



Bromelain-Based Debridement Molecular Mode of Action

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Disclosures

- Studies funded by MediWound Ltd.
- Dr. Klinger is the Chief R&D Officer at MediWound Ltd.

The Importance of Debridement

Remove necrotic and non-vital tissue that impairs repair process

Remove senescent cells from wound bed

Remove non-migratory cells from ulcer edge

Control excessive or abnormal bacterial load

Allow improved availability of growth factors

Allow wound assessment (e.g., depth, tunnels)

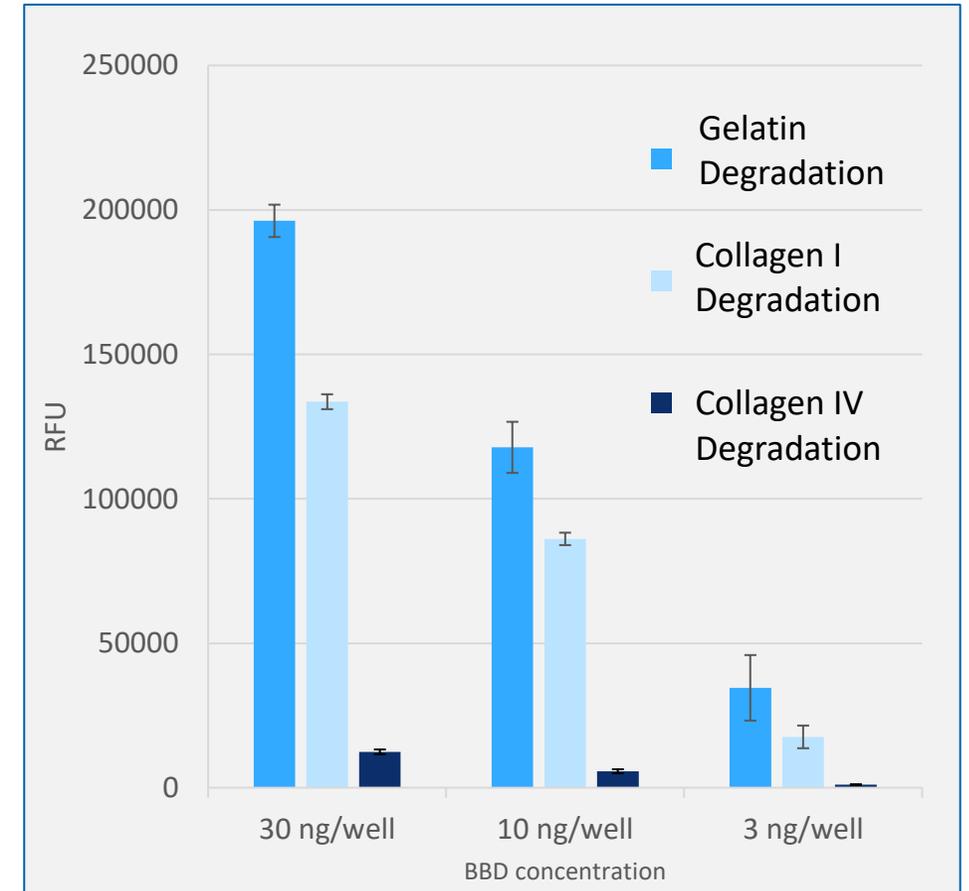
Manage and control the pathology

BBD - Bromelain Based Debridement

- BBD – a mixture of proteolytic enzymes enriched with bromelain, derived from the stem of pineapple plant
- BBD is the active ingredient in NexoBrid[®] and EscharEx[®]
 - *NexoBrid[®], FDA/EMA approved for eschar removal in second and third-degree thermal burns*
 - *EscharEx[®] - Investigational biological product in late-stage clinical development in venous leg ulcers (VLU) and and diabetic foot ulcers (DFU)*

BBD Degrades Denatured Collagen

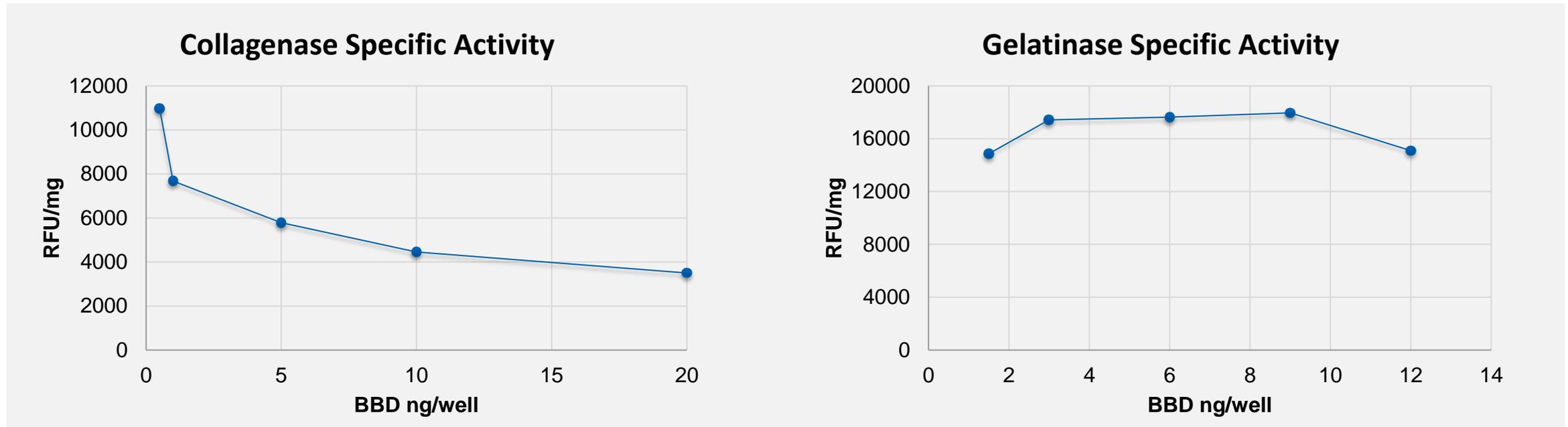
- Eschar in **burn wounds** consists primarily of gelatin, a denatured form of collagen
- In **chronic wounds**, MMPs degrade intact collagen, leading to denatured, non-functional collagen that impairs wound healing
- BBD degrades gelatin at a much faster rate than collagen type I and IV (Indicated by stronger fluorescent signal (RFU))
 - Collagen type I (abundant in the skin)
 - Collagen type IV (abundant in the basement membrane and should be preserved)



BBD activity was evaluated using fluorescently labeled native and denatured collagen

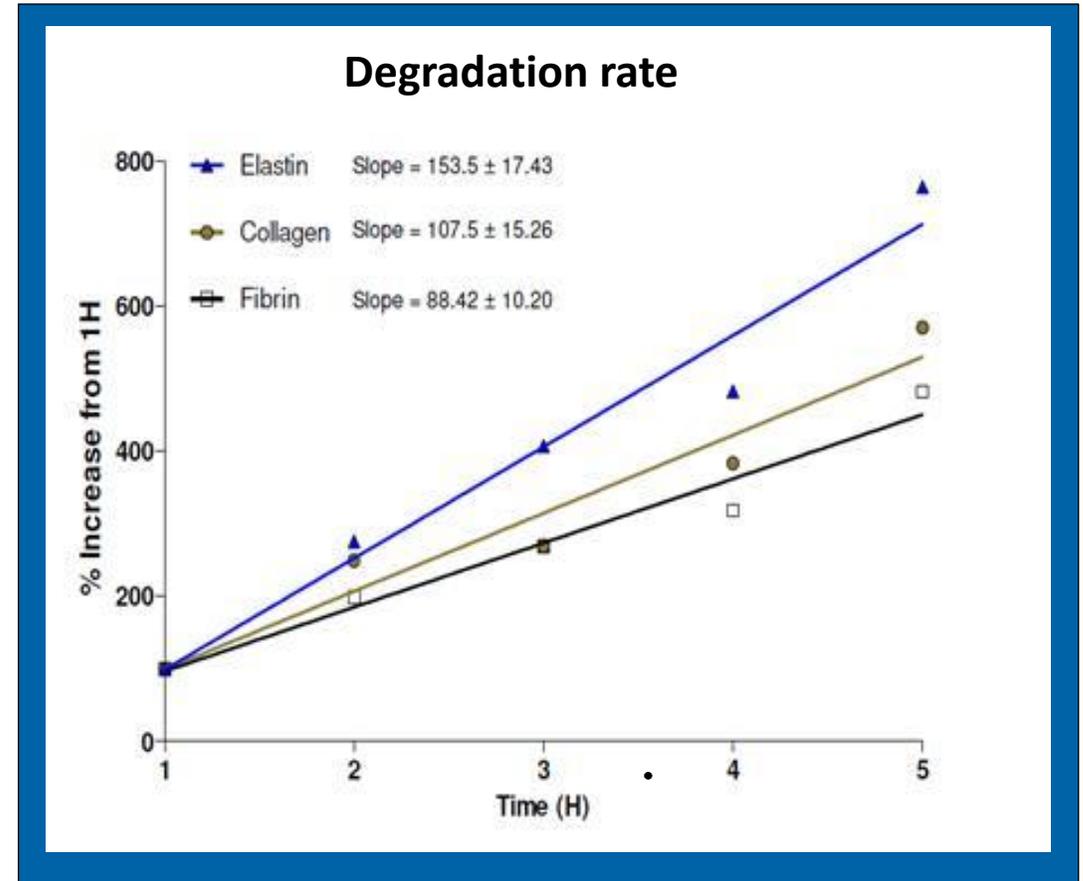
Protease Inhibitors Control BBD's Enzymatic Activity

- Collagenase specific activity, measured by RFU/BBD concentration, decreased with increasing BBD concentration, indicating the presence of protease inhibitors within the BBD mixture
- The presence of protease inhibitors in BBD's mixture was confirmed by LC-MS/MS analysis
- Gelatinase specific activity was not affected by BBD concentration, suggesting a higher affinity of BBD to gelatin



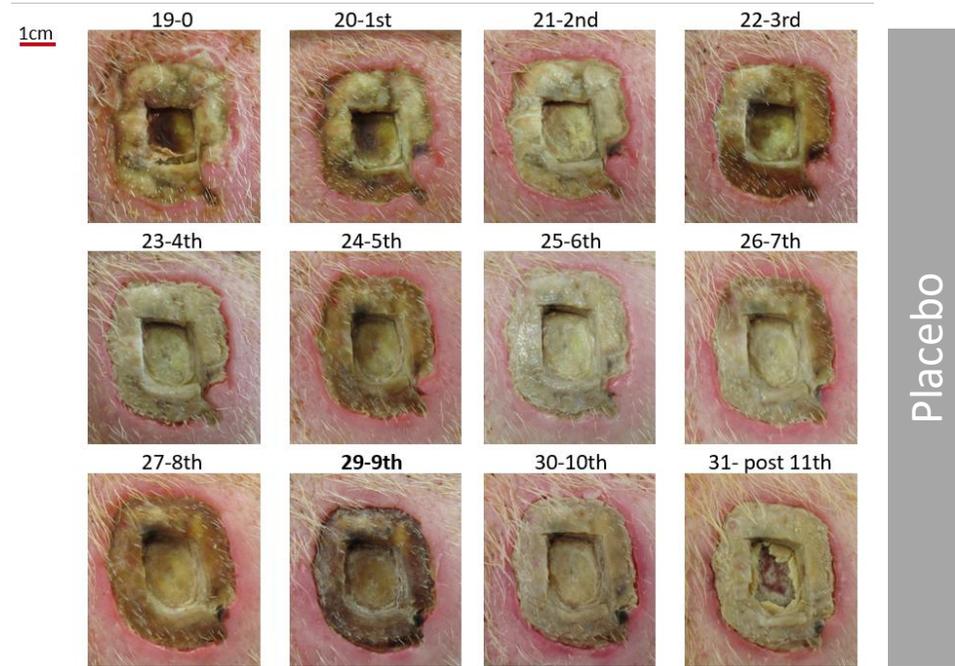
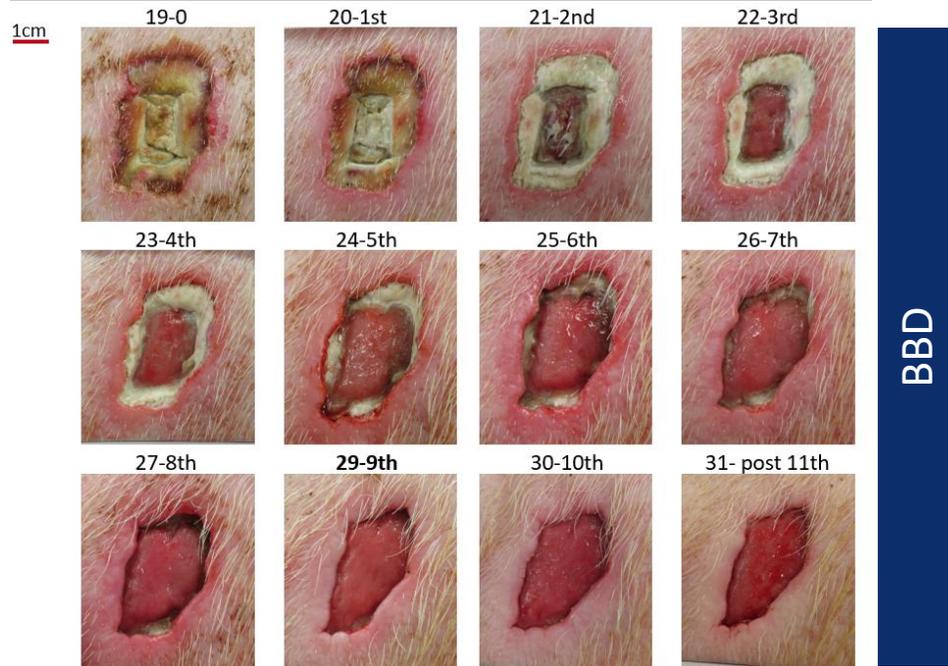
BBD Removes Over-Secreted ECM Proteins

- ECM proteins e.g., fibrin, collagen, elastin are over-secreted in chronic wounds
- Accumulation of these degraded proteins prevents the progression to normal healing
- BBD enzymes degrade over-secreted ECM proteins and facilitate the removal of various denatured proteins from the wound bed



In vitro degradation of fluorescently labeled proteins by BBD, using Franz cells

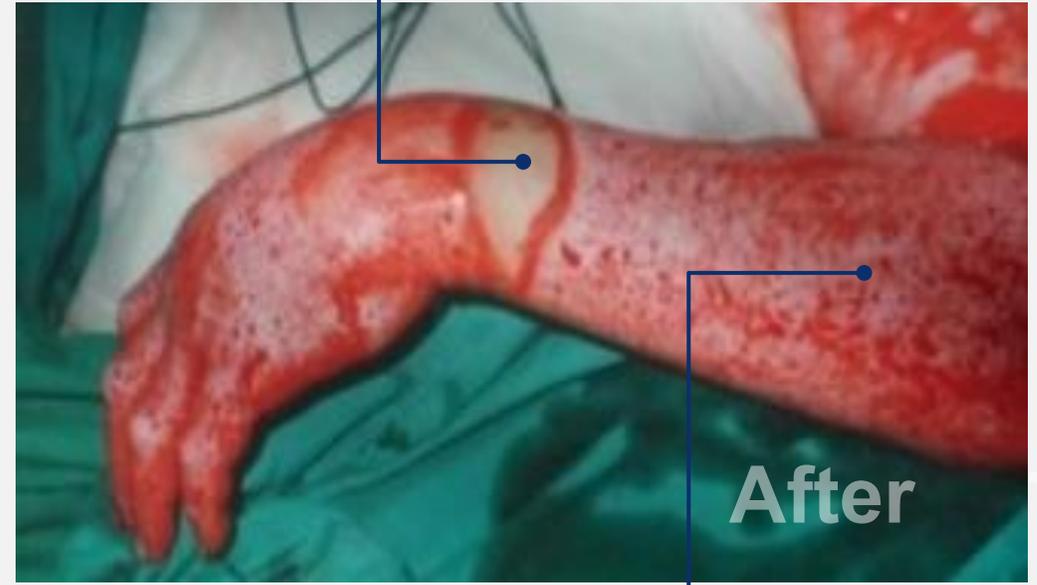
BBD Effectively Debrides Hard-to-Heal Wounds in a Pig Model



Complete debridement and granulation tissue formation are achieved within eight daily BBD treatments, demonstrating superiority over placebo

Clinical Evidence

BBD Selectively Removes Eschar in Deep Burns

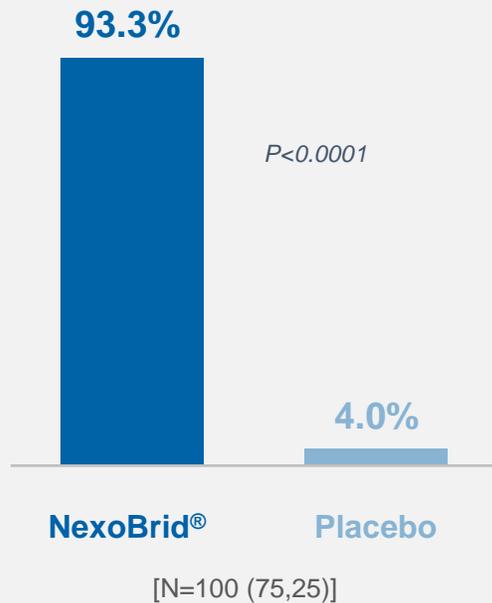


Intact skin preserved

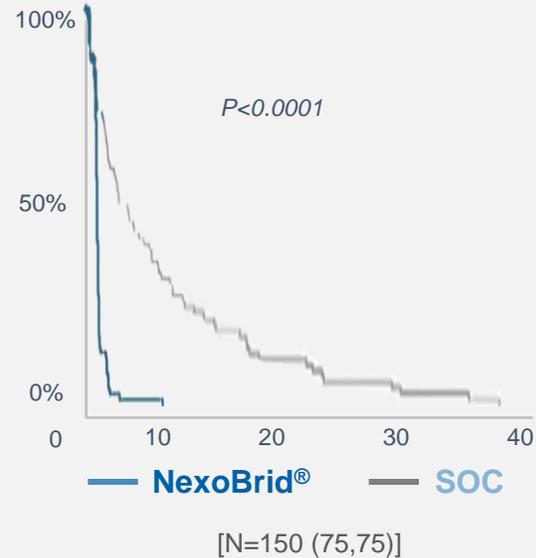
Non-injured dermis preserved

Phase 3 Studies Demonstrated Superiority¹ in Burns

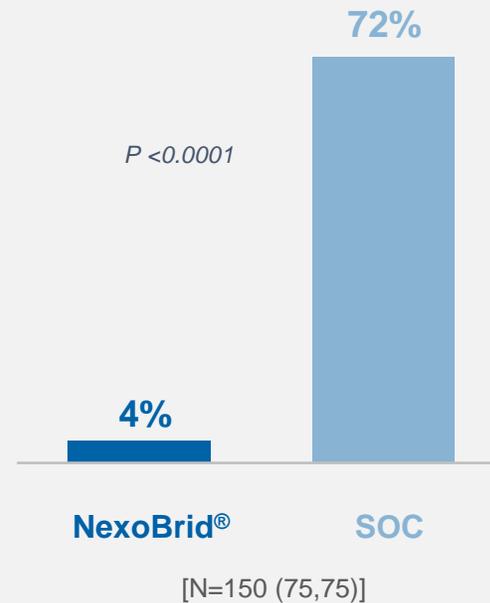
Incidence of complete eschar removal



Time to complete eschar removal (days)



Incidence of surgical eschar removal



Blood loss



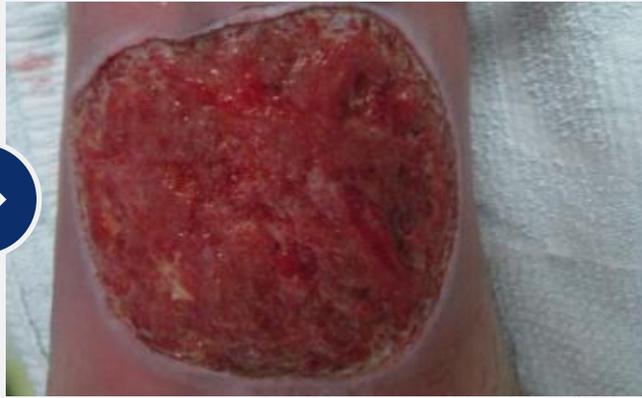
1. Shoham et al. 2023; Journal of Burn care & Research

EscharEx - Enzymatic Debridement within Days

Before



After



VLU

Venous Leg Ulcers

(Complete Debridement – 3 days)



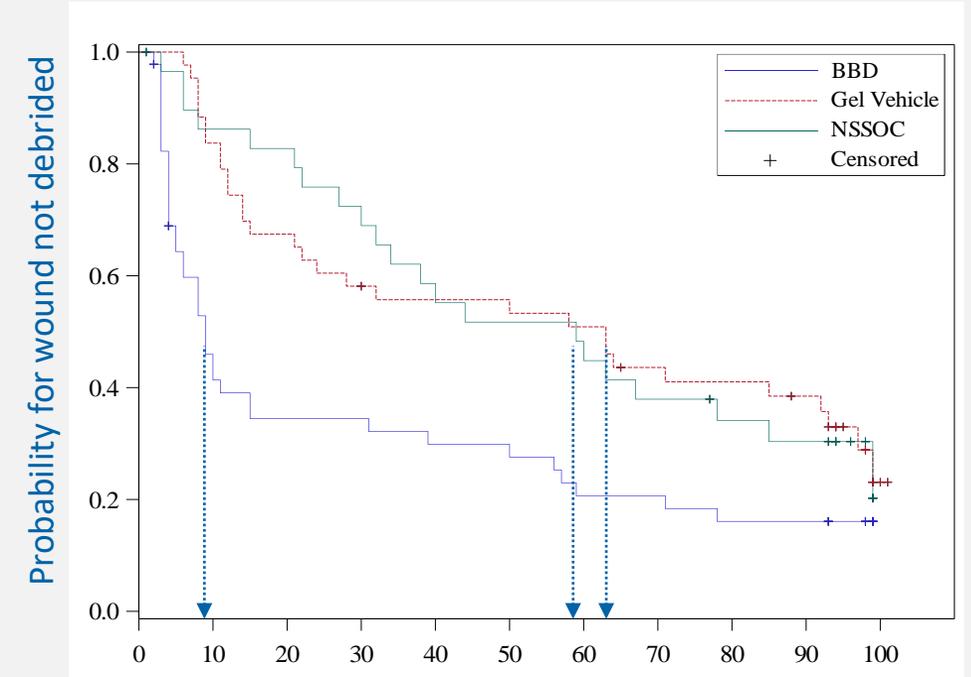
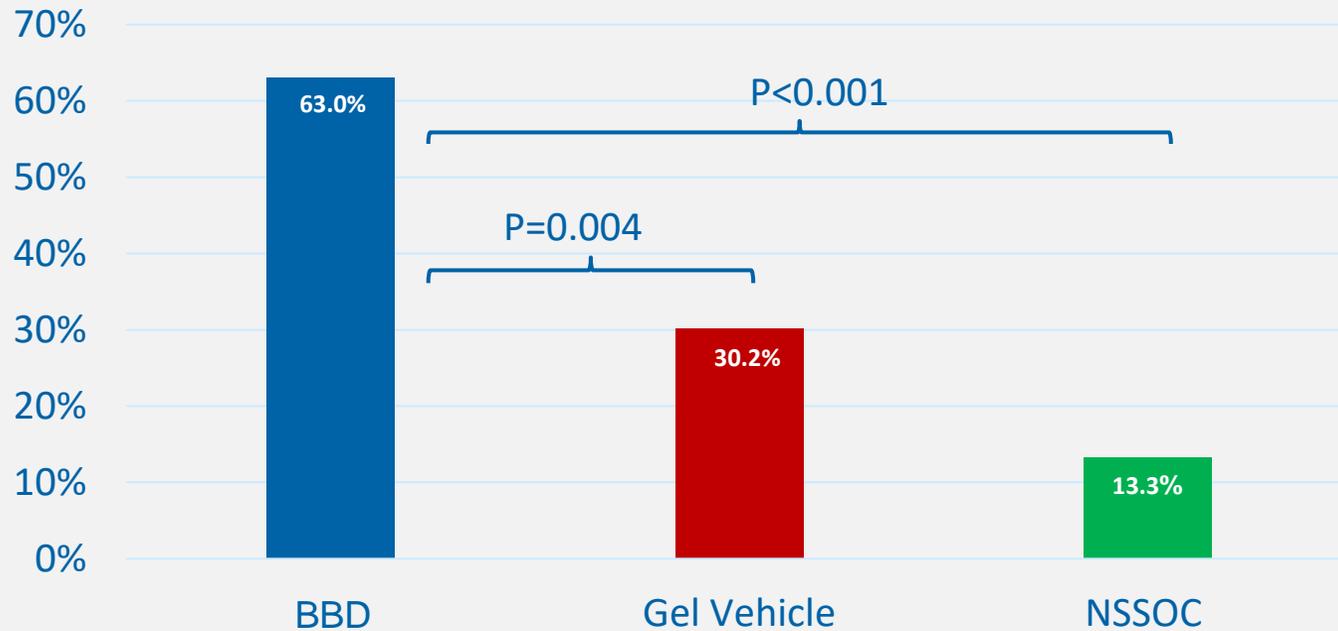
DFU

Diabetic Foot Ulcers

(Complete Debridement – 4 days)

Phase 2 Demonstrated Superiority¹: VLU Debridement

Complete Debridement Within the Daily Treatment Period (2 weeks)

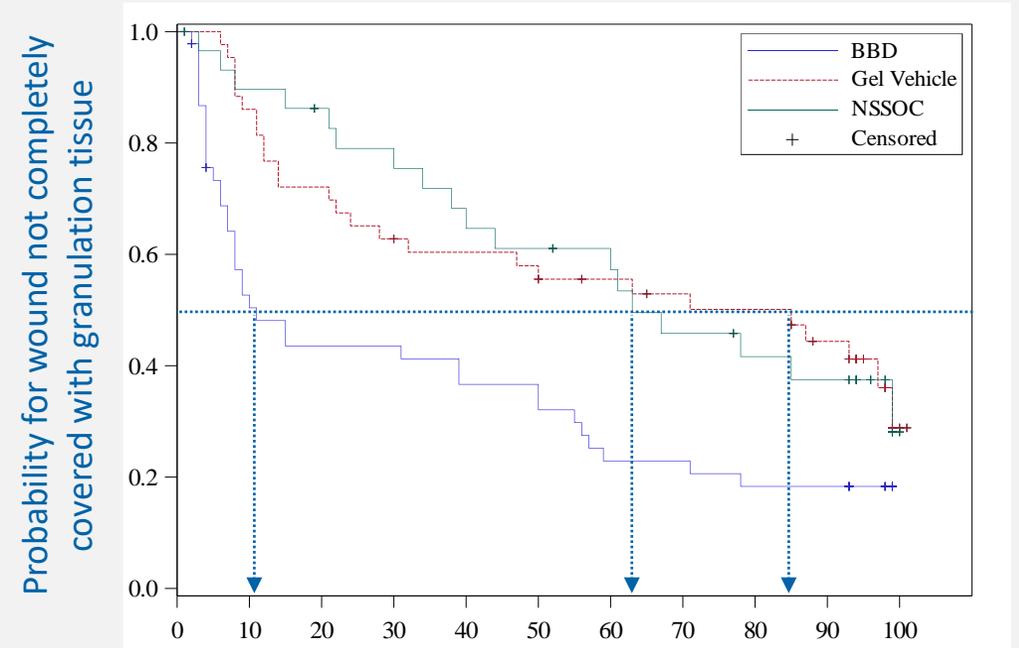
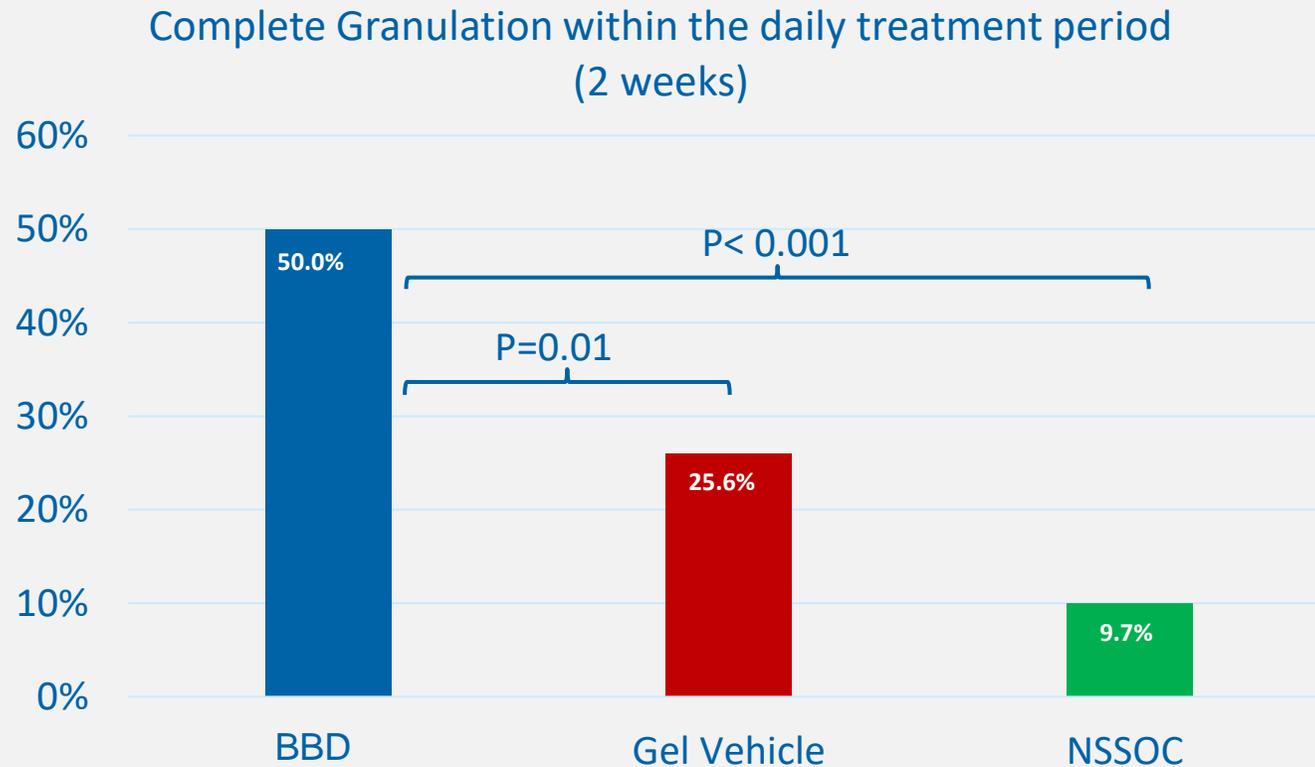


Time to complete debridement (days)

BBD: 9 days vs:

- **NSSOC: 59 days, P=0.016**
- **Gel Vehicle: 63 days, P=0.004**

Phase 2 Demonstrated Superiority¹: VLU Granulation



Time to complete granulation (days)

BBD: 11 days vs:

- **NSSOC: 63 days, P=0.011**
- **Gel Vehicle: 85 days, P=0.004**

Summary

- In-vitro studies demonstrate that BBD's complex enzymatic mixture has a highly selective multi-target proteolytic activity
- The debriding activity of BBD was demonstrated in preclinical models as well as in patients with burns and in patients with chronic wounds
- The enzymatic mixture composition is an important and unique attribute of BBD that enables fast and effective complete debridement of wounds exhibiting various forms of denatured proteins and nonviable tissues