Utilization of Real-World Data to Design and Implement a Phase III Pivotal Randomized Controlled Trial (COVER DFUs) Evaluating the Treatment of Diabetic Foot Ulcers with Exposed Structures with a Novel Biologic

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Introduction

There is a global public health epidemic of diabetes, which is leading to the development of diabetic foot ulcers (DFUs) in up to 170 million affected patients in their lifetime.[1,2] The annual direct costs of diabetic foot disease, nearly an astounding $80 billion, are comparable to those of cancer in the United States (US).[1] As few as 1 out of 4 DFUs are healed at 12 weeks,[3,4] 19% of ulcerations result in lower extremity amputations (LEAs),[5] and their 5-year mortality rate is greater than 50%.[6]

Recent guidance, statements, and actions by the US Food and Drug Administration (FDA) have encouraged the pursuit of the Biologics Licensing Application (BLA) pathway for human cells, tissues, or cellular or tissue-based products (HCT/Ps) wound care therapies. Approval under the BLA pathway requires substantial evidence of effectiveness and safety demonstrated by at least two adequate and well-controlled clinical studies. Such studies often require a significant amount of time and resources to conduct. There has not been a biologic drug approved for the use in chronic wounds in over 20 years. Most advanced dressings currently available are distributed under the 510k device or 361 HCT/Ps regulatory pathways, which may require little to no formal clinical studies.[7] Randomized controlled trials (RCTs) may not adequately represent real-world patient populations, complicating the application of their results to clinical practice.[8] In an effort to design a clinically relevant RCT for the BLA of a novel autologous heterogeneous skin construct (AHSC) to treat non-infected DFUs with exposed deep structures **[Closure Obtained with Vascularized Epithelial Regeneration (COVER) DFUs, NCT05372809]**, an in silico analysis of a sponsor-initiated large multi-institutional wound registry was performed to inform the trial design.

Methods

The U.S. Wound Registry (USWR) was analyzed to determine trial characteristics. The USWR is a 501(c)(3) nonprofit organization listed in ClinicalTrials.gov and recognized for quality reporting by the National Registry of Registries and the Centers for Medicare and Medicaid Services.[9] The registry uses an electronic health record purpose-built for wound care (Intellicure, Inc., The Woodlands, TX) that collects all patient and wound data at point-of-care using structured programming and language, thereby continuously generating real-world evidence for research purposes.[9,10]

There were 14,552 Wagner 2 DFUs (extending into tendon, tissue, bone, or capsule) available in the USWR. After setting the area range gate to 1-10 cm^2, 5,875 DFUs were available in the analysis. Initial area was coded as follows: 1-2 cm^2 (1); 2.01-4 cm^2 (2); and 4.01-10 cm^2 (3). Exposure of tissue level was coded into 4 categories: skin (partial or full thickness) (1); fat/subcutaneous (2); tendon/muscle (3); and bone (4). Healing was coded as "yes" or "no", with any wound healed within 16 or 24 weeks coded as "yes". Amputations were coded as nonhealed.

Two healing analyses were done using logistic regression to analyze the healing odds at 16 and 24 weeks stratified by ulcer severity. In the first healing analysis, a logistic regression was constructed using healed at 16 weeks as the dependent variable and area category and depth of tissue exposed category as independent variables. In the second healing analysis, initial area was coded as follows: 1.01-4 cm^2 (1); and 4.01-10 cm^2 (2). Exposure of tissue level was coded into 3 categories: fat/subcutaneous (1); tendon/muscle (2); and bone (3). There were 2,773 DFUs analyzed after excluding ulcers with skin as tissue level exposure. The second healing analysis was repeated using healed at 24 weeks as the dependent variable and area category and depth of tissue exposed category as independent variables.

Results

Tables 1a and 1b summarize the results of the logistic regression analyses of healing odds at 16 and 24 weeks. In Table 1a, after adjusting for tissue level exposed, the odds of larger Wagner 2 DFUs healing within 16 weeks compared to small wounds (1-2 cm^2) were substantially lower (0.74 and 0.58, respectively). P values are not shown, because the odds ratio (OR) and the associated 95% confidence intervals (CIs) clearly show that the larger the wound, the lower the odds are of the wound healing.

Table 1. Logistic regression analysis of odds of healing stratified by diabetic foot ulcer severity

Table 1a. Odds of healing at 16 weeks

Variable	B	Odds Ratio	95% CI	
			Upper	Lower
Initial area				
2.01-4 cm^2	-0.180	0.84	0.74	0.94
4.01-10 cm^2	-0.426	0.65	0.58	0.74
Level of tissue exposure				
Fat/subcutaneous	-0.005	0.995	0.87	1.14
Tendon/muscle	-0.602	0.55	0.42	0.72
Bone	-0.580	0.56	0.41	0.78
Constant	-0.296	0.74		

Table 1b. Odds of healing at 24 weeks

Variable	B	Odds Ratio	95% CI	
			Upper	Lower
Initial area				
4.01-10 cm^2	-0.169	0.85	0.73	0.98
Level of tissue exposure				
Tendon/muscle	-0.296	0.74	0.55	1.01
Bone	-0.490	0.61	0.42	0.90
Constant	-0.079	0.92		

Table 2. Key characteristics of the COVER DFU randomized controlled trial to strengthen the trial design and for regulatory review

Design Element	COVER Trial Protocol
Sample size needs to be adequately powered at ≤80%	Sample sizes of 50 in each treatment group (n = 100) achieve 82% power to detect a difference of 0.30 between the group proportions of 0.25 and 0.55 at a significance level (alpha) of 0.05 using a 2-sided z-test with continuity correction
Randomization needs to be stratified and allocation concealed	1:1 randomization will be stratified using a permuted block design by wound size and wound depth with blinded allocation provided via an interactive web response system using a (pseudo-)random number generator
Study population needs to be representative of patients with DFUs	Only Wagner 2 DFUs measuring 1.0-10.0 cm^2 but without ischemia are included.[a]
Recruitment delays should be mitigated by selection of multiple study sites	Up to 20 study centers will participate and enroll patients
Primary endpoint must be complete wound healing	Primary endpoint is complete wound healing (based on FDA definition) at 24 weeks to accommodate the longer healing times of Wagner 2 DFUs[a]
Blinding	A blinded assessor will validate wound healing status. Blinding of treating investigator and patient not technically or ethically feasible.

COVER Trial Design Considerations

Table 2 summarizes the key trial design characteristics of the COVER DFU trial for regulatory review under the BLA pathway. Subjects eligible for the study after screening and a 2-week run-in period will be randomized 1:1 to AHSC and standard of care or standard of care only using stratification. Randomization will be performed within each stratum, so that treatment allocation is as balanced as possible within each of the 'fixed' blocks.

Sample Size: In DFU RCTs, a sample size needs to be sufficiently large for the primary outcome(s) to have a statistical power of at least 80% in regard to treatment group differences.[11,12] In the COVER trial, the sample size was calculated at 50 in each study (100 subjects total) to achiever 82% power to detect a difference in the proportion of DFUs healed at 24 weeks of 0.30 between the group proportions of 0.25 and 0.55 at a significance level (alpha) of 0.05, using a 2-sided z-test with continuity correction.[13]

Primary Endpoint: Complete Wound Healing: The FDA gold standard for the primary endpoint in wound research is complete wound closure defined as 100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirement, confirmed at 2 visits 2 weeks apart.[14,15] When performing the primary endpoint healing assessment, a blinded assessor or blinded adjudication is advised to reduce bias, given that blinding study providers and subjects to treatment arms is often not feasible or ethical in chronic wound research.[11,14,15]

Given that the COVER trial will only include the more severe Wagner 2 DFUs, and the duration required by the FDA for safety data acquisition, a longer healing trajectory was incorporated into the follow-up time of 24 weeks. Digital planimetry will measure ulcer size during 2 separate healing assessments. Closure is determined by the treating investigator and confirmed in person by a blinded assessor and validated by a blinded adjudicator evaluating high resolution photography. At each study visit, the treating investigator and blinded assessor will assess healing based on the following questions:

- Is the wound 100% reepithelialized, without pink, red, yellow, or black slough or dried exudate concealing the surface of the skin and does the wound not require a dressing?
- Is the entire skin surrounding the former wound skin either normal in color, pink or red, callused, or macerated but without signs of an ulcer in the tissue that surrounds the former wound (i.e., no excoriations, no marginal recurrence)?
- Is there complete absence of exudate, meaning there cannot be any clear, serous, serosanguinous or purulent drainage?
- Is there absence of clinical signs of infection in or around the former wound site?

All questions must be answered "yes" for the index ulcer to be considered completely healed. After healing is first observed, the wound photographs will be forwarded to an independent validator, who will confirm closure.

Appropriate Statistical Analysis of Endpoints: Adequate statistical analysis of healing outcomes is also needed in DFU trial design to ensure the certainty of outcomes[11,16] Stratified variables used in randomization need to be employed in adjusted analysis of primary outcomes to prevent inflated p values (larger p values than would be obtained using proper analysis) and CIs that are too wide, which can result in the study being underpowered and incorrectly suggest that the therapy is not beneficial. Similarly, when there are multiple endpoints, multiplicity adjustment is also needed to ensure that secondary endpoints do not suffer from type I errors in which it appears an endpoint is statistically significant when in fact it is not significant.

Recruitment Issues in DFU Trials: A final consideration that should be made to DFU trial design is the difficulty of recruiting patients, with recruitment periods often stretching for very long periods of time, delaying trial completion.[8,14,17] Because of strict inclusion criteria, there can be a lack of eligible patients.[17,18] The inclusion of more study centers in the trial protocol may help overcome recruitment barriers. The COVER protocol involves 20 US study centers to mitigate delays due to recruitment issues.

Conclusion

The trial protocol inclusion of more severe wounds of patients enrolled at 20 study centers, real-world analysis for randomization stratification, blinded healing assessment, adequate power, and robust statistical analysis are measures to reduce trial bias and uncertainty of outcomes and ensure the study population is more representative of the real-world population with DFUs. The COVER DFUs trial protocol may assist in improving chronic diabetic foot ulcer research and generating stronger evidence to support the safety and effectiveness of novel, innovative wound products.

References

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