MediWound

EscharEx®
Next-Generation of Enzymatic Debridement

KOL Event

July 12th, 8:00am ET

Robert J. Snyder, DPM

John C. Lantis, MD

Cyaandi R. Dove, DPM

Kevin Feng

KOL Event on EscharEx - Agenda

Presenter	Topic
Ofer Gonen, CEO	Welcome & introduction
Robert J. Snyder, DPM, MBA, MSc[1]	U.S. wound care debridement practice; the unmet medical need
John Lantis, MD[2]	EscharEx clinical evidence and potential role; Phase 2 study results
Robert J. Snyder, DPM, MBA, MSc	Pharmacology study results; biofilm opportunity overview
Cyaandi Dove, MD[3]	Case series from the Pharmacology study; EscharEx potential as a 1st line therapy
Kevin Feng, Oliver Wyman	U.S. Market research insights: landscape analysis and strategic opportunities
Ofer Gonen, CEO	Closing remarks
KOL Panel	Expert Q&A session

(1) Chief Medical Director, EscharEx program

(2) Consultant; Principal Investigator in the Phase II Study

(3) Principal Investigator in the Phase II and Pharmacology studies

Debridement as the centerpiece of wound management and discussion of current unmet medical needs

Robert J. Snyder, DPM, MSc, MBA, CWSP, FFPM FRCPS(G)
Chief Medical Director, EscharEx Program, Mediwound
Dean, Professor and Director of Clinical Research
Barry University School of Podiatric Medicine

It All Begins with Debridement- Pivotal First Step

Promoting epithelialization of chronic wounds has been applied to wound management as a priority

- *D: Debridement of nonviable tissue*
- *I: Management of Inflammation and Infection*
- *M: Moisture control*
- *E: Environmental and Epithelialization assessment*

The primary goal of debridement is to remove all the devitalized tissue from the wound bed to promote wound healing.

- Debridement is also used for removal of biofilm, bioburden along with senescent cells
- Chronic, non-debrided tissue becomes a “petri dish” for higher bacterial load which leads to infective processes and poor healing

Debridement Purpose

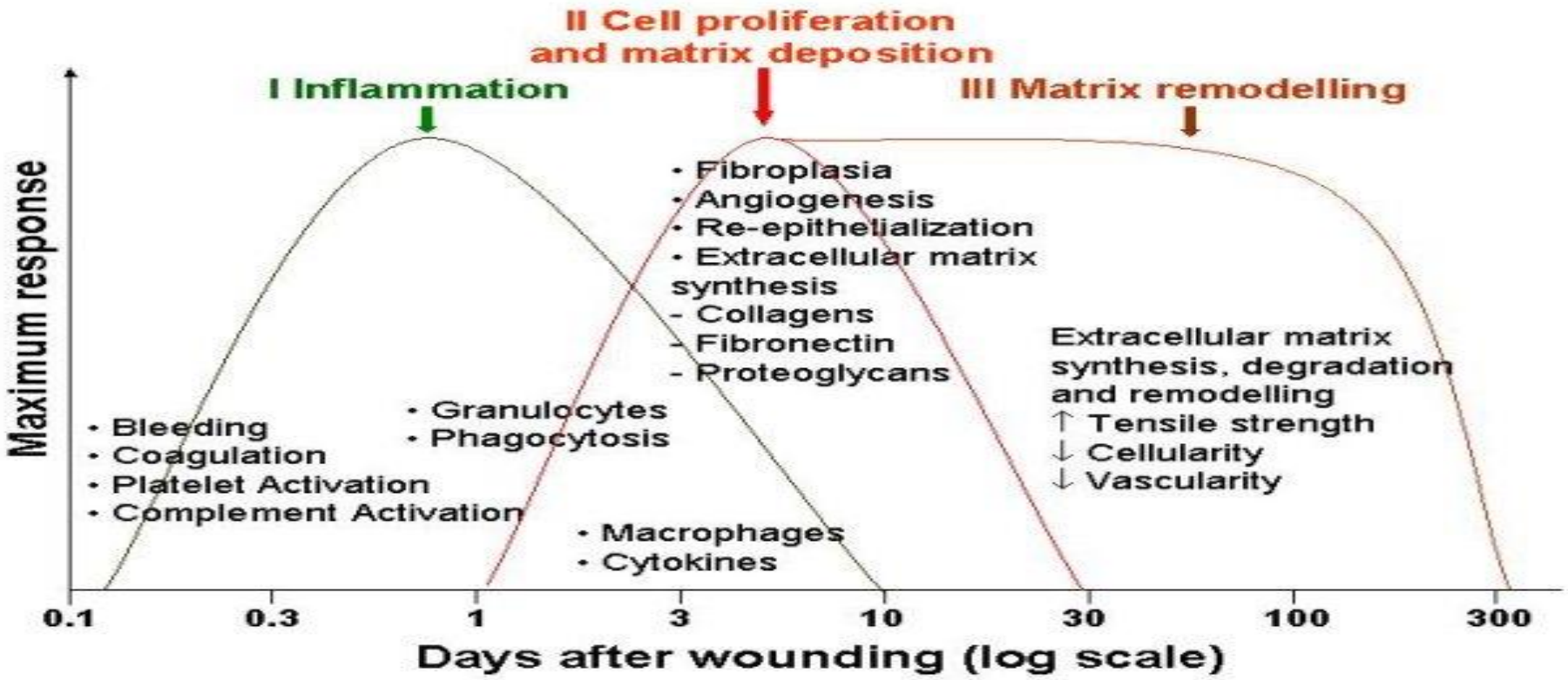
The underlying pathogenic abnormalities in chronic wounds cause a continual build-up of non-viable tissue

Optimum debridement should achieve a balance between the removal of necrotic tissue and preservation of healthy tissue and not inhibit subsequent healing

O'Brien M: Methods of debridement and patient focused care. J Comm Nurs 17(11): 17-25, 2003.
G.S.Schutz, et al., Wound bed preparation: a systemic approach to wound management, Wound Rep Reg Supplemental, 2003;11:1-28

Wound healing Schematic

Balance between production and degradation of molecules



Chronic: balance is lost and degradation plays a large a role

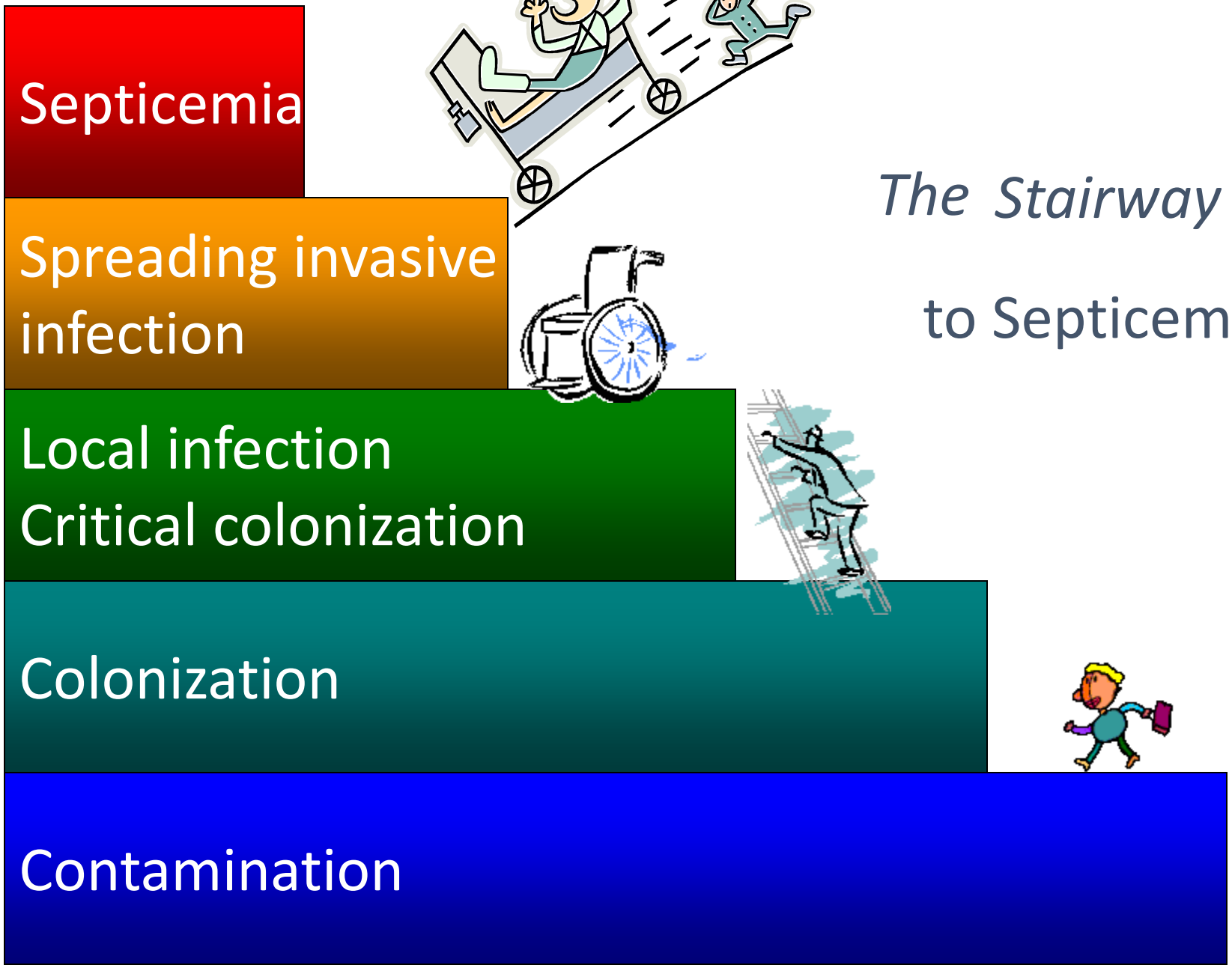
Why Debride

- Necrotic tissue impairs the wound repair process
- Senescent cells must be removed from wound bed
- To remove non-migratory cells from the ulcer edge
- To control excessive or abnormal bacterial load
- May allow for improved availability of growth factors
- To evaluate for abscess and or tunnels
- To manage and control the pathology

Mulder GD, Vande Berg JS. Cellular senescence and matrix metalloproteinase activity in chronic wounds. JAPMA 2002;92(1):3407.

Sibbald R, Williamson D, Orsted H, et al. Preparing the wound bed-debridement, bacterial balance, and moisture balance. Ost/Wound Manag 2000;46(11):14-22, 24-8, 30-5.

The Stairway to Septicemia

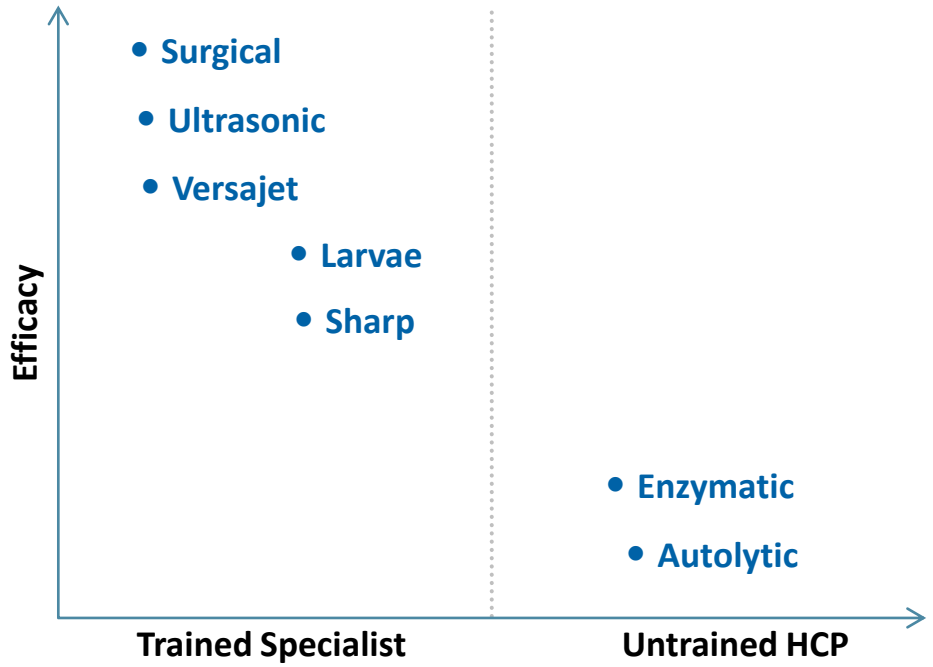


Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis 17:91-96. 2004.

Debridement in Out-patient Management

++ Fast and effective

− Specialist time
Pain / anesthesia
Bleeding risk



\+ Use in conjunction with sharp
Most can apply
Use on wounds with PAD
Use in painful wounds
Move on to advanced treatment sooner

−
Not all wounds appropriate
More frequent application
Many still need sharp debridement

Significant Medical Need for Rapid and Effective Debriding in Outpatient Settings

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The Unmet Need and Rationale for Development

A rough prevalence rate of chronic non-healing wounds in developed countries is 1-2% of the general population

Routine care of non-healing chronic wounds starts with debridement- the necessity to induce the functional process of tissue repair

Sharp is the dominant debridement method used. Non-sharp debridement techniques are primarily used adjunctive to sharp or reserved for patients considered ineligible for sharp

There is a clear unmet need for an effective & easy to use non-sharp product for debridement of chronic wounds

EscharEx®

EscharEx is a new biological product developed for debridement of non-viable tissue in patients with hard-to-heal wounds (DFUs and VLUs)

EscharEx active pharmaceutical ingredient is a complex and concentrate mixture of proteolytic enzymes enriched in bromelain, derived from the stem of pineapple plant

The mechanism of action of the product is mediated by the proteolytic activity of the enzymes' mixture which allows debridement of non-viable necrotic tissue in hard-to-heal wounds

EscharEx Clinical Evidence

John C. Lantis, M.D.
Mount Sinai West Hospital and Icahn School of Medicine

EscharEx®

- **EscharEx** is a new biological product under development for debridement of non-viable tissue in patients with DFUs and VLUs
- EscharEx active substance is a complex mixture of proteolytic enzymes enriched in bromelain extracted from the pineapple stems
- The same active substance of NexoBrid, a drug product approved in EU and ROW for debridement of 2nd and 3rd degree burns. Phase 3 study in the US (named DETECT) completed successfully
- EscharEx is supported by the pre-clinical and clinical data generated for NexoBrid regulatory approval
- The mechanism of action (MOA) of EscharEx is mediated by the proteolytic activity of the enzymes
- The enzymatic mixture composition is an important and unique attribute of the product that enables fast and effective complete debridement of wounds exhibiting various forms of denatured proteins and devitalized tissues

Phase 2 Completed Study[1]

Study Objectives:

To asses the safety and efficacy of EscharEX-01 compared to Gel Vehicle

Study Design

Study conducted in Israel and Hungary, completed October 2017

Stage I

- Prospective, Randomized, Assessor blinded, multicenter Controlled - EscharEx vs. Gel Vehicle (2:1)
- 73 Patients: venous leg ulcers, diabetic lower extremity ulcers and traumatic/post operative wounds
- Treatment: 5% EX-01 up to 10 applications of 4 hrs each, up to 6M follow-up

Stage II

- 38 Patients: venous leg ulcers, diabetic lower extremity ulcers
- Treatment: 2.5% EX-01 up to 8 applications of 24 hrs/3 times a week

Endpoints

Primary endpoint

- **Stage I:** Incidence of complete debridement of non-viable tissue vs. Gel Vehicle
- **Stage II:** Safety of EX-01 over extended period of application

Secondary endpoints

- Time to complete debridement; granulation tissue; incidence and time to wound closure; QoL

Safety

- Local and systemic safety and tolerability

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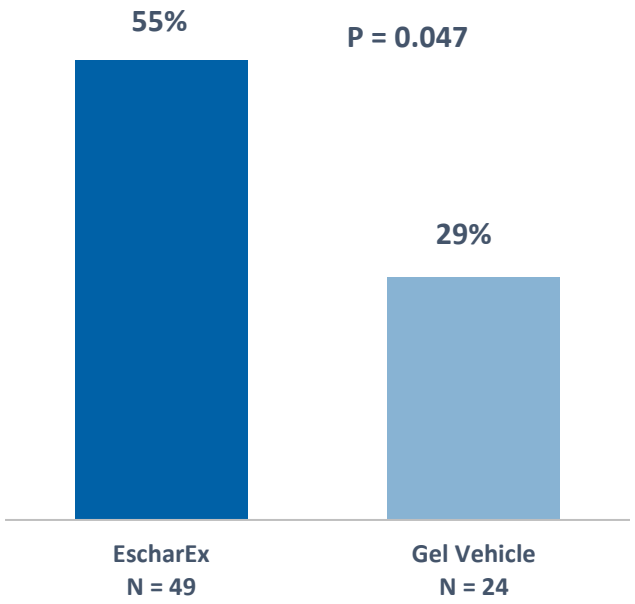
[1] *Bromelain-based enzymatic debridement of chronic wounds: Results of a multicentre randomized controlled trial, Shoham et al, Wound Rep Reg. 2021;29:899–907.*

Stage 1- Baseline Characteristics

- Seventy three (73) patients were randomized:
    - 23 Diabetic lower extremity ulcers, 24 VLU and 26 post trauma non-healing wounds
- Age was not significantly different between study groups
- Slightly more female subjects were treated with EscharEx, while more male subjects were treated with Gel Vehicle - differences were not significant
- VLU and Trauma/post-op wounds treated with EscharEx (mean 33.6cm^2; SD 29.7) while larger in size than wounds treated with Gel Vehicle (mean 25.8cm^2; SD 22.4) - differences were not significant
- Per etiology, wounds treated with EscharEx (mean 72.8 wks; SD 163) were older than wounds treated with Gel Vehicle (mean 30.8 wks; SD 41) - difference was not significant in the 'All' group

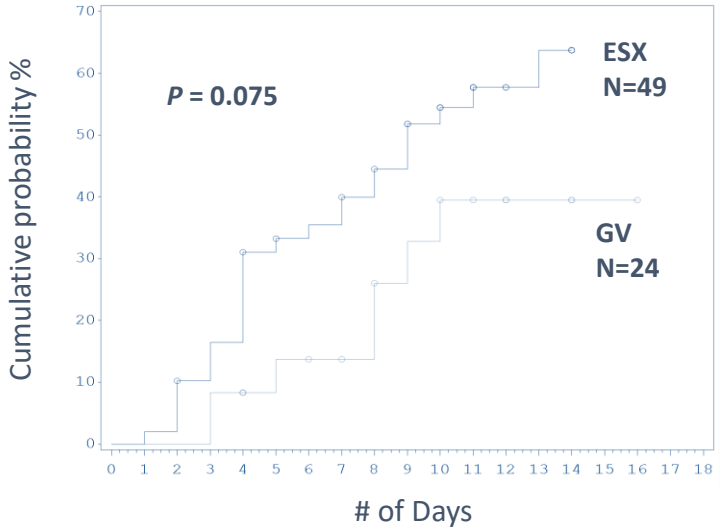
Study Met its Primary Endpoint

Incidence of complete Debridement*



Significantly higher incidence of complete debridement

Time to complete debridement**



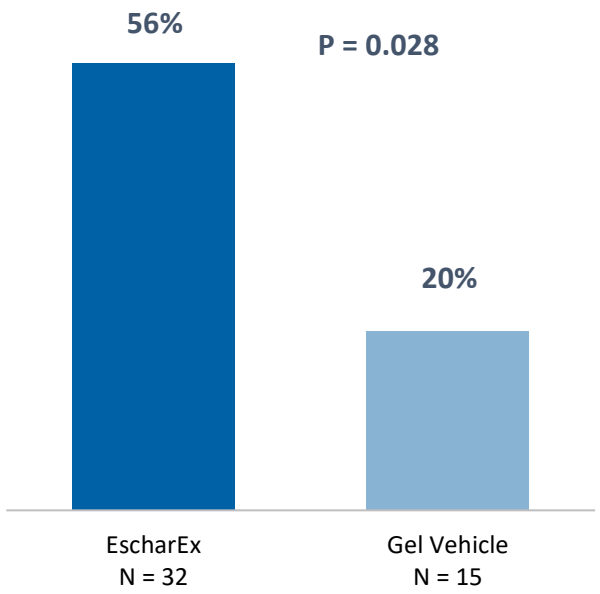
Shorter time to achieve complete debridement

>90% of the patients who completed debridement with EscharEx were debrided within 7 days (after 4-5 daily applications)

*With up to 10 daily applications
**Kaplan-Meier survival analysis with log rank p-value

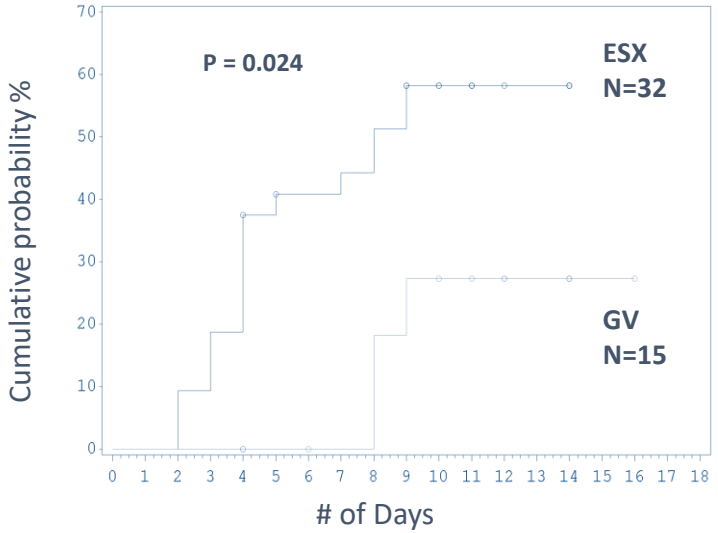
VLUs and DFUs Post-Hoc Analysis

Incidence of complete debridement*



Significantly higher incidence of complete debridement

Time to complete debridement**



Shorter time to achieve complete debridement

*With up to 10 daily applications
**Kaplan-Meier survival analysis with log rank p-value

Stage 2 - Safety

No. of patients treated	38
Etiology	• Venous leg ulcers • Diabetic lower extremity ulcers
Study drug	• **2.5%** EscharEx vs. gel vehicle, 2:1
Debridement	• Up to 8 applications, **24 or 48/72 hrs** each (2 cohorts)
Follow up	• 12 weeks, or until wound closure + 2 weeks durability
Primary analysis	• Safety (study not powered for efficacy)

- Most of the AEs were mild to moderate and unrelated to treatment
- No differences were observed in the rate of systemic AEs between treatment groups
- Treatment-related AEs were local, mild to moderate and reversible (e.g. maceration, erythema, and edema at the peri-wound)

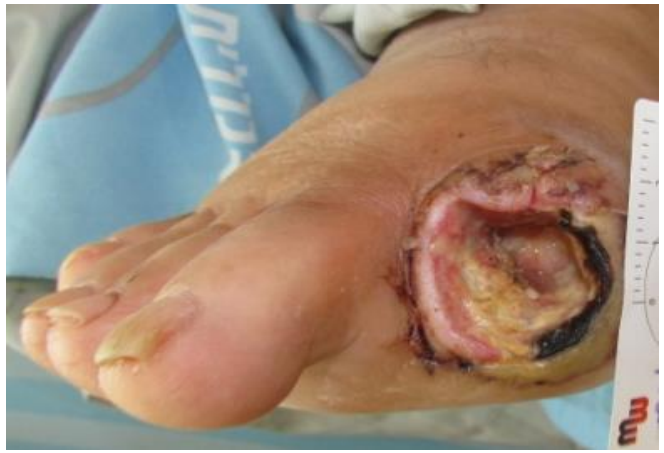
Summary

- Patients' baseline characteristics were similar between the arms. Patients in EscharEx arm had on average larger and older wounds (yet not statistically significant)
- The study met its primary efficacy endpoint
- **Patients treated with EscharEx demonstrated a significantly higher incidence of complete debridement compared to patients treated with gel vehicle (EscharEx: 55% vs. gel vehicle: 29%, p=0.047)**
    - *Complete debridement was achieved earlier in patients treated with EscharEx*
    - *The effect was even greater in diabetic lower extremity ulcers and in venous leg ulcers*
- **EscharEx was safe and well tolerated in all tested doses and dosing regimens**

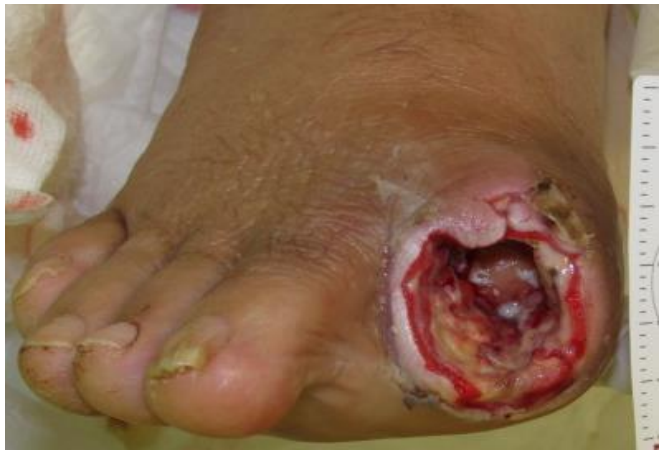
The overall data demonstrate a favourable benefit/risk ratio

Case Study

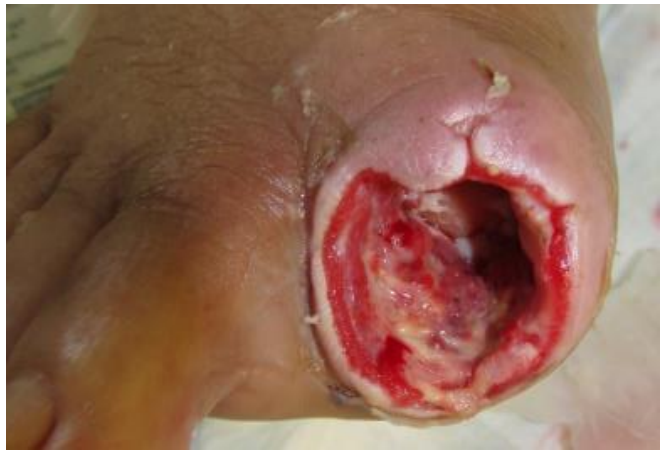
DFU pre-existing 6 weeks (EX-01; 4hr daily treatments)



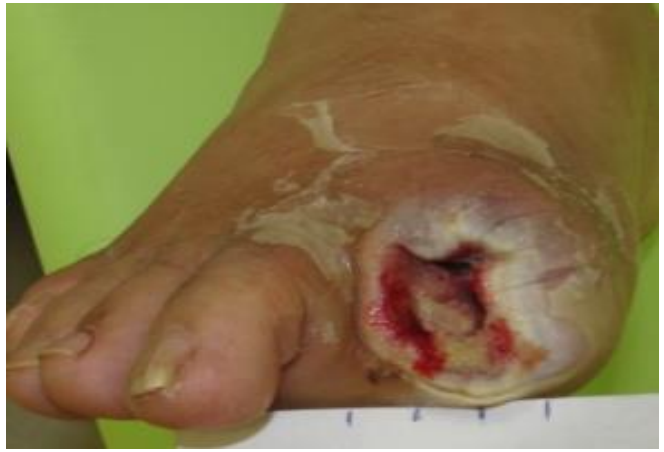
Before EscharEx



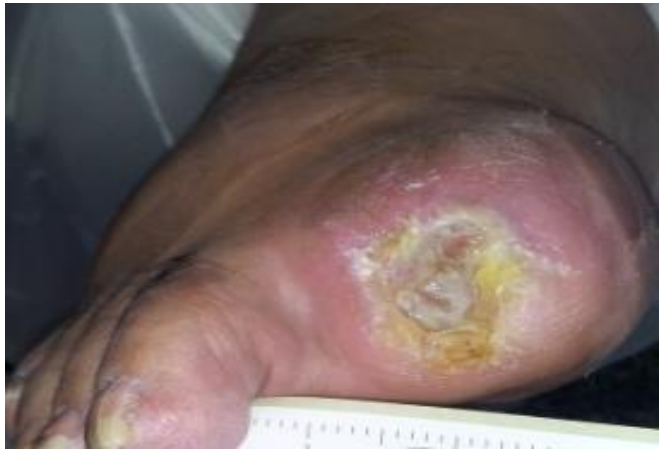
Post 2nd EscharEx treatment



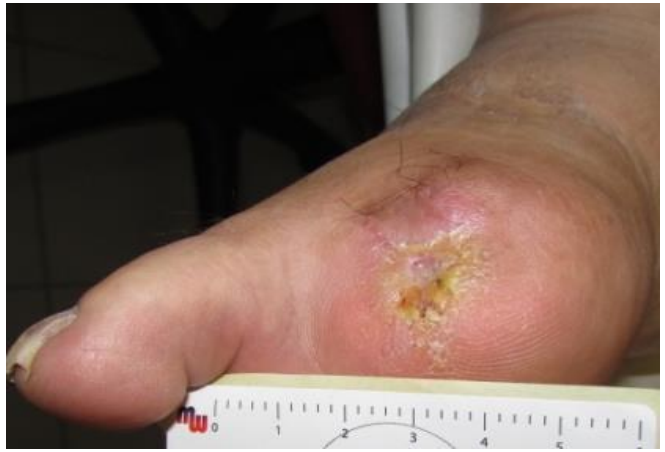
Post 4th EscharEx treatment



1 week post debridement



8 weeks post debridement



5 months post debridement

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2nd Generation EscharEx (EX-02) - Product Profile

- Advanced formulation with improved physicochemical properties (Homogenous and viscosity)
- High potency and favorable safety profile
- More convenient for user (enhance compliance)
  - *Daily applications*
  - *Easier to prepare and administer*
  - *Fit current medical practice*

Phase II Completed Study in VLU Patients

Study Objectives:

To assess safety and efficacy of EscharEx compared to Gel Vehicle (placebo control) and non-surgical SOC*

Study Design

- A multicenter (USA, Israel and Swiss), prospective randomized assessor blinded study for treatment of venous leg ulcers (VLUs)
- Sample size: 120 VLU patients (EX-02; Gel Vehicle; non-surgical SOC), 3:3:2 ratio
- Treatment: 5% EX-02 up to 8 applications of 24 hrs each
- Pre-defined interim assessment after 80 pts completed treatment
- Stages of analysis:
- First stage (Topline) - Primary endpoint after EscharEx and Gel Vehicle pts completed debridement
- Second stage - secondary, exploratory and safety endpoints

Endpoints

Primary endpoint

- Incidence of complete debridement of non-viable tissue vs. Gel Vehicle

Secondary endpoints

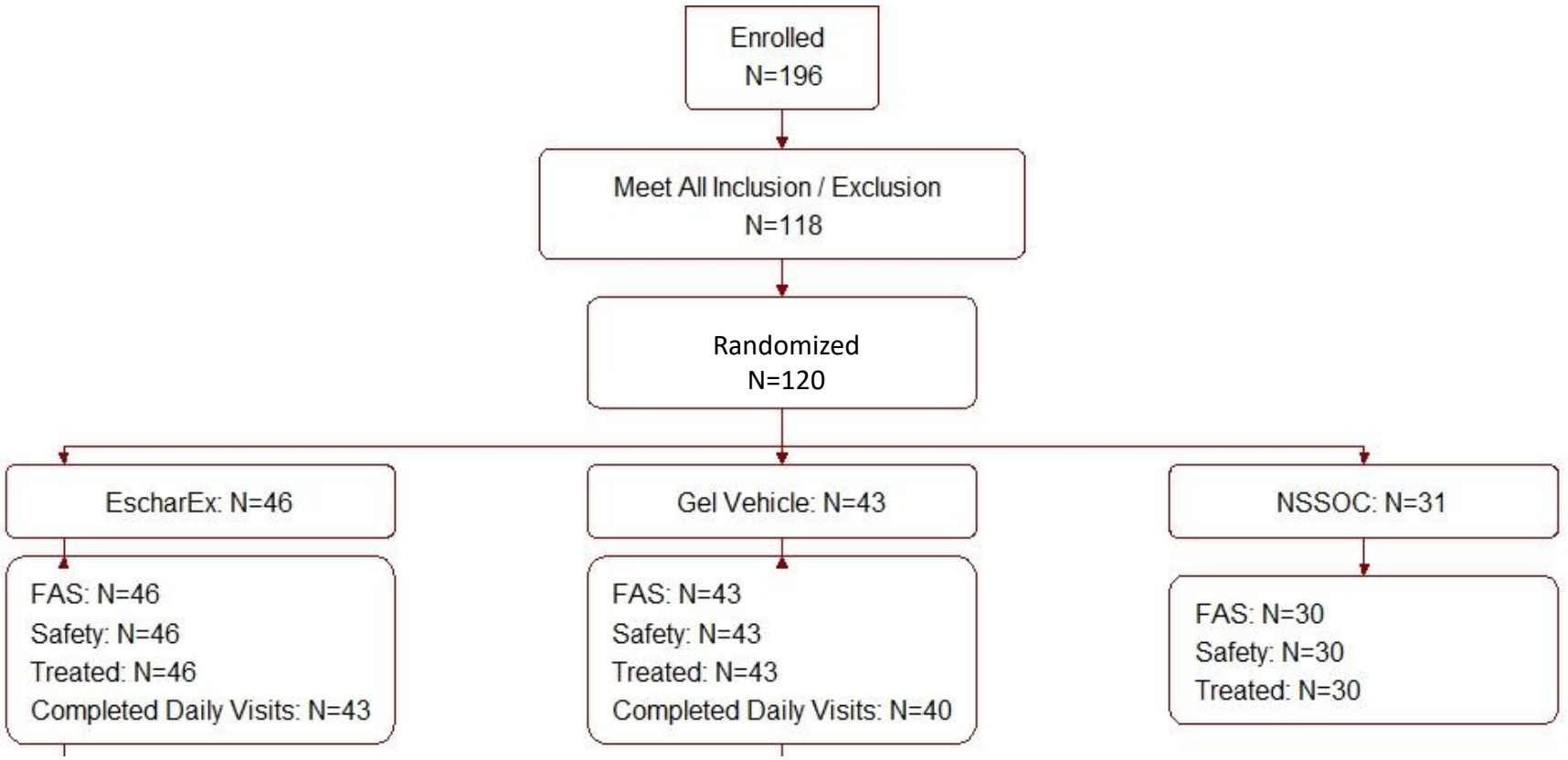
- Time to complete debridement; pain & wound area reduction; granulation tissue; wound QoL;

Safety

- Local and systemic safety and tolerability;
- Incidence and time to wound closure

*Non-surgical standard of care – enzymatic or autolytic debridement

Subject Disposition



The randomization was stratified by two levels of wound size and three levels of pain at baseline, blocked by region. Following FDA's feedback it was decided to re-weigh the study groups so the final randomization ratio is 3:3:2 for EX-02: Gel Vehicle: NSSOC. Keeping in mind that 1:1:1 randomization ratio was used for approximately first 45 subjects (~15 subjects per group), we specify 2:2:1 randomization ratio for the rest of the study. This modification yielded a 3:3:2 randomization ratio at the end of the study.

Patient Baseline Characteristics

Patient baseline characteristics were comparable across all study arms

Parameter	EscharEx (N=46) Mean (SD)	Gel Vehicle (N=43) Mean (SD)	NSSOC (N=30) Mean (SD)	All (N=119) Mean (SD)
Age (years)	65.6 (12.5)	62.0 (12.6)	65.6 (12.5)	64.3 (12.6)
Weight (kg)	98.0 (27.8)	105.1 (26.8)	95.7 (23.7)	100.0 (26.5)
Height (cm)	174.5 (9.9)	175.1 (10.8)	170.5 (14.4)	173.7 (11.5)
BMI (kg/m^2)	31.9 (7.4)	34.2 (8.0)	32.8 (6.8)	33.0 (7.5)

Gender, ethnicity and race were comparable across all study arms

Parameter		EscharEx (N=46) n (%)	Gel Vehicle (N=43) n (%)	NSSOC (N=30) n (%)	All (N=119) n (%)
Gender	Male	26 (56.5)	27 (62.8)	11 (36.7)	64 (53.8)
	Female	20 (43.5)	16 (37.2)	19 (63.3)	55 (46.2)
Ethnicity	Hispanic or Latino	10 (21.7)	13 (30.2)	7 (23.3)	30 (25.2)
	Not Hispanic or Latino	36 (78.3)	30 (69.8)	23 (76.7)	89 (74.8)
Race	White	38 (82.6)	36 (83.7)	20 (66.7)	94 (79.0)
	Black or African American	7 (15.2)	6 (14.0)	9 (30.0)	22 (18.5)
	Asian	1 (2.2)	0	1 (3.3)	2 (1.7)
	American Indian or Alaska Native	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	1 (2.3)	0	1 (0.8)

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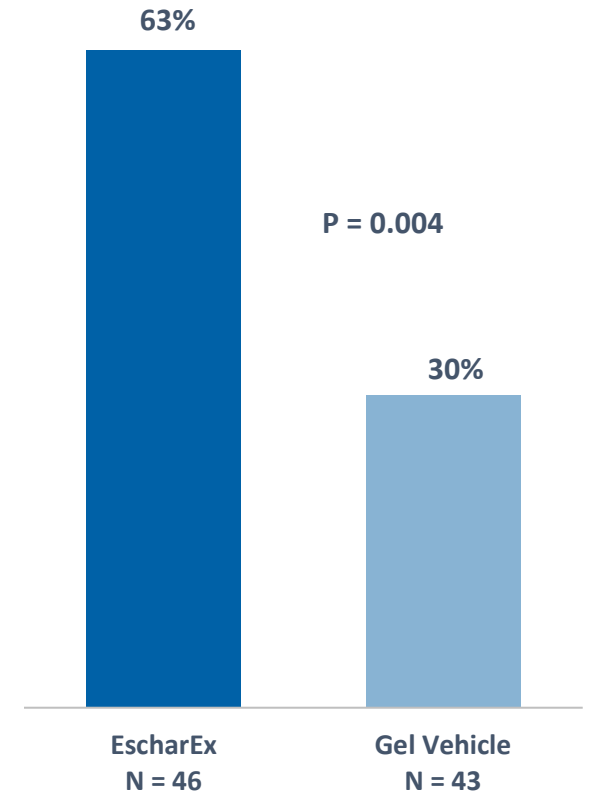
Wound Baseline Characteristics

Wounds treated with Gel Vehicle were older and larger in size than wounds treated with EscharEx and NSSOC, yet not statistically different

Parameter	EscharEx (N=46) Mean (SD)	Gel Vehicle (N=43) Mean (SD)	NSSOC (N=30) Mean (SD)	All (N=119) Mean (SD)
Wound Age (weeks)	26.8 (20.5)	39.5 (27.6)	25.7 (20.7)	31.1 (24.0)
Wound Size (cm^2)	13.3 (20.4)	18.9 (18.1)	14.7 (20.1)	15.7 (19.5)
Percent of Non-Viable Tissue per Clinical Evaluation (%)	72.2 (13.7)	77.7 (14.8)	68.4 (16.7)	73.2 (15.2)

Primary Endpoint - Incidence of Complete Debridement



Significantly higher incidence of complete debridement

- **Primary endpoint met with high degree of statistical significance**
- **Significantly higher incidence of complete debridement achieved with up to 8 daily applications (within 14 days): 29/46 patients treated with EscharEx (63%) vs. 13/43 patients treated with gel vehicle (30%)**

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Covariate Analysis (1/2)

EscharEx superiority over Gel Vehicle remained statistically significant after adjustment for pre-specified covariates ascribed for patient baseline characteristics

		EscharEx (N=46)		Gel Vehicle (N=43)		Arm P-Value	Interaction Covariate P-Value
		N	n (%)	N	n (%)		
Patient Age, split by median	Age ≤ 62.8 years	21	14 (66.7%)	24	8 (33.3%)	**0.002**	0.958
	Age > 62.8 years	25	15 (60.0%)	19	5 (26.3%)		
Gender	Male	26	19 (73.1%)	27	9 (33.3%)	**0.003**	0.531
	Female	20	10 (50.0%)	16	4 (25.0%)		
Baseline Pain Level	NPRS ≥ 7	12	8 (66.7%)	16	5 (31.3%)	**0.004**	0.774
	1< NPRS <7	20	11 (55.0%)	17	3 (17.6%)		
	NPRS ≤ 1	14	10 (71.4%)	10	5 (50.0%)		

Covariate Analysis (2/2)

EscharEx superiority over Gel Vehicle remained statistically significant after adjustment for pre-specified covariates ascribed for wound baseline characteristics

		EscharEx (N=46)		Gel Vehicle (N=43)		Arm P-Value	Interaction Covariate P-Value
		N	n (%)	N	n (%)		
Wound Age, split by median	Age ≤ 28 weeks	30	16 (53.3%)	20	4 (20.0%)	**0.0008**	0.703
	Age > 28 weeks	16	13 (81.3%)	23	9 (39.1%)		
Wound Size*	Small: 2-40 cm^2	42	27 (64.3%)	39	13 (33.3%)	**0.002***	0.336
	Large: 40-100 cm^2	4	2 (50.0%)	4	0 (0.0%)		

*Cochran–Mantel–Haenszel test was used instead of logistic regression, due to 0% result.

Exploratory Analyses:

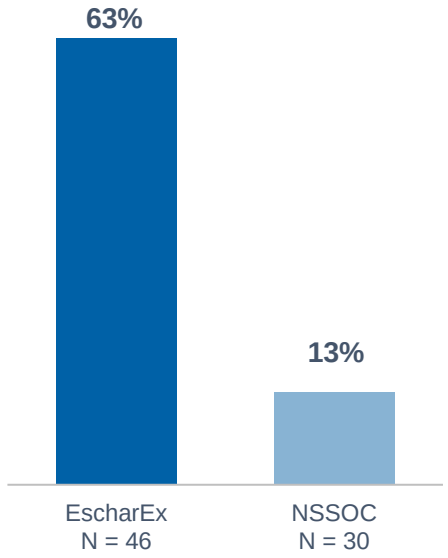
- When adjusting for continuous wound size, the rates are 61.7% vs 30.9% (p=0.006)
- When adjusting for continuous wound age, the rates are 65.9% vs 27.1% (p=0.001)

Poolability Across Regions

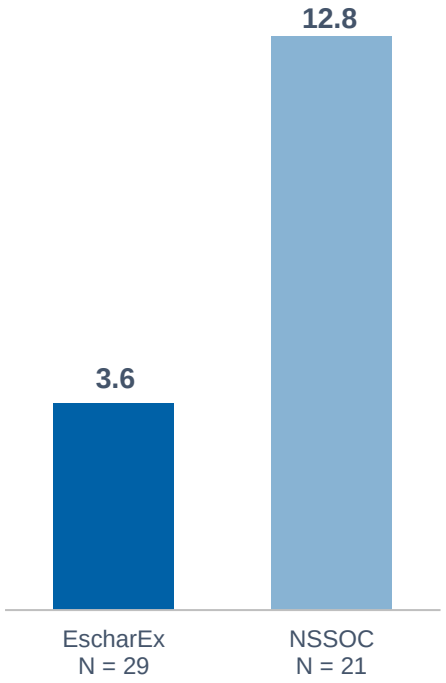
EscharEx superiority over Gel Vehicle remained statistically significant after adjustment for pre-specified covariate ascribed for regions

Covariate		EscharEx (N=46)		Gel Vehicle (N=43)		Interaction Covariate P-Value
		n (%)	N	n (%)		
US Sites		18 (58.1%)	31	9 (30.0%)	30	0.514
Non-US Sites		11 (73.3%)	15	4 (30.8%)	13	

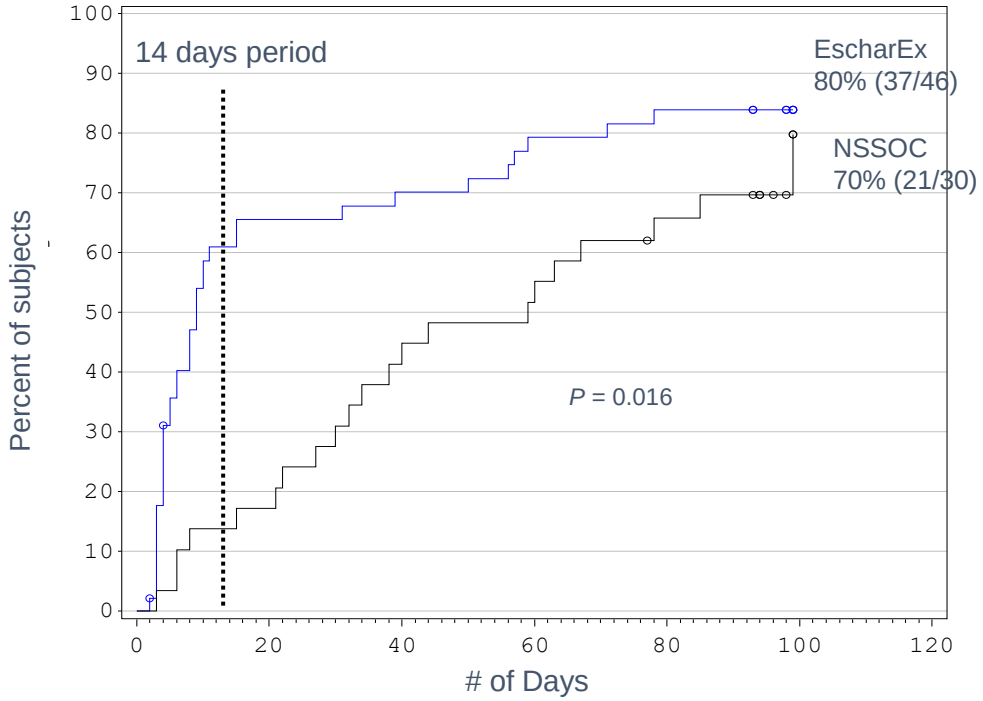
Improvement Over SOC



Incidence of complete debridement*



Average # of applications to achieve complete debridement



Time to achieve complete debridement**

Estimated median time to achieve complete debridement: EscharEx- 9 days vs. NSSOC - 59 days

*w/i up to 8 daily applications
**Kaplan-Meier survival analysis with log rank p-value

NSSOC – non-surgical standard-of-care

EscharEx vs. Gel Vehicle

Statistically significant higher incidence of at least 75% granulation tissue
Comparable reduction in pain, reduction in wound area and in wound QoL
Statistically significant shorter time to achieve complete debridement

	EscharEx (N=46)		Gel Vehicle (N=43)			P value
		95% CI (%)		95% CI (%)	Diff.	
Incidence (N(%)) of at least 75% granulation (1)	42 (93.3%)	81.7, 98.6	24 (55.8%)	39.9, 70.9		<0.0001
Estimates of Raw NPRS Change from Baseline to Twice-Weekly Visits (2)	1.53	0.81, 2.26	1.08	0.34, 1.82	0.45	0.4
Raw Change in Wound Size at 2-Weeks Post Last Treatment (3)	3.27	-0.35, 6.88	2.31	-1.49, 6.11	0.96	0.72
Raw Change in Total Quality of Life at 2-Weeks Post Last Treatment (4)	0.6	0.4,0.8	0.5	0.3,0.7	0.0	0.789
Estimated median time to achieve complete debridement (5)	9 days		63 days			0.004

1 P-value was calculated using 2-sided Fisher's exact test
2 P-Value was calculated using a mixed model repeated measures model, adjusted for baseline pain
3 P-Value was calculated using one-way analysis of covariance: Change in Wound Size = Baseline Wound Size + Group
4 P-value was calculated using one-way analysis of covariance: Change in Total QoL = Baseline QoL + Group
5 Kaplan Meier log-rank p-value

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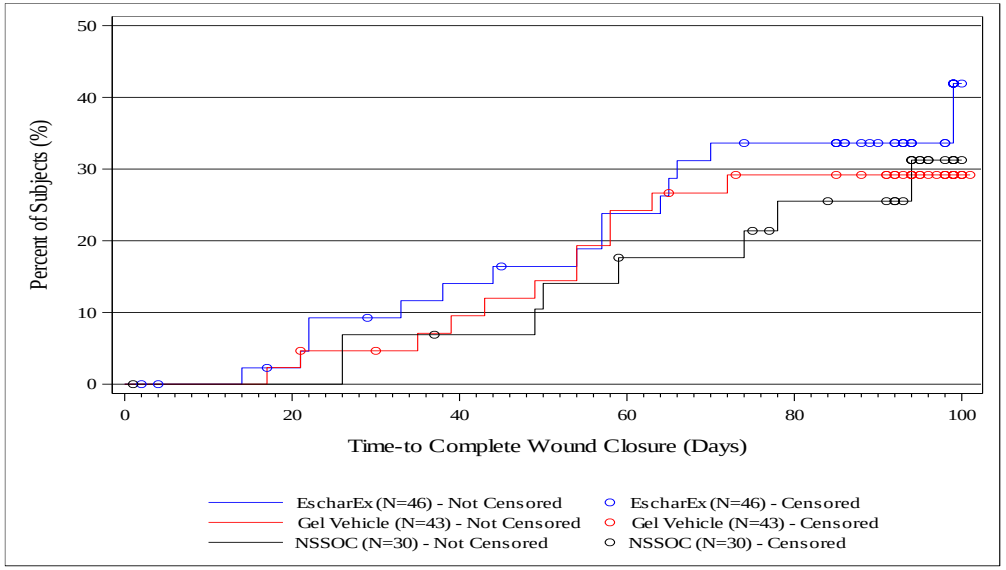
No Deleterious Effect on Wound Closure

Comparable time to complete wound closure compared to patients treated with gel vehicle and NSSOC

Kaplan-Meier Statistics	EscharEx (N=46)	Gel Vehicle (N=43)	NSSOC (N=30)
25th Percentile (days)	64.0	63.0	78.0
25th Percentile 95% CI (days)	33, 99	43, NE	49, NE
Log Rank Test P-Value		0.53	0.47



Non-inferior incidence rate of complete wound closure compared to patients treated with gel vehicle and NSSOC

EscharEx (N=46)			Gel Vehicle (N=43)				NSSOC (N=30)			
Total N	Complete Wound Closure, n (%)	95% CI (%)	Total N	Complete Wound Closure, n (%)	95% CI (%)	P-Value	Total N	Complete Wound Closure, n (%)	95% CI (%)	P-Value
46	15 (32.6%)	19.5, 48.0	43	12 (27.9%)	15.3, 43.7	0.0056	30	8 (26.7%)	12.3, 45.9	0.0094

CI=confidence interval.
Percentage was calculated from the overall number of subjects in each treatment group.
P-Values were calculated using Farrington and Manning (1990) non-inferiority test with non-inferiority margin 20%.

MediWound

Safety

EscharEx was well-tolerated and overall safety was comparable between the arms

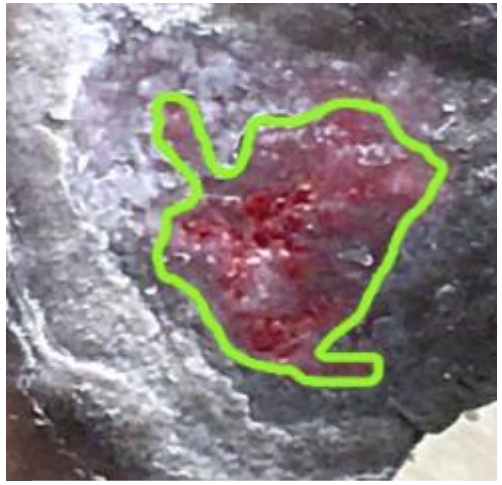
- Independent Data Monitoring Committee reviewed the safety data of all 120 patients along the study
- No safety concerns were identified in the study population
- No differences were found in reported adverse events and no serious adverse event was related to study treatment

Case Study

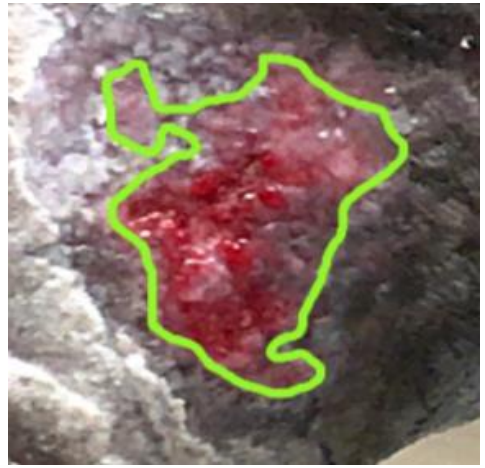
VLU pre-existing 1 month (EX-02; 24hr daily treatments)

Before EscharEx

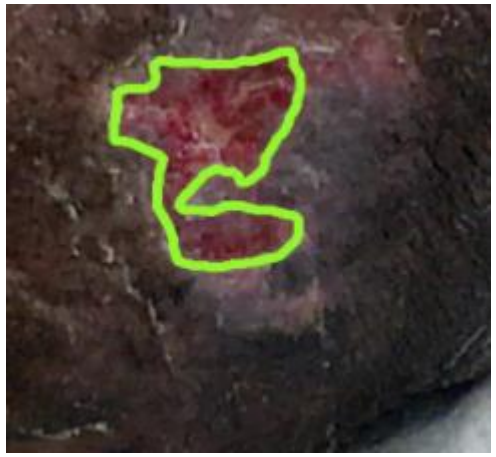
Post 1st treatment



Post 2nd treatment

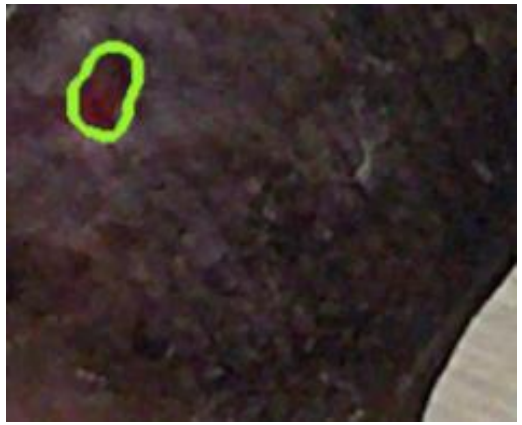


Post 3rd and last treatment



5 days post last treatment

2 weeks post last treatment



12 weeks post last treatment

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Summary and Conclusion

- Patients' baseline characteristics were similar between the arms. Patients in Gel Vehicle arm had on average larger and older wounds
- **The study met its primary efficacy endpoint**
  - Patients treated with EscharEx demonstrated a significantly higher incidence of complete debridement compared to patients treated with gel vehicle (EscharEx: 63% vs. gel vehicle: 30%, p=0.004)
  - Complete debridement was achieved within up to 8 daily applications performed in the first 2 weeks of the study
  - The efficacy of EscharEx compared to Gel Vehicle was consistent across subgroups defined by patients' and wounds baseline characteristics as well as by different regions
- **EscharEx demonstrated significant improvement over the non-surgical SOC**
- **EscharEx was well-tolerated and overall safety was comparable between the study arms**

PharmEx Clinical Pharmacology Phase 2 Trial
A 'Triple Threat': Managing Biofilm/ Bioburden

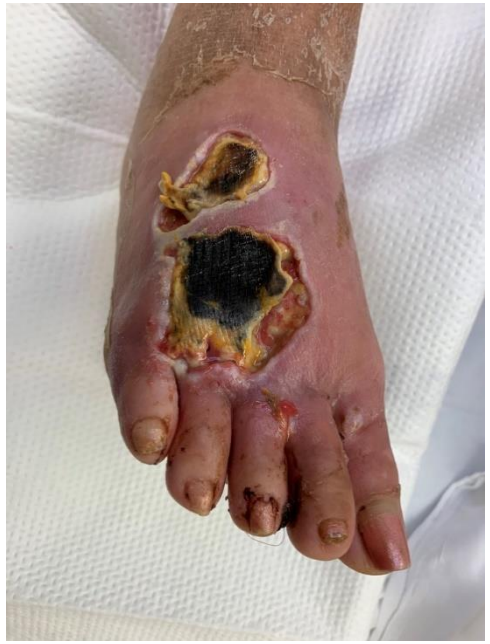
Robert J. Snyder, DPM, MSc, MBA, CWSP, FFPM FRCPS(G)
Chief Medical Director, EscharEx Program, Mediwound
Dean, Professor and Director of Clinical Research
Barry University School of Podiatric Medicine

Objectives

- Learn about the ongoing clinical pharmacology study regarding EscharEX
- Review interim study results
- Discuss an overview of managing biofilm/bioburden in chronic wounds
- Review bromelain and its effect on biofilm
- Describe why EscharEX may be a ‘Triple-Threat’ to chronic wounds

What is the Problem

- ”Microbial infections are the single most important cause of chronic, non-healing wounds. Chronic wound infections typically form biofilms, which are notoriously recalcitrant to conventional antibiotics..” (Kadam et al 2019)
- “Bacterial biofilms are an ever-growing concern for public health, featuring both inherited genetic resistance and a conferred innate tolerance to traditional antibiotic therapies...” (LuTheryn et al 2019)



Kadam et al (2019)Biomedicines, *7*(2), 35
LuTheryn et al (2019)Microbial Biotechnology, *13*(3), 613–628

MediWound

Infection Complicates the Treatment of Wounds and Impedes the Healing Process by:

- Damaging tissue[1]
- Reducing wound tensile strength[1]
- Inducing an undesirable inflammatory response[2]

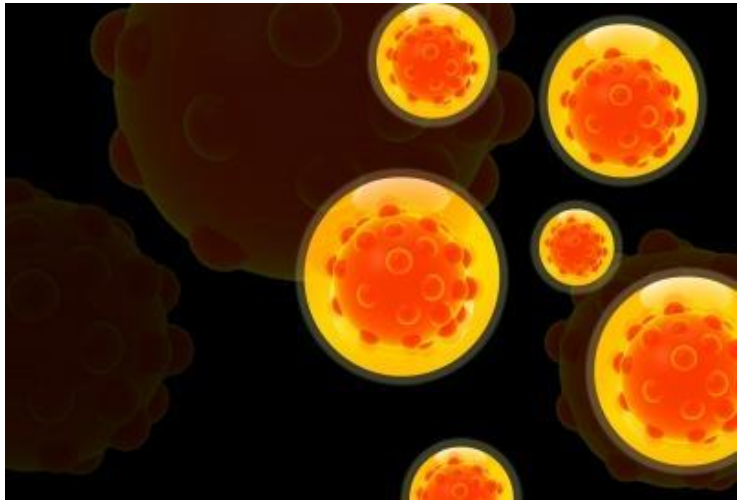


Image courtesy of renjith krishnan/ FreeDigitalPhotos.net

Thus, controlling or preventing infection is essential in order for the healing process to progress normally

1. *Wright JB Hansen DL, Burrell RE. The comparative efficacy of two antimicrobial barrier dressings: In vitro examination of two controlled release of silver dressings. Wounds 1998; 10(6): 179-188.*
2. *Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of Acticoat** antimicrobial barrier dressing. J Burn Care Rehabil 1999; 20: 195-200.*

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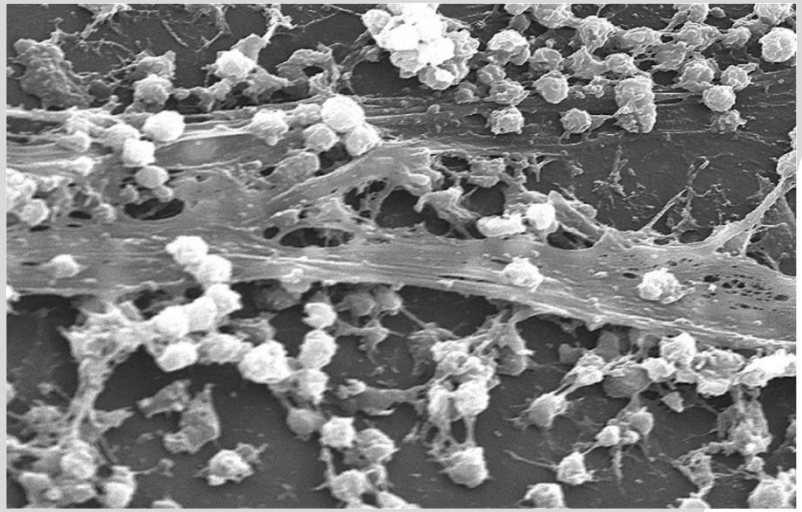
What is Biofilm?

Biofilm is a community of pathogens enveloped within a complex structure of entangled polymers strengthened with metallic bonds



Source image: https://phil.cdc.gov/Details.aspx?pid=7488

Image courtesy of CDC/Rodney M. Dolan, PhD. and Janice Haney Carr

Community of pathogens

Multiple species of bacteria and fungi living together

Entangled polymers

Microbes secrete a protective matrix called EPS (extracellular polymeric substance) made from polymers including proteins, glycolipids, polysaccharides and DNA.

Metallic bonds

Metallic ions bind polymers of the EPS together forming a resilient barrier.

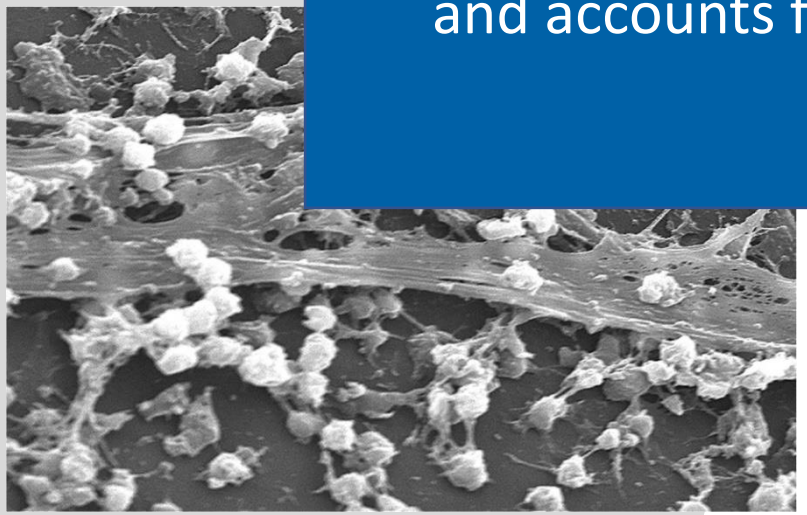
1. Wright JB Hansen DL, Burrell RE. The comparative efficacy of two antimicrobial barrier dressings: In vitro examination of two controlled release of silver dressings. Wounds 1998; 10(6): 179-188.

*2. Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of Acticoat** antimicrobial barrier dressing. J Burn Care Rehabil 1999; 20: 195-200.*

What is Biofilm?

Biofilm is a community of pathogens enveloped within a complex structure of entangled
with metalli

The glycocalyx protects the bacteria from antibiotics and accounts for the persistence of the infection



Source image: https://phil.cdc.gov/Details.aspx?pid=7488

Image courtesy of CDC/Rodney M. Dolan, PhD. and Janice Haney Carr

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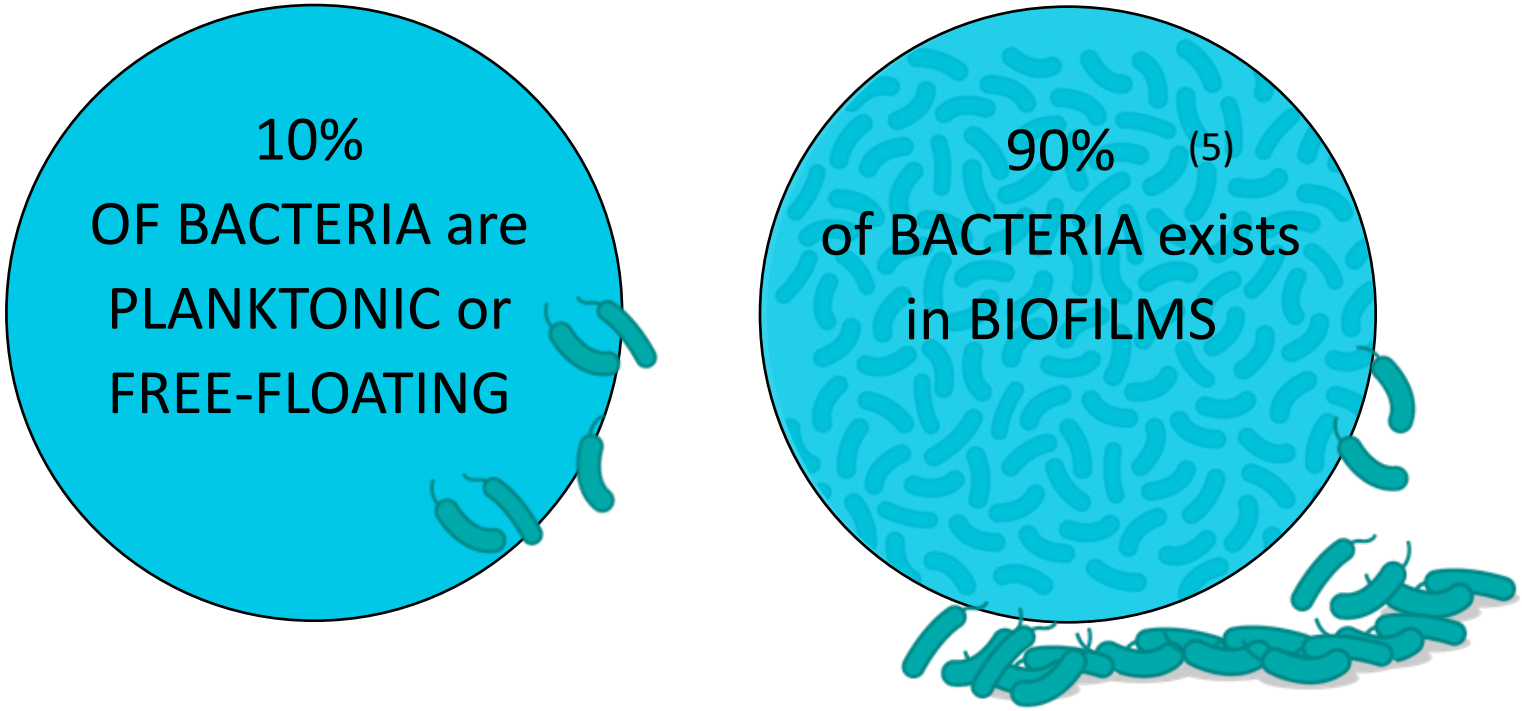
*2. Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of Acticoat** antimicrobial barrier dressing. J Burn Care Rehabil 1999; 20: 195-200.*

Most Bacteria Exist Within Biofilms



(5)

Bacteria protected by biofilm EPS (extracellular polymeric substance) can be 1000x more tolerant to antibiotics than planktonic bacteria.

Snyder RJ et al (2017) Wounds, 29 (6 sup): S1-S1

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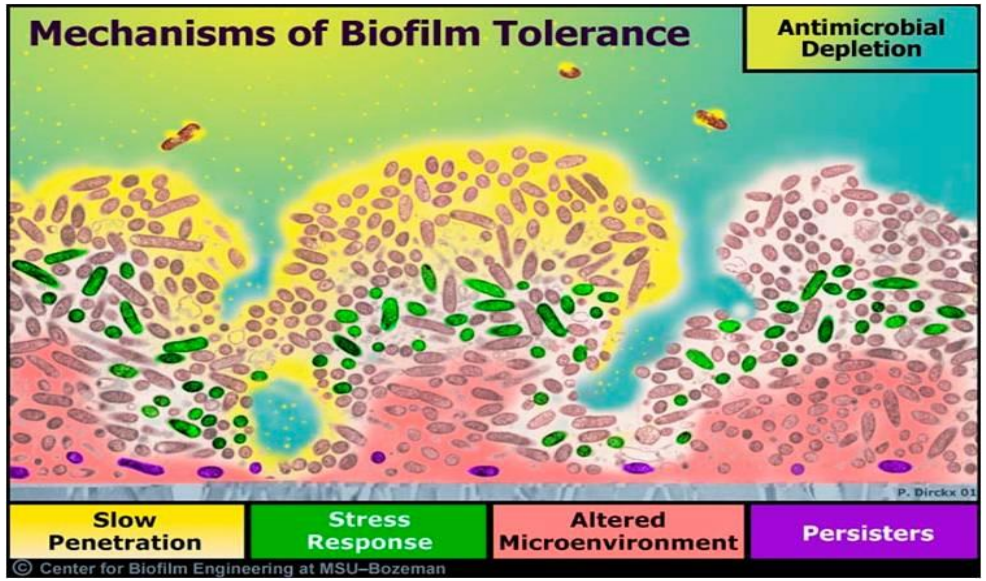
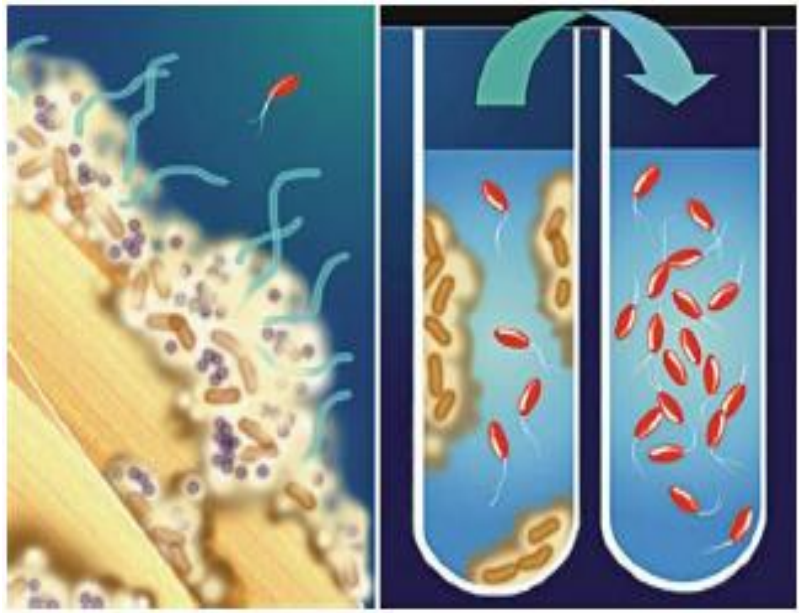
Biofilms Don’t Play Fair

- Difficult to culture
- Tolerant of biocides
- Tolerant of antibiotics
- Capable of regenerating





Biofilm phenotype highly adapted for survival in the harshest of environments

The Benefits of Bromelain

- Nancy J Millenbaugh et.al established a Staphylococcus aureus biofilm model that mimicked wound like conditions
- The antibiofilm activity of four enzyme compounds reviewed
- **Bromelain reduced biofilm mass by 98%**
- Scanning electron microscopy confirmed detachment of the biofilm EPS and bacteria from growth surfaces
- Overall, results indicated that enzymes such as **Bromelain** may be an effective means of eradicating biofilms and a promising strategy to improve treatment of multidrug-resistant bacterial infections

Enzymatic degradation of in vitro *Staphylococcus aureus* biofilms supplemented with human plasma

Introduction

Clinical Pharmacology Study: PharmEx

A prospective study performed to evaluate the clinical performance and pharmacology effect of EscharEx (EX-02 formulation) in debridement of lower leg ulcers (VLU and DFU): Clinical Phase II

PharmEx - Overview

Pharmacology study

Study Objectives	Assess the pharmacological effect of EscharEx in patients with VLU and DFU
Study Design	• Single arm • Open label • 12 patients recruited @ 3 sites in the U.S. • Duration – up to 8 treatment applications + 2 weeks follow-up • Punch biopsies and wound fluids will be taken before and after complete debridement
Data Collection	**Clinical performance** Safety and efficacy - Incidence and time to complete debridement **Effect on biofilm** Reduction of biofilm **Anti- Inflammation** Bacterial load reduction **Wound progression** Bio-markers (e.g. cytokines, MMPs)

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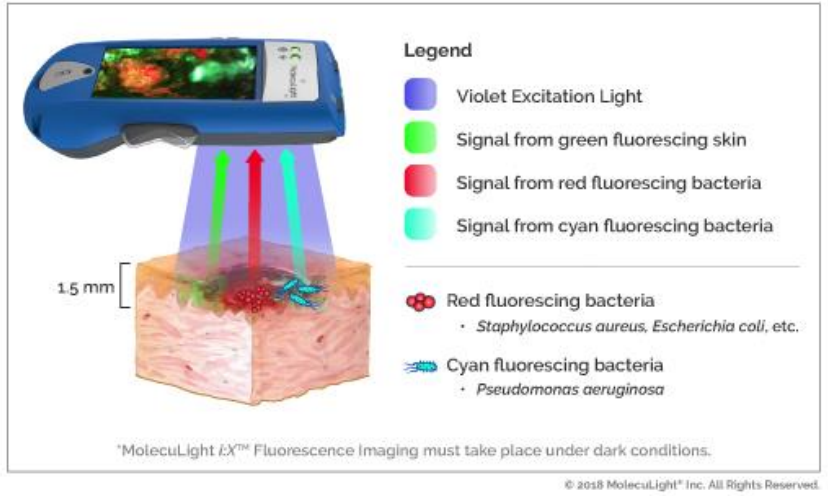
Bacterial Load Reduction

- Changes in bacterial load throughout debridement were measured with the Moleculight imaging device (MolecuLight Corp, Pittsburg, PA)
- The area of fluorescence, indicating bacterial burden, was calculated in pixels by counting and summing the red fluorescence pixels and cyan fluorescence pixels
- The area of pixels was then converted to cm^2 by finding the pixel to area ratio from the fluorescent image via the corresponding detected area in the wound measurement image
- Most bacteria fluoresce red, Pseudomonas uniquely fluoresces cyan



[1] *Moelleken M, Jockenhöfer F, Benson S, Dissemond J. Prospective clinical study on the efficacy of bacterial removal with mechanical debridement in and around chronic leg ulcers assessed with fluorescence imaging. Int Wound J. 2020 Aug;17(4):1011-1018.*

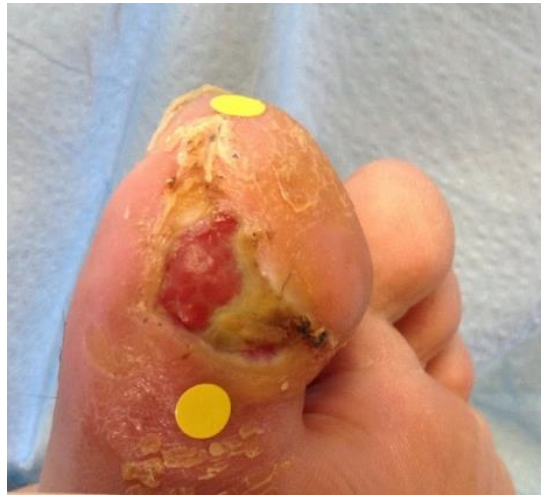
Bacterial Load Reduction – Example

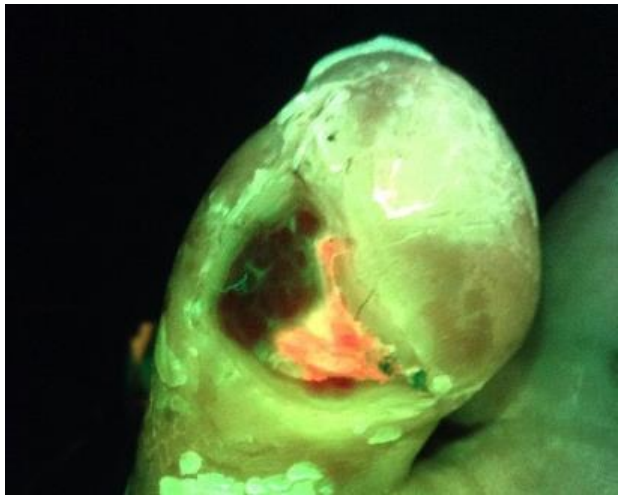
Subject 104-004

Pre Treatment

Red fluorescence area:

0.84 cm^2

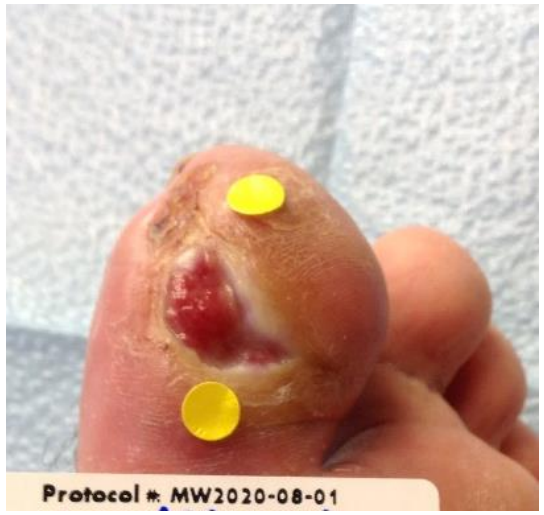


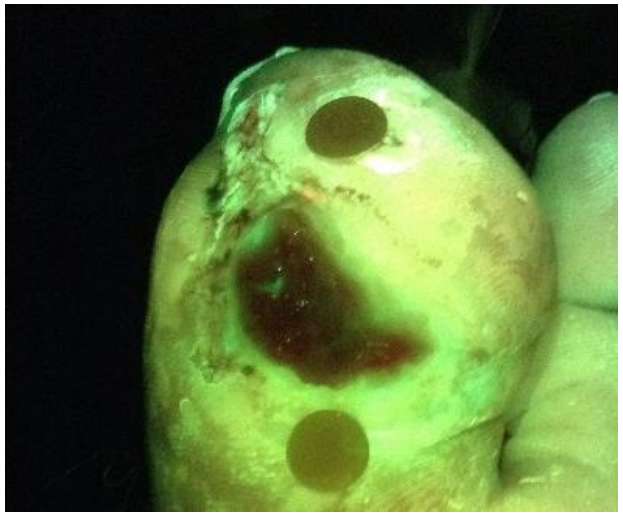


Post treatment

Red fluorescence area:

0.2 cm^2





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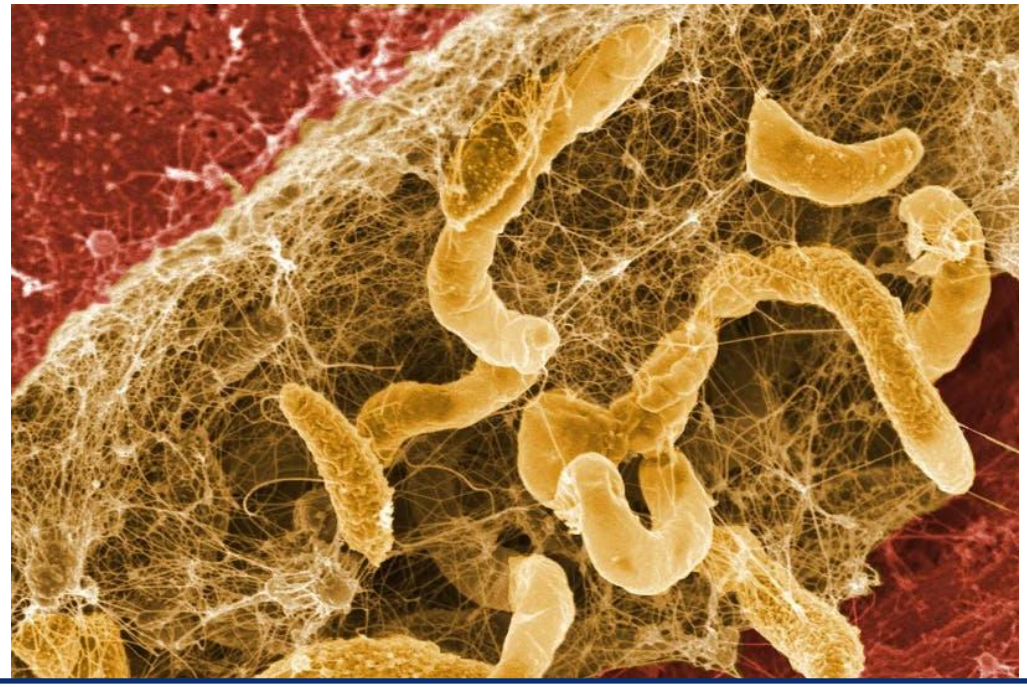
Biofilm Reduction

- Wound punch biopsies (3 mm) are collected before and after treatment for analysis of biofilm presence.
- Moleculight fluorescence imaging was utilized to identify the highest fluorescence area to obtain the biopsy.
- Biopsy samples are frozen cut into 5 mm-thick sections using a cryostat, placed on slides and stored at -70°C
- The sections were stained and examined using a confocal scanning laser microscope (CSLM)



Representative images of each specimen was semi-quantitatively characterized based on the following scale (a ranking of 2 or higher is considered positive for biofilm)

0 - No microorganisms observed

1 - Single individual microorganisms

2 - Small micro-colonies (10-100 cells) of microorganisms

3 - Large micro-colonies (>100 cells) of microorganisms

4 - Continuous film of microorganisms

5 - Thick (> 10 um) continuous film of microorganisms

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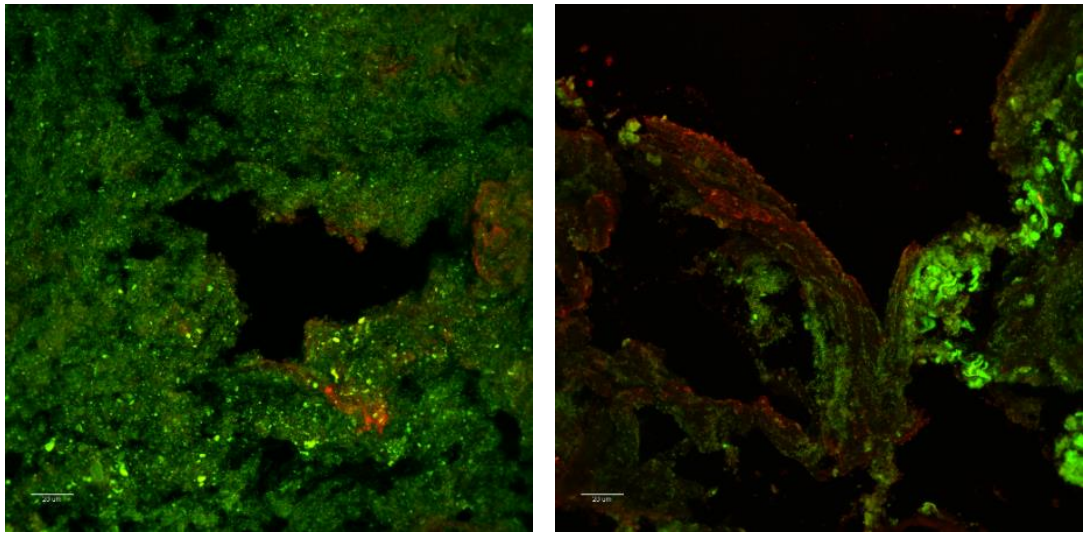
Biofilm Reduction – Example

Subject 101-001

Pre-Treatment

Biofilm score: 5

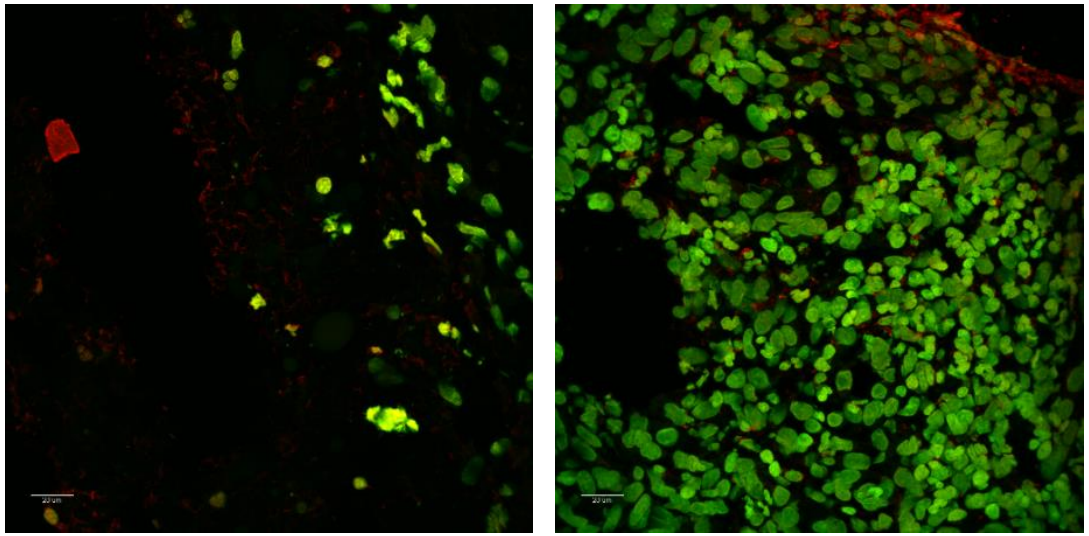
(Thick continuous film of microorganisms)



Post treatment

Biofilm score: 1

(Single individual microorganisms)



MediWound

Summary of Results

Clinical performance outcomes

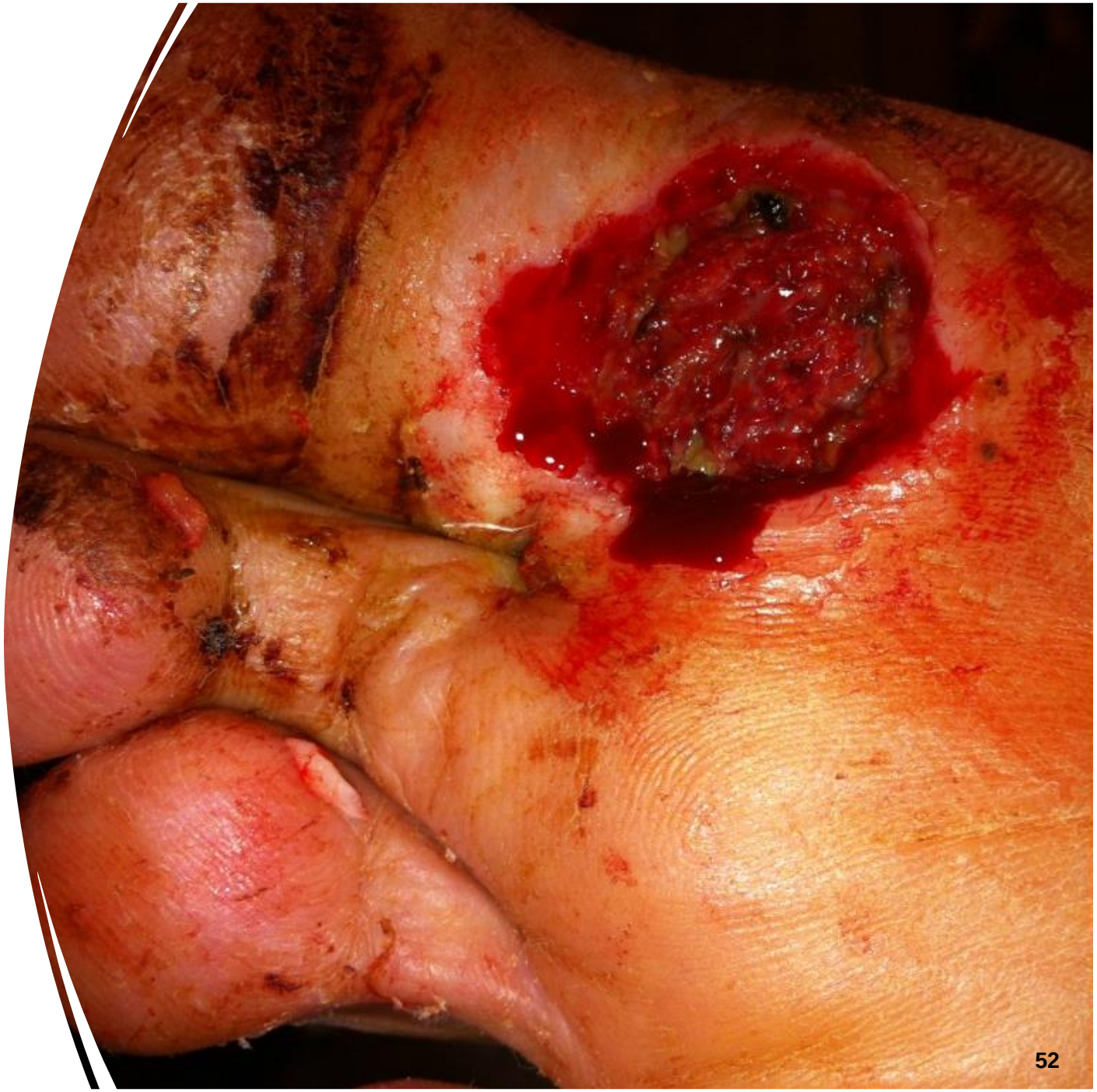
- ✓ 70% of patients achieved complete debridement during the treatment period within up to 8 applications
- ✓ On average, complete debridement was achieved after 3.9 applications of EscharEx
- ✓ Significant debridement of wounds during the treatment period (average of 84.9% NVT removed)
- ✓ Significant decrease in wound size by the end of two weeks follow-up (average of 35%)
- ✓ EscharEx is safe and well tolerated

Pharmacology measures

- ✓ In all patients that were positive for biofilm at baseline, the biofilm was reduced substantially to single individual microorganisms or completely removed
- ✓ Seven patients had positive red fluorescence at baseline and average red flouresance was reduced from 1.69 cm^2 pre-treatment to 0.60 cm^2 post treatment
- ✓ Biomarker analysis from wound fluid is on-going (MMPs, cytokines, chemokines and GFs)

EscharEX as a ‘Triple Threat’

- ✓ Efficient wound debridement may convert a chronic wound into one that is acute
- ✓ Bromelain could disrupt biofilm bacteria
- ✓ Bromelain could decrease planktonic bacteria



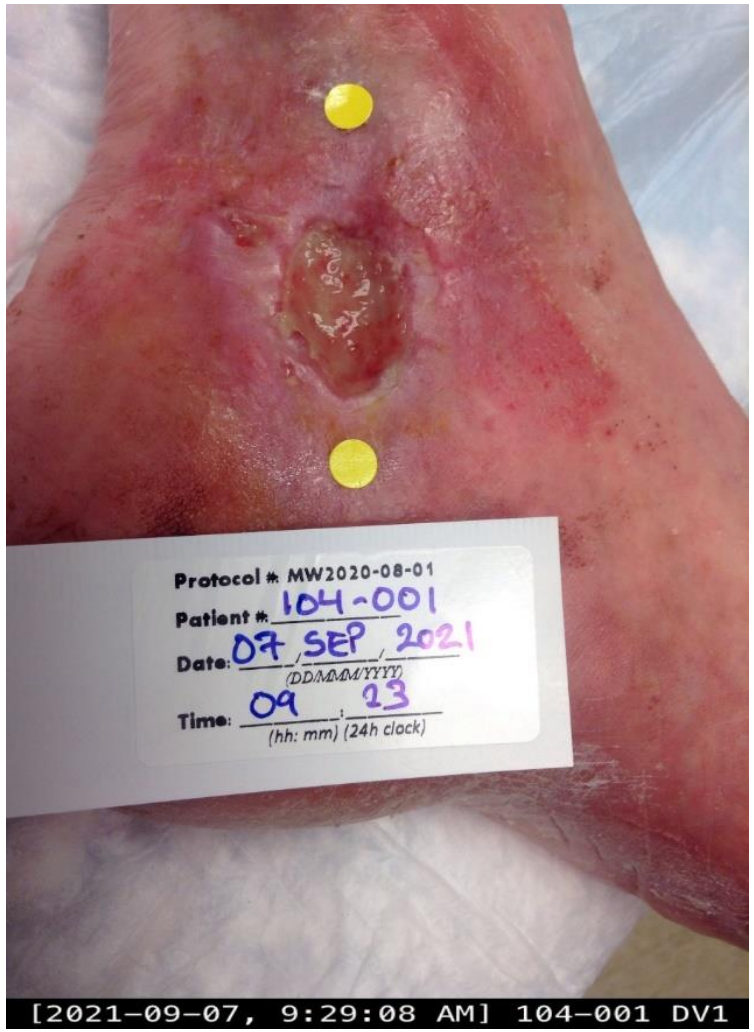
PharmEx Clinical Pharmacology Phase 2 Trial Treatment Photos

Cyaandi R. Dove, DPM
Advanced Wound & Ankle Center, Las Vegas

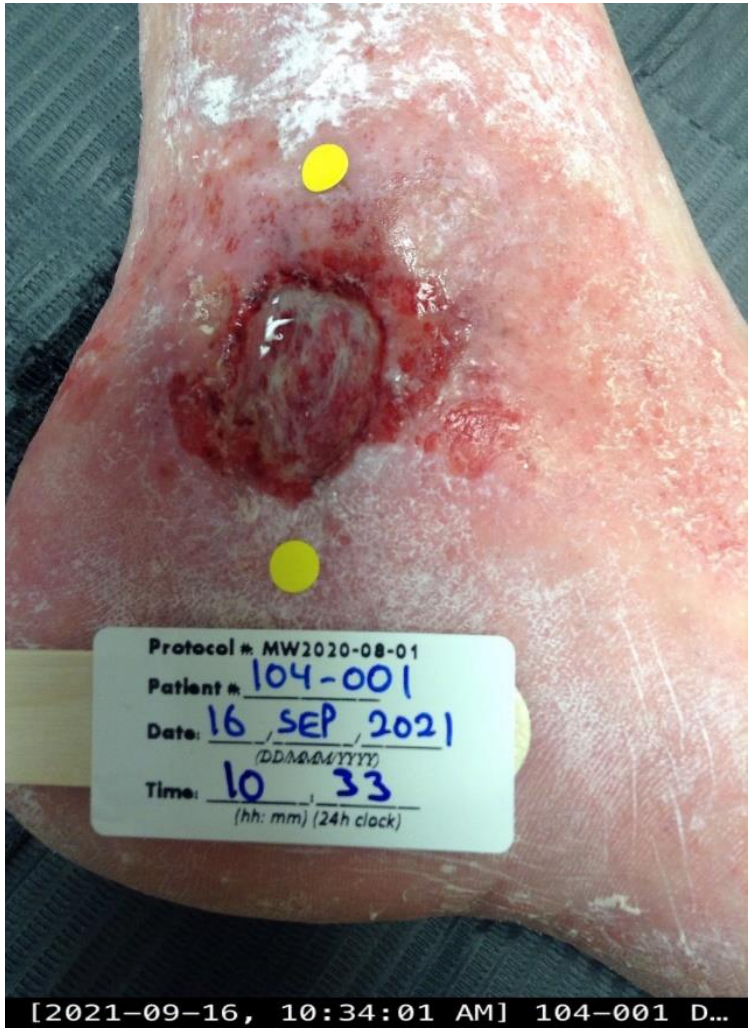
MediWound

104-001
VLU

Pre-treatment #1, 07 Sep 2021 – 75% NVT



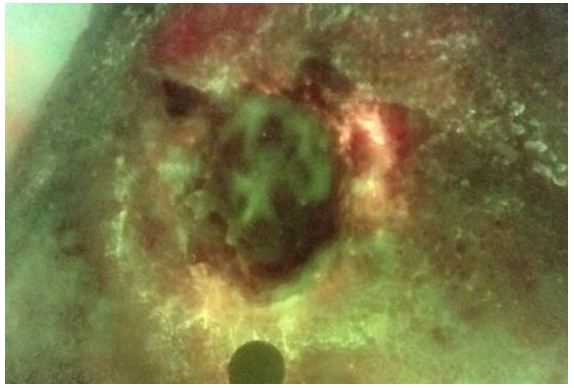
Post-treatment #6, 16 Sep 2021 – 0% NVT (Complete ER)



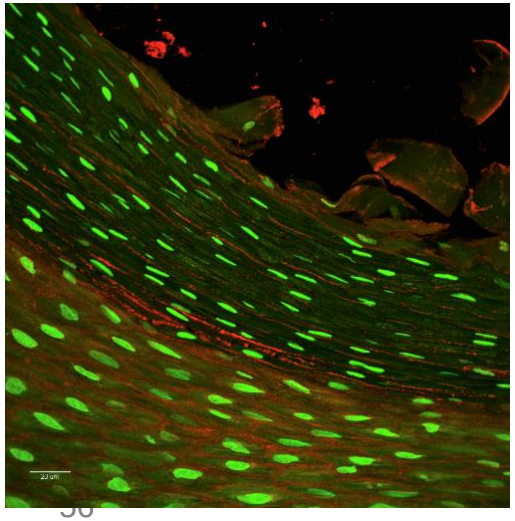
MediWound

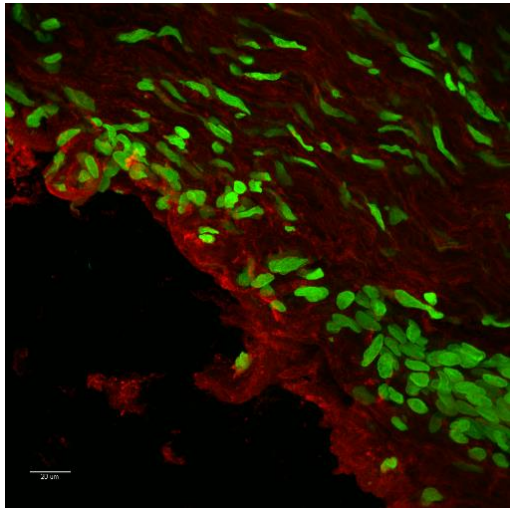
Pre-treatment

Moleculight



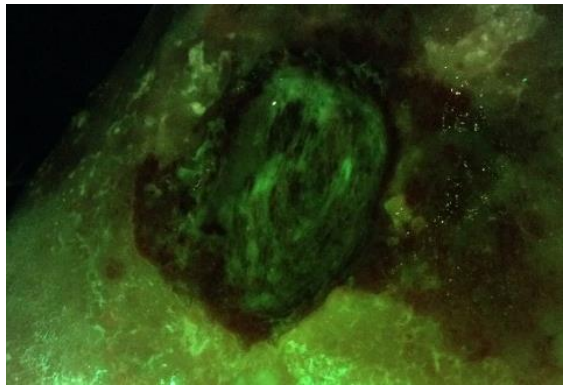
Biofilm score: 1 (Single individual microorganisms)



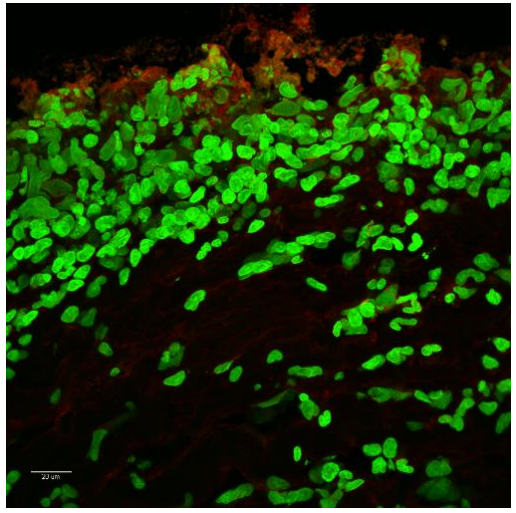


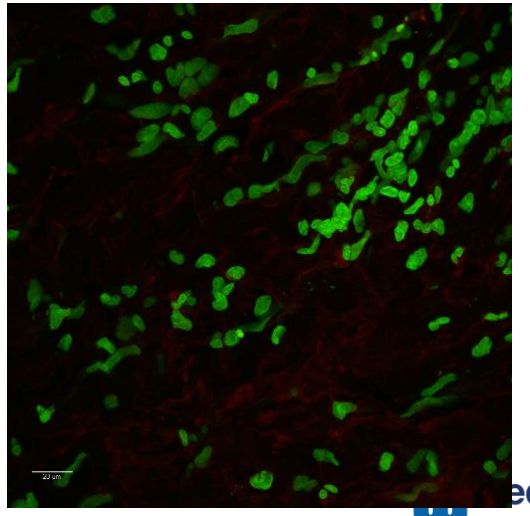
Post-treatment

Moleculight



Biofilm score: 1 (Single individual microorganisms)

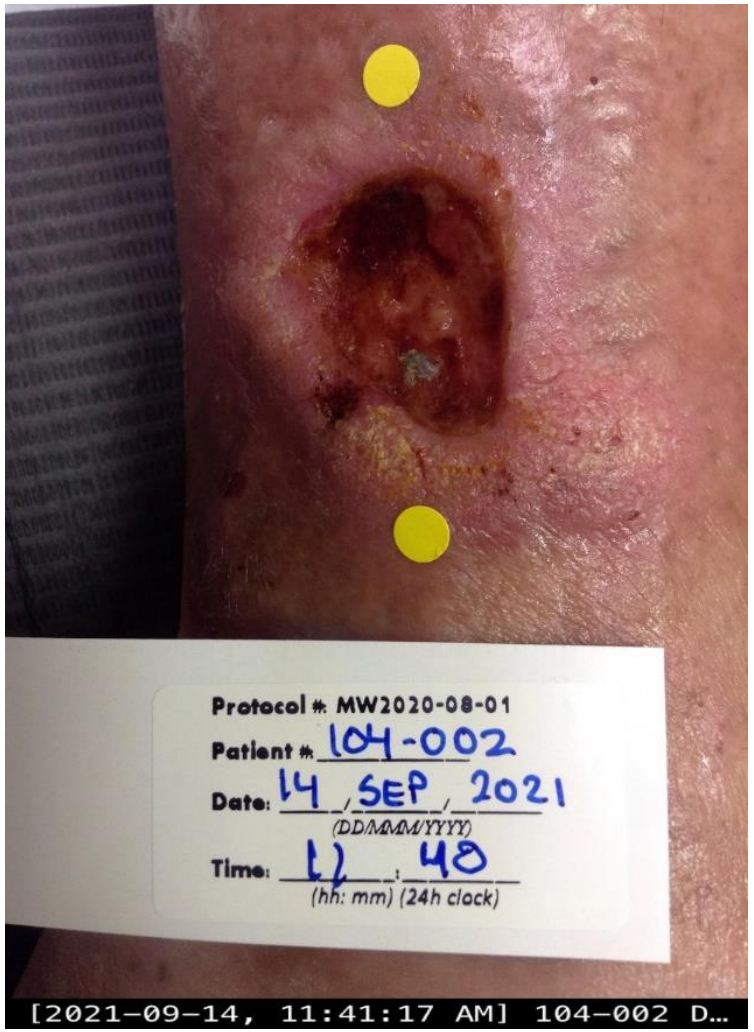




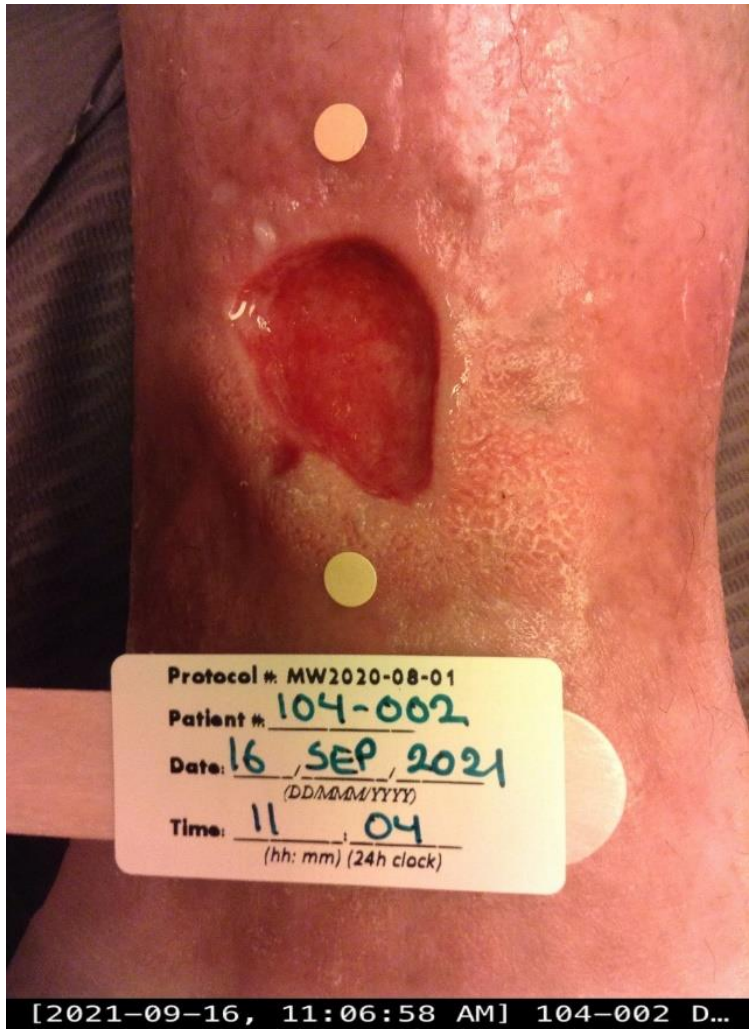
MediWound

104-002
VLU

Pre-treatment #1, 14 Sep 2021 – 70% NVT



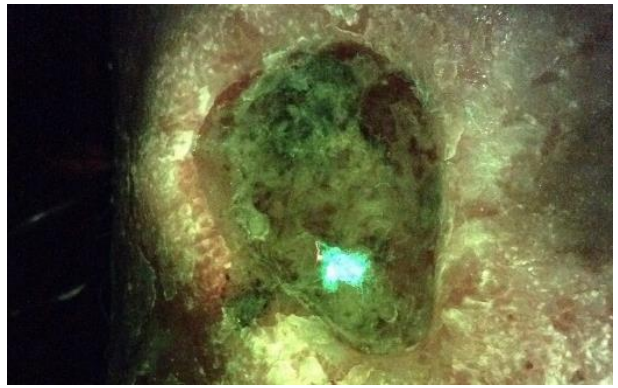
Post-treatment #2, 16 Sep 2021 – 0% NVT (Complete ER)



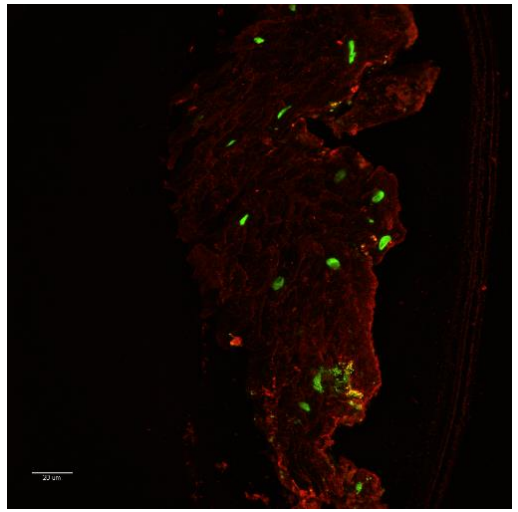
MediWound

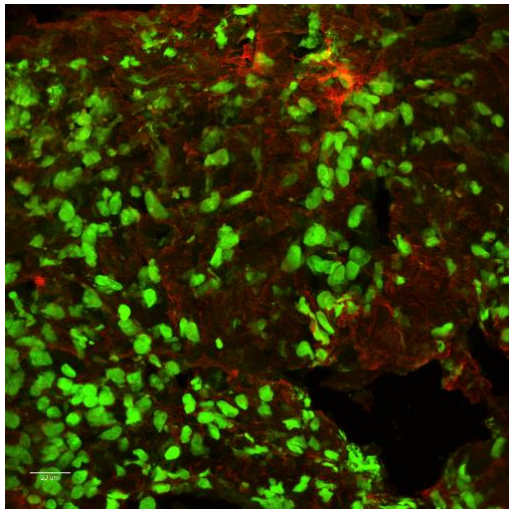
Pre-treatment

Moleculight



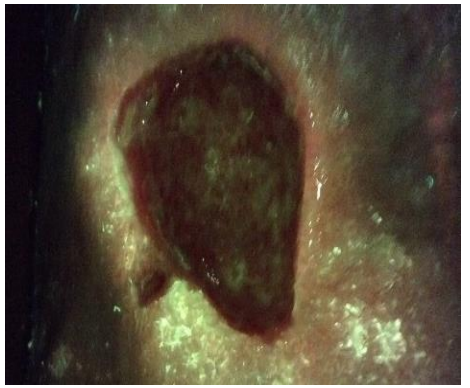
Biofilm score: 2 (Small microcolonies of microorganisms)



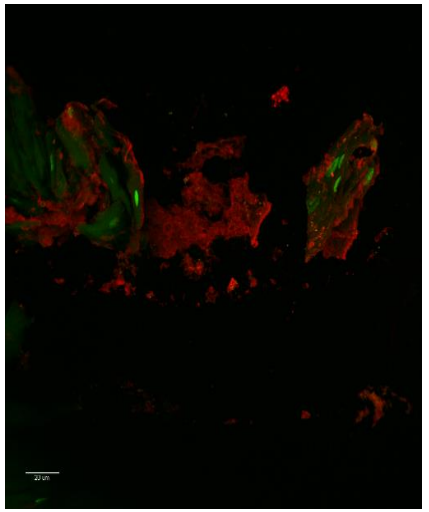


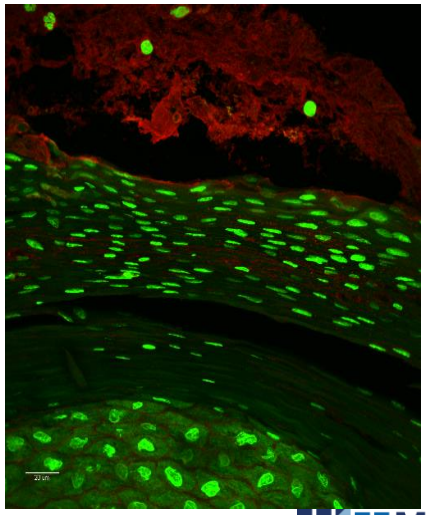
Post-treatment

Moleculight



Biofilm score: 1 (Single individual microorganisms)



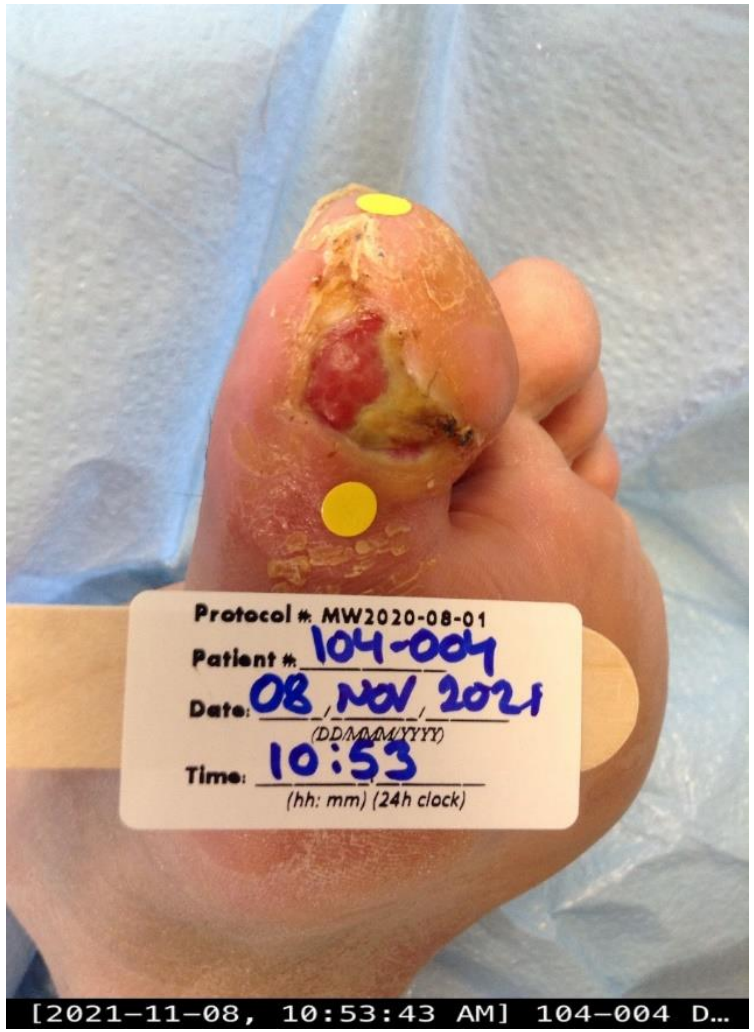


MediWound

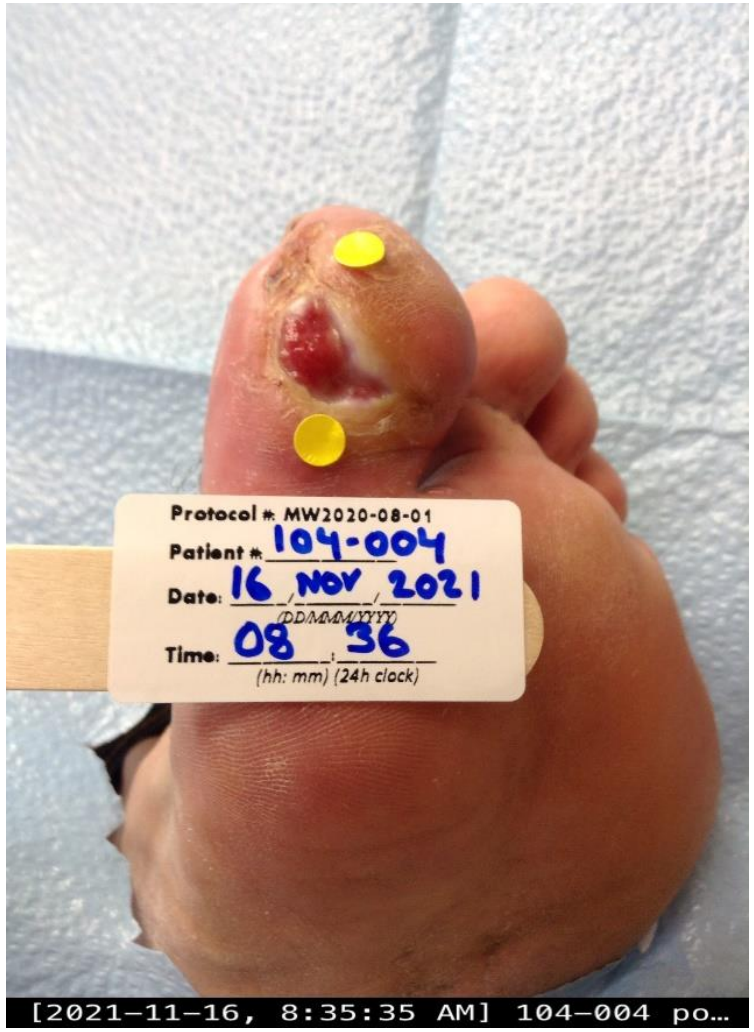
MediWound

104-004
DFU

Pre-treatment #1, 08 Nov 2021 – 70% NVT



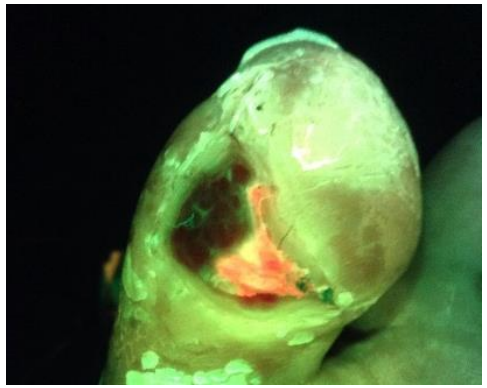
Post-treatment #5, 16 Nov 2021 – 0% NVT (Complete ER)



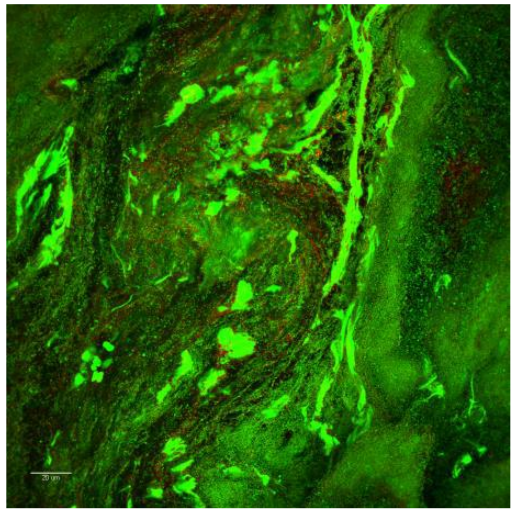
MediWound

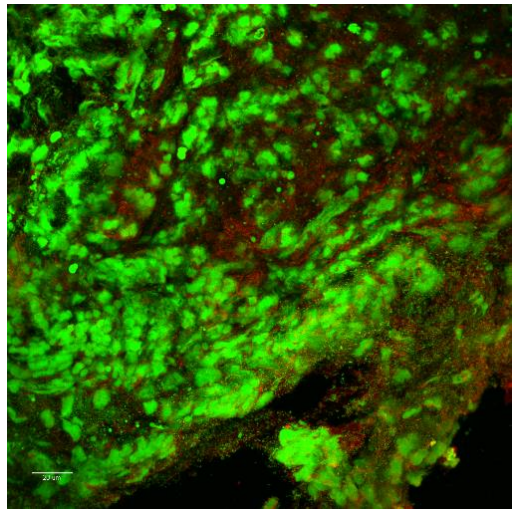
Pre-treatment

Moleculight



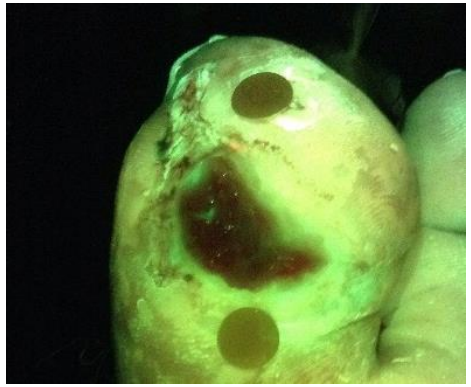
Biofilm score: 5 (Thick continuous film of microorganisms)



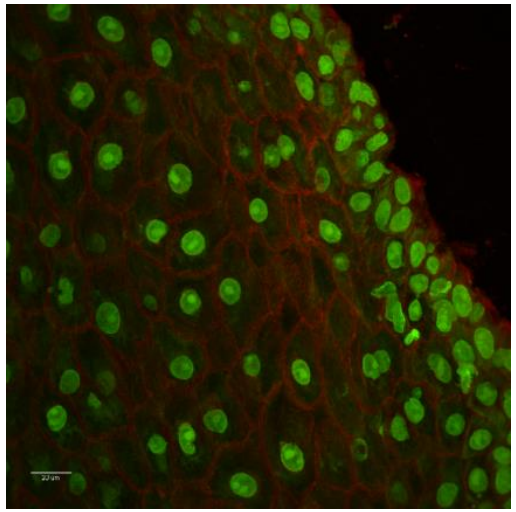


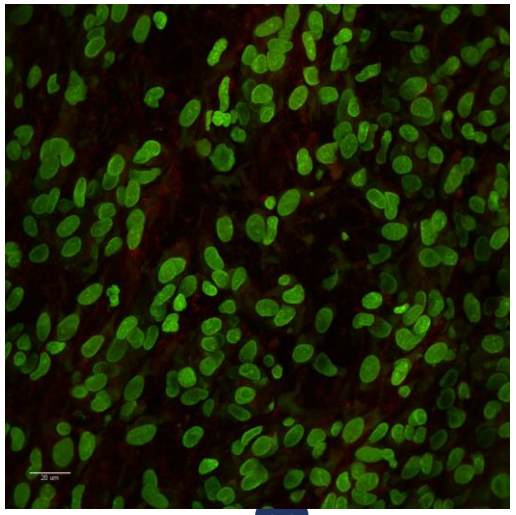
Post-treatment

Moleculight



Biofilm score: 1 (Single individual microorganisms)



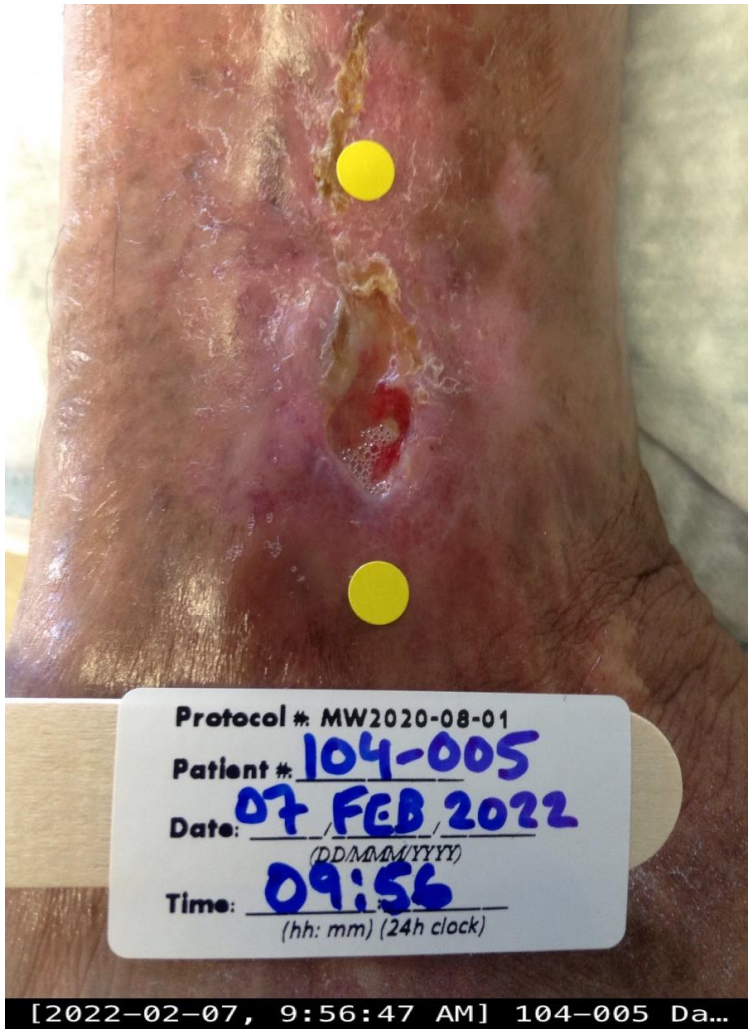


MediWound

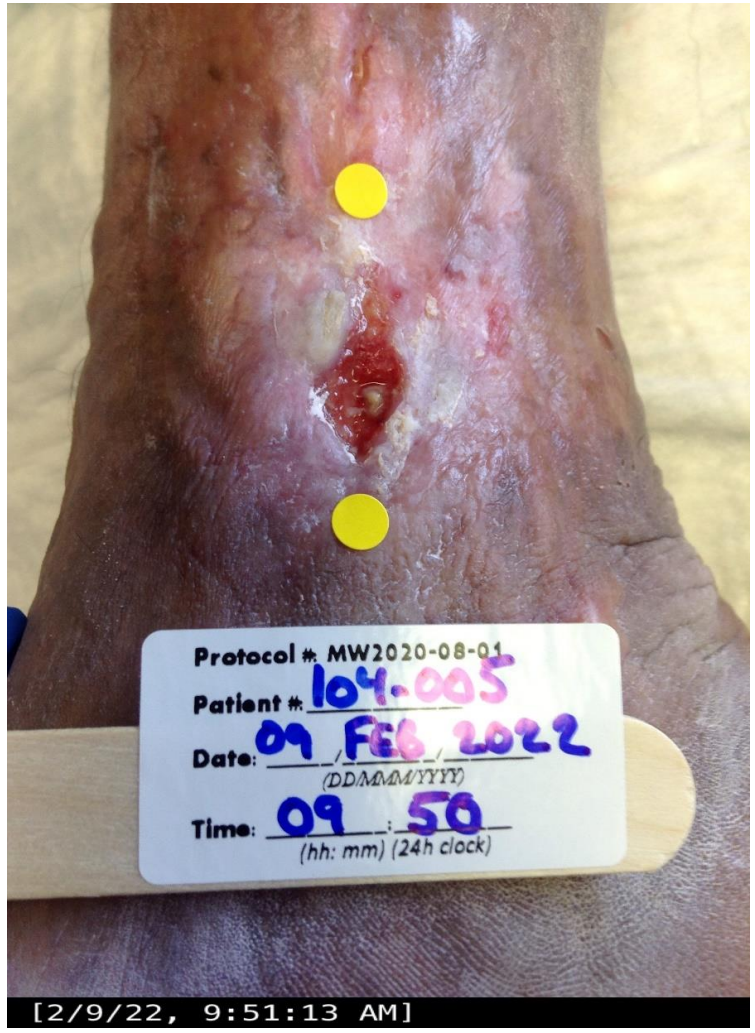
MediWound

104-005
VLU

Pre-treatment #1, 07 Feb 2022 – 80% NVT



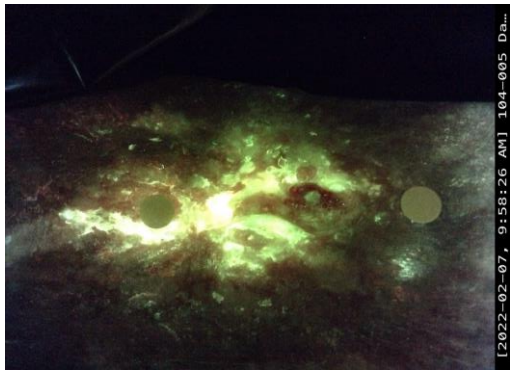
Post-treatment #2, 09 Feb 2022 – 0% NVT (Complete ER)



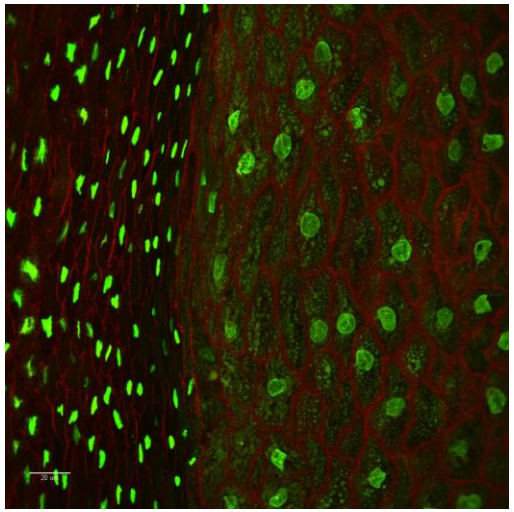
MediWound

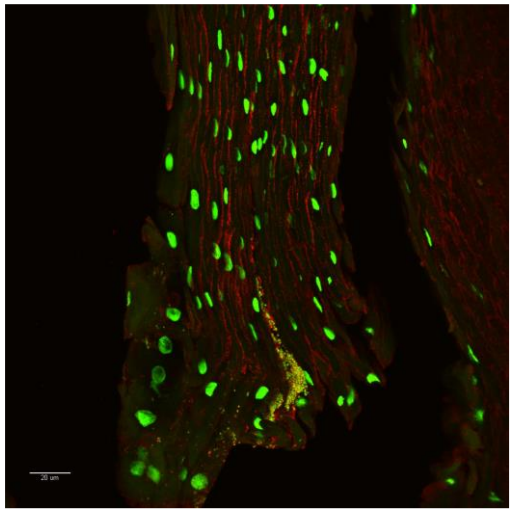
Pre-treatment

Moleculight



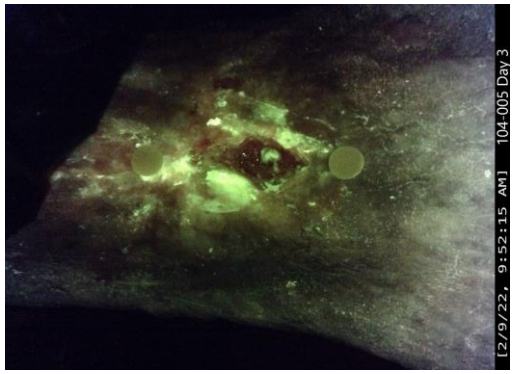
Biofilm score: 3 (Large microcolonies of microorganisms)



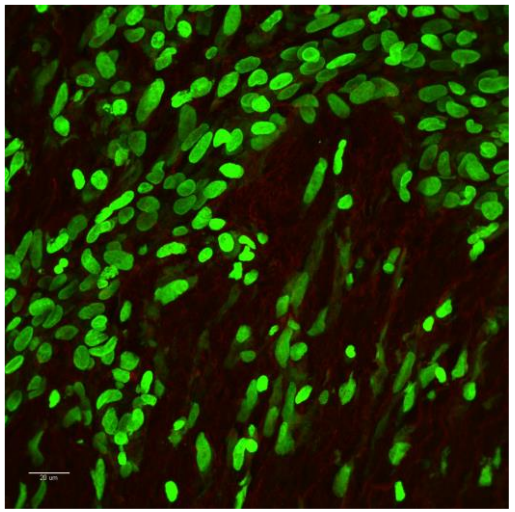


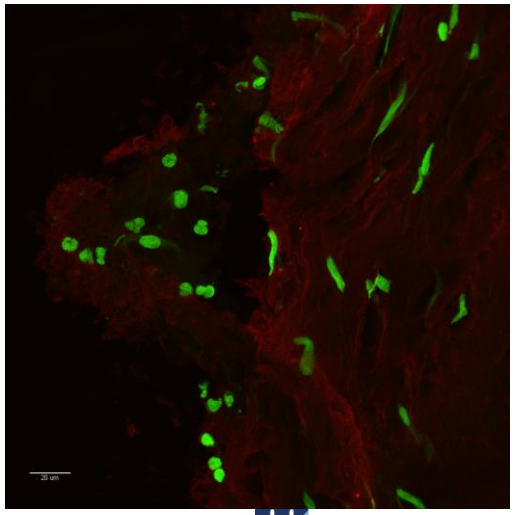
Post-treatment

Moleculight



Biofilm score: 0 (No microorganisms observed)



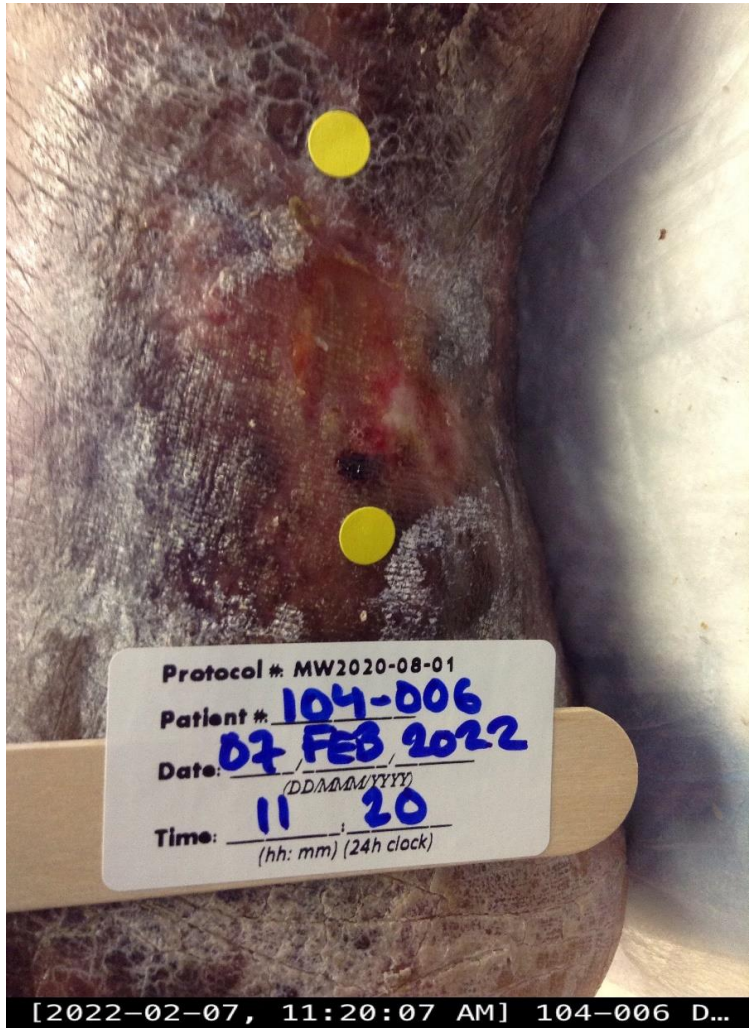


MediWound

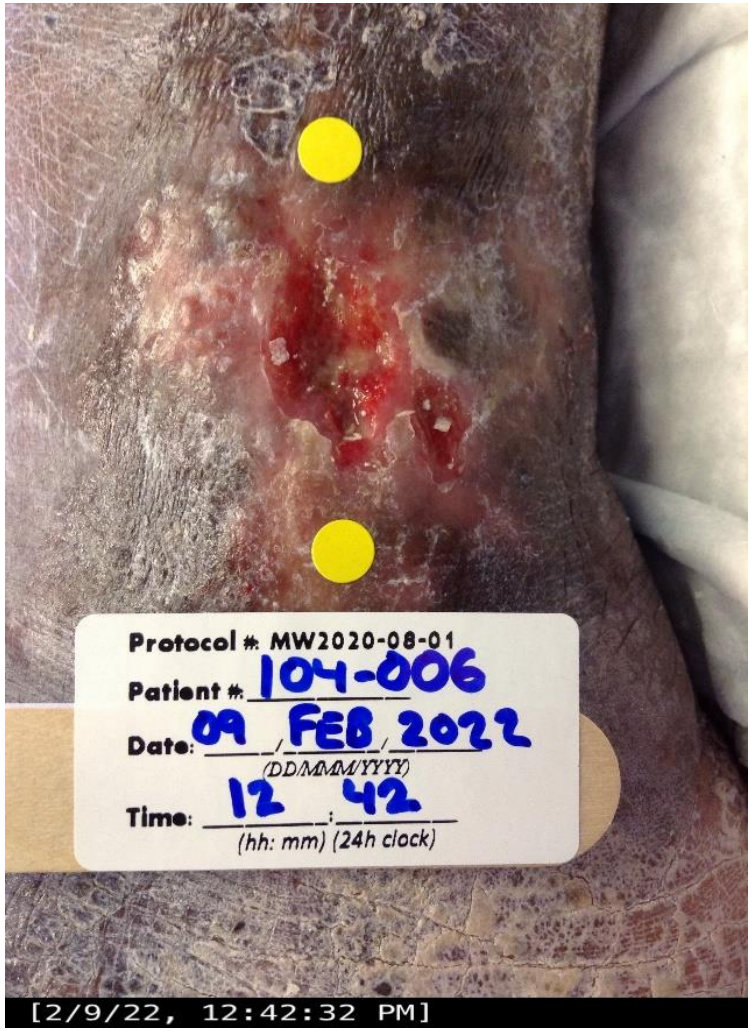
MediWound

104-006
VLU

Pre-treatment #1, 07 Feb 2022 – 85% NVT



Post-treatment #2, 09 Feb 2022 – 0% NVT (Complete ER)



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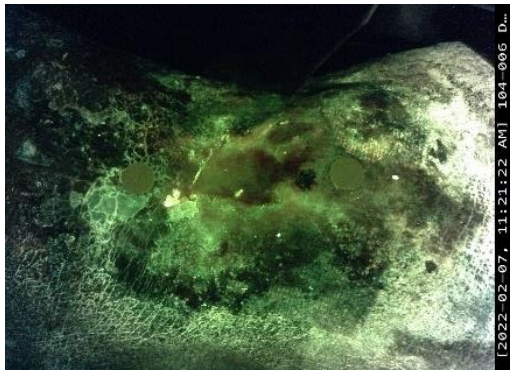
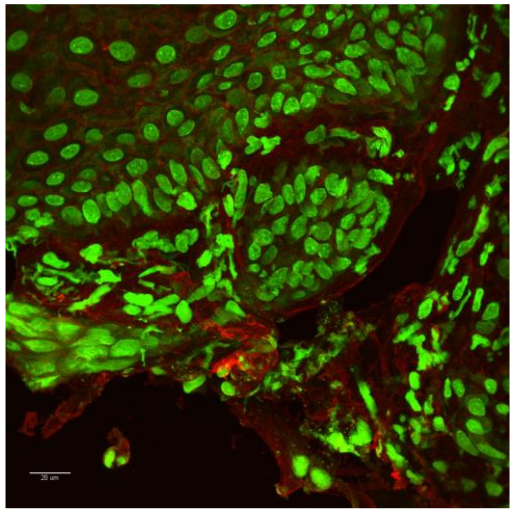
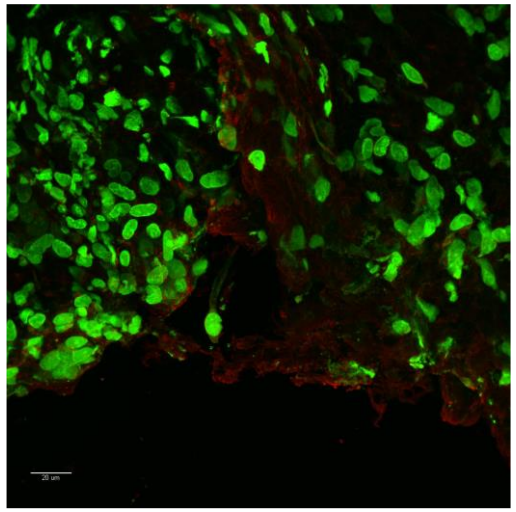
Pre-treatment

Moleculight



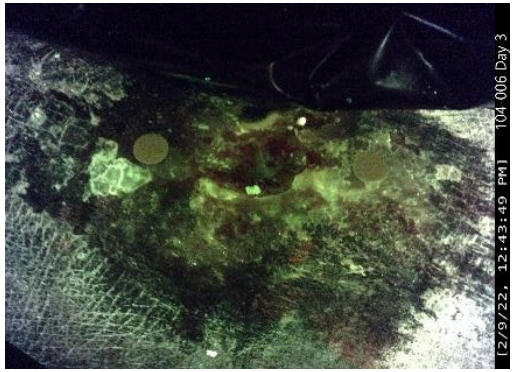
Biofilm score: 2 (Small microcolonies of microorganisms)



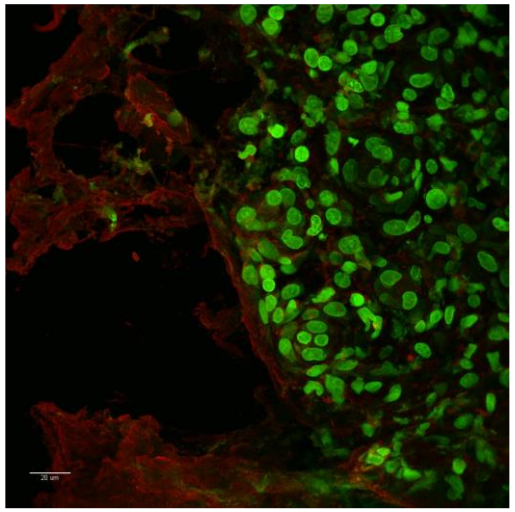


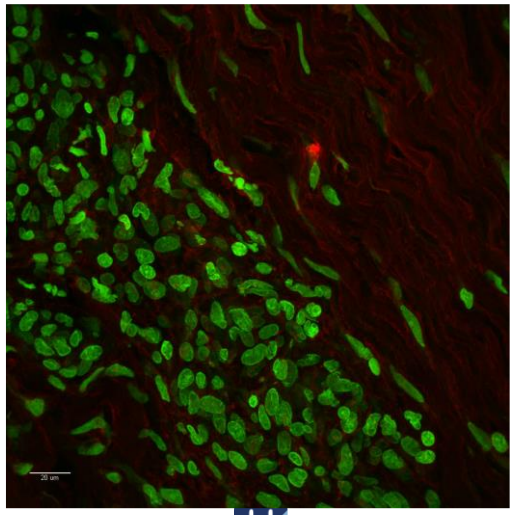
Post-treatment

Moleculight



Biofilm score: 1 (Single individual microorganisms)





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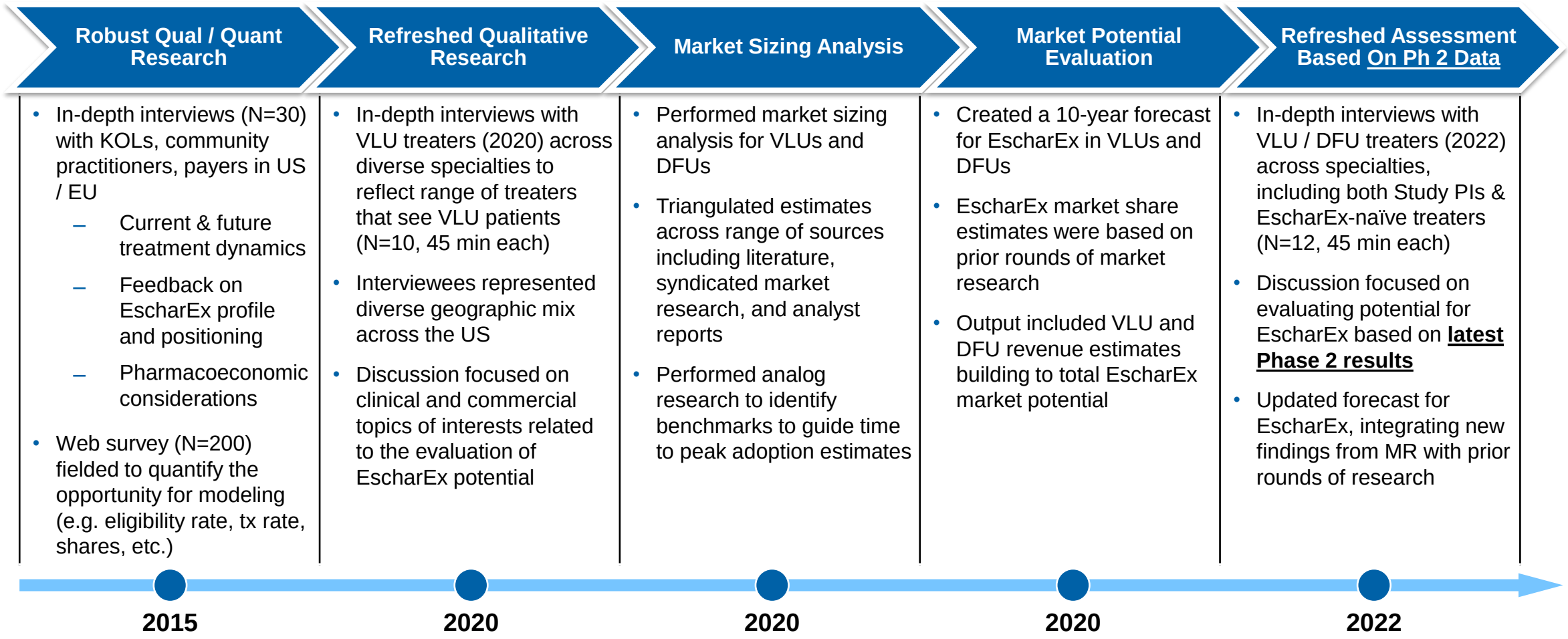
Market Landscape Analysis & EscharEx Market Potential

Kevin Feng
Oliver Wyman

Market Research Has Been Comprehensive



Comprehensive and step-wise evaluation of EscharEx Potential based on latest clinical development plan & data

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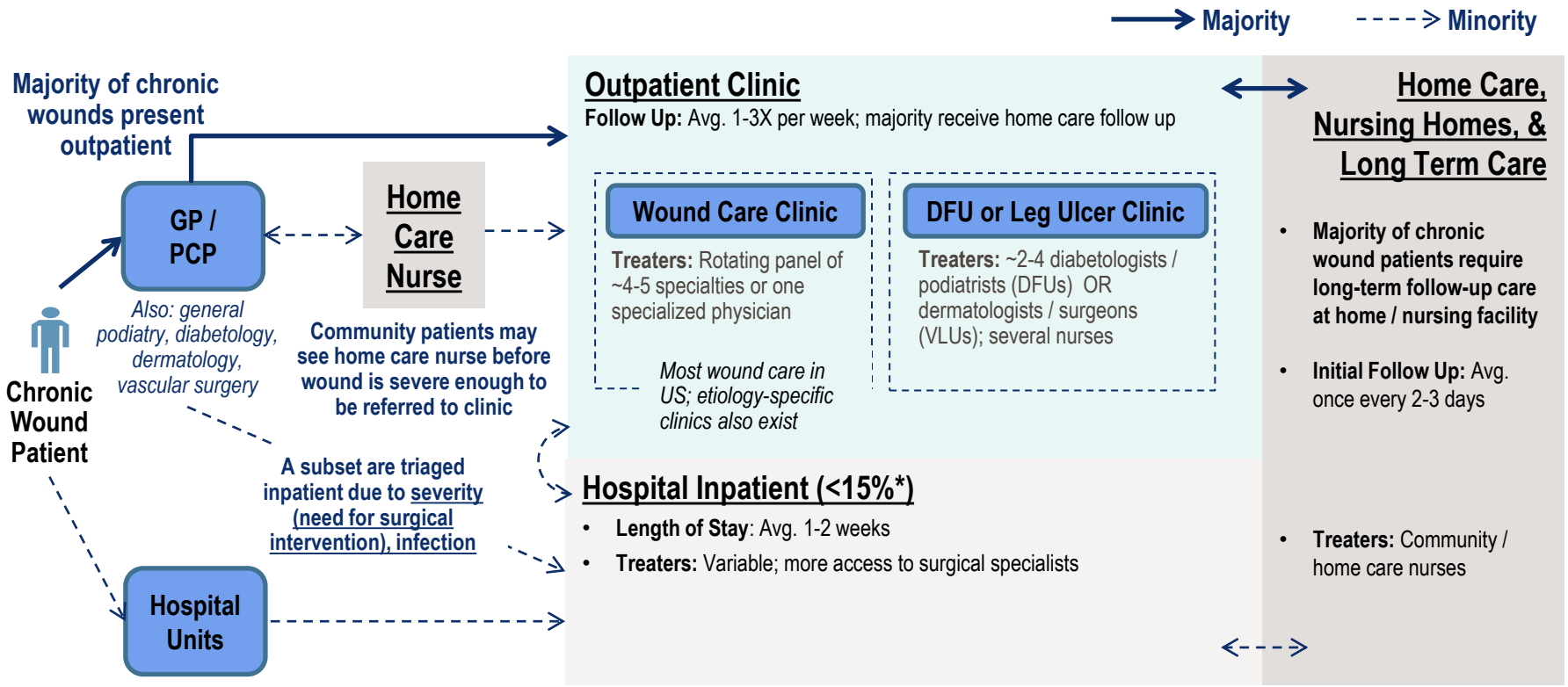
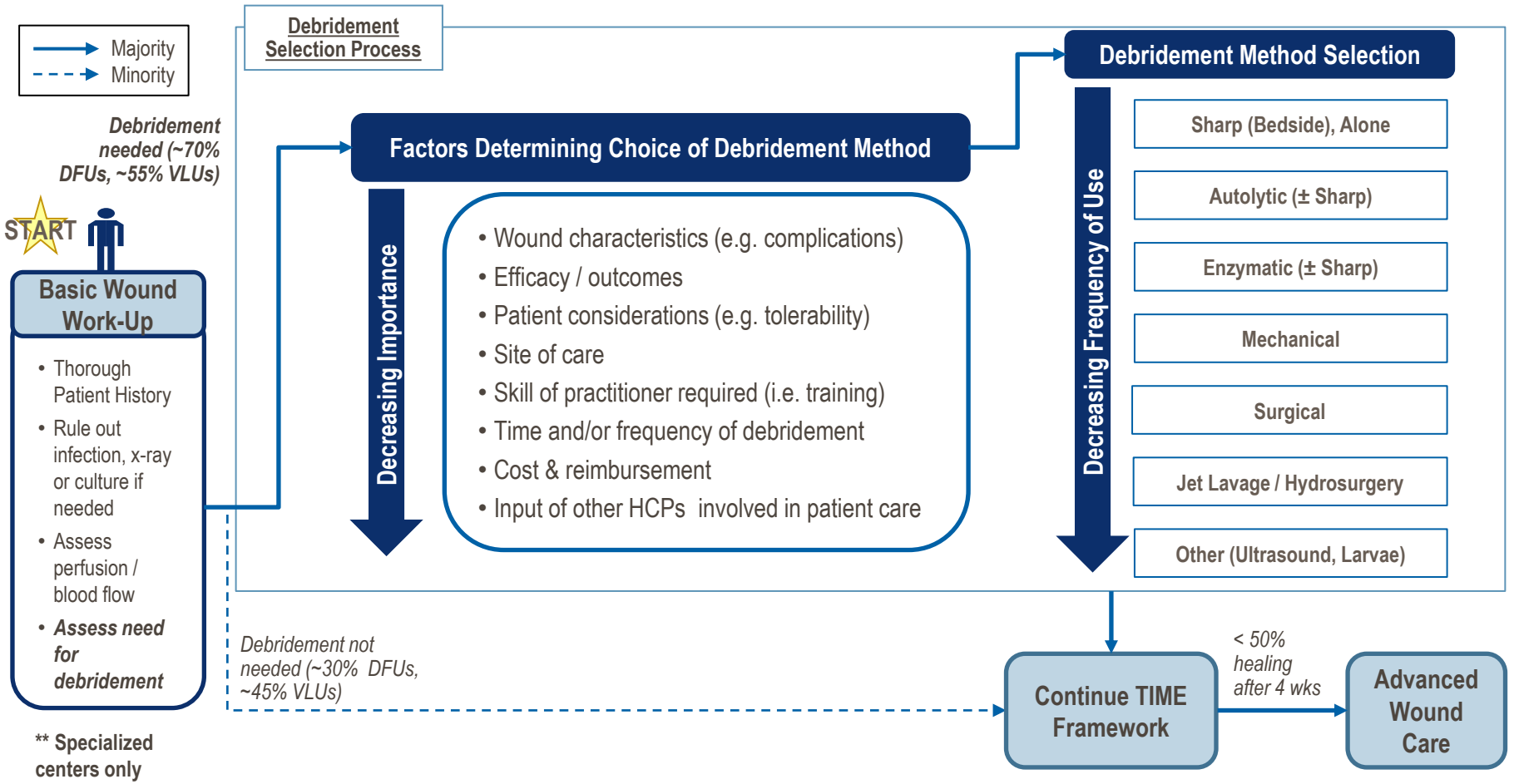
Chronic Wound Patient Journey: Key Sites of Care



Most chronic wounds in the U.S. are treated outpatient with follow-up visits 1-3x per week

*15% present in academic setting w/ more complex wounds; overall % inpatient likely lower

Debridement is SOC, But Method Is Not Standardized



Wound characteristics, efficacy, and patient considerations are top influencers of choice

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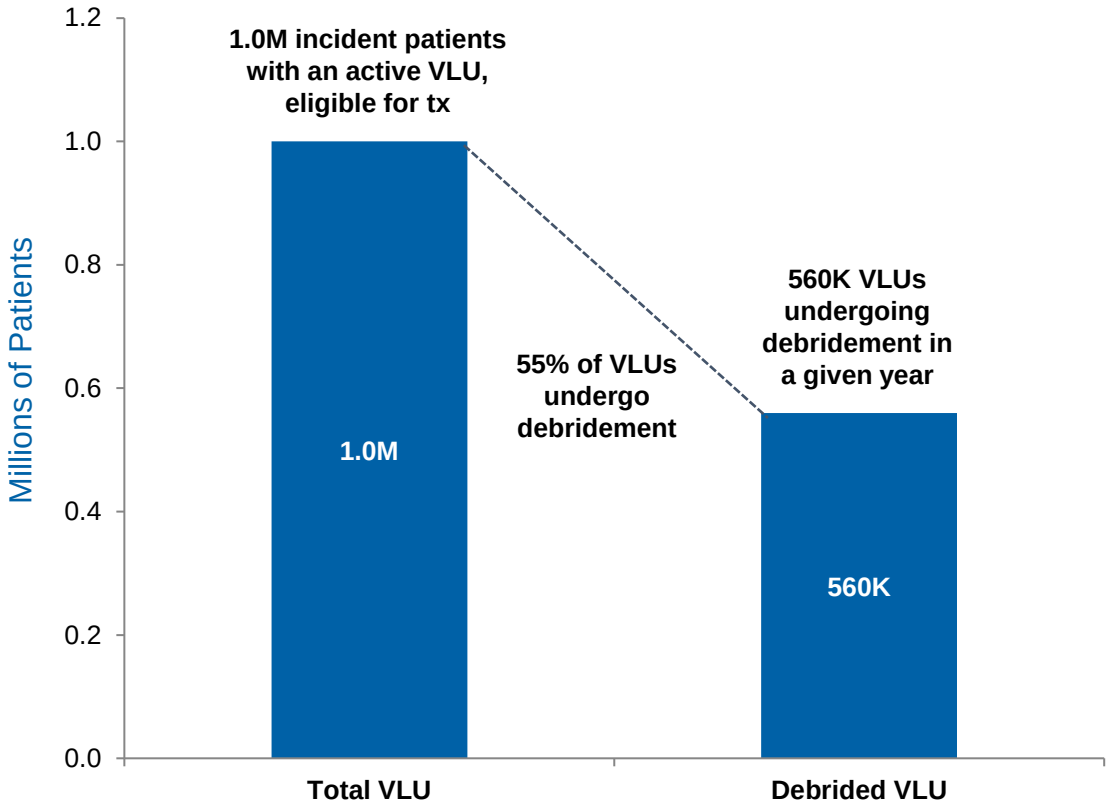
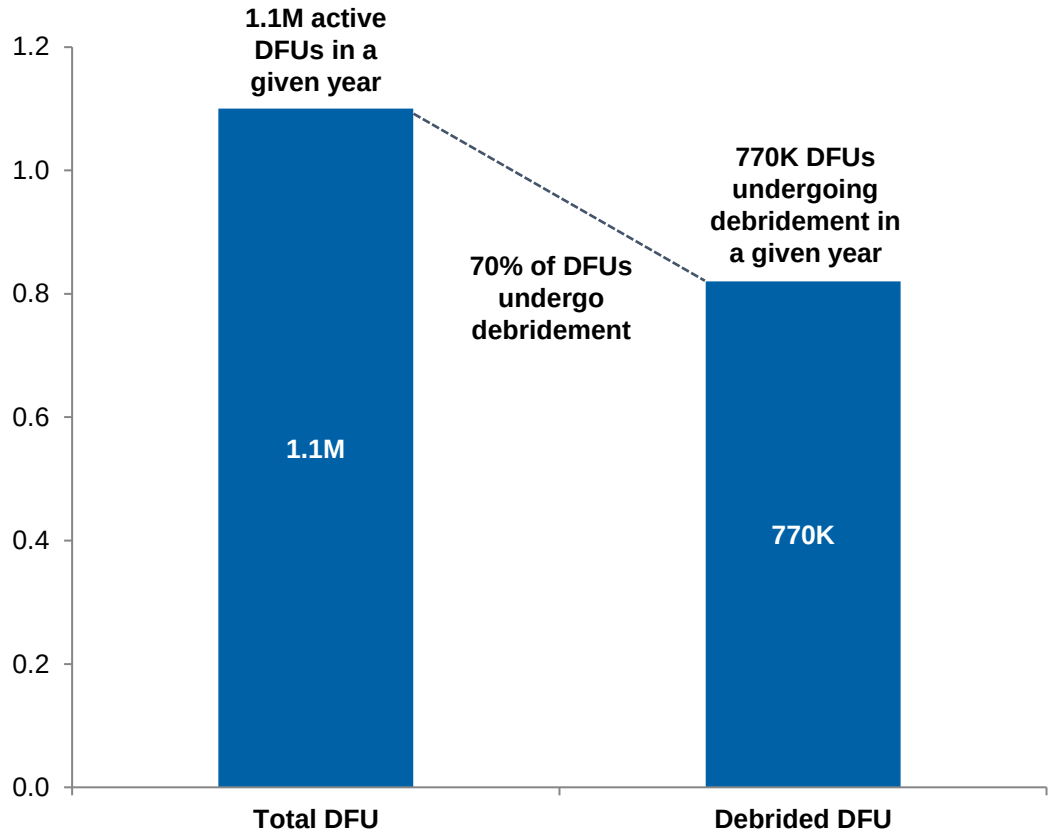
Triangulation Indicates 1M VLUs and 1.1M DFUs Annually Eligible for Debridement

2022 US VLU Epidemiology Estimate



2022 US DFU Epidemiology Estimate



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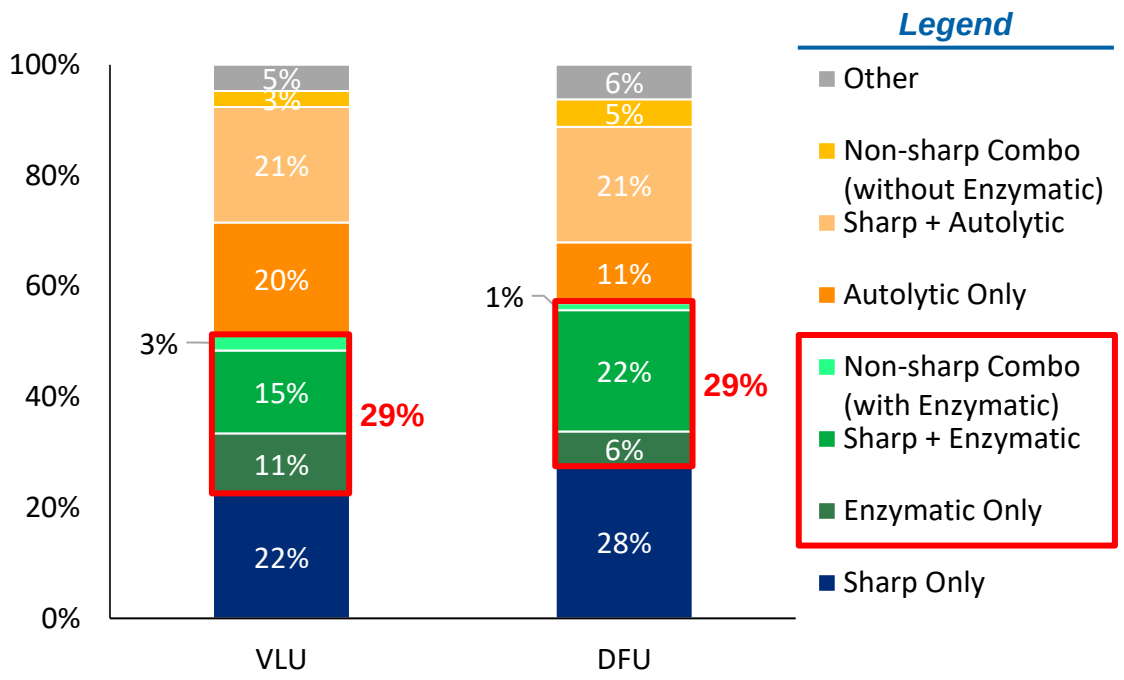
VLU Debridement Approach Driven By Site Of Care; Sharp Remains SoC Across Wound Care Clinics

Current Debridement Practices*



Commentary

- **All VLU patients seen at WC clinics will undergo debridement**
  - In contrast, in home health setting only 1/3 VLUs are debrided; other 2/3 of patients have wounds that are caught and managed early by nurses, and thus can heal without needing debridement
- **Choice of debridement technique is highly dependent on site of care**
  - Surgeons and clinicians at wound care clinics, regardless of medical specialty, **perform sharp debridement as SOC for all patients**
  - In other specialty practices, such as dermatology, **clinicians much more split between sharp vs. non-sharp**
  - Nursing home / home health settings depend enzymatic or autolytic
- While sharp is SoC at WC clinics, **pain can be a barrier to use** (particularly in VLUs), leading HCPs to defer to a topical instead
- **Sharp + enzymatic / autolytic combinations** are also commonly used, with sharp used as primary method (e.g. 1-2x per week) and topical as maintenance (applied in between sharp visits)

*"All DFU / VLU patients get sharp debridement. **If they are able to tolerate it, it is probably the most effective debridement** method of removing nonviable tissue, as well as bioburden in the wound. "*

– Podiatrist #5 (Non-PI)

*"Some of the wounds are more superficial, **sometimes the topical agent alone is enough**...if they are not responding, yeah, then we would have to step it up and go to a different method, probably add sharp debridement in "*

– Dermatologist #2 (Non-PI)

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*Estimates are based on small study (N=12)

Source: OW Primary Research (6/2022)

Current Enzymatic Use is Limited, Due to Perception of Low Efficacy and High Cost

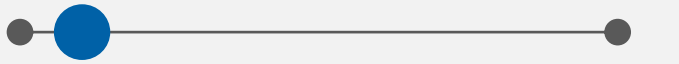
Current Enzymatic SOC Perception

Efficacy

Safety

Dosing & Administration

Cost



Commentary

- **Efficacy**: HCP opinion of enzymatic efficacy generally ranges from **very low to moderate**; most still utilize to some degree but **note limited efficacy due to slow speed of debridement**
  - Efficacy may be **further reduced if unable to comply** with recommended 1x daily regimen
  - A few HCPs cited **Panafil as a much faster enzymatic debrider**, prior to recall
- **Safety**: Considered very safe, with minimal AEs / pain
- **Dosing & Administration**: Generally **considered easy to use / apply**, given potential for self or care-giver application; recommended regimen is typically **1x / day**
  - Slow speed of debridement **leads to extended use** (average of 6-8 weeks), which can also influence **patient compliance** with daily regimen
- **Cost**: High cost often cited as **major disadvantage relative to efficacy**,
  - Average cost of ~$298 / 30g tube, reimbursed under pharmacy benefit; prior research showed patients use ~6-8 tubes on average (total cost of treatment ~$2000)

*"**Enzymatic use is a little bit of an expense thing**. It is a little bit of an availability thing that sometimes it is just harder to get, **so that I use them less partly for that reason**. I do think they **probably work a little bit better than autolytic**, but **I am not honestly even sure of that."***

– Dermatologist #2 (Non-PI)

*"It is efficacious compared to Vaseline... **But is it tremendously efficacious? Tremendously helpful? I question that notion**… Oftentimes, **my patients cannot afford it**, or the patient has to pay most of it because **their prescription plan may or may not cover it**."*

– Podiatrist #2 (Non-PI)

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Source: OW Primary Research (6/2022)

HCPs Report Significant Need For Faster, More Efficacious Topical Debridement Agent

Unmet Need

- Physicians note that while sharp is efficacious and affordable, **there remain situations where sharp cannot be utilized**, driving unmet need for efficacious and affordable non-sharp alternatives:
  - **Speed**: Ideal product should work faster than current topical modalities, as speed of debridement cited by most HCPs as greatest unmet need
  - **Affordability**: Novel agent should be affordable and similar to current alternatives; experts note higher cost or lack of coverage by insurance as deterrents to using current modalities
  - **Application frequency / duration:** Daily application over long periods of time required by current enzymatic treatment; alternative ideally requires fewer applications
- **Gap in market remains after recall of papain products** (seen as much more effective than current enzymatic SoC), which were used commonly when sharp was not suitable

*"**I would like to see a product that actually works within a reasonable period of time**. Not eight weeks but maybe something within four weeks. Even with compliant patients with a wound that's a couple centimeters in diameter, it's going to take eight weeks. **It shouldn't take that long.***

–Podiatrist #1 (Non-PI)

Pipeline

- A few physicians have noted interest in few products in the pipeline (e.g. hydro-debriders, topical stem cell agents); however, most HCPs have **limited optimism or knowledge of therapeutic agents in the pipeline**

*"Enzymatic is not great at debriding everything and it takes a long time …something **that will debride faster is what we are looking for**. Sharp is really the only fast debridement modality, but it is not always applicable. I**f we had something that was able to debride the wound faster without causing pain, that would be ideal**."*

–Podiatrist #4 (PI)

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Source: OW Primary Research (6/2022)

EscharEx Perceived As Highly Efficacious, Demonstrating Clear Benefit Over Current Options

EscharEx Perception by Attribute

Primary Endpoint	Incidence to complete debridement
Secondary Endpoint	Time to achieve complete debridement
	# applications needed for debridement
	>75% Granulation tissue incidence
Pharmacology	Biofilm Score
	Bacterial load via fluorescence
Wound Closure	Incidence of wound closure
	Time to wound closure

Commentary

- **Perception of efficacy is extremely favorable**, with HCPs immediately noting EscharEx's faster speed of debridement vs. current agents
- **Primary and secondary clinical endpoints** believed to be most important, with clearest benefit demonstrated by **incidence of and time needed to achieve complete debridement**
- **Pharmacology data** seen as helpful in **supporting clinical endpoints**, though less important than primary / secondary
  - HCPs often expect lower biofilm / bacterial load as natural consequence of better debridement (and thus may not emphasize importance of seeing pharmacology data)
  - However, a few physicians noted **biofilm score / bacterial load has been emerging** with increasing level of importance in wound healing field
- Few HCPs want to see **superior efficacy in wound closure**, given faster debridement should translate to faster wound closure; however, **most believe that a superiority endpoint is not essential** for a debridement agent, and **comparable incidence / time data is sufficient**
  - If **superior efficacy for wound closure** was shown, HCPs believe this may support even further adoption of Product X and justify higher costs

*"**The product looks like it works very well**. They are basically saying you only need five applications of this product to get the wound to a granular bed, **which is great because you do not usually see that**."*

–Podiatrist #5 (PI)

*"I think **biofilm is increasingly important** because of literature supporting better ways of trying to break bioburden down. It is more on my radar today than it was 10 years ago or even two years ago. **It's innovative in a way to keep that as one of your endpoints**. "*

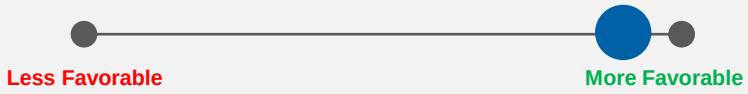
–Podiatrist #6 (PI)

Source: OW Primary Research (6/2022)

Minimal Issues with EscharEx Safety Or Dosing & Administration

EscharEx Perception by Attribute

Safety



Dosing & Administration

Commentary

- **Safety:** Most HCPs raised minimal issues with safety profile (perceiving as safe), with several noting how crucial safety is when considering high opinion of enzymatic agent's safety today
  - A few HCPs requested additional data surrounding pain (or absence of pain) upon application, highlighting importance of patient comfort
- **Dosing & Administration:** Perceived as favorable, particularly given short regimen (daily applications for 5 days) compared to current enzymatic agent and potential for home-application
  - **Potential for range of 5-8 applications did not raise any concerns**, as even 8 days is significantly faster than current enzymatic agent; few HCPs noted minor benefit with 7 or fewer days, to fit logistically into weekly clinical visits
  - HCPs also amenable to first application in clinic, followed by subsequent home applications

*"There were no adverse events. There were no allergic reactions to the product. **It seems like it is a safe product to use**. 120 patients to evaluate the tolerability and safety of the product, it is a good study. "*

–Podiatrist #5 (PI)

*"**My perception wouldn't change from 5 to 8 applications**. I mean current enzymatic treatment, it's 100 applications, you know. So, they could go to 20 applications, and it still wouldn't make any difference to me."*

–Dermatologist #2 (Non-PI)

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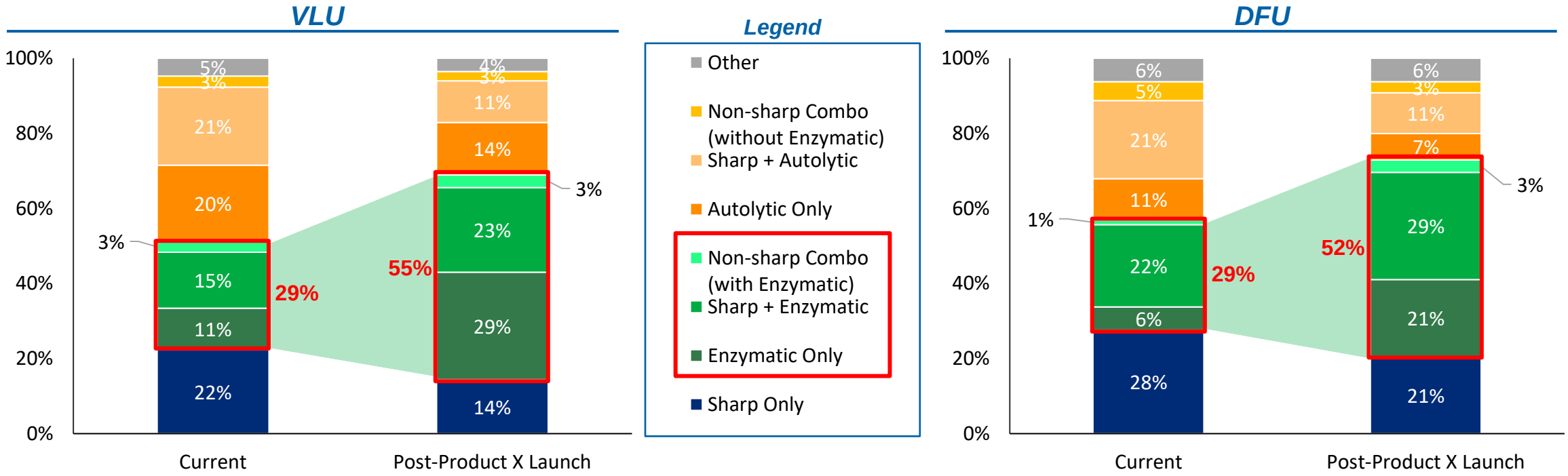
Source: OW Primary Research (6/2022)

Given Strong Profile of EscharEx, HCPs Reported Expansion of Enzymatic Use Drawing From Other Classes

Future Debridement Practices



- HCPs expect **aggressive expansion of enzymatic segment across VLUs & DFUs,** with slightly **higher use in VLUs** given **additional barrier that pain** poses to sharp use; similarly, HCPs expect greater use of enzymatic only in VLUs (vs. DFUs), but greater use of sharp + enzymatic in DFUs (vs. VLUs)

EscharEx is anticipated to draw share from all other debridement modalities (including sharp only, autolytic only, and sharp + autolytic)

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Source: OW Primary Research (6/2022)

U.S. Market Opportunity

~2.1M
VLU and DFU patients eligible for debridement in a given year

55% - 70%
Percentage of wounds debrided

43%
Percentage debrided by enzymatic methods
(Research indicates that EscharEx can expand enzymatic market (~20% debrided by enzymatic methods today) if superior to current enzymatic agent and more cost effective)

70%
Anticipated EscharEx market share based on superiority
5 Years-to-Peak Share

CoT: $1,500 (base) / $1,800 (upside) / $1,200 (downside)
CoT: based on 5 applications on average @ $300 per application

- **EscharEx TAM for VLUs and DFUs is estimated at ~$2B in the U.S.**
- **Market research and physician feedback suggest that EscharEx potential market share at ~30%**

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Market potential estimates based on above assumptions, and does not account for market access and other considerations that may impact actual figures and are subject to EscharEx approval b FDA. EscharEx is an investigational drug under development, not approved in any jurisdiction

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Corporate Update

Ofer Gonen, CEO

Why MediWound?

EscharEx® presents huge market potential

- **EscharEx** fills an unmet medical need for a rapid, effective, non-surgical debriding agent, for outpatient settings
- **EscharEx** is based on a clinically & commercially validated enzymatic technology platform (NexoBrid®)
- **EscharEx** is superior to non-surgical standard-of-care
- **EscharEx** is headed for global approval for VLUs and DFUs
- **EscharEx** generates significant interest from strategic players
- **EscharEx** sets a new bar for efficacy, enabling it to become a 1st line therapy with 30% share of a $2B market

MediWound's **Corporate Strategy**

EscharEx®	**The focus** Pursue an accelerated regulatory pathway Global approach Strategic alternatives
NexoBrid®	**On track** BLA resubmission, BARDA & Vericel collaboration, commercial global expansion
MW005	**On track** Positive data readout, strategic alternatives