DE NOVO CLASSIFICATION REQUEST FOR MEDLINE ART SKIN HARVESTING SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Semi-automated autologous skin graft harvesting and application device. A semi-automated autologous skin graft harvesting and application device is a handheld electromechanical surgical instrument that extracts autologous skin graft tissue from a healthy donor skin site and deposits it to a recipient site. The device extraction and deposition functions are automated and are activated by the user. The device is not intended for treatment of full-thickness burns.

NEW REGULATION NUMBER: 21 CFR 878.4795

CLASSIFICATION: Class II

PRODUCT CODE: QYK

BACKGROUND

DEVICE NAME: Medline ART Skin Harvesting System

SUBMISSION NUMBER: DEN210049

DATE DE NOVO RECEIVED: October 19, 2021

SPONSOR INFORMATION:

Medline Industries, Inc.
Three Lakes Drive
Northfield, IL 60093

INDICATIONS FOR USE

The ART (Autologous Regeneration of Tissue) Skin Harvesting System is intended for the harvesting and application of autologous, full thickness micrografts for wounds where autologous skin grafting would be appropriate.

LIMITATIONS

The sale, distribution, and use of Medline ART Skin Harvesting System are restricted to prescription use in accordance with 21 CFR 801.109.

The Medline ART Skin Harvesting System is contraindicated for management of full-thickness burns. Donor sites may not include any of the following:

- Areas in one of the following anatomical regions: face, scalp, neck, hands, feet, ears, ankles, elbows, genitals, breast, axilla, perianal area, areas with bony prominences or tendons;
- Areas where the skin is unhealthy or non-intact;
- Areas where the total thickness of the skin and subcutaneous fat is less than 5 mm.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The device is a handheld surgical skin tissue harvesting system that uses an array of coring needles to acquire full thickness skin tissue columns (hereafter referred to as "micrografts" or "microcolumns") from an appropriate healthy donor site for deposition onto an appropriate recipient treatment site (Figure 1). The procedure is minimally invasive and both the tissue acquisition (i.e., "harvest") and deposition (i.e., "scatter") processes are automatically performed by a handheld device as described below.

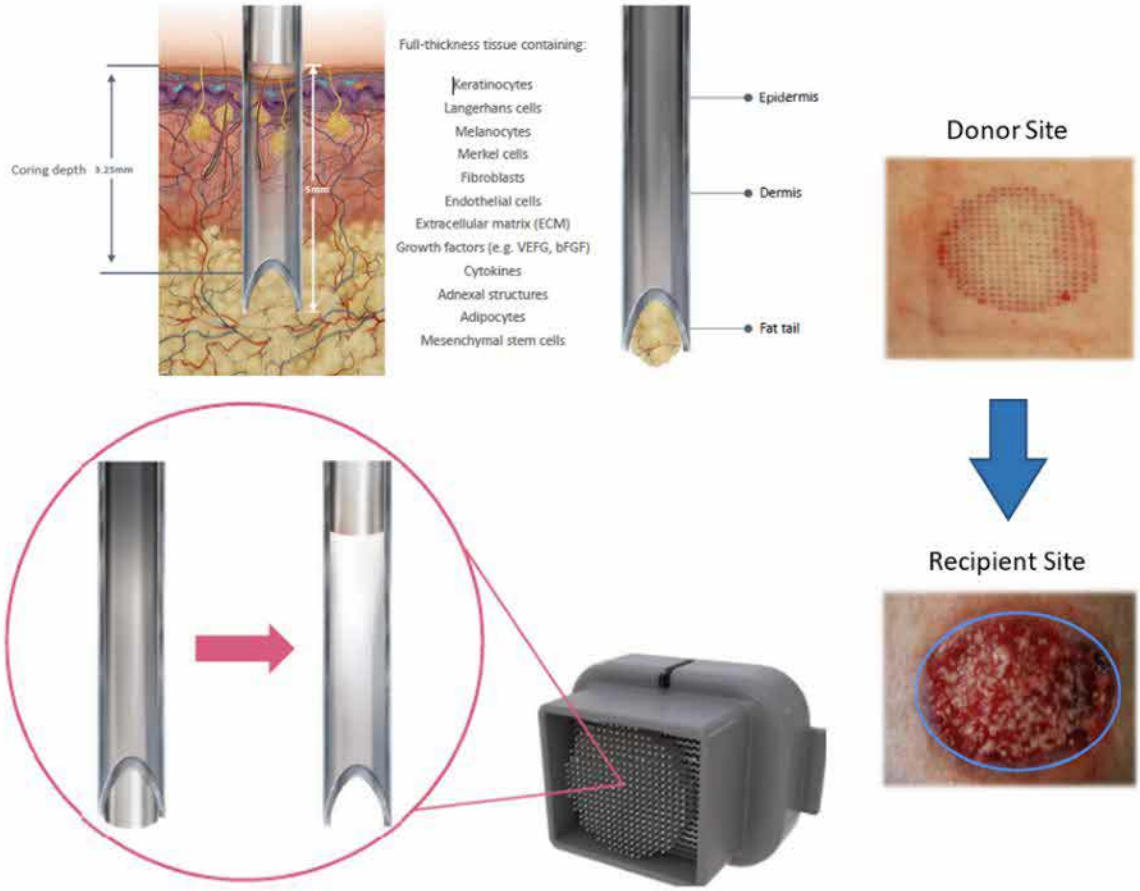

Figure 1. Principle of Operation

The device consists of three components: (1) a non-sterile, reusable handheld device; (2) a sterile, single-patient use needle cartridge containing the needle array for harvesting skin micrografts from

the patient donor site; and (3) a sterile, single-patient use handheld protective sleeve to cover the handheld device (Figure 2). The handheld device uses embedded software to control the operation of the cartridge using user-activated tactile buttons and trigger (Figure 3). The sterile sleeve protects the handheld device from soilage and provides a physical barrier between the non-sterile handheld device and the patient.

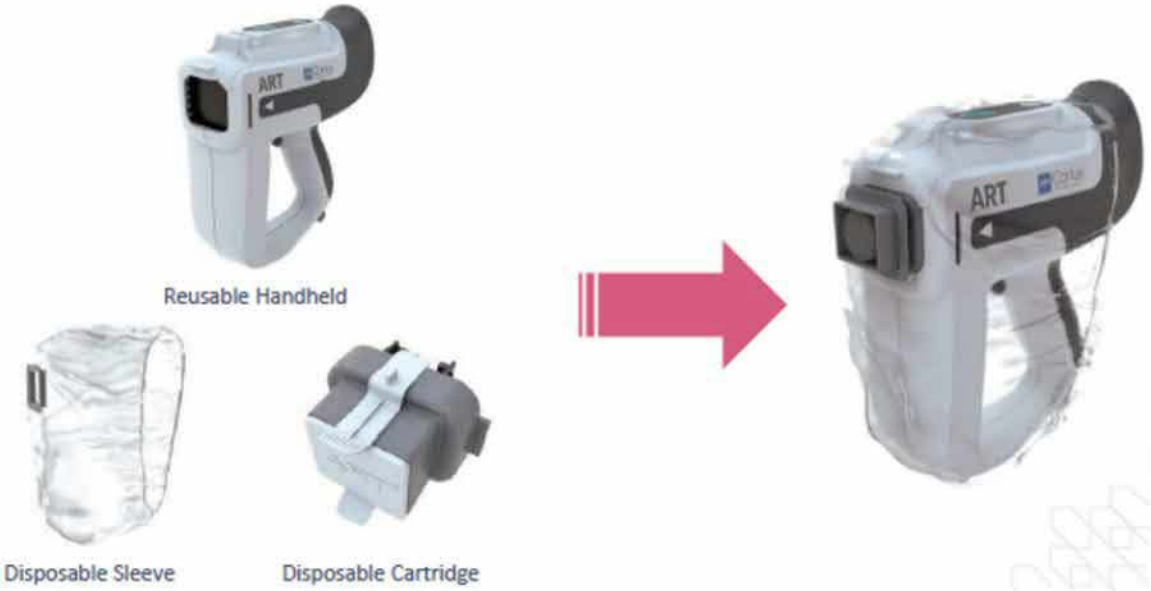

Figure 2. Device Components

Figure 3. Handheld Unit Features

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Medline ART Skin Harvesting System is comprised of a non-sterile, non-patient-contacting handheld unit and patient-contacting sterile needle cartridge and protective sleeve. The patient-contacting components are categorized as having surface contact with

breached/compromised skin for limited (<24 hour) contact duration and the sponsor has provided acceptable documentation to support the following biocompatibility endpoints according to the relevant FDA guidance documents and standards:

- FDA Guidance for the *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices -Part 1: Evaluation and testing within a risk management process"*
- Cytotoxicity - MEM Elution Test (ISO 10993-5)
- Sensitization - Guinea Pig Maximization Test (ISO 10993-10)
- Irritation - Primary Dermal Irritation Test (ISO 10993-10)
- Acute Systemic Toxicity (ISO 10993-11)
- Material-Mediated Pyrogenicity (ISO 10993-11)
- Hemolysis (ASTM F756-13)

Additionally, a systemic toxicity assessment was conducted using a porcine abdomen model.

The results demonstrate that the Medline ART Skin Harvesting System is biocompatible.

SHELF LIFE/STERILITY

Medline ART Skin Harvesting System handheld unit: The handheld unit is non-sterile and is not intended to be sterilized. Cleaning and disinfection validation was demonstrated by testing.

Needle cartridge and Protective sleeve: The single-patient use needle cartridge and handheld protective sleeve are packaged and sterilized via gamma radiation in accordance with ASTM F1980-16 to a sterility assurance level (SAL) of 10^{-6}. The shelf-life of these components was verified to be 1 year based on real time (needle cartridge) and accelerated (protective sleeve) aging.

As noted in the labeling, the device should not be used in oxygen rich environments. Additionally, a risk assessment was provided to address all safety concerns associated with electromagnetic compatibility, wireless, electrical, mechanical, and thermal safety.

SOFTWARE/CYBERSECURITY

The handheld device contains software and hardware that control the motion of the needle and pin arrays in the needle cartridge component for harvesting tissue microcolumns from the donor site and dispersing microcolumns onto the recipient site. The sponsor has provided all relevant documentation to address a Moderate Level of Concern according to the following FDA guidance documents and standards:

- FDA Guidance for the Content of Premarket Submission for Software Contained in Medical Devices (May 11, 2005)
- AAMI 62304:2006 - Medical device software - Software life cycle processes
- AAMI 62304 amendment 1:2015 – Medical device software – Software life cycle processes
- AAMI TIR 80002-1 :2009- Medical device software risk management

- ISO 14971:2019 Medical devices - Application of risk management to medical devices

Software documentation and testing demonstrates that the software will operate in a manner described in the specifications. The hazard analysis characterized software risks. No cybersecurity risks were identified. The submission describes verification and validation testing to address the potential hazards with satisfactory results. The software documentation contains sufficient detail to provide a reasonable assurance that the software will operate in a manner described in the specifications and all testing and results were adequate to meet the above standards.

ELECTROMAGNETIC COMPATIBILITY (EMC) & ELECTRICAL SAFETY

The handheld device is controlled by embedded software and contains electrical hardware to control the user interface and the motion of the needle and pin arrays in the cartridge component during the harvesting and scattering procedures. Additionally, the device contains various electromechanical subsystems to help ensure that the device is used in a safe manner in accordance with its intended use. The handheld unit is powered by a 120 VAC (60Hz) grounded power supply.

Testing was performed in accordance with the following standards to support the electrical safety concerns associated with the subject device.

- IEC 60601-1:2012 Medical Electrical Equipment Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-6:2010 Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability
- IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices

Testing was performed in accordance with the following standards to support the electromagnetic compatibility of the subject device.

- IEC 60601-1-2:2014 (4th Edition) Medical Electrical Equipment Part 1-2: General requirements for basic safety and essential performance collateral standard: Electromagnetic compatibility
- IEC 61000-4-2:2008 Electromagnetic compatibility (EMC) – Part 4-2: Testing and measurement techniques – Electrostatic discharge immunity test
- IEC 61000-4-3:2006:AI:2007/A2:2010 Electromagnetic compatibility (EMC) – Part 4-3: Testing and measurement techniques – Radiated, radio-frequency, electromagnetic field immunity test
- IEC 61000-4-4:2012 Electromagnetic compatibility (EMC) – Part 4-3: Testing and measurement techniques – Electrical fast transient/burst immunity test
- IEC 61000-4-5:2014 Electromagnetic compatibility (EMC) – Part 4-5: Testing and measurement techniques –Surge immunity test
- IEC 61000-4-6:2013 Electromagnetic compatibility (EMC) – Part 4-6: Testing and measurement techniques – Immunity to conducted disturbances, induced by radio-frequency fields

- IEC 61000-4-8:2009 Electromagnetic compatibility (EMC) – Part 4-8: Testing and measurement techniques – Power frequency magnetic field immunity test
- IEC 61000-4-11:2004 Electromagnetic compatibility (EMC) – Part 4-11: Testing and measurement techniques – Voltage dips, shorts interruptions and voltage variations immunity tests
- EN 55011:2009/A1:2010, CISPR 11:2010 Industrial, scientific and medical equipment. Radiofrequency disturbance characteristics. Limits and methods of measurement

The provided documentation and testing demonstrate that the hardware will operate safely in the intended environments for clinical use. Where necessary, i.e., when patients are fitted with an active implanted medical device, warning labels have been added to inform users to not use the device on patients with such devices. The electrical safety and electromagnetic compatibility documentation is of sufficient detail to provide a reasonable assurance that the device in accordance with the specifications.

PERFORMANCE TESTING: BENCH

TRANSPORTATION TESTING

Testing was performed to demonstrate the functionality and suitability of the final finished and sterilized Medline ART Skin Harvesting System packaging post-transit. Transportation testing study was carried out in accordance with ISTA-3A (simulated ship tests for drop and vibration of all device components), ASTM D4169-16 (all device components), and ASTM D4332-14 (non-sterile handheld only) using unaged samples, as life cycle and stability testing adequately established that the integrity of the device, including its packaging, is maintained throughout the subject device's shelf-life.

DESIGN VERIFICATION TESTING

Design Verification testing was performed to demonstrate that the following criteria in the final finished device were met:

- The device can be properly set up by the user. (i.e., the needle cartridge can be loaded appropriately, the handheld protective sleeve fits over handheld device, etc.)
- Visual and dimensional inspection of the fully assembled Medline ART Skin Harvesting System meets specifications.
- Duration of the harvesting steps are within specification.
- No particulates larger than 0.2 mm^2 are shed from the handheld or cartridge during the first three harvest and scatter cycles on a new cartridge.
- Opening of the handheld device loading door functions properly while the handheld protective sleeve is attached.
- The needle cartridge performs as intended for at least 3 harvest/scatter cycles.
- Usability Testing: testing was conducted to demonstrate users can perform all critical tasks when using the User Manual.

DURABILITY TESTING

Life cycle testing was performed on the handheld unit to demonstrate that the electrical and mechanical function of the handheld unit meets reliability and durability

specifications over its expected service life. Testing on human cadaver legs demonstrated that the handheld unit functions as intended for at least 1,000 collection and scatter cycles, with the adherence to the established maintenance schedule. A conservative service life of 2 years is based on a use scenario of 250 use cycles per year.

PERFORMANCE TESTING- ANIMAL WOUND HEALING STUDY

A full thickness porcine wound healing study was performed on the subject device to investigate the safety and effectiveness of the subject device as an alternative to traditional Split Thickness Skin Grafting (STSG) using a dermatome. In corroboration with reports in the published literature this study was also used to demonstrate healing after uncontrolled tissue orientation deposition at the graft site and to determine whether the orientation of the micrografts impacted healing (e.g., due to potential uneven scarring, uneven pigmentation, and cyst or granuloma formation).

Wound Model

The device is intended for use on various wound types, excluding full-thickness burns, where autologous skin grafting would be appropriate. In clinical practice, the standard procedure is to achieve hemostasis and manage exudate prior to undergoing any grafting procedure, as excessive exudate and fluid beneath a graft can jeopardize graft take. To model this initial bed preparation, full thickness wounds were created on each animal 2-3 days prior to the grafting procedure. Therefore, each of 18 female Yorkshire pigs received 6 full thickness wounds measuring 40 mm diameter (3 wounds per side), on Study Day -2, i.e., 2-3 days prior to grafting. Recipient sites were tattooed around their perimeter and covered with Adaptic non-adherent dressing, sterile gauze squares, and TegaDerm film dressing. The dressings were then covered with PetFlex.

Methods

On Day 0 (±1 day), the bandages were removed from the donor sites and the sites were observed, measured, and photographed. Donor tissue for the subject device (ART donor sites) and control (STSG donor sites) groups, respectively located on the upper back and hindquarters of each animal, were aseptically acquired using the ART Skin Harvesting device or dermatome.

Donor skin tissue was harvested from at least four donor sites using the subject device. Microcolumns from at least two donor sites were scattered onto a single recipient site. If during either of the two donor harvests the ART device did not deploy at least approximately 50% of its full capacity or if a system malfunction caused it to be unable to scatter tissue, a third ART harvest was performed in the vicinity of the allocated donor site area. Additional ART harvests were performed as needed to provide approximately 50% coverage of the recipient site. Recipient sites were covered with a thin layer (approximately 2 mm thickness) of (b)(4) gel, followed by Adaptic Non-Adhering Dressing, and Optifoam Adhesive Foam Dressing. Bandages were further secured with (b)(4), and the animal wrapped with (b)(4).

Control tissue (approximately 1" x 2" or approximately 12.9 cm^2, 16/1000" deep) was harvested from two donor sites. Harvested skin was meshed and stretched/expanded to a

1:2 ratio and cut to fit the recipient sites wound bed geometry and sutured to the edges of the recipient site. The recipient sites were covered with a thin layer (approximately 2 mm thickness) of (b)(4) gel, Adaptic Non-Adhering Dressing, and Optifoam Adhesive Foam Dressing (in that order). A gauze square was placed on top of the Adaptic and a suture bolster created on top of the site to apply pressure to aid in keeping the graft adhered to the site to ensure graft take. (b)(4) Transparent Film Dressing was placed over the bolster, bandages were further secured with (b)(4), and the animal wrapped with (b)(4)

All subject device and control donor sites were covered with Adaptic Non-Adhering Dressing, a gauze square, and (b)(4) Transparent Film Dressing (in that order). Bandages and dressings were changed on Days 3(+/- 1 Day), 7(+/- 1 Day), 14 (+/- 1 Day), 21 (+/- 1 Day), 28 (+/- 1 Day), 35 (+/- 1 Day), and 42 (+/- 1 Day). Wounds and adjacent skin were scored visually at each dressing change for erythema, edema, re-epithelialization, wound contracture, fluid/exudate, slough/necrosis and any notable macroscopic observations (i.e., hemorrhaging, and discoloration). The following internal scale was used for erythema, edema, slough/necrosis, and granulation:

0 = None
1 = Minimal: Re-epithelialization covering 1-25% of wound
2 = Slight: Epithelium covering up to 26-50% of wound
3 = Moderate: Epithelium covering up to 51-75% of the surface of the wound
4 = Marked: Epithelium covering >75% of the surface area of the wound
5 = Complete re-epithelialization. 100% of surface of wound

Wound cross-sectional diameters were measured and circumferences calculated. Wound contracture was also quantified based on the tattooed circumference normalized to Day -2. Sites were re-bandaged per protocol after all observations/measurements were complete.

Donor Site Outcomes

Re-epithelialization at the donor site following tissue harvesting using the ART device versus STSG is presented in
Figure 4. Donor site outcomes On Day 4, 53% (20 out of 38 sites) of STSG donor sites received erythema scores of 1-3 compared with 29% (27 out of 94) of ART donor sites that received an erythema score of 1 (i.e., 71% of ART donor sites had no noticeable erythema at Day 4). Also on Day 4, 61% of ART donor sites received a re-epithelialization score of a 2 or 3 while 74% of STSG donor sites received a re-epithelialization score of 0 or 1.

On Day 7, 74% of ART donor sites received a re-epithelialization score of 4 or 5 while 33% of STSG scored similarly.

No other notable differences were observed between donor sites from either group from Days 14 through to the end of the study.

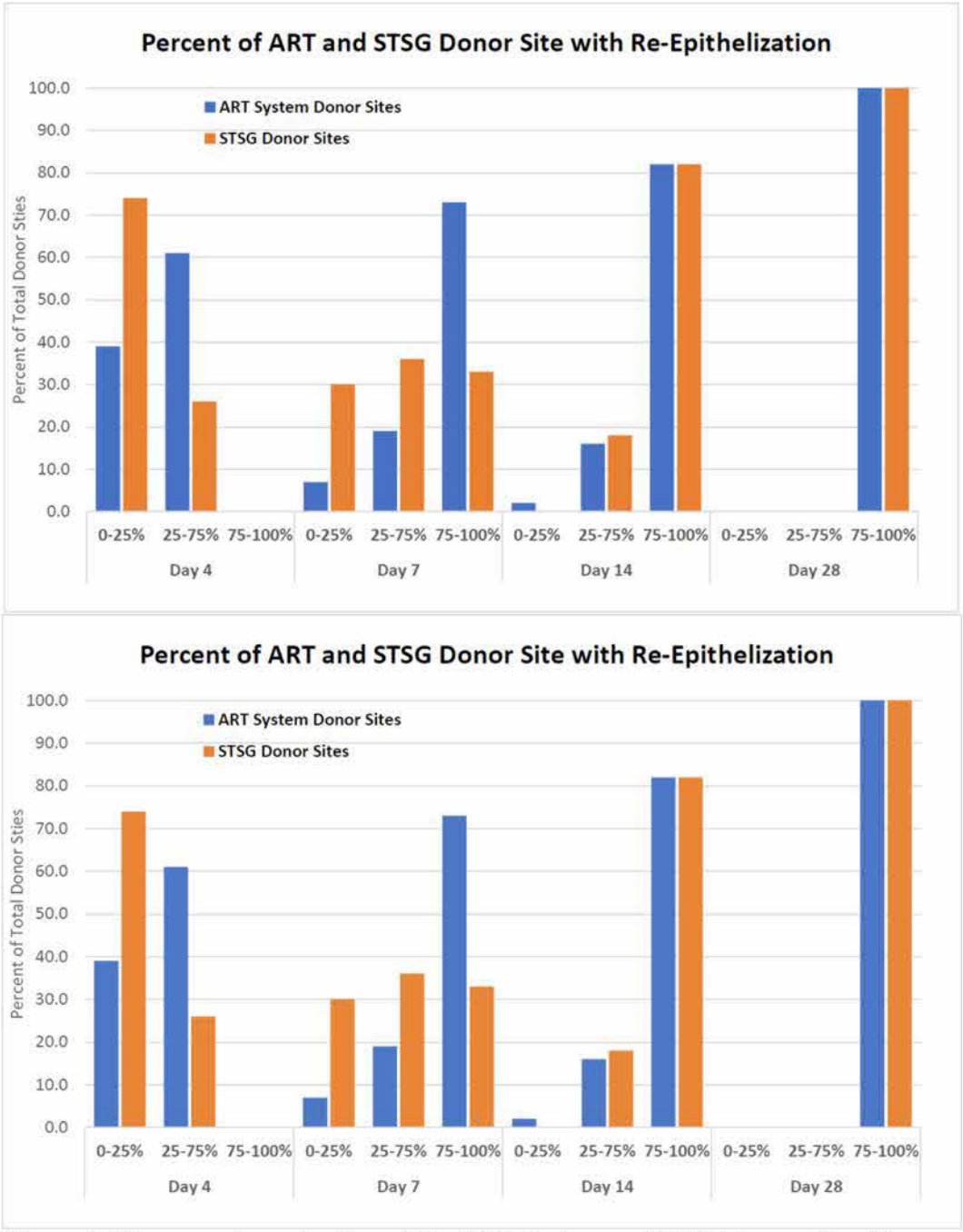

Figure 4. Macroscopic evaluation of the ART System and STSG donor sites. The results show that the ART System donor sites healed at an accelerated rate compared to the STSG donor sites. On Day 4, 61% of the ART System donor sites reached 25-75% re-epithelization compared to 26% of the STSG donor sites (P=0.0395). By Day 7, 73% of the ART System donor sites reached 75-100% re-epithelization compared to 33% for the STSG donor sites (P= 0.0014). Both the ART System donor sites and STSG donor sites reached 75-100% re-epithelization by Day 28.

The above macroscopic scores were also observed histologically, where both donor sites were healed by Day 7. Additionally, at Day 21, epidermal rete ridges were observed only

in the ART donor sites, granulation tissue was more pronounced in the STSG donor sites, with ART donor sites having stroma that appeared to be normal, better-organized collagen deposition and less irritation than STSG sites.

Recipient Sites Outcomes

Overall circumference and rate of occurrence of necrotic tissue/slough at recipients sites receiving no treatment, ART-harvested micrografts, or STSG are compared on **Error! Reference source not found.** and Table 1. Temporal Progression of Recipient Site Circumferences. Change in wound circumference from Day 0. Negative values indicated wound contraction.

Treatment		Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Untreated	Mean	-3.19	-5.99	-5.53	-5.38	-4.63	-1.60
	SD	1.19	1.72	1.48	2.73	1.33	2.45
ART	Mean	-2.54	-5.87	-4.55	-3.55	-2.79	-1.02
	SD	1.41	2.03	1.15	1.40	1.96	1.78
STSG	Mean	-0.82	-2.26	-2.22	-0.44	0.51	1.59
	SD	1.15	2.39	1.91	1.24	1.63	1.21

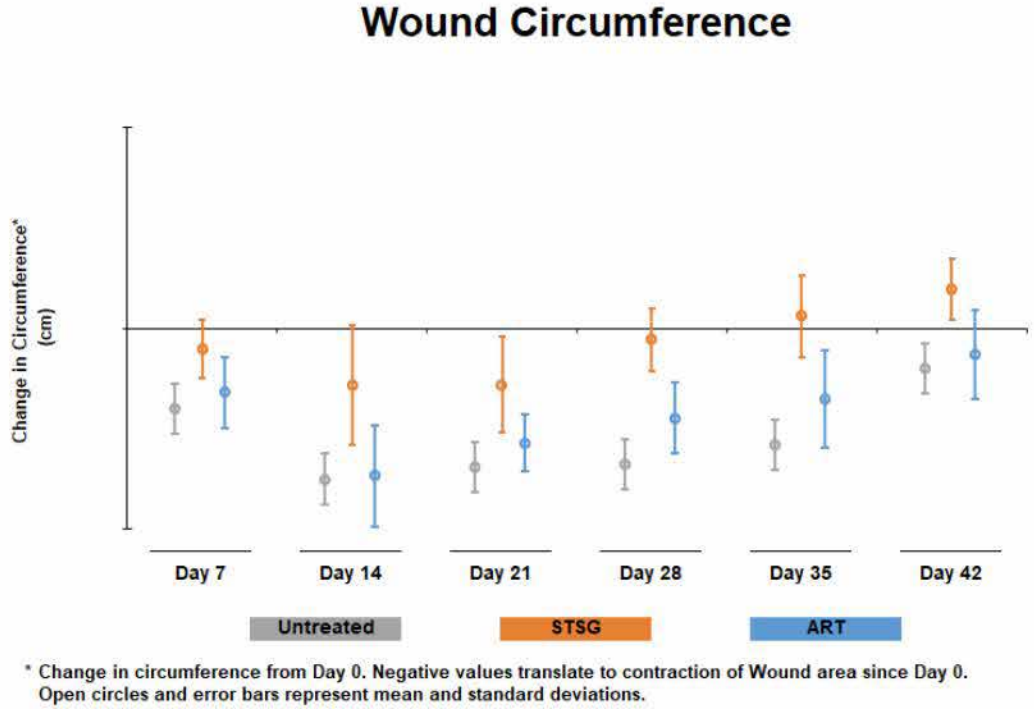

Figure 2. Temporal Progression of Recipient Site Circumferences. Change in wound circumference from Day 0. Negative values indicated wound contraction.

Table 2, respectively. Wound contracture for STSG graft recipient sites was significantly less than that seen in the ART graft recipient sites through Day 21 (i.e., when normalized to Day 0 tattoo circumference) or Day 28 (i.e., when normalized to Day 0 wound circumference. At Day 21, the ART tattoo has a -0.64cm standard deviation (SD) from Day 0 baseline compared to 0.14cm SD for the STSG. At day 28, the ART wound within

the tattoo has -3.55cm SD of contraction compared to -0.44cm SD. Maximum contracture was seen in all treatment types by Day 14.

Table 1. Temporal Progression of Recipient Site Circumferences. Change in wound circumference from Day 0. Negative values indicated wound contraction.

Treatment		Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Untreated	Mean	-3.19	-5.99	-5.53	-5.38	-4.63	-1.60
	SD	1.19	1.72	1.48	2.73	1.33	2.45
ART	Mean	-2.54	-5.87	-4.55	-3.55	-2.79	-1.02
	SD	1.41	2.03	1.15	1.40	1.96	1.78
STSG	Mean	-0.82	-2.26	-2.22	-0.44	0.51	1.59
	SD	1.15	2.39	1.91	1.24	1.63	1.21

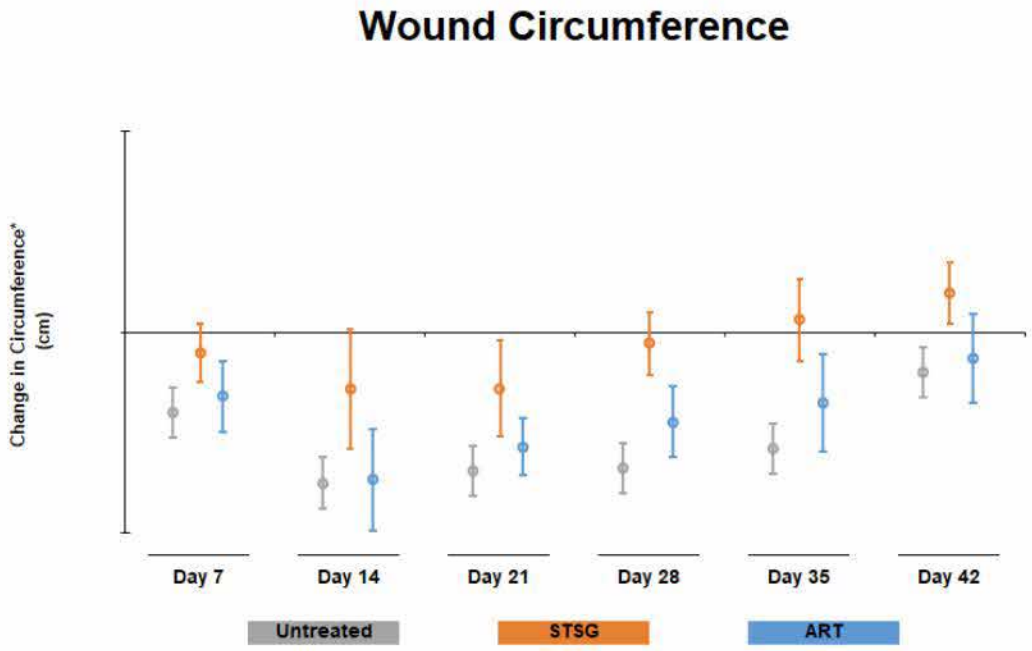

Figure 2. Temporal Progression of Recipient Site Circumferences. Change in wound circumference from Day 0. Negative values indicated wound contraction.

Table 2. Adverse events were reported as necrotic tissue/slough at the recipient site on a scale of 1-4 (minimal to marked). The ART System recipient sites had less adverse events than the STSG recipient sites. On Day 7, 72% of the STSG recipient sites had necrotic tissue/sloughing compared to only 14% of the ART System recipient sites (P=0.0001). By Day 14, 39% of the STSG recipient sites had necrotic tissue/slough compared to 0% of the ART System recipient sites (P=0.0006). There was no significant (NS) difference between ART System recipient sites and STSG recipient sites from Day 21 to Day 42. In addition, there were a total of 3 adverse events reported for the STSG donor sites (data not shown).

Day of Evaluation	ART Recipient Sites	STSG Recipient Sites	Untreated Recipient Sites	P value*
Day 0	0	0	0	NS
Day 7	17	72	14	P=0.0001
Day 14	0	39	0	P=0.0006
Day 21	4	9	13	NS
Day 28	8	0	8	NS
Day 35	0	0	8	NS
Day 42	0	0	0	NS

On Day 7, ART and untreated sites scored similarly for erythema (25% of untreated sites scored a 1 vs 28% of ART sites scored 1 and 3% scored 2) and necrosis (17% of ART sites scored 1 or 2 vs 14% of untreated sites receiving a score of 1 or 2), while 41% of STSG sites scored 2 or higher for these parameters (42% scored between 1 and 3 for erythema and 72% scored between 1 and 4 for necrosis). Purulent exudate was observed at a higher rate in untreated recipient sites than in either ART or STSG sites. Edema was observed in 47% of ART sites (scores ranged from 1 to 3), compared to 31% of untreated sites (scores ranged from 1 to 2). ART sites scored higher for re-epithelialization (69% of ART sites scored between 2 and 4) compared to untreated sites (50% of untreated sites scored between 2 and 4).

On Day 14, ART sites scored lower for erythema (16% scored 1 – 2) than untreated (26% scored 1 – 2) or STSG (46% scored 1 – 3) sites. ART and untreated sites scored similarly for edema (17% of sites in both groups scored 1 and 8% of untreated sites scored 2) while STSG sites scored higher (30% scored 1 or higher). Necrotic tissue/sloughing was not observed in ART or untreated sites; however, 38% of STSG sites scored between 1 and 4. Re-epithelialization scores for ART sites (25% scored 5) fell between those of their untreated (8% scored 5) and STSG (57% scored 5) counterparts.

On Day 21, 46% of the ART sites scored 5 for re-epithelialization whereas the 17% of the untreated sites scored a 5 for re-epithelialization and 83% of the STSG sites scored a 5 for re-epithelialization.

On Day 28, untreated and STSG scored higher for erythema (17% of both scored 1) than ART sites (8% scored 1.) ART site scores for re-epithelialization (67% scored 5) fell between untreated (33% scored 5) and STSG (92% scored 5) site scores.

On Day 35, 100% of ART and STSG sites had fully healed, i.e., re-epithelialization scores of 5. Among untreated specimens, only 58% scored 5, while 25% scored 4, and 16% scored 2 or 3.

On Day 42, all ART and STSG sites scored 5 for re-epithelialization, while only 75% of untreated sites scored 5 and 25% of the remaining untreated sited scored 4. This was corroborated histologically. Additionally, rete ridges were only observed in 25% ART recipient sites and 92% of the STSG sites. Granulation tissue was found to be most mature in STSG sites, followed by the ART sites. Collagen was slightly more organized at STSG sites compared to ART. Similarly, there were more ART sites exhibiting organized collagen compared to untreated sites. More STSG sites had minimal but scattered elastin deposition while pattern of elastin deposition was predominantly similar at ART/untreated sites. Overall inflammation scores in the superficial wound bed were predominantly minimal (score =1), with no evidence of necrosis (except at one untreated site, which scored 2). In the deep dermis, sites treated with the ART device were observed to have lower inflammation (54% scored 1 and 46% score 2) that sites treated with either STSG (42% score 1, 50% score 2, and 8% scored 3) or untreated controls (33% scored 1, 60% scored 2, and 7% scored 3). Overall, inflammation was predominantly minimal, with no evidence of necrosis (except at one untreated site) at all sites (superficial wound bed). Granuloma/microgranuloma formation involving entrapped adipocytes/dressing material/possible bacteria was observed at ART (6 of 13), STSG (5 of 12) and untreated (4 of 15) sites.

Overall, based on macroscopic and histopathology healing parameters, ART recipient sites demonstrated improved and faster healing compared to nongrafted sites and fewer adverse events than the STSG-grafted sites (Figure 5). There was greater wound contracture observed in the ART recipient sites compared to STSG sites.

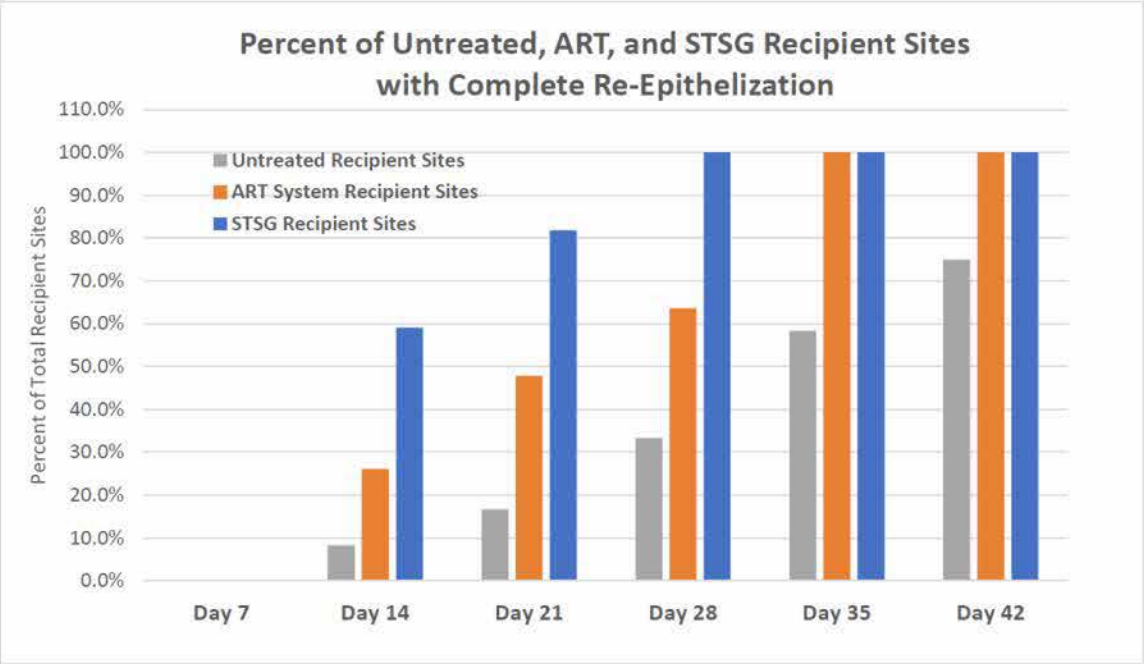

Figure 5. Macroscopic evaluation of the ART System, STSG, and Untreated recipient sites. The results show that the ART System recipient sites healed at an accelerated rate compared to the Untreated recipient sites. On Day 14, 26% of the ART System recipient sites reached complete re-epithelization compared to 8% of the Untreated recipient sites. By Day 21, 48% of the ART System recipient sites reached complete re-epithelization compared to 17% of the Untreated recipient sites. Complete re-epithelization was achieved by Day 28 for the STSG recipient sites and by Day 35 for the ART System recipient sites. As expected, the STSG recipient sites had the highest level of complete re-epithelization from Day 14 to Day 42. The Untreated recipient sites did not reach complete re-epithelization.

HUMAN FACTORS/USABILITY TESTING

Human factors/usability (HF/U) testing was performed using the subject device in two simulated use studies to demonstrate that the Medline ART Skin Harvesting System is safe and effective for its intended use, users, and use environments.

The first study involved 18 nurse or doctor (HCPs) users who were trained in accordance with the User Manual and Medline available in-service training program prior to using the device in the simulated environment. Testing demonstrated that users were able to read and understand the instructions and adequately perform the collection/scattering procedure. Users successfully completed all critical tasks at >95% achievement rates, with 8 of the 10 critical tasks being performed at a 100% success rate.

A second user study was performed to include seven (7) physicians and eight (8) surgical podiatrists with a larger number of podiatrists (who are the user population most likely to benefit from the device), add an eight-hour period between user training and device use to simulate training decay, to redefine all critical tasks as such regardless of whether their probability of occurrence is low, and to refine the user manual and training program. In

this user study, a success rate of 97.5% was achieved, with users completing 585 out of 600 total tasks without difficulty or use errors.

All of the participants were able to:

- Press cartridge against donor site
- Initiate harvest
- Maintain position during harvest
- Recognize completion of harvest
- Press scatter button
- Hold at appropriate distance from wound
- Initiate scatter

In cases with poor donor site selection, the device completed a less effective harvest retrieving fewer full thickness microcolumns because the needles do not puncture to their full depth, or because less than 20 rows of needles get deployed. In rare cases, the device also jammed and required servicing. While the HF/U study demonstrated that every single task evaluated was performed at a success rate well above the criteria (80% of the time), these risks are mitigated through training.

CLINICAL INFORMATION

The risks and benefits of the subject device were primarily demonstrated by the preclinical study data. As supplemental evidence, clinical study data provided confirmatory information to support that the results in the preclinical study can be translatable to humans.

For general demonstration of safety and effectiveness, two clinical studies were conducted on an early version of the device, which consisted of a handheld unit that was not controlled by software and a needle array having only 22 needles arranged in two rows. Of note, per the June 2006 FDA Guidance for Industry, "Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment", "Complete wound closure is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart". Of note, the wounds observed in these two studies did not align with FDA's recommendation from the guidance, in that the wounds were not confirmed at two consecutive study visits 2 weeks apart. As such, this supplemental clinical data were evaluated as confirmatory information to support overall use of the device in humans and would not support wound healing as defined in the guidance.

- Study 1 consisted of 25 patients who had undergone excisional surgery of skin malignancies on the ear, scalp, forehead, nose, thigh, and calf were treated with device. Post-excision of tumors and initial granulation of wounds, micrografts were seeded and inspected up to 8 weeks. 96% (n=22) of subjects completing the study (N=23) reached complete re-epithelialization, on average within 5.7 weeks. Following treatment, 96% of subjects healed completely by 8 weeks, and no infections, secondary ulceration, or hypo/hyperpigmentation were observed in the study.

- Study 2 consisted of 12 patients with recalcitrant, pre-amputation wounds that had been unresponsive to standard of care and/or advanced therapies. Eleven patients completed the study (6 diabetics, 5 non-diabetics; 1 smoker and 10 non-smokers; two patients developed infections that were resolved by the end of the study) and the twelfth patient, who developed an infection during the study, discontinued participation from the study after the 6-week examination. Wounds included 9 venous leg ulcers (VLU) and two diabetic foot ulcers (DFU) with an average chronicity of 8.75 months. Following treatment, 8 subjects showed rapid healing and achieved complete re-epithelialization, 2 subjects showed steady initial healing that leveled off by the end of the 8-week follow-up period (these wounds were 66% and 53% re-epithelialized by the end of the 8-week study), the wound of one subject increased in size after treatment and then returned to a healing trajectory. Seven wounds showed a 40% closure by four weeks.

One clinical study (NCT05076578) was conducted on the final finished subject device between September 2021 and February 2022. The study consisted of two groups, each having 10 participants. Of note, per the June 2006 FDA Guidance for Industry, "Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment", "Complete wound closure is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart". Of note, the wounds observed in this study did not align with FDA's recommendation from the guidance in that the wounds were not confirmed at two consecutive study visits 2 weeks apart. As such, this supplemental clinical data were evaluated as confirmatory information to support overall use of the device in humans and would not support wound healing as defined in the guidance.

- **Group A** consisted of 10 (4 males and 6 females) healthy volunteers characterized by the following comorbidities: Fibromyalgia (n=1), Depression (n=1) and a History of Deep Vein Thrombosis (n=1). Beginning at the screening visit, all subjects' donor sites were managed by washing with soap and water at each dressing change. An adhesive post-operative dressing was applied to all donor sites. Tissue was acquired from donor sites (average of 200 micrografts per harvest) in the thigh (n=3), calf (n=5), and upper buttock (n=2) under local anesthesia. The study group participants underwent tissue acquisition only and did not receive treatment. The sponsor reported minimal pain associated with the procedure with no adverse events reported. Donor sites were monitored for the duration of the study and were found to re-epithelialize without complication within 7-10 days following tissue acquisition.

- **Group B** consisted of 10 subjects (7 males and 3 females) having chronic wound(s) present for a minimum of 4 weeks (wound duration ranged from 4-312 weeks and averaged 71 weeks). Study participants had the following comorbidities: Type II Diabetes (n=4), Type I Diabetes (n=1), COPD (n=1), Insomnia (n=1), GERD (n=1), Hypertension (n=2), Diabetic Neuropathy (n=4), and Venous Insufficiency (n=1).

Wounds were treated with one harvest/scatter cycle and, although the number of micrografts deposited to each recipient site was not a measured data point in the study, the study director reported that, on average, 200 micrografts were deposited per harvest cycle in Group A. Treated wounds included DFU, VLU, pressure ulcers (PrU), and other etiologies. The success criterion was based on the number of wounds achieving a percentage area reduction (PAR) of 40% or greater in 4 weeks. Although not formally part of the study's success criteria, the number of micrografts per harvest was additionally counted. Deposition of at least 50% of micrografts per harvest/deposition cycle was observed for all applications, which was considered to meet requirements.

Donor tissue was acquired from thigh (n=3), calf (n=3), and upper buttocks (n=4) using procedures similar to Group A. Recipient wounds were dressed with a nonadherent dressing and a secondary foam dressing. The brands were left to the discretion of the investigator. Wound care followed standard procedures.

After treatment, recipient sites were monitored for 4 weeks in weekly follow-up visits, during which time, wounds in 5 subjects (50%) achieved complete re-epithelialization (PAR of 100%) during the study. One subject had partial closure (PAR of 2.5%) of the wound. Two subjects experienced a slight increase (PAR of -14% and PAR of -0.27%) in their wound size. Two patients were lost to follow up. Utilizing intention-to-treat analysis, there was a mean 49% reduction in wound area from baseline to week 4.

On the basis of PAR, which measures the percent area reduction of the wound via re-epithelialization by cells proliferating from the seeded micrografts, the results of the above small-scale human studies demonstrate safety, feasibility, and healing outcomes that it is an indirect measure of wound healing. The graft take rates for the SOC (STSG) alternative treatment is a measure of complete coverage of the wound at the first dressing change following surgery. This measurement is subject to change upon evaluation at subsequent dressing changes. Even though these two are not directly related, the study authors used re-epithelialization scoring as a scale to compare PAR and graft take. No donor site morbidity was observed, and a substantial number of subjects achieved a reduction in wound size following the procedure. It is also noted that the procedure takes less time than traditional STSG and can be performed under local anesthesia in a clinic setting. Subjects reported minimal pain during and after tissue harvest.

LABELING

The Medline ART Skin Harvesting System needle cartridge sterile package consists of a formed PETG tray and cover, with a (b)(4) lid heat-sealed onto the tray. The handheld protective sleeve sterile package is a (b)(4) pouch. Four sealed ART needle cartridge trays and four sealed ART sleeve pouches are packaged in a labeled clay-coated newsback display box.

The Medline ART Skin Harvesting System labeling meets the labeling requirements of 21 CFR 801.109 for a prescription device. It contains the indications for use, prescription only symbol,

device description, contraindications, general warnings and precautions, summary of clinical data, instructions for use including disposal instructions, potential adverse events, storage conditions, and symbols and markings. Furthermore, the packaging includes a shelf life for the device.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with the use of a semi-automated autologous skin graft harvesting and application device.

Risks to Health	**Mitigation Measures**
Delay in healing	*In vivo* performance testing
Device malfunction resulting in injury	Performance testing Software verification, validation, and hazard analysis Electrical safety testing
Failure of the user to select an adequate donor site resulting in increased donor site morbidity	Labeling
Infection	Sterilization validation Reprocessing validation Shelf life testing Labeling
Adverse tissue reaction	Biocompatibility evaluation
Interference with other medical devices resulting in malfunction of either device	Electromagnetic compatibility testing Electrical safety testing Software verification, validation, and hazard analysis Wireless coexistence testing Labeling
User error resulting in injury	Human factors evaluation Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the semi-automated autologous skin graft harvesting and application device is subject to the following special controls:

(1) *In vivo* performance testing must demonstrate that the device performs as intended under anticipated conditions of use in a clinically relevant wound model, including evaluation of normal wound healing.

(2) Performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Ability of the device to extract target tissue to the intended depth;
   (ii) Ability of the device to extract target tissue without damage to underlying structures; and
   (iii) Ability of the device to deposit extracted tissue at the recipient site.

(3) The patient-contacting components of the device must be demonstrated to be biocompatible.

(4) Software validation, verification, and hazard analysis must be performed for any software components of the device.

(5) Performance data must support the electrical safety, electromagnetic compatibility (EMC), and wireless coexistence of the device.

(6) Performance data must validate the reprocessing instructions for the reusable components of the device.

(7) Performance data must demonstrate the sterility of the patient-contacting components of the device.

(8) Performance data must support the shelf life of sterile device components by demonstrating package integrity and device functionality over the identified shelf life.

(9) Human factors/usability evaluation must be performed to confirm that the user can correctly use the device based solely on the device labeling.

(10) Labeling must include:
   (i) Instructions on preparation of donor sites and treatment of recipient sites prior to and following use of the device;
   (ii) Validated reprocessing instructions for any reusable device components; and
   (iii) A shelf life.

BENEFIT RISK DETERMINATION

DISCUSSION OF BENEFIT

The Medline ART Skin Harvesting System is intended for the harvesting and application of autologous, full thickness skin micrografts for wounds where autologous skin grafting would be appropriate, excluding full-thickness burns. One of the benefits of this device is that it increases the accessibility of skin grafting to more patients allowing a wider variety of healthcare providers the ability to perform the procedure outside of wound care and burn center facilities. Other benefits that were demonstrated in the animal study include faster donor site healing and less donor site inflammation than the split-thickness skin graft (STSG) donor site. At Day 7, 73% of ART donor sites had re-epithelialization scores of 4 or 5 while 33% of STSG donor sites received a similar re-epithelialization score of 4 or 5. There were no remarkable gross differences observed between ART donor sites and STSG donor sites beyond Day 14. Also, when compared to no grafting of the recipient site, the ART skin graft healed the animal wound at day 35 while the no graft site was only 58% re-epithelialized at the same timepoint. The STSG healed the wound at a faster rate than the ART skin graft with 92% of the STSG sites scoring 5 for re-epithelialization at Day 28 and 67% of the ART sites scoring 5 for re-epithelialization. However, both ART skin graft and the STSG wounds were 100% re-epithelialized at day 35 showing no delay in healing when compared to the standard of care at that time point.

DISCUSSION OF RISK

The device was tested in optimal conditions using cadaver leg skin as well as a healthy pig model. Even under these conditions, the study participants sometimes had difficulty following the precise instructions and applying the proper amount of pressure necessary to deploy the needles, resulting in the collection of fewer than the minimum target of 50% of the 316 total micrografts that can be collected per harvest cycle. In the real-world, where the environment is less than optimal (i.e., poor lighting or poorly trained assistant), with patients with co-morbidities, or the patient is moving, operating the device may be more difficult. These real-world scenarios make it more likely for device harvest failures which puts the patient at risk for increased morbidity at the donor site due to the need to acquire additional donor tissue or partial treatments of the wound due to an application of fewer micrografts than would be optimal to ensure vigorous healing. If the practitioner is unable to harvest the graft successfully, then the device will not be able to accomplish the proposed Indications for Use due to an increased risk of delayed healing and/or infection. These risks are mitigated by the human factors study, the User Manual, and the ART™ Training Template (Training for users prior to using the ART™ system and performing any procedures).

There is a risk that we do not completely understand how wounds heal in different patient populations, with co-morbidities, and in different Fitzpatrick skin types. There are risks of delayed or non-healing, hyper- and hypo-pigmentation, as well as hypertrophic and keloid scar formation. Although the device has been evaluated in a limited number of clinical studies to treat chronic wounds on diabetic patients, patients undergoing cancer treatment, and otherwise healthy patients, large-scale prospective clinical trials have not been conducted on the subject device.

Therefore, there is uncertainty in clinical use, and we do not fully understand how this device performs in patients with co-morbidities, different Fitzpatrick skin types, patients susceptible to hypertrophic and keloid scarring, and hypo and hyperpigmentation. Additionally, there is uncertainty in how the device collected full thickness micrografts would perform in the general population, which may also include patients suffering from other conditions such as: connective tissue disorders, nutritional deficiencies, and other systemic disorders. However, successful wound management is dependent on patient optimization based on their unique conditions and co-morbidities, effective site selection, preparation, grafting application, and wound care follow-up. These risks are addressed by the labeling and human factors evaluation. While there was no observed infection in the clinical studies for the device, there is a risk with any skin grafting procedure of infection. The risk of infection is mitigated by validation of the sterilization of the device, validation of the reprocessing procedure for the device, as well as evaluation and confirmation of the shelf life of the device. Further, the User Manual mitigates the risk of infection by providing the user with instructions on how to safely use and reprocess the device.

There is the risk that the microarray is not complete or is insufficient to adequately cover the graft area. Published data acquired from wound centers demonstrated subject device use with wounds reported as having a median area of 1.50-2.88 cm^2 undergoing treatment. This risk is mitigated by in vivo performance testing of the subject device. Preclinical studies on healthy pigs assessed the performance of the device on wounds measuring 4.0 cm in diameter and 12.56 cm^2 area, demonstrating the effectiveness of the device on wounds measuring more than 4 times the median

wound size seen in literature. Furthermore, using the ART Skin Harvesting device, graft tissue is acquired from only 10% of the total donor site area. Therefore, while the possibility that wounds larger than the median-sized may be encountered, additional harvest cycles can be performed to acquire the necessary graft tissue. Additionally, the risk of insufficient microarray collection is also mitigated by human factors evaluation and performance testing to ensure that the device usability is adequate and that the device can adequately harvest and deploy the micrografts. Moreover, the device is limited to use by a licensed healthcare professional, which mitigates this risk by ensuring that sound clinical judgement on the quantity of tissue needed for grafting. Labeling instructions also mitigate this risk, by informing the user of how to safely use the device.

Lastly, there is the risk of interference with other Active Implanted Medical Devices in proximity of the Medline ART Skin Harvesting System. The patient's pacemaker or defibrillator could fail during the procedure and the patient could suffer a major complication such as a stroke, myocardial infarction, or death. These are serious adverse events that have been adequately mitigated through performance testing and labeling.

DISCUSSION OF BENEFIT-RISK

The benefit of this device is automation, accessibility, reproducibility, and use outside of specialty centers for skin harvesting with dispersal of the skin graft into a prepared wound bed. This would ordinarily require technical training with specialized operative equipment to perform this advanced surgical procedure. Although there have not been any randomized, controlled clinical studies performed with this device to demonstrate that the device is equivalent or superior to a standard of care (e.g., split-thickness skin grafting), the available data from the limited human clinical studies demonstrated that use of the device can lead to healing of chronic wounds that have been adequately prepared for grafting. These clinical data are further supported by testing performed on healthy pigs. Together, the clinical and animal performance data have demonstrated equivalent healing, to complete re-epithelialization of wounds undergoing treatment with the ART Skin Harvesting Device compared with wounds treated with split-thickness skin grafts or wounds receiving a sham treatment (e.g., in healthy pigs, full thickness wounds treated with either the subject device or STSG were completely healed in 35 days, as compared to only 58% and 75% of sham-treated wounds at 35 and 42 days, respectively). Additional benefits of the subject device are that it is less technically demanding than the currently available standard(s) of care and is more widely available to a larger pool of healthcare providers; access to this device benefits a larger number of patients with various wound types.

A risk of this device comes from the complexity of the device. There are a several steps required to accomplish the final task of completing the skin graft. If the environment is less than optimal, there is the risk that adverse events, such as incomplete harvest because of failure to adequately stretch the skin of the donor site, deploy the needles, or firmly apply the device to the patient without proper assistance may take place. Many of the adverse events may be dependent upon experience with the device. Therefore, the risks are mitigated through proper training and user experience, instructions for use, and labeling of the device.

The risk of interference with other Active Implantable Medical Devices (e.g., pacemakers, defibrillators, etc.), has been mitigated by electrical safety, electromagnetic compatibility (EMC), and wireless coexistence testing on the subject device to demonstrate its safety and that it will not

cause a malfunction of other Active Implantable Medical Devices due to electromagnetic interference. A device specific user training program has been established by the sponsor to ensure that all users are trained on the proper use of the device. This training program will include clear instruction to not use the device on patients having the noted Active Implantable Medical Devices.
Two risks were identified that could result in injury to the patient: user error and device malfunction. The risk of user error has been mitigated by human factors/usability evaluation to confirm that users are able to use the device in a safe and effective manner following device-specific training with instructions in the proposed labeling. The risk of device malfunction has been mitigated through bench performance testing under the anticipated conditions of use. Under these conditions, the subject device was shown to be capable of harvesting full thickness skin grafts without damage to underlying physiological structures and depositing the extracted tissue at the target recipient site as intended by the user.

The risk of a delay in healing has been mitigated by in vivo performance testing in a full thickness pig wound healing study where wound healing was characterized using the subject device and demonstrate that wounds healed with less erythema, contraction, and inflammation and faster compared to nongrafted sites and had fewer adverse events than comparable sites treated with STSG.

Assessing the performance of split-thickness grafting is not a straightforward process. There are many factors that affect the take of a split-thickness skin graft. Most importantly is the thickness of the split-thickness graft which can vary from thin (0.15 - 0.3mm), to intermediate (0.3 - 0.45mm), to thick (0.45 -0.6mm). The thicker the donor graft, the higher the risk of the graft not re-vascularizing and graft non-take. Also, graft take is highly dependent upon the recipient wound bed. Variables such as whether the wound is acute or chronic factors into graft take as well as the health of the wound (i.e., hypertrophic granulation tissue, poor vascularity, bioburden, or patient-related comorbidities such as malnutrition and anemia). Finally, while STSG is the SOC that is being used to evaluate the healing performance observed in wounds treated with the subject device, the metric of that performance between the two is defined differently. In the case of split-thickness skin grafting, wound healing is defined on the basis of "graft take". The process of "graft take" involves three steps which include imbibition, inosculation, and finally, revascularization. If all three steps do not occur, the graft will not survive. This is contrast to the micrograft "take". As the micrografts are seeded on the wound bed, the individual cells divide and spread to coalesce into a sheet to cover the wound bed. Therefore, for the subject device, wound healing is defined on the basis of the percentage of wound area reduction (PAR) resulting from the proliferation of newly seeded skin cells in the applied micrografts. While these performance metrics are fundamentally different measurements, both grafting processes determine ultimate success based on 100% re-epithelialization of the wound. Therefore, in this measure, the two methods are comparable via the Re-epithelialization Scoring scale described by the study author. As such, the animal studies showed that both the ART grafted wounds and the split-thickness skin grafted wounds were 100% re-epithelialized at 35 days.

Some clinical scenarios and conditions are difficult to evaluate in animal studies such as determining the relative risks and benefits in patients with co-morbidities including diabetes, hypertension, hyperlipidemia, connective tissue disorders, abnormal scarring (hypertrophic or

keloid scarring), and pigmentary abnormalities may require human testing. There is uncertainty with both the risks and benefits of device use in the general diverse patient population. The device has not been tested in the real-world setting on patients with varying co-morbidities and conditions, FSTs, predilection for hyper- or hypopigmentation and abnormal scarring.

The risk of infection has been mitigated with a declared shelf life and clear language in the labeling instructing users how reusable components of the subject device are to be reprocessed following use. The shelf life and reprocessing instructions are supported by validation studies to demonstrate that the established sterilization methods and reprocessing instructions can ensure that all patient-contacting components of the device are sterile, that the reusable components of the device are able to be cleaned and disinfected effectively for the anticipated lifetime of use of the subject device. Additionally, shelf-life testing performed on the subject device support the integrity of the packaging and functionality of the device over its claimed shelf life.

The risk of adverse tissue reaction has been mitigated with testing to ensure that all patient-contacting components of the device are demonstrated to be biocompatible.

In summary the benefits of providing another treatment option to health care providers, increased accessibility, a new tool available to additional providers, and demonstrated wound healing of both the donor and recipient sites outweighs the risks observed for this device.

Patient Perspectives
This submission does not include specific information on patient perspectives for this device.

Benefit-Risk Conclusion
In conclusion, given the available information above, for the following indication statement:

> The ART® (Autologous Regeneration of Tissue) Skin Harvesting System is intended for the harvesting and application of autologous, full-thickness skin micrografts for wounds where autologous skin grafting would be appropriate.

The probable benefits outweigh the probable risks for the Medline ART Skin Harvesting System. The device provides benefits, and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Medline ART Skin Harvesting System is granted and the device is classified as follows:

> Product Code: QYK
> Device Type: Semi-automated autologous skin graft harvesting and application device
> Regulation Number: 21 CFR 878.4425
> Class: II