CLOSER LOOK

MEMORANDUM

Applied Biologics announces first site activation in phase 3 trial evaluating BIOxHEAL for chronic diabetic foot ulcers – September 1, 2026

Patient enrollment expected to begin shortly; BIOxHEAL is being developed as a short-course biologic therapy with weekly administration

Scottsdale, Arizona-based Applied Biologics announced today the activation of the first clinical research site in its phase 3 trial for its lead clinical asset BIOxHEAL, a treatment for chronic diabetic foot ulcers (DFUs). Today's announcement marks the biologic's transition from clinical preparation into active execution, with patient enrollment expected to begin shortly.

The RCT will take place across multiple centers and compare BIOxHEAL plus the standard of care against the standard of care alone in patients with non-healing DFUs. We are enthusiastic to see this advancement of an investigational treatment for DFUs, which precede 80% of lower extremity amputations among individuals with diabetes.

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DFUs represent a significant complication of diabetes, affecting millions worldwide

BIOxHEAL is a biological, tissue-based treatment for DFUs, which affect ~18.6 million people worldwide each year, including ~1.6 million people annually in the US. Approximately one-third of individuals with either T1D or T2D are estimated to develop a foot ulcer during their lifetime. DFUs develop through a complex interaction of neuropathy, impaired wound healing, and peripheral arterial disease (PAD). Moreover, these chronic wounds are extremely prone to infection due to the body's hyperglycemic environment, with at least 20% of infections resulting in some form of amputation. Worldwide, DFUs are the leading cause of atraumatic lower extremity amputations.

BIOxHEAL aims to treat DFUs on a cellular level by leveraging natural regenerative processes; nascent competitive landscape evolves

BIOxHEAL is being developed under the FDA Biologics License Application (BLA) pathway; the tissue-based therapy aims to supplement established standards of care by providing biologic exposure to the wound environment. Instead of covering the wound, BIOxHEAL aims to work at the cellular level to stimulate tissue regeneration and improve vascularization. The weekly treatment is intended to act alongside established standards of care for DFU wound management. Clinical response and continued presence of the unhealed target ulcer will determine the duration of the short-course biologic therapy. Along with DFUs, other potential indications under investigation include venous leg ulcers (VLUs) and pressure injuries.

Competitive Landscape expanding, though reimbursement remains challenging

Although "breakthroughs" seem few and far between, multiple companies have worked in and around diabetic foot ulcers and wound healing over time, working to slow and /or prevent amputations over time. While the return on

avoiding these complications altogether is sizable, given the vast population at risk and the investments needed, the competitive landscape remains challenged, with a few bright spots.

- As we reported in July, Merakris Therapeutics is one company aiming to address unmet needs in this arena. The company received an NIH Direct-to-Phase II SBIR Grant to advance the development of its injectable MTX-001 for DFUs in July 2026.
- Convatec has a broad advanced wound-care portfolio with several technologies specifically targeting DFUs. Most notably, the company is launching ConvaNiox, a nitric oxide-generating antimicrobial and antibiofilm dressing for hard-to-heal wounds, with an initial focus on DFUs. The company received regulatory approval in 2025 and planned a broader launch in 2026.
- Smith+Nephew has a broad advanced wound-management portfolio spanning several approaches used in DFU care. Its offerings include OASIS extracellular matrix products for chronic wounds, including DFUs, SANTYL enzymatic debridement, and CENTRIO platelet-rich plasma, which is intended to support the healing of DFUs.
- Solventum, formerly 3M Health Care, has a substantial presence in advanced wound care, including technologies used in the management of DFUs. Its portfolio spans negative-pressure wound therapy, including V.A.C. Therapy, as well as advanced wound dressings and other wound-management products.
- Mölnlycke Health Care also specifically addresses DFUs within its wound-care portfolio, with products spanning wound dressings, infection management, and pressure offloading. The company emphasizes a comprehensive approach to DFU management encompassing wound preparation, infection control, and protection throughout healing.

As with so much innovation around diabetes and obesity, the linchpin often stems from issues related to access and affordability. We spoke at length in 2024 with Drs. DavidArmstrong and William Padula about proposed Medicare coverage related to changes to foot ulcer treatment reimbursement. They highlighted skin substitutes, which had significant upside compared to other treatments in our view – see key takeaways and specific highlights from the interview itself:

- On the prevalence of diabetic foot ulcers and related complications
- On the cost-effectiveness of skin substitutes
- On the potential treatment consequences of this Medicare proposal
- On alternative treatments for diabetic foot ulcers
- On ways to become involved in advocacy
- On the opportunity cost of efficacious treatment

We will be back after some more research on the competitive landscape outside Merakris, Convatec, and skin substitutions – we will also do some further research on data around amputations and how that is changing given more recent and positive interventions. We are very interested in how the economics are looking, given that Dr. Armstrong highlighted when we spoke that a whopping one-third of the direct costs associated with diabetes care in the US are attributed to foot treatment — more than the total direct costs of treating cancer in the US.

In closing, we'd like to stress a statement by Dr. Padula in our 2024 interview, when he characterized the population of those with DFUs as a "large but quiet" population, emphasizing both potential upside as well as downside that could emerge related to DFUs, and advocated for that policy to facilitate change. We were very moved when he asserted that it is the community's obligation to contact government representatives and CMS to advocate on behalf of patients, reiterating that the voices of HCPs and patients are necessary to amplify the message.

Close Concerns' Questions

1. Given the substantial burden of diabetic foot ulcers across patient populations, how will Applied Biologics approach patient recruitment to ensure that the study population reflects the diversity of patients affected by DFUs?
2. On the trial enrollment front, in terms of trial logistics, how many sites does Applied Biologics ultimately expect to

participate in the phase 3 trial?

-- *by Kayla Cao, Kayla Mathieu, Monica Oxenreiter, and Kelly Close*