A Phase 2 Open-Label Single-Arm Study to Assess the Effect of SNF472 on Wound Healing in Calciphylaxis (Calcific Uremic Arteriolopathy) Patients

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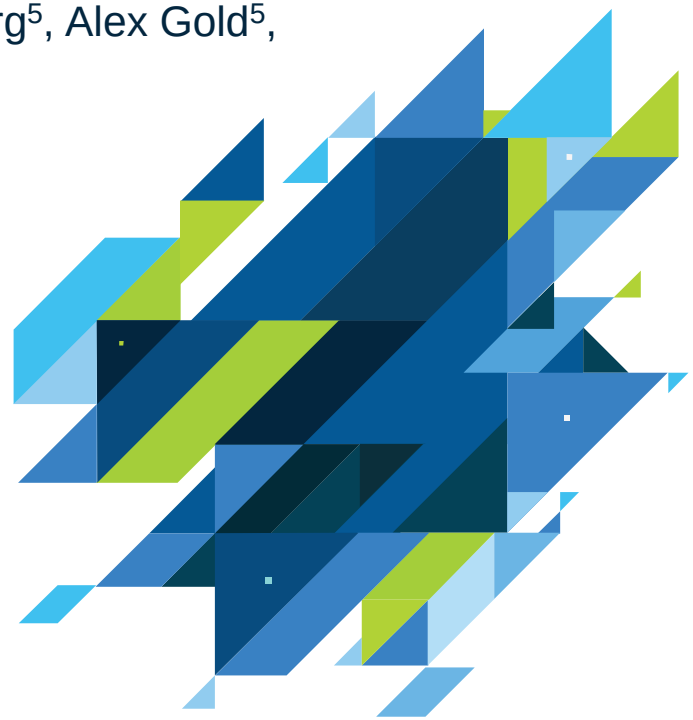


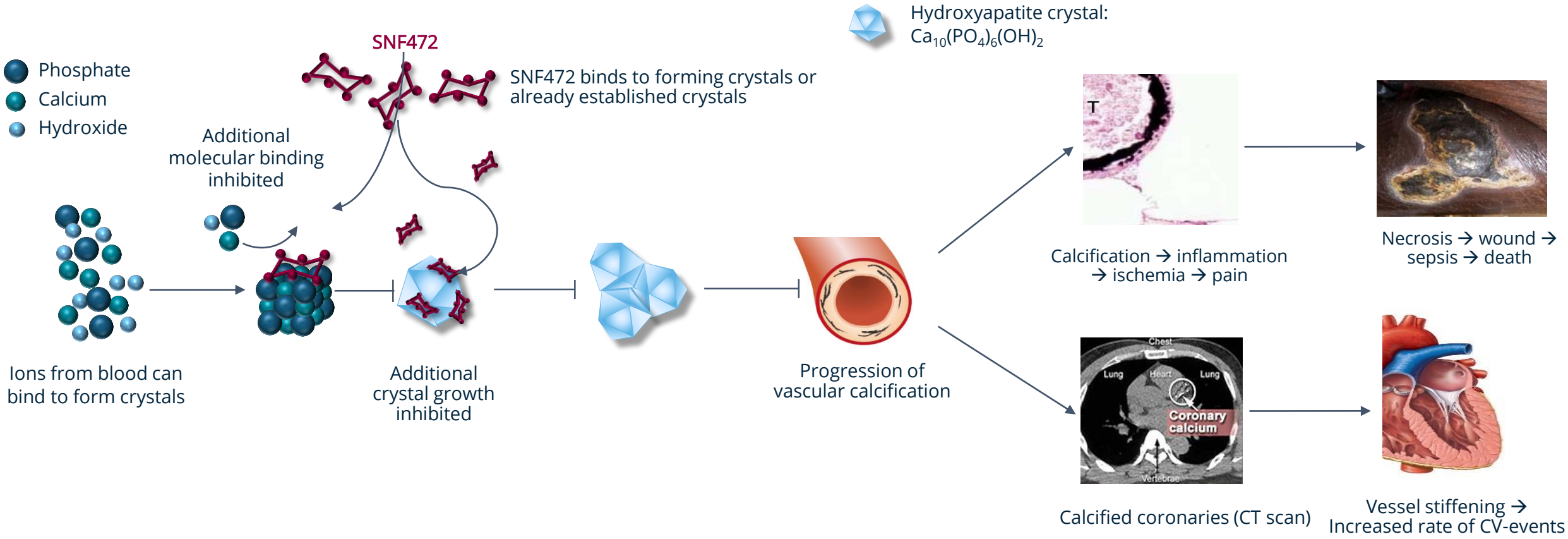
Introduction

- **Calcific uremic arteriolopathy (CUA), also called calciphylaxis**
  - Rare, severe form of vascular calcification in patients with ESRD
  - Progressive, painful necrotic skin ulcers resulting from calcification of small vessels
  - 1-year mortality rate of 55% and overall mortality of approximately 80%
  - No approved therapies exist

- **SNF472 is being developed to treat CUA in patients with ESRD on hemodialysis**
  - SNF472 is an intravenous formulation of myo-inositol hexaphosphate (IP6)
  - Selectively inhibits the formation and growth of hydroxyapatite (HAP) crystals, the final common pathway in the pathophysiology of vascular calcification

[1]Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. New England Journal of Medicine. 2018:378:1704-1714.

Simple and Elegant Physiochemical Mechanism of Action



- **SNF472 blocks new Ca-crystal formation and ongoing crystal growth**
- **Does not interfere directly with calcium and phosphate blood levels**

Study Design

Single-arm, Open-label study

- 12-week treatment period and a follow-up visit at Week 13
- SNF472 administered via the dialysis circuit during each dialysis session (3x per week)
  - 400-900 mg based on body weight category
- “Standard of care” CUA treatment per each site’s customary procedures

Key Entry Criteria

- On hemodialysis with newly diagnosed or newly recurrent CUA within 5 weeks of study start
- Diagnosis based on either clinical symptoms or a combination of symptoms and a tissue biopsy

Efficacy Measures

- Would Healing:
  - Bates-Jensen Wound Assessment Tool (BWAT)[1], a validated wound healing assessment tool
  - Qualitative wound image assessments
- Pain: Visual Analog Scale
- Quality of Life: Wound QoL

[1]Bates-Jensen B and Sussman C. Tools to measure wound healing. Chapter 5 in Wound Care: A collaborative practice manual for health professionals. Sussman C, Bates-Jensen B, eds. Lippincott Williams & Wilkins. Philadelphia, PA. 2012;131-61.

Study Endpoints

Primary Endpoint – Wound Healing

- Change from Baseline to Week 12 in the total BWAT score

Secondary Endpoints

- Wound Healing:
  - Change from Baseline by visit in the total BWAT score
- Pain:
  - Change from Baseline to Week 12 in the Pain Visual Analog Scale (VAS)
- Quality of Life:
  - Change from Baseline to Week 12 in the Wound Quality of Life (QoL) total score and in the subscales (body, everyday life, psyche)

Wound Healing as Measured with the Bates-Jensen Wound Assessment Tool (BWAT)

- A validated, objective, quantitative tool that can be applied systematically across sites
- Evaluates 13 characteristics of wounds:
  - Size
  - Depth
  - Edges
  - Undermining
  - Necrotic tissue type
  - Necrotic tissue amount
  - Surrounding skin color
  - Exudate type
  - Exudate amount
  - Peripheral tissue edema
  - Peripheral tissue induration
  - Granulation tissue
  - Epithelialization
- Each characteristic is rated on a scale of 1 to 5
- Possible range of total BWAT score is 13 – 65
- BWAT was selected based on regulatory guidance to use a quantitative method to measure wound healing

[1]Bates-Jensen B and Sussman C. Tools to measure wound healing. Chapter 5 in Wound Care: A collaborative practice manual for health professionals. Sussman C, Bates-Jensen B, eds. Lippincott Williams & Wilkins. Philadelphia, PA. 2012;131-61.

Subject Disposition

Population / Disposition	n (%)
ITT	14 (100%)
Completed study/ Per Protocol	11 (79%)
Early discontinuation	3 (21%)
Reasons for discontinuation:	
Subject withdrew consent	1 (7%)
Death	1 (7%)
Withdrew from dialysis (led to death)	1 (7%)
Adverse event	0
Lost to follow-up	0

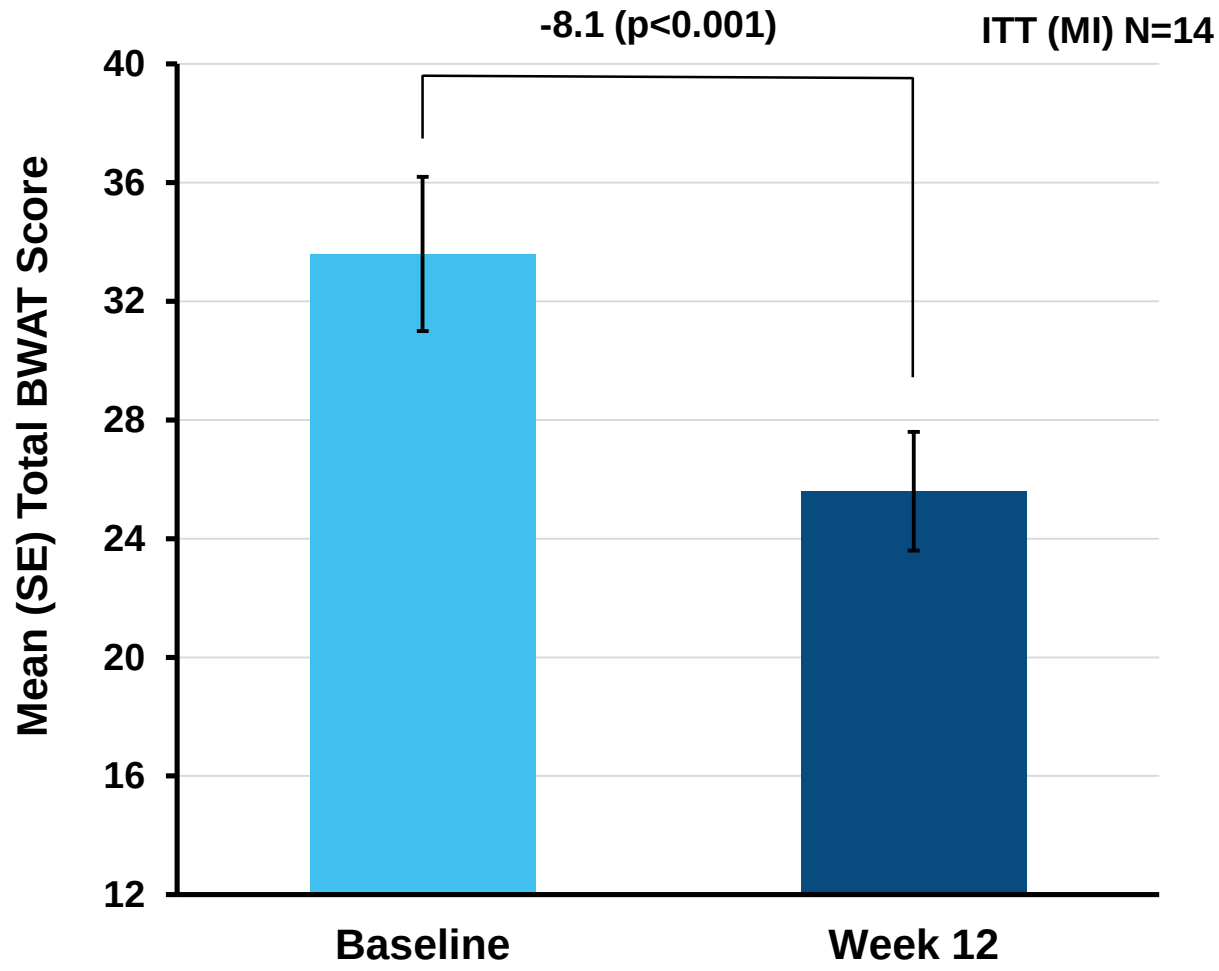
ITT, Intent-to-treat population

Demographics and Baseline Characteristics (ITT Population, N=14)

Parameter		Mean (SE)	Range
Age (years)		61 (3.8)	34 - 90
Years on Hemodialysis		3.8 (1.2)	0.03 -15
			n (%)
Sex	Male		3 (21)
	Female		11 (79)
Race	White		10 (71)
	American Indian / Alaska Native		2 (14)
	Black / African American		2 (14)
Baseline Conmeds	Warfarin[a]		2 (14)
	STS[b]		11 (79)

[a]One of the 2 subjects receiving warfarin at baseline stopped warfarin at Week 3.
[b]STS, sodium thiosulfate. 1 additional subject initiated STS at Week 7, 1 subject stopped STS at Week 2, others continued on STS along with SNF472.

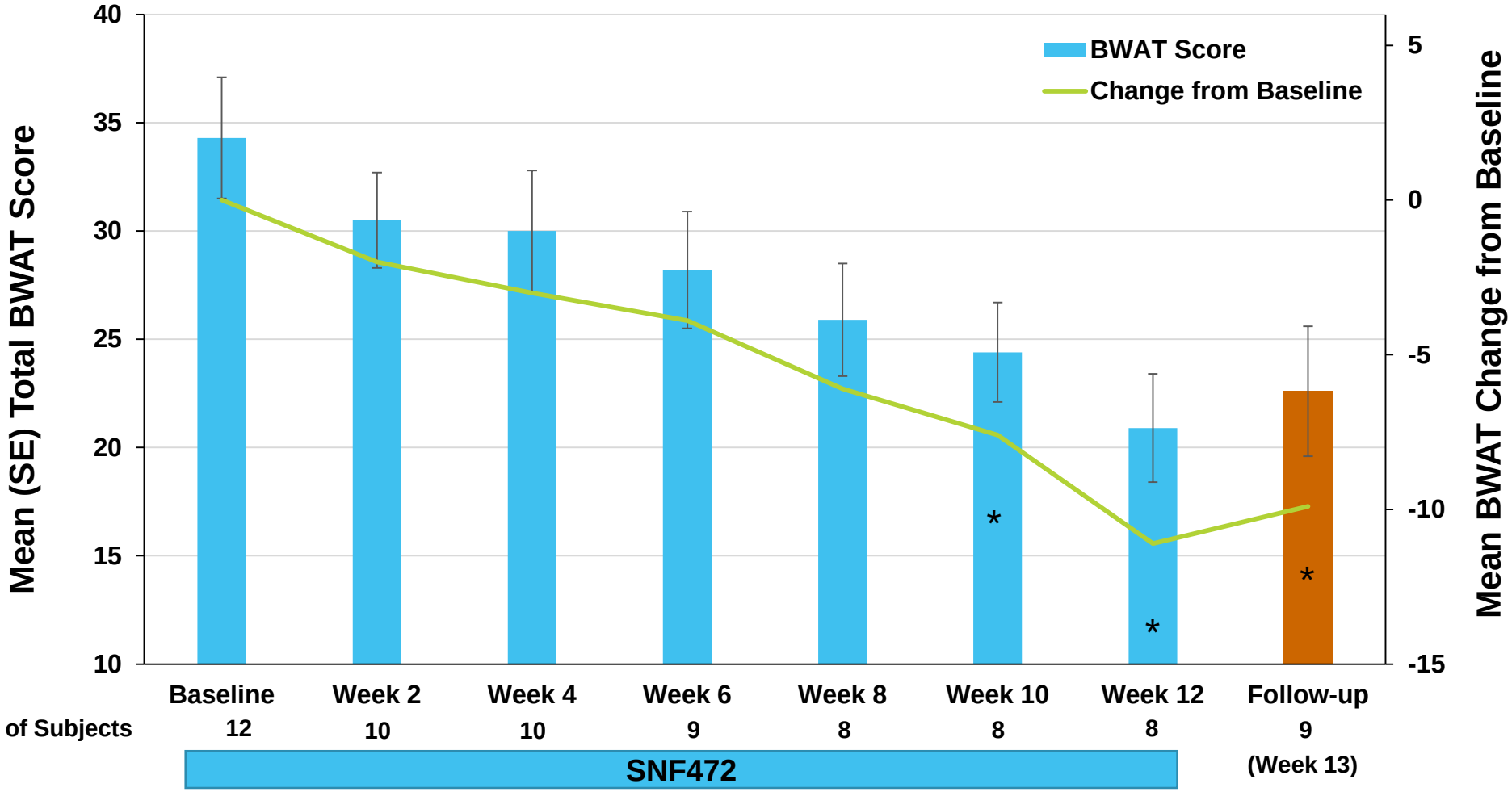
Primary Endpoint: Wound Healing Measured by Total BWAT Statistically Significant Improvement from Baseline to Week 12



ITT (MI), Intent-to-treat population with multiple imputation

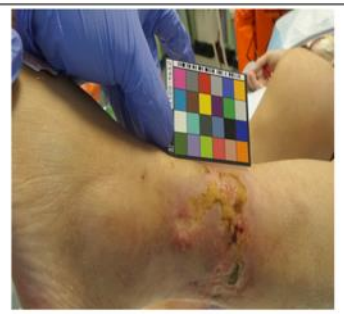
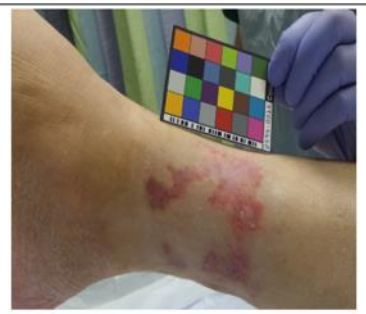
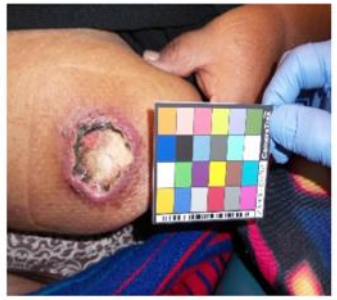
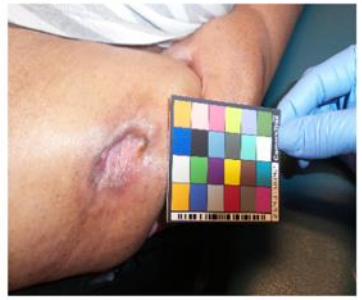
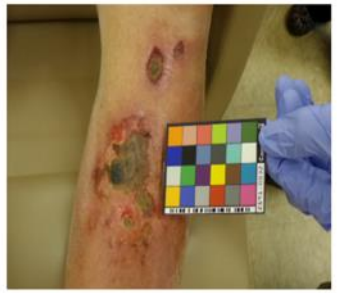
Secondary Endpoint: BWAT Over Time
Consistent Reduction in BWAT Score Over Time

Change from Baseline in Total BWAT Score by Week for the Primary Lesion – ITT Observed



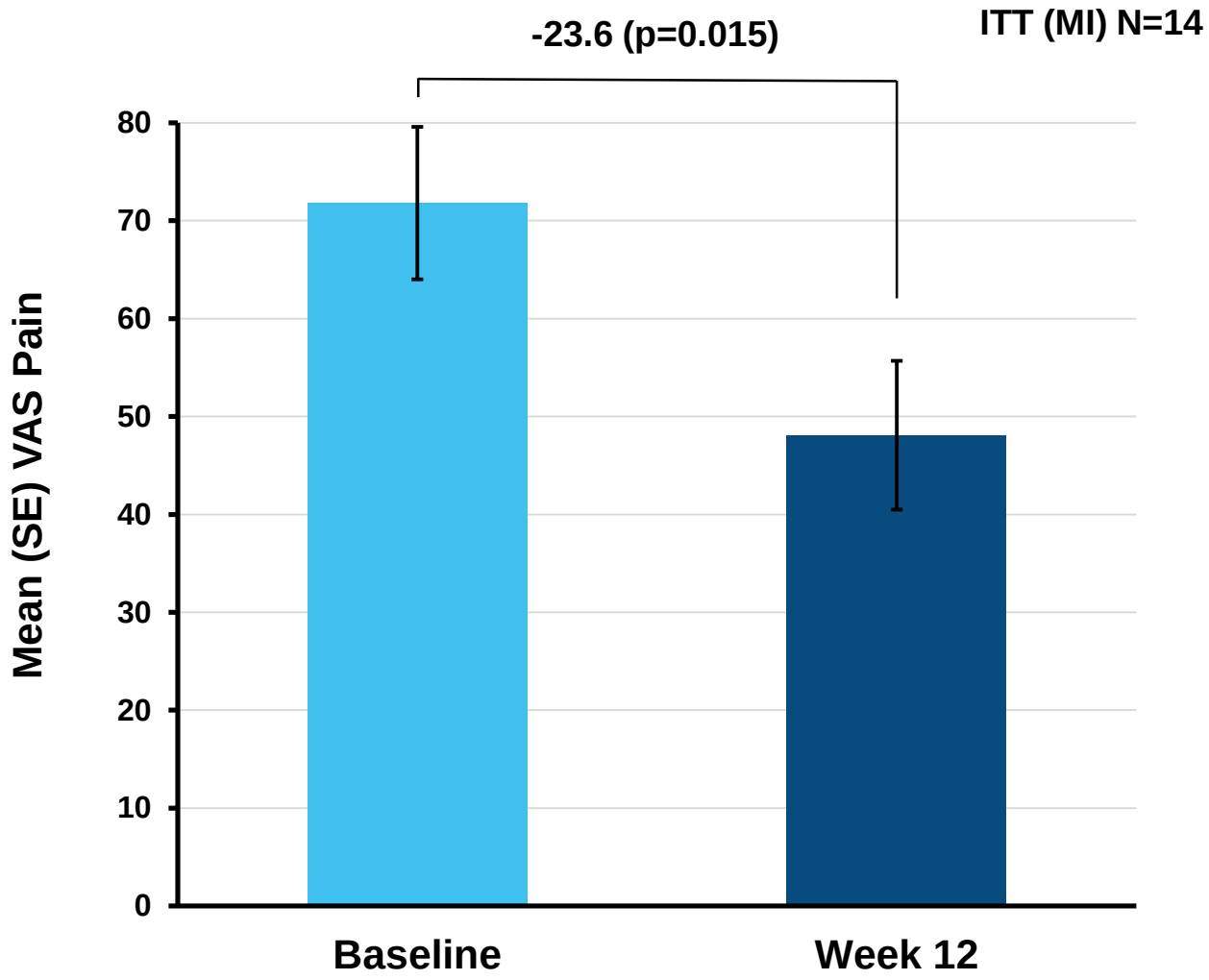
*p<0.05 change from baseline

Secondary Endpoint – Qualitative Wound Image Assessment Examples of How Experts Evaluated Wound Development

Subject ID	Baseline	Week 12	Assessment
Subject 1			Improved
Subject 8			Improved
Subject 6*			Worsened

*SNF472 plasma concentration was below the limit of quantification in Subject 6 who had significant lesion worsening. Plasma SNF472 was in the expected range in all other subjects.

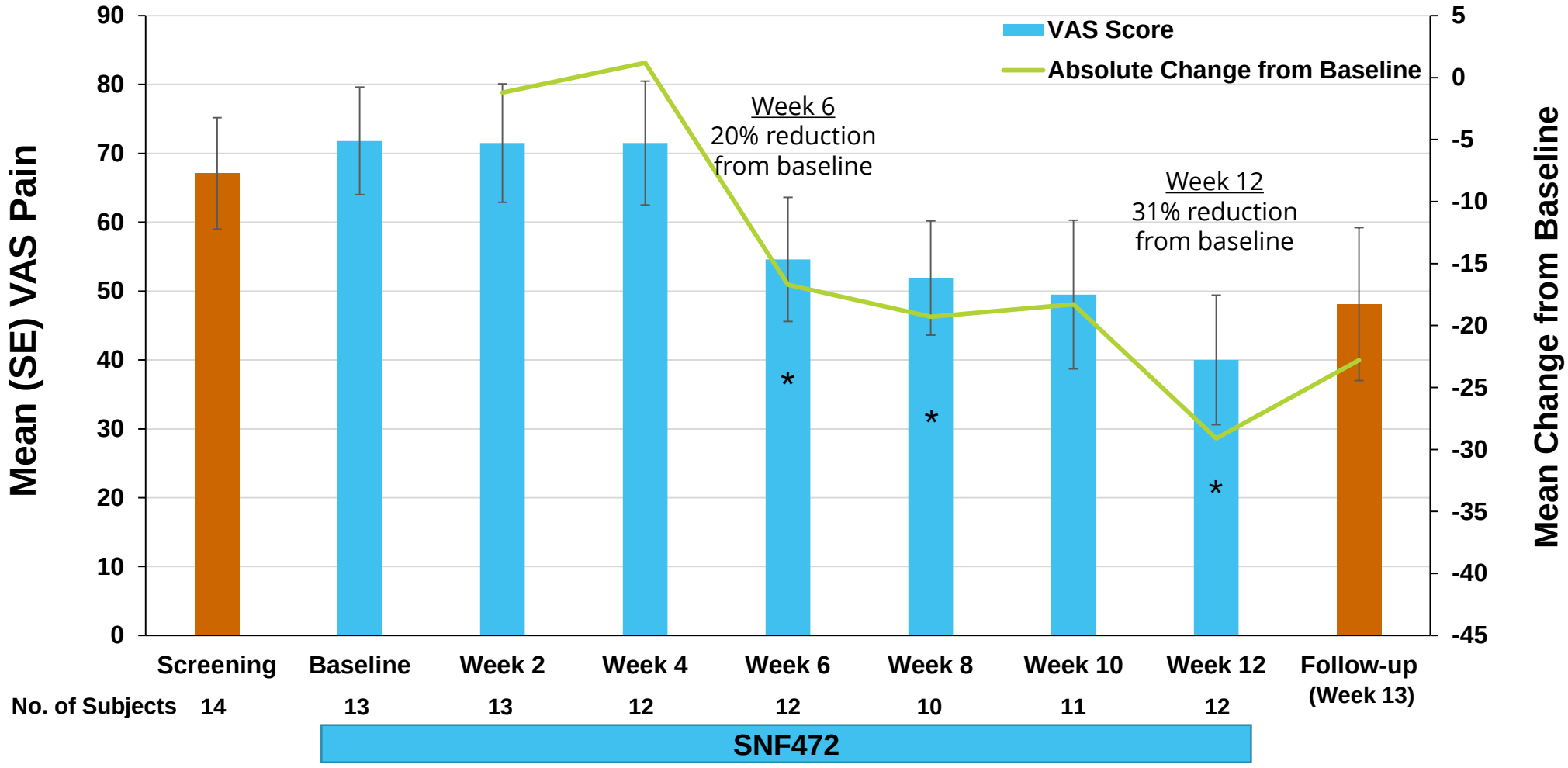
Secondary Endpoint: Statistically Significant Reduction in Pain from Baseline to Week 12 Using VAS



ITT (MI), Intent-to-treat population with multiple imputation

Secondary Endpoint: Pain VAS Over Time Consistent Reduction Was Observed from Week 6

Change from Baseline in Pain VAS By Week - ITT (observed)



*p<0.05 change from baseline

Safety and Tolerability

Adverse Events

- 14 subjects reported 79 treatment-emergent adverse events

Serious Adverse Events and Deaths

- 13 SAEs were reported for 7 subjects, including 2 deaths:
  - Cellulitis, fluid overload, haematemesis, gangrene (wet), gangrene (dry), pulmonary edema, hypertensive emergency, abdominal wound dehiscence, sepsis, urinary tract infection, pyrexial infection due to leg ulcers
  - One death due to cardiogenic shock, one death after withdrawal from hemodialysis (cardiorespiratory arrest)

Laboratory and ECG Data

- No clinically significant changes in any lab or ECG parameter

Conclusions

- This was the first multicenter, international, prospective, interventional study of CUA
- SNF472-treated subjects showed statistically significant and clinically meaningful improvements in wound healing and pain
- SNF472 was generally well tolerated with adverse events consistent with the study population

Perspectives

- A Phase 3 randomized placebo-controlled trial of SNF472 for CUA is in planning stages
- A Phase 2 study to assess the ability of SNF472 to reduce cardiovascular calcification in ESRD is in progress

Thank you!