up
- A quarter of the wound actually got bigger over 3 months
- Will anxiously await 6 months results; however, future biologic therapies may require addressing multiple pathways

THANK YOU!