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Aurix Gel Is an Effective Intervention for Chronic Diabetic Foot Ulcers: A Pragmatic Randomized Controlled Trial

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ABSTRACT

BACKGROUND: Autologous platelet-rich plasma products can significantly vary with respect to platelet concentration, the presence of additional cellularity, and the use of additives. Therefore, the utility of each formulation for treating chronic wounds needs to be established.

OBJECTIVE: To establish the efficacy of up to 12 weeks of treatment with Aurix hematogel for healing diabetic foot ulcers against usual and customary care including any wound modality in 129 patients using a Medicare Coverage with Evidence Development paradigm.

METHODS: This pragmatic randomized controlled trial was conducted in 28 real-world outpatient wound care sites using an inclusive design that included participants with various health risks, comorbidities (eg, peripheral arterial disease, smoking), and any wound severity (Wagner 1–4).

RESULTS: Kaplan-Meier analysis showed a significant (log-rank $P = .0476$) time-to-heal advantage, with 48.5% of wounds healing with Aurix hematogel compared with 30.2% with usual and customary care. A higher percentage of healing was observed for Aurix across all wound severities (Wagner grade 1–4). Subgroup analysis revealed a significant healing advantage for Aurix when treating wounds accompanied by peripheral arterial disease and a demonstrated advantage for smokers.

CONCLUSIONS: This first Coverage with Evidence Development study in wound care demonstrates the effectiveness of Aurix for treating diabetic foot ulcers in Medicare beneficiaries.

KEYWORDS: Aurix gel, chronic wounds, Coverage with Evidence Development, diabetic foot ulcer, hematogel, Medicare, pragmatic trial, platelet-rich plasma, wound healing

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INTRODUCTION

The incidence of diabetes continues to grow, and diabetic foot ulcers (DFUs) are significant burden on healthcare economics.[1] Despite the availability of a wide range of drugs and medical devices for the treatment of chronic DFUs, healthcare providers still encounter significant challenges in healing many patients. Differences in patient health status, including the presence of various comorbidities, contribute to the disparate response to clinical interventions and widely variable healing outcomes for DFUs.

Although the FDA has evaluated a number of therapies indicated for nonhealing ulcers, the assessments are based on data from conventional clinical studies that typically limit patient enrollment based on highly restrictive inclusion/exclusion criteria.[2] For example, three of the four published randomized controlled trials (RCTs) on chronic DFUs identified by the authors of this article included only Wagner grades 1 and 2 ulcers.[3–5] Patients with common health risks such as smoking or comorbidities such as peripheral arterial disease (PAD) were also excluded.

A more recent study supporting platelet-based technology for healing chronic ulcers targeted hard-to-heal DFUs;[6] however, final enrollment included mostly superficial DFUs (87%), with an additional 10% of ulcers probing to tendon and only 3% probing to bone. Patients with common comorbidities such as PAD were excluded from participating, and the authors acknowledged that the patient population likely was not representative of those typically seen within a wound clinic. Although such tightly controlled studies are valuable tools for assessing safety and efficacy, they generally do not provide data that can serve as a robust predictor of clinical effectiveness across broader patient populations.[7]

To improve patient access and develop data more generalizable to broader Medicare populations, the Centers for Medicare & Medicaid Services (CMS) has established the Coverage with Evidence Development (CED) paradigm. Under CED, Medicare

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provides reimbursement coverage for promising new or existing therapies and services while data investigators collect health outcomes data to inform future coverage decisions.[8] Studies designed with inclusive patient enrollment and treatment protocols that more closely reflect everyday practice are encouraged. To date, 23 CED programs either have been completed or are ongoing.

Presented here is the first clinical study conducted under CED that addresses the effectiveness of wound healing modalities, specifically the National Coverage Determination on Autologous Blood-Derived Products for Chronic Non-Healing Wounds (NCD 270.3).[9] To provide context, Table 1 presents important study design elements and operational aspects of a conventional RCT as compared with a pragmatic RCT conducted to evaluate "effectiveness" under CED.

Autologous Blood-Derived Products for Wound Care

Autologous blood-derived products for healing chronic wounds have garnered attention from healthcare providers for many years.[10,11] Although it is well established that platelets release a full complement of biomolecules regulating processes critical for tissue regeneration,[12,13] the benefit of platelet-based therapies in wound care is a topic of debate.[14,15] This is partially attributable to the variety of technologies used to obtain platelets from a sample of patient blood.[16] Importantly, the majority of these technologies have been cleared by the FDA for a specific orthopedic indication[17] and were not developed or approved for use in wound care.

The platelet concentration and the presence of accompanying white blood cells are dependent on the device used, and this has a meaningful impact on concentrations of cytokines, chemokines, and growth factors within platelet-rich plasma (PRP) samples.[18] Further, research has demonstrated that PRP containing lower concentrations of platelets can promote proliferation and differentiation responses important for soft and hard tissue healing, and PRP containing higher concentrations of platelets can have opposite effects.[19–22] Therefore, to achieve the most meaningful health outcomes using autologous blood therapies, it is important to match the choice of technology with the intended indication.

While noting these differences in PRP preparations, recent clinical studies have supported the efficacy of platelet-based therapies for the treatment of chronic wounds.[23–28] A recent systematic review of the literature related to chronic DFUs concluded "that the topical application of PRP for DFUs results in statistically superior healing rates and lower complication rates compared to controls."[29] Expanding on this understanding, the CED program implemented by CMS as defined within NCD 270.3 is intended to evaluate the merit of different autologous blood therapies for treating nonhealing ulcers, specifically in the population of Medicare beneficiaries.

Table 1.

COMPARING CONVENTIONAL AND PRAGMATIC RCTS UNDER THE CED PARADIGM

Study Activity	Conventional RCT	Pragmatic RCT
General operations		
Responsible for conduct of study	Sponsor responsible	Sponsor responsible
Institutional Review Board oversight	Yes	Yes
Informed consent	Yes	Yes
Investigator research background[a]	Experienced	Most naïve; some experienced
Data collection and monitoring	Sponsor responsible	Sponsor responsible
Designated study coordinator	Yes	No
Study design		
Protocol development	Sponsor/FDA	Sponsor/CMS
Inclusion/exclusion criteria[b]	Narrow population (limited)	Diverse population (all comers)
Multicenter	Not always	Yes
Financial aspects		
Cost of therapy	Sponsor responsibility	Medicare reimbursement
Physician fee	Sponsor responsibility	Medicare reimbursement
Facility fees	Sponsor responsibility	Medicare reimbursement
Patient copay	None	20% standard Medicare rules
Patient incentives	Sponsor responsibility	Not allowed per Medicare rules
Research payment to providers	Sponsor responsibility	Not allowed per Medicare rules
Research payment to hospital/facility	Sponsor responsibility	Not allowed per Medicare rules
Regulatory oversight	FDA	CMS (and FDA if use is off label)

Abbreviations: CMS, Centers for Medicare & Medicaid Services; CED, Coverage with Evidence Development; RCT, randomized controlled trial.

[a]Differences in investigator research experience and access to designated study coordinators can present challenges to enrollment, protocol adherence, and data collection.

[b]Although a pragmatic study targets enrollment of all comers, Medicare rules preventing the sponsor from providing patient, provider, and hospital incentives impact enrollment and patient compliance. This is further impacted by the requirement most patients will have to contribute a 20% copay for medical care.

Aurix Therapy (Nuo Therapeutics Inc, Gaithersburg, Maryland), a biodynamic hematogel, consists of a proprietary formulation of platelets and pharmaceutical-grade reagents produced using the Aurix System at the patient point of care. Based on a double-blind RCT,[3] the system has been cleared for use by the FDA specifically for exuding wounds.[30] The body of peer-reviewed evidence supporting Aurix as a treatment for chronic ulcers includes both comparison and observational studies evaluating healing outcomes of 390 chronic wounds treated in sites of care including outpatient wound centers, Veterans Affairs hospitals, and long-term acute care facilities.[31–35]

As a complement to this body of evidence, presented here is the first multicenter, pragmatic RCT conducted under CED to evaluate the Aurix System for healing chronic DFUs exclusively among Medicare beneficiaries. The aim of the study was to evaluate healing outcomes associated with the "real world" use of Aurix hematogel when administered by providers within typical environments at participating sites of care.

MATERIALS AND METHODS

Study Design

This study was approved by CMS and conducted under the CED program to evaluate the "on-label" use of Aurix along side usual and customary care (UCC) as compared with UCC only to treat chronic DFUs in an intended total study population of 760 patients in up to 100 sites across the US. The Aurix and UCC and UCC-only groups were randomized at a ratio of 1:1 at 28 investigative sites contributing to the data collection. The study was conducted with institutional review board oversight, and written informed consent was obtained prior to any study-related procedures. Patient participation was limited to Medicare beneficiaries with at least one nonhealing DFU.

In standard clinical practice, differences in the patient demographics, provider skillsets, and approaches to UCC in various wound centers are variables that can influence treatment outcomes. To evaluate the hematogel as used in clinical practice, investigator training was limited to instruction on the International Conference on Harmonisation Good Clinical Practice guideline, the CED protocol, and specific steps for the production and application of Aurix. Further, unlike conventional RCTs, recruitment and documentation of data were the responsibility of investigators and available support staff. The sponsor's clinical specialists and clinical affairs teams were made available upon request to provide support for the appropriate preparation and application of Aurix and to clarify any questions related to the study protocol.

On average, participants receiving Aurix were treated twice a week for the first 2 weeks and once a week thereafter while under active treatment, but the actual frequency of treatment was determined by the clinician. In the UCC-only arm of this study, investigators were instructed to use any treatment modality or combination of available treatment modalities so long as the treating clinician and patient considered it to be in the best interest to heal the chronic ulcer; for example, hyperbaric oxygen therapy for Wagner grades 3 to 5 DFUs. Additional care in the Aurix and UCC group was restricted as discussed in the following sections.

Wound closure was defined as complete epithelialization in the absence of drainage and without the need for wound dressings. The primary endpoint was complete wound healing after 12 weeks of treatment. Additional analysis includes the proportion of healed DFUs in the treatment period. Immediately prior to randomization and again at the end of the 13-week study period, quality-of-life data were collected using the Quality of Life with Chronic Wounds short-form instrument (W-QOL).[36] Correlation of changes in W-QOL scores and wound trajectory will be presented in a subsequent publication.

Source data were gathered from centers using the Net Health WoundExpert (Pittsburgh, Pennsylvania) electronic medical record (EMR). In this case, deidentified data were captured by ITS Integrations (Columbia, South Carolina) via direct electronic transfer of records from the EMR to a third-party database. Of the 28 participating wound centers, 8 did not use WoundExpert, and case report forms were used for data capture instead. Independent statisticians from Amarex Clinical Research (Germantown, Maryland) and PharmaData Associates (Piscataway, New Jersey) developed the statistical and data analysis plan.

Participants

Prior to any study-related procedures, investigators obtained institutional review board-approved written informed consent from the participants. Patients were allowed to withdraw from the study at any time. Study participants had to

- be 18 years or older,
- have Medicare as their primary insurance coverage,
- have type 1 or type 2 diabetes,
- have a Wagner grade 1 through 5 DFU located on the dorsal, plantar, medial, or lateral aspect of the foot or heel that was at least 1 month old,
- have a debrided ulcer size between 0.5 and 50 cm^2,
- have a demonstrated off-loading regimen,
- have demonstrated inadequate progress toward healing (as determined by the provider) following active treatment with UCC at the investigative site for a minimum of 2 weeks immediately prior to screening, and
- have adequate venous access for periodic blood draws (necessary for Aurix administration).

Study exclusion criteria were developed with consideration of Aurix's FDA-approved labeling and included potential sensitivity

to Aurix components (calcium chloride, bovine thrombin, ascorbic acid). This included patients on chemotherapeutic agents; patients with malignancy in the wound area; patients with or patients who had a serum albumin of less than 2.5 g/dL, platelet count of less than 100×10^9/L, and/or hemoglobin of less than 10.5 g/dL.

Patient participation was precluded in the presence of another wound that could interfere with treatment of the index ulcer. Patients were required to self-report using the W-QOL and therefore could not be cognitively impaired. Clinically infected DFUs must have been treated (per the Infectious Disease Society of America Guidelines or another algorithm) before the participant could be randomized to a treatment arm. In this case, antibiotics were administered for at least 48 hours with the continued use of traditional wound care until the infection exhibited clinical signs of antibiotic response, at which point randomization could proceed following thorough cleansing of the wound bed.

Randomization

After meeting all study inclusion/exclusion criteria and providing written informed consent, participants were immediately randomized for study participation. (The full list of study activities is presented in Supplemental Table 1, http://links.lww.com/NSW/A21.) Randomization and treatment could occur on the same day as the screening visit or at any time within 7 days of the successful completion of screening. In the event randomization did not take place within the allowed 7-day window, a 30-day waiting period was required before patients could be rescreened for participation.

Using a 1:1 randomization ratio, eligible patients were randomly assigned to receive Aurix and UCC or UCC only. Randomization codes were generated electronically by Amarex Clinical Research using mixed blocks of sizes 2 and 4. For this open-label study, randomization certificates including the codes and treatment assignment groups were distributed to providers using the Amarex Clinical Research WebView platform.

Study Procedures

Gel preparation and application. The Aurix System comprises a small, purpose-built, portable centrifuge for separating platelets and plasma from other blood constituents, a reagent kit providing pharmaceutical grade additives to create a fibrin gel containing activated platelets, and a wound dressing kit supplying the accessories required for venous access as well as for preparing and applying the bioactive Aurix gel.

Venipuncture was performed to obtain 5 to 20 mL of blood, and the blood sample was centrifuged for approximately 1 minute to produce a platelet/plasma fraction that was harvested directly into a mixing chamber. Pharmaceutical-grade reagents were sequentially introduced into the mixing chamber and then gently inverted, typically for 15 to 30 seconds, to produce a gel with appropriate consistency for application. The gel was immediately applied to the wound bed, and a barrier cream was placed on intact skin surrounding the wound. A nonadherent contact dressing was placed over the Aurix gel, and the wound was covered with a nonabsorbent dressing. An absorbent layer was then secured over the wound for wound exudate.

Patient assessments. Prior to initial treatment, patients were required to fill out the W-QOL short form for a baseline wound-specific quality-of-life assessment. Regardless of the randomized assignment, standard-of-care practices were required as part of UCC for both study groups. Investigators were instructed to follow the Standard of Care Considerations for Chronic Cutaneous Ulcers as described in the 2006 FDA Guidance and were provided information pertaining to appropriate debridement, off-loading, maintenance of a moist wound environment, management of infection, wound cleansing, and nutrition support including blood glucose control.

At each patient visit, investigators recorded vital signs, conducted symptom-guided physical examinations as necessary, imaged the wound with digital photography, and assessed wound infection as well as the need for debridement and moisture management. Wound measurements (length, width, depth) were performed at each visit. To ensure a standardized approach for obtaining wound measurements, investigators were instructed to establish a "clock face" over the wound bed in which 12:00 was oriented toward the patient's head. The length and width of the wound were to be always considered from 12:00 to 6:00 and from 3:00 to 9:00, to reduce subjectivity.

Participant adherence was assessed, and additional patient education about the protocol was provided when needed. Off-loading method(s) and concomitant medications (antibiotics only) were documented. Investigators were asked to document treatment-emergent adverse events (TEAEs).

Treatment visits. Following wound assessments, either Aurix and UCC or UCC only was administered. The UCC-only group was treated with therapies that the provider and patient determined were in the best interest of healing. All patients received standard of care that could include the use of semiocclusive dressings or hydrocolloid dressings with or without an absorbent dressing. For the UCC-only group, the use of chemically impregnated dressings was allowed. Standard of care alone or in combination with advanced wound care such as hyperbaric oxygen, negative pressure, cellular and/or tissue-based products, and any other healing modality, with the exception of autologous blood products, was permissible in the UCC-only arm of this study.

Investigators were encouraged to schedule UCC visits in accordance with the treatment regimen as prescribed at the clinical site. For example, while patient treatments within the UCC-only group generally were scheduled to occur on a weekly basis, the use of

other therapies such as daily treatment with hyperbaric oxygen was allowed. Further, a continuum of care or treatment algorithm, such as the daily delivery of hyperbaric oxygen along with periodic application of an advanced dressing, was allowed. All wound care provided in the UCC-only group was documented.

All patients randomized to the Aurix and UCC group received standard of care and Aurix hematogel. Unlike the UCC-only arm of the study, the use of materials containing any active ingredient in this group was prohibited (eg, methylene blue, gentian violet, zinc oxide, silver, hydrogen peroxide, acetic acid, or iodine). Patients were to receive two Aurix applications in each of the first 2 weeks of treatment followed by one application every week thereafter.

Given the pragmatic nature of this study and the intent to gather data on Aurix as it may be used in clinical practice, a single treatment for each week during the 12-week treatment period was acceptable if patients were unable or unwilling to make two treatment visits within each of the first 2 weeks. Further, understanding that a single treatment modality may not be sufficient to bring all DFUs to complete closure in a cost-effective manner and considering the range of wound severities and comorbidities, the present study was powered with intent to collect data to assess the benefit of Aurix both as a stand-alone therapy and when used as part of a continuum of care or a defined treatment algorithm at the discretion of the patient and provider. Therefore, additional advanced wound care was allowed in the Aurix and UCC treatment group. The types and frequency of wound care used in the UCC-only group, as well as for concomitant care in the Aurix and UCC group, are listed in Table 2 and discussed later.

End-of-treatment and posttreatment visits. Week 13 of the study protocol was the scheduled end-of-treatment visit, which included all assessments as previously conducted for each weekly treatment visit. Participants also completed an end-of-study W-QOL for comparison with the baseline measurement.

Wound closure was assessed at each patient visit. Patients with index wounds that did not close after completing 12 weeks of Aurix treatment were to return to the clinic for the week 13 visit to document healing status. If the index ulcer closed prior to week 13, the treatment visit where closure was observed and documented was considered the end-of-treatment visit.

When the determination of complete closure was made, a follow-up visit was scheduled approximately 2 weeks later to confirm closure. If closure was not confirmed at this follow-up visit, patients were to continue their treatment assignment for the duration of the planned 13-week study period. In cases in which ulcers did not achieve complete healing but demonstrated at least 50% wound area reduction after 12 weeks of treatment, treatment could continue for up to 20 weeks at the discretion of the patient and provider. Data for treatment beyond 12 weeks were collected for separate analysis as a tertiary endpoint.

Table 2.

CONCOMITANT CARE

Wound Care	Aurix and UCC, n (%)	Healed, n (%)	UCC only, n (%)	Healed, n (%)
Total patients	66 (100)	32 (48.5)	63 (100)	19 (30.2)
Received standard of care only	51 (77.3)	26 (51.0)	29 (46.0)	8 (27.6)
Received advanced therapies	15 (22.7)	6 (40.0)	34 (54.0)	11 (32.4)
CTP only	0 (N/A)	0 (N/A)	12 (19.0)	4 (33.3)
HBO only	10 (15.2)	3 (30.0)	8 (12.7)	4 (50)
NP only	2 (3.0)	1 (50.0)	2 (3.2)	0 (N/A)
HBO and CTP	0 (N/A)	0 (N/A)	4 (6.3)	2 (50)
HBO and NP	2 (3.0)	2 (100)	1 (1.6)	0 (N/A)
HBO, CTP, and NP	1 (1.5)	0 (N/A)	1 (1.6)	1 (100)
NP and CTP	0 (N/A)	0 (N/A)	5 (7.9)	0 (N/A)
Not recorded	0 (N/A)	0 (N/A)	1 (1.6)	0 (N/A)

Abbreviations: CTP, cellular and/or tissue-based products; HBO, hyperbaric oxygen; N/A, not applicable; NP, negative pressure; UCC, usual and customary care.
Note: Standard of care includes the use of semi-occlusive dressings or a hydrocolloid dressing with or without an absorbent outer dressing. The use of chemically impregnated dressings was allowed in the UCC-only group but prohibited in the Aurix and UCC arm as described.

RESULTS

The enrollment of 760 patients was planned to provide statistical power for detailed subgroup analysis. However, because of many unanticipated challenges to enrollment (see the Discussion section), the sponsor agreed with a request by CMS to analyze the available data for the intent-to-treat (ITT) population that randomized 66 patients to Aurix and UCC and 63 patients to the UCC-only arm of the study. The ITT population includes all patients randomized to the study and who returned to receive at least one treatment and postbaseline ulcer measurement.

Twenty-eight facilities across the US participated in this study, representing both physician offices (n = 2) and outpatient wound treatment centers (n = 26) designated by CMS as Place of Service (POS) 11 and POS-22, respectively. The disparity in the number of participating POS-22 and POS-11 sites of service was primarily attributable to reimbursement hurdles (also addressed in the Discussion section). To evaluate the effectiveness of Aurix as it is generally used in clinical practice, sites representing diverse urban and rural geographies were selected indepedent of the investigator and wound center staff's previous clinical research experience. Designated study coordinators were present in only 2 of the 28 clinical sites, because those sites had active research programs. The remaining 26 sites relied on the clinical support staff and investigators to enroll participants and document health outcomes data.

Patient Demographics and Baseline Characteristics

Characteristics of the study population are reported in Table 3 and include age, race, sex, and health status (both health risks and

Table 3.

PATIENT DEMOGRAPHICS

Characteristics	Aurix and UCC (n = 66)	UCC-only (n = 63)
Mean age, y	64.7	66.9
Sex, n (%)		
Male	51 (77.3)	49 (77.8)
Female	15 (22.7)	14 (22.2)
Race, n (%)		
White	57 (90.5)	54 (81.8)
Black	4 (6.3)	5 (7.6)
Asian	0 (0.0)	2 (3.0)
Other	2 (3.2)	5 (7.6)
Health risks/comorbidities, n (%)		
Smoking	38 (57.6)	29 (46.0)
PAD	26 (39.4)	30 (47.6)
Immunosuppression	4 (6.1)	4 (6.3)
Renal failure	8 (12.1)	7 (11.1)
Arthritis	2 (3.0)	3 (4.8)
Transplant recipient	5 (7.6)	2 (3.2)
None	15 (22.7)	19 (30.2)

Abbreviations: PAD, peripheral artery disease; UCC, usual and customary care.
Note that while sums of n (%) values for sex and race will correlate 1:1 with the study group population, patients frequently have multiple health risks/comorbidities. In this case the sum of n (%) values correlate with each occurrence of the particular health risk/comorbidity observed.

comorbidities). The mean age was similar for patients randomized to the UCC-only and Aurix and UCC study groups: 66.9 and 64.7 years, respectively. Sex and race were also balanced between treatment groups. The study enrolled predominately male participants, 77.8% in the UCC-only group and 77.3% in the Aurix and UCC study group. The enrolled population was predominately white, 81.8% of participants in the UCC-only group and 90.5% of participants in the Aurix and UCC group. No other race category exceeded 7.6% in either study arm.

One or more health risks and comorbidities affected 73.6% of the enrolled participants with DFUs. A history of smoking, present in 46% of the UCC-only participants and 57% of the Aurix and UCC group, as well as PAD, present in 47.6% of the UCC-only participants and 39.4% of Aurix and UCC participants, were most prevalent within the study population. Immunosuppression, renal failure, arthritis, and previous transplant were represented in both study groups, with prevalence ranging from 3% to 12%.

Wound Size and Severity

Average wound area prior to the first study treatment was 4.1 cm^2 for the Aurix and UCC group and 5.6 cm^2 for the UCC-only group. The distribution of small (<1 cm^2), intermediate (>1 to ≤7 cm^2), and large (>7 cm^2) ulcers was approximately the same for each treatment group (Supplemental Table 2, http://links.lww.com/NSW/A22). Small ulcers accounted for approximately 29%, intermediate-sized ulcers for approximately 53%, and large DFUs for approximately 18% of wounds in each treatment group. All Wagner grade wound severities were allowed in this pragmatic study. The majority of wounds within each of the treatment groups were of intermediate severity, including 48.5% Wagner grade 2 and 44.4% Wagner grade 3 ulcers.

Concomitant Care

Table 2 displays the different treatments used in the two study groups and the associated healing rates. In the Aurix and UCC group, 51 of 66 participants (77.3%) received only standard of care compared with 29 of 63 participants (46.0%) in the UCC-only group. The percentage of patients healed in the Aurix and UCC and UCC-only groups who received only standard of care were 51.0% and 27.6%, respectively. In combination with advanced care, the percentage of patients healed in for the Aurix subgroup was 40% compared with 32.4% in the UCC-only subgroup. Advanced care was used more frequently in the UCC-only group, with 34 of 63 participants (54%) receiving the additional care compared with 15 of 66 (22.7%) in the Aurix treatment group.

Interestingly, although hyperbaric oxygen was the predominant form of advanced care used in the Aurix subgroup (13 of 15 participants), cellular and/or tissue-based products were the predominant form of advanced care used in the UCC-only subgroup (22 of 29 participants). The use of different combinations of advanced care was more frequent in the UCC-only subgroup (11 of 34 participants) as compared with the Aurix subgroup (3 of 15 participants).

Analysis of Effectiveness

In this study, 48.5% of participants treated with Aurix and UCC healed within the 13-week study period compared with 30.2% of participants treated with UCC only (Table 4, $P = .034$). Further, greater percentage of ulcers healed in the Aurix treatment group for all Wagner categories (Table 5). Kaplan-Meier analysis of the time to heal for the Aurix and UCC and UCC-only groups over the 13-week study period was performed, censoring those cases where healing was not observed within the 13-week time period. Figure 1 shows a separation of the survival curves at approximately 6 weeks

Table 4.

COCHRAN-MANTEL-HAENSZEL TEST COMPARING THE PROPORTION OF PATIENTS HEALED BETWEEN THE TREATMENT GROUPS WITHOUT STRATIFICATION

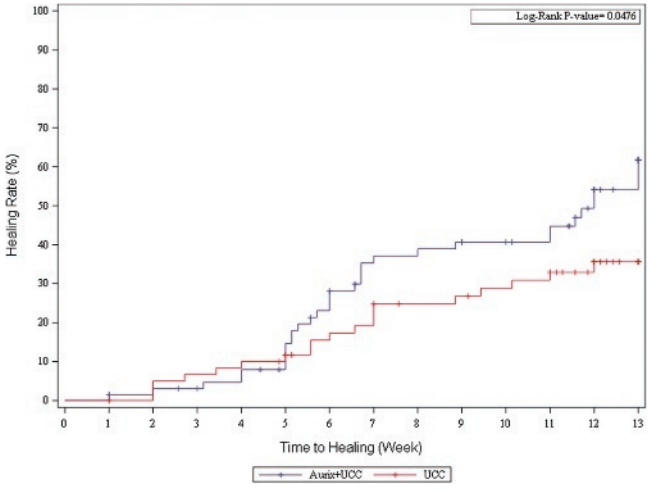
Treatment	Healed, n (%)	Not Healed, n (%)	Total
Aurix and UCC	32 (48.5)	34 (51.5)	66
UCC-only	19 (30.2)	44 (69.8)	63
Total	51	78	129

Odds Ratio	95% Confidence Limits		*P*
2.1796	1.0579	4.4906	.034

Abbreviation: UCC, usual and customary care.

Figure.

KAPLAN-MEIER AND LOG-RANK TEST COMPARING TIME TO HEALING BETWEEN THE AURIX AND UCC AND UCC-ONLY TREATMENT GROUPS



Healing was considered for analysis if achieved within 13 weeks after initial treatment (patients who were randomized, received study treatment, and provided at least one postbaseline ulcer measurement). The time-to-heal advantage for Aurix was statistically significant.

and $P = .0476$, indicating a statistically significant time-to-heal advantage for Aurix.

Patients with wounds that did not heal after 12 weeks of Aurix treatment but who experienced at least a 50% reduction in wound area were allowed to continue Aurix treatment for up to 20 weeks. The group with extended treatment included eight patients, two of whom healed within the 20-week period. The small number of participants in the extended treatment group does not provide sufficient data for additional analysis.

Smoking and PAD status. The percentage of patients with PAD in the UCC-only group was 47.6% compared with 39.4% in the Aurix and UCC group (Table 3). However, this imbalance did not confer negative bias on the UCC-only group. In fact, the percentage of participants with PAD that healed in the UCC-only group was 30.0% (Table 6), the same as the overall healing rate for the entire UCC-only group, 30.2% (Table 4). When stratified by baseline PAD status (Table 6), 53.9% of participants in the Aurix arm healed compared with 30% in the UCC-only group ($P = .0319$; odds ratio [OR], 2.2; 95% confidence interval [CI], 1.0699–4.5742). Cox regression comparing time to healing with PAD status as a covariate (Supplemental Table 3, http://links.lww.com/NSW/A23) also shows that Aurix provides a significant ($P = .0486$) healing advantage for participants with PAD (hazard ratio [HR], 1.8; 95% CI, 1.004–3.135).

Similarly, despite a health risk of smoking in 57.6% of participants in the Aurix and UCC group compared with 46% in the UCC-only group, smoking did not confer a negative bias on the Aurix and UCC group. Healing for smokers in the Aurix and UCC group was 65.8%. Although numerically larger than the UCC-only group (34.5%), the difference was not significant (Table 6).

Concomitant antibiotics and healing. Healing in both groups by concomitant antibiotic use was assessed (Supplemental Table 4, http://links.lww.com/NSW/A24). Eighty-five of the participants

Table 5.

TOTAL WOUNDS AND WOUNDS HEALED BY WAGNER GRADE AND INTERVENTION

	Aurix and UCC		UCC only	
Wagner grade	No. of wounds	Healed, n (%)	No. of wounds	Healed, n (%)
1	3	1 (33.3)	7	2 (28.6)
2	32	16 (50.0)	19	5 (26.3)
3	27	12 (44.4)	31	9 (29.0)
4	4	3 (75.0)	6	3 (50.0)
All grades	66	32 (48.5)	63	19 (30.2)

Table 6.

COCHRAN-MANTEL-HAENSZEL TEST COMPARING THE PROPORTION OF PATIENTS HEALED BETWEEN THE AURIX AND UCC AND UCC-ONLY TREATMENT GROUPS STRATIFIED BY PAD (A) OR SMOKING (B)

(A)

	Treatment	Healed, n (%)	Not Healed, n (%)	Total
Participants with PAD	Aurix and UCC	14 (53.85)	12 (46.15)	26
	UCC-only	9 (30.00)	21 (70.00)	30
	Total	23	33	56
Participants without PAD	Aurix and UCC	18 (45.0)	22 (55.0)	40
	UCC-only	10 (30.3)	23 (69.7)	33
	Total	28	45	73
	Odds Ratio	95% Confidence Limits		*P*
	2.2123	1.0699	4.5742	.0319

(B)

	Treatment	Healed, n (%)	Not Healed, n (%)	Total
Participants who smoked	Aurix and UCC	25 (65.8)	13 (34.2)	38
	UCC-only	10 (34.5)	19 (65.5)	29
	Total	35	32	67
Participants who did not smoke	Aurix and UCC	7 (25.0)	21 (75.0)	28
	UCC-only	9 (26.5)	25 (73.5)	34
	Total	16	46	62
	Odds Ratio	95% Confidence Limits		*P*
	1.9869	0.9510	4.1513	.0657

Abbreviations: PAD, peripheral arterial disease; UCC, usual and customary care.

(66%) in this study did not receive antibiotic treatment during the study period. The use of antibiotics correlated with a decrease in healing for both treatment groups. In the absence of antibiotics, 55% of participants healed in the Aurix and UCC group and 35.6% in the UCC-only group. When antibiotics were administered, the healing rate dropped to 38.5% in the Aurix and UCC group and 16.7% in the UCC-only group. The odds of healing remained higher in the Aurix and UCC group than the UCC-only group (P = .0193; OR, 2.4368; 95% CI, 1.154–5.1457) after controlling for the effect of antibiotic use. Cox regression analysis comparing time to healing between the Aurix and UCC and UCC-only groups with antibiotic use as a covariate shows that participants without antibiotic use healed faster than participants with antibiotic use (P = .0114; HR, 1.861; CI, 1.053–3.290). After adjusting for antibiotic use, the Aurix and UCC over UCC-only HR of healing is 1.861 (P = .0325), indicating that the time to healing was shorter for the Aurix and UCC patients than for the UCC-only patients.

Safety

In this pragmatic study, on-site clinical monitors were not used to facilitate the documentation of TEAEs. The investigators were instructed to capture TEAEs within the EMR or case report form during the patient encounter. All of the spontaneously recorded TEAEs are presented in Supplemental Table 5, http://links.lww.com/NSW/A25. The TEAEs included seven serious adverse events, none of which were judged to be treatment related. The serious adverse events included two amputations in the UCC-only treatment group. No amputations were documented for the Aurix and UCC treatment group. Only one of the TEAEs was even suspected to be related to the treatment. Specifically, a participant in the UCC-only treatment group developed a new ulcer resulting from the placement of a total contact cast.

Durability of Healing

Assessment of wound healing durability was limited to a 2-week wound healing confirmation visit. However, the inability to provide patients with transportation, copay reimbursement, and/or other incentives under Medicare rules contributed to limited return visits for the 2-week follow-up. Documented 2-week healing confirmation visits included 20 participants from the Aurix and UCC group (two wounds reopened) and five participants from the UCC-only group (one wound reopened). The small number of participants who returned after initial healing precluded statistical analysis.

DISCUSSION

This landmark study is the first of its kind in wound care conducted under the Medicare CED program. The results indicate that Aurix provides advantages for healing chronic DFUs, specifically in the Medicare population. Further, this study provides useful insight for developing operational strategies for CED programs both within and beyond the field of wound care.

Study Operations and Enrollment

This pragmatic study was intended to gather health outcomes data for Aurix as typically used for chronic wounds. Accordingly, the trial's inclusion/exclusion criteria were intentionally limited to provide access for a broader population of Medicare beneficiaries. The study was designed to minimally impact the day-to-day delivery of care, which varies depending on the clinical site (Supplemental Table 1).

Data elements required for analysis of study endpoints were established for consistency with those most commonly documented for patient encounters within the WoundExpert EMR. This simplified the direct transfer of source data to the study database and obviated the need for case report forms in a majority of investigative sites. Considering the study design was inclusive and data collection was relatively seamless, the expectation was that patient enrollment would be significantly more efficient than in a conventional RCT.[2] This unfortunately was not the case; many unique aspects of the CED paradigm (Table 1) presented unanticipated hurdles to study enrollment.

For example, conventional RCTs generally rely on a sponsor to provide resources for most if not all study treatments, transportation to and from treatment facilities, and the time and effort required to perform study-related activities. In contrast, CMS policy under CED is that Medicare can only reimburse for study treatments, physician's fees, facility fees, and other claims directly related to patient care. Because treatments and services are covered under CED, study sponsors, investigative sites, and patients must follow Medicare rules. Under those rules, sponsors are prohibited from making payments to patients, providers, or institutions affiliated with the investigative sites for any activities within the normal scope of patient care.

In the present study, this had important repercussions for patient participation, provider engagement, and study site retention. The vast majority of study candidates with or without secondary insurance, other than certain Medicaid plans, were responsible for a standard 20% Medicare Part B copay for all treatments administered throughout the study. Because a majority of secondary insurance payers would not cover treatment under CED, the sponsor pursued and obtained an advisory opinion from the Office of the Inspector General, which allowed investigative sites to waive copay requirements pursuant to stipulated provisions. These activities failed to have the intended effect. Over the 3½-year study enrollment period and despite an estimated 800 insurance verifications after clinical eligibility screening, many patients could not access this program and certain demographics

were underrepresented (Table 3) within the 129-participant ITT population.

In addition to this patient consideration, the requirements of CED had unexpected consequences on provider engagement and study site retention. The CED was first established in 2006, and CMS's commitment to and the rules of CED are well established.[8] However, CED has yet to be widely implemented, and it was the sponsor's experience that stakeholders did not have an equal and shared understanding of the program. Although CMS updates published mandates for payments to be made for products and services provided under the CED program on a yearly basis, in certain cases, Medicare Administrative Contractors appeared to exercise discretion with respect to actual payment to facilities and providers under this wound care CED. This was especially problematic for reimbursement in the physician's office setting and resulted in this site of service being significantly underrepresented in this CED effort. Adding complexity, infrastructure used by certain facilities and providers to submit claim information required modification by technical staff to handle the elements needed to identify CED-related activity. The end result of these compounding factors was long payment cycles or the complete absence of payment for the physician and/or facility.

Unsurprisingly, this resulted in significant attrition of investigators and clinical sites. Over the course of this CED program, 48 investigative sites were either trained or completed site initiation and were open for enrollment. Immediately prior to data analysis, the number of actively participating sites was three. The sponsor's experiences with secondary insurance payment and claims denials by Medicare Administrative Contractors may be unique in the CED experience in that the use of autologous blood products for wound care is associated with a long-standing noncoverage decision by CMS. Nonetheless, this may be instructive to future CED programs that may be well served by a sponsor's thorough consideration of mechanisms for coding and claim submission at potential investigative sites, as well as the secondary insurance payer mix within the reimbursement landscape.

Effectiveness

At the suggestion of CMS, compelled by slow progress, this pragmatic study was opened for analysis prior to enrollment of the intended 760 participants. Although the current 129-patient dataset does not support many of the planned subgroup analyses, it does allow for a meaningful analysis of the primary and some secondary endpoints and provides compelling effectiveness data.

The large average starting wound area and range of wound sizes enrolled in this study are notable (Supplemental Table 2). The inclusion/exclusion criteria in this study were not intended to force equal enrollment of all wound severities; a substantial majority of wounds enrolled for both the UCC and Aurix and UCC groups were Wagner grades 2 and 3 involving ligament, tendon, deep fascia, or bone (Table 5). Although the numbers of wounds in these Wagner categories are similar between the groups, there is bias against the Aurix and UCC group, which enrolled 10% more of these severe ulcers than the UCC-only group (Table 5).

The authors believe that the preponderance of severe wounds enrolled in this study is greater than the distribution seen in most wound centers. One possible explanation for the prevalence of severe wounds is that the study provided investigators a treatment opportunity for hard-to-heal DFUs that previously could not be addressed effectively with other healing modalities. Nonetheless, the present study addresses a mix of wound sizes, severities, and comorbidities that is problematic for healing and remains unaddressed in other published RCTs. Further, although the wound distribution was mostly Wagner grades 2 and 3 ulcers, Wagner grades 1 to 4 wound severities were represented in both groups (Table 5).

Considering that the range of comorbidities and the severity of wounds evaluated in this study are a first for an RCT in wound care, the healing benefit ($P = .034$; OR, 2.1796; 95% CI, 1.0579–4.4906) observed for Aurix (Table 4) and Kaplan-Meier time to heal (log-rank $P = .0476$) presented in Figure 1 are notable. This is especially true considering a recently published RCT showing that another autologous blood technology achieved a 34% healing rate for a majority of superficial wounds over a 20-week study period in the absence of serious comorbidities.[6] In comparison, the overall healing rate (48.5% of wounds) in the Aurix treatment group was achieved within a 13-week study period with larger and more severe wounds, some involving tendon and bone (Table 5). The observation that the Kaplan-Meier curves for the Aurix and UCC and UCC-only treatment groups separate at about 6 weeks shows an approximate two-fold healing advantage at the end of the 13-week study period. This is striking considering that published double-blind RCT data show earlier separation of healing curves when Aurix was compared with saline hydrogel.[3]

The authors suggest that the relatively and more frequent use of advanced care within the UCC-only arm of this study may have contributed trial noise that included early healing responses within the initial weeks of treatment. However, that cannot adequately be explored with the number of patients available for this analysis. This notwithstanding, Kaplan-Meier analysis supports the hypothesis that Aurix hematogel provides a significant time-to-heal benefit compared with UCC including one or more advanced treatment modalities.

An important and unexpected finding was that while smoking or a baseline diagnosis of PAD did not meaningfully impact the overall healing rate of 30.2% observed in the UCC-only group (Table 4), numerically higher healing rates in these two subgroups

were observed in participants treated with Aurix (53.8% and 65.8%, respectively; Table 6). The increased healing observed for participants with PAD was significant (P = .0486; Supplemental Table 3). Although unexpected, investigators hypothesize that the improved healing of smokers and participants with PAD may lie in the activation of platelets; that is, the topical application of Aurix serves to bypass the lack of perfusion to deliver a natural complement of growth factors and other biomolecules that facilitate tissue regeneration. Future studies exploring the long-term durability of wound healing specifically in patients with these comorbidities would be of value.

Given the wide range of DFU severities and underlying comorbidities often are seen at wound centers, efficient and cost-effective wound healing may sometimes require different healing modalities within a continuum of care. In this study, advanced care was allowed in both treatment arms, and analysis was conducted for treatments performed in the presence or absence of such care. Presented in Table 2, the overall healing rate for the Aurix and UCC group with and without advanced therapies was 48.5%; this is approximately the same as the percentage healed when Aurix was used only with standard of care (51%).

Interestingly, when advanced care was added, the percentage healed in the Aurix and UCC group declined to 40%. However, the limited sample size (15 of 66 patients) is not sufficient for robust statistical testing and subsequent interpretation. In contrast, the majority of patients (34 of 63) in the UCC-only group were provided with one or more forms of advanced care, and the observed healing rate for this group was 32.4%. This is higher than the 27.6% observed for the UCC-only group in the absence of advanced care, but substantially lower than the 51% healing observed for Aurix when delivered with standard of care only. Therefore, it is possible that Aurix may not only provide a healing benefit, but also an economic benefit by reducing the need for expensive advanced care options.

Critically, this study evaluated wound healing, including large and severe wounds, in the presence of difficult comorbidities. Significant healing benefit was established in terms of the proportion healed (Table 4) and time to healing (Figure 1), as well as for healing wounds of patients with PAD (Supplemental Table 3). Aurix confers a unique healing benefit not provided by other modalities. This view is consistent with the notion that Aurix hematogel bypasses a lack of perfusion to provide a bioactive gel containing platelets that deliver appropriate growth factors and other biomolecules important for regeneration.[37–39]

Limitations

The open-label design of this study prohibited blinding of the treating clinicians and participants, which may have introduced unintentional bias. Although the inclusion/exclusion criteria were not as restrictive as most published studies and RCTs, they prohibited inclusion of all patients normally seen in an outpatient wound setting.

The determination of durability past 2 weeks could not be studied adequately because the mechanics of CED requiring a patient copay made it unlikely that patients would return to the clinic after wound closure for an observational assessment. This would be an important subject for future study because wound reopening is common in patients with PAD and diabetes.

Innovation

Aurix is a unique point-of-care system for producing a bioactive hematogel. As compared with conventional RCTs carried out in wound care, limited inclusion/exclusion criteria in this study allowed for the enrollment of patients with a range of comorbidities and wound severities. Investigators retained autonomy to employ treatments according to their standard protocols, including advanced therapies such as cellular and/or tissue-based products and negative-pressure wound therapy. The results are therefore more easily extrapolated to the typical wound care setting and population of Medicare patients with DFUs.

CONCLUSIONS

This article represents the first pragmatic CED RCT in wound care. Based on the authors' experience, the CMS CED paradigm is a promising tool for establishing the effectiveness of therapies and informing coverage decisions. However, its implementation requires that the CMS, sponsors, investigators, and even potential patients understand the reimbursement landscape and mechanisms including, but not limited to, the payer mix and the methods that planned investigative sites may use for claim submission.

Although many hurdles to enrollment were encountered over the course of this CED study, analyses of the 129-patient ITT dataset support the effectiveness of Aurix when used to treat chronic DFUs in the Medicare population. These results indicate that Aurix, alone or in combination with other advanced therapies, improves healing of chronic DFUs of all severities, even in the presence of serious comorbidities, in the Medicare population as compared with UCC as provided in an outpatient wound center. ●

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