SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Interactive Wound and Burn Dressing

Device Trade Name: Orcel™ (Bilayered Cellular Matrix)

Applicant's Name and Address: Ortec International, Inc.
3960 Broadway, 2nd Flr.
New York City, NY 10032

Premarket Approval (PMA) Application Number: P010016

Date of Panel Recommendation: July 17, 2001

Date of Notice of Approval of Application: August 31, 2001

II. INDICATIONS FOR USE

OrCel™ is indicated for the treatment of fresh, clean split thickness donor site wounds in burn patients.

III. DEVICE DESCRIPTION

OrCel™ is a bilayered cellular matrix in which normal human allogeneic skin cells (epidermal keratinocytes and dermal fibroblasts) are cultured in two separate layers into a Type I bovine collagen sponge. Donor dermal fibroblasts are cultured on and within the porous sponge side of the collagen matrix while keratinocytes, from the same donor, are cultured on the coated, non-porous side of the collagen matrix. OrCel™ serves as an absorbable biocompatible matrix that provides a favorable environment for host cell migration and has been shown to contain the following cell-expressed cytokines and growth factors: FGF-1 (bFGF), NGF, GM-CSF, IL-1α, IL-1β, IL-6, HGF, KGF-1 (FGF-7), M-CSF, PDGF-AB, TGF-α, TGF-β1, TGF-β2, and VEGF. OrCel™ is not intended to be a human skin replacement and does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles. DNA analysis performed on two OrCel™ -treated donor site patient tissue samples showed no trace of allogeneic cell DNA after two or three weeks respectively.

OrCel™ is manufactured under aseptic conditions from human neonatal foreskin tissue. The donor's mother is tested and found to be negative for syphilis and for human viruses,

including CMV, HSV I & II, HTLV I & II, Hepatitis B&C, HIV 1&2, EBV and HHV-6. The donor's fibroblast and keratinocyte cells are tested and found to be negative for viruses and retroviruses (including HTLV I&II, Hepatitis B, HIV 1&2, EBV, and HHV-6), bacteria, fungi, yeast, mycoplasma, and tumorigenicity. The donor cells are tested and are found to be normal human cells using karyology, isoenzyme, growth and morphological analyses. Prior to cell seeding, the matrix is cross-linked and then coated on one side with a thin gel layer prepared from acid-soluble collagen. The final product is tested for morphology, cell density, cell viability, sterility, mycoplasma, and physical container integrity. All animal derived reagents are tested for: viruses, bacteria, fungi, yeast, and mycoplasma before use, and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE).

The device measures approximately 6 cm x 6 cm (minimally 36 cm^2). A non-adherent mesh is placed on both aspects of the device to protect the cells. The device is packaged in a plastic tray with protein-free packaging medium containing DMEM, water for irrigation, sodium bicarbonate, folic acid solution, HEPES buffer, L-Glutamine, MEM non-essential amino acids, and sodium hydroxide to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterility barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-18° C (for up to 72 hr.).

IV. CONTRAINDICATIONS

- OrCel™ is contraindicated for use on clinically infected wounds.
- OrCel™ is contraindicated in patients with known allergies to bovine collagen.

The warnings and precautions can be found in the OrCel™ labeling, which is available on the FDA web site at *http://www.fda.gov/cdrh/pdf/p010016.pdf*.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Split thickness skin grafting is a frequently used technique in the management of serious burns. Once it has been determined that a burn patient will require split thickness autografting, a donor site is selected. Donor sites are areas of healthy, non-injured skin, which are harvested for autograft use, thereby leaving an open wound requiring coverage. There are many dressing options for donor sites in the postoperative period. The type of dressing selected depends on the size of the donor site created, the anatomic location on the body surface, and the proximity to other wounds. Treatments include dry, fine-meshed gauze or impregnated fine-meshed gauze (e.g., with scarlet red), hydrocolloid dressings, and biologic and synthetic wound dressings.

VI. ADVERSE EFFECTS

In two within-patient studies comparing OrCel™ with a control semi-permeable biological wound dressing, a total of 90 patients were evaluated for safety after treatment of split thickness donor sites in burn patients. Table 1 lists all reported adverse events related to the treated donor sites. Table 2 lists all systemic adverse events with a frequency greater than two events. Because all patients received both OrCel™ and control treatments, attributing causality for systemic adverse events to a specific treatment was not feasible

Table 1: Adverse Events Related to the Treated Donor Sites

Adverse Events	Donor Site	
	OrCel™	Control
Pain	6 (6.7%)	6 (6.7%)
Pruritus	4 (4.4%)	5 (5.6%)
Itching	2 (2.2%)	2 (2.2%)
Infection	1 (1.1%)	2 (2.2%)
Rash Pustular	1 (1.1%)	----
Tenderness to palpation	1 (1.1%)	----
Blisters	----	1 (1.1%)
Bullous Eruption	----	1 (1.1%)
Conversion to full thickness wound	----	1 (1.1%)
Excision & regrafting of donor site	----	1 (1.1%)

Table 2: Systemic Adverse Events With a Frequency >2 Occurrences

Adverse Events	Frequency
Constipation	19 (21.1%)
Anaemia	13 (14.4%)
Insomnia	12 (13.3%)
Fever	11 (12.2%)
Vomiting	10 (11.1%)
Infection	9 (10.0%)
Nausea	9 (10.0%)
Pharyngitis	8 (8.9%)
Pruritis	8 (8.9%)
Hyperglycaemia	7 (7.7%)
Agitation	6 (6.7%)
Sepsis	6 (6.7%)
Anxiety	5 (5.6%)
Atelectasis	5 (5.6%)
Hypernatraemia	5 (5.6%)
Relaxation Of Scar	5 (5.6%)
Thrombocythaemia	5 (5.6%)
Diarrhea	4 (4.4%)
Dyspnea	4 (4.4%)
Dyspepsia	4 (4.4%)
Rehabilitation NEC	4 (4.4%)
Thrombocytopenia	4 (4.4%)
Death	4 (4.4%)
Depression	3 (3.3%)
Hypokalaemia	3 (3.3%)
Hypotension	3 (3.3%)
Urinary Tract Infection	3 (3.3%)
Edema	3 (3.3%)
Other Local Destruc Skin	3 (3.3%)
Pulmonary Infiltration	3 (3.3%)
Scar	3 (3.3%)
Skin Malformation	3 (3.3%)
Pneumothorax	3 (3.3%)

A total of four patients died, three during the pivotal study and one during the pilot study. Two patients had Adult Respiratory Distress Syndrome (ARDS). Both patients had predisposing respiratory conditions in their medical conditions prior to study start. The third patient had bacterial sepsis secondary to burn injuries resulting in death. The fourth patient had septic shock and multi-system organ failure secondary to burn injuries resulting in death.

VII. MARKETING HISTORY

OrCel™ has been approved under a Humanitarian Device Exemption for use in patients with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the release of hand contractions (i.e., "mitten" hand deformities).

OrCel™ is not marketed nor has it been withdrawn from marketing in any other country.

VIII. SUMMARY OF NONCLINICAL LABORATORY STUDIES

An overview of the nonclinical studies conducted on OrCel™ and the acellular collagen sponge is presented below.

In an *in vitro* assay, OrCel™ stimulated the release of cytokines into culture media. *In vivo* wound closure was examined in male severe combined immuno-deficient (SCID) mice and female athymic nude mice. For male SCID mice, OrCel™ produced approximately 60% wound contracture and complete epithelialization in eight of twelve animals. In a range-finding study using OrCel™ with different cell densities, a trend toward greater wound closure was observed in nude mice treated with medium and high cell density OrCel™ than with acellular or low cell density OrCel™.

The collagen sponge coated with collagen gel was shown to be biocompatible in *in vitro* cytotoxicity and *in vivo* tests under the conditions of the studies. There was no evidence of cytotoxicity when extracted material from the coated collagen sponges was incubated with mouse connective tissue NCTC 929 cells (elution and agar diffusion assays). An extract of the coated collagen sponge was not a hemolytic agent when tested in rabbit red blood cells. In guinea pigs, undiluted extracted material from the coated collagen sponge did not produce sensitization. Intracutaneous and acute systemic toxicity studies performed in rabbits and mice, respectively, resulted in comparable responses between extracts of the collagen sponge coated with collagen gel and control materials. Similarly, intramuscular implantation of the coated sponge into rabbits with observations up to 90 days post-implantation resulted in no significant differences between the control material and coated sponge. Both produced negative to mild reactivity, but the collagen sponge coated with collagen gel was more rapidly resorbed. The coated sponge was not mutagenic, and an extract of the coated collagen sponge did not produce a pyrogenic response in rabbits.

A full thickness skin wound study was conducted in swine comparing the wound closure rates for the collagen sponge and control material. Skin wounds made in swine revealed similar rates of wound closure for collagen sponges and the control material; complete resorption of the sponge was reported by day 30.

Data collected in murine models of full-thickness wound closure revealed 60% wound contracture and complete epithelialization in 67% of male SCID mice at 14 days post-

treatment with OrCel™, and a trend toward greater wound closure with higher cell densities of OrCel™ in female nude mice. In an *in vitro* assay, several of the cytokine expression levels measured in OrCel™, such as GM-CSF and VEGF, lead to accumulated concentrations in OrCel™ culture medium in the nanogram per milliliter level, which is significant.

With respect to biocompatibility, i*n vitro* assays confirmed a lack of cytotoxicity and hemolysis. And, extracted material from the coated sponge did not produce sensitization, mutagenicity, pyrogenicity, or adverse intracutaneous, acute systemic, or sustained intramuscular effects. In a swine model, comparable resorption and wound closure were observed between control materials and the collagen sponge.

IX. SUMMARY OF OF THE CLINICAL INVESTIGATIONS

A pilot and pivotal study were conducted on donor sites in patients requiring split thickness skin autografting for the management of burn injuries. Both studies were prospective, evaluator-masked, randomized and controlled. They were matched-pair design (i.e., each patient had two designated donor sites of equivalent surface area) and donor sites were randomized allowing each patient to receive a single application of OrCel™ and a control semi-permeable biological wound dressing.

PILOT STUDY

STUDY DESIGN

The pilot study was a single center, within patient control trial. The objective was to examine preliminary safety data and evaluate performance of OrCel™ in management of split thickness donor sites in burn patients. Patients in this study were 10 years of age and older and had burns involving at least 10% but not greater than 60% of total body surface area. The total donor surface area comprised a minimum of 72 cm^2 and a maximum of 144 cm^2. Patients were followed through post-treatment Day 28.

PRIMARY ENDPOINT

The primary outcome measure was the time (days) to wound closure (100% re-epithelialization). Re-epithelialization was defined as the visible presence of a dry, opalescent-pink external surface representing the newly formed outer cornified layer of the epidermis, which, in the Investigator's assessment, no longer required a dressing or protective covering. Wound closure was evaluated using computerized planimetric analysis and validated through photographic review. Photographs were assessed by three blinded independent burn experts to determine if clinical re-epithelialization was present.

Safety was assessed by recording adverse events, donor site pain and itching assessments, and the incidence of infection, wound cultures, and laboratory measurements.

DISPOSITION OF PATIENTS/DEMOGRAPHY

A total of eight subjects were enrolled into a single center. Seven patients completed the study and one patient had a serious adverse event, which resulted in death that was judged by the Investigator to be unlikely related to study treatments.

Five (62.5%) patients were African American, and three (37.5%) were Caucasian. Mean age of the patients was 41.3 years (range 10 to 84 years); mean height was 66.8 inches (range 51 to 72 inches); and mean weight was 145.1 pounds (range of 83 to 221 pounds).

ANALYSIS AND RESULTS

Efficacy Results

The Kaplan-Meier estimates of the percent of 100% wound closure patients from computerized planimetric analysis and from the Investigator's assessment showed a statistically significant difference in 100% wound closure time between OrCel™ and the control treatment (p=0.034), with shorter 100% wound closure times observed with OrCel™. At least 50% of the patients had 100% wound closure by both planimetric analysis and Investigator's assessment by Day 12 with OrCel™, while 50% of the patients had 100% wound closure by Day 25 with the control treatment.

Safety Results

All eight patients had at least one adverse event. One patient died and 12 serious adverse events were reported. The most frequent adverse events were fever (3 patients, 37.5%) and constipation (3 patients, 37.5%).

PIVOTAL STUDY

STUDY DESIGN

The pivotal study was a multi-center study evaluating the safety and effectiveness of OrCel™ in the treatment of split thickness donor sites burn patients. The main criteria for inclusion in the pivotal study were:

- patients 1 year of age and older
- the presence of burns involving at least 10% but not greater than 80% of total body surface area including burns of thermal (flame, scald and contact), chemical and friction etiology
- donor sites treated had to be virgin areas and could be located on anterior or posterior non-articulated surface areas
- total (investigational treatment and control) donor surface could be between 72 cm^2 to 360 cm^2 in patients greater than 3 years of age and 36 cm^2 to 180 cm^2 in patients less than 3 years of age

The main criteria for exclusion were:

- patients with sepsis with hemodynamic instability requiring pressor support or a microbiology report of positive blood cultures drawn within 48 hours prior to surgery
- severe inhalation injury requiring PEEP > 20 and Fi02 > 60% within 12 hours prior to surgery
- trauma score
- treatment with systemic corticosteroids during the 30 days prior to injury
- immunosuppressive, radiation or chemotherapy during the three months prior to injury
- history of allergy or sensitivity to collagen material
- history of insulin-dependent diabetes accompanied by glycosylated hemoglobin A1C > 10%.

Split thickness donor sites were to be selected according to the Investigator's routine surgical practice, guided by donor site availability with an attempt to identify to similar donor sites on each patient. Discrete, contiguous, non-articulated sites were used. Split thickness autografts were harvested between 0.006-0.014 inch depth.

A total of 82 patients were enrolled at 12 study sites. All 82 patients were included in the intent-to-treat (ITT) and safety populations. The per-protocol (PP) population consisted of 74 patients (90.2%) and excluded the 8 patients in the ITT population with major protocol violations. Sixty patients (73%) completed the study and 22 patients (27%) discontinued study before the week 24 visit. Table 3 below provides a patient accounting for the study.

Table 3: Patient Accounting

Prospective sample size: ITT	100
Prospective sample size: Evaluable	85
Patients Enrolled: ITT	82
Completed Study: Evaluable	60
Number of OrCel™ Sites Re-cropped	3
Major Protocol Violations	8
Discontinued Patients	22
• Adverse event	3
• Protocol violation	0
• Withdrew consent	0
• Lost to Follow-up	16
• Other	3
# Patients in Effectiveness Population: PP	74
# Patients in Safety Population	82

TREATMENT PROTOCOL

In patients under three years of age, up to 2 OrCel™ devices were applied and, in patients over three years of age, up to 4 OrCel™ devices were applied. Patients were treated with a one-time application of the OrCel™. OrCel™ was applied to the donor site, secured with staples according to the investigator's discretion, and covered with a non-adherent, moisture retentive synthetic material, gauze wrap and Ace conforming bandage. The outer dressing was removed every 48 to 72 hours, and backing irrigated with saline until post-operative day 7 when backing removal was attempted. Patient evaluations were performed at screening, day 0 (pre and post harvest), 3, 7, 14, 21, 28, and week 12 and week 24.

STUDY ENDPOINTS

The primary effectiveness endpoint was time to 100% wound closure (complete re-epithelialization) as determined by photography. One hundred percent wound closure was defined as the visible presence of a dry, opalescent-pink external surface representing the newly formed outer cornified layer of the epidermis, which, in the Investigator's assessment, no longer required a dressing or protective covering.

The secondary effectiveness endpoints were:

- time to complete wound closure as determined by computerized planimetric assessment of unhealed wounds
- time to complete wound closure as determined by investigator through clinical assessment
- the rate of wound closure as determined by the percent change in wound area from baseline as determined by planimetric data
- time to readiness for recropping as assessed by the investigator
- time to actual recropping of an original donor site

Safety variables that were compared between the two treatments were: incidence of donor site specific adverse events, scar outcome, pain and itching scores, and incidence of donor site infection and breakdown, time to actual recropping, and recrop outcome.

ANALYSIS AND RESULTS

The days to healing data was censored at day 32 post surgery.

Effectiveness Results

Days to 100% Wound Closure

Time to 100% wound closure is presented in Table 4 for the ITT (N=82) and PP (N=74) populations and the three methods of assessment.

Table 4: Median and Mean Days to 100% Wound Closure

	Median Days to Wound Closure*			Mean (SD) Days to Wound Closure		
	OrCel™	Control	p-value**	OrCel™	Control	p-value+
Photographic ITT	15.0	22.0	0.0006	18.0	22.4	<0.0001
Photographic PP	15.0	21.0	0.0009	17.8	22.1	<0.0001
Planimetric ITT	12.0	17.0	<0.0001	13.7	19.3	<0.0001
Planimetric PP	12.0	16.0	<0.0001	13.4	18.7	<0.0001
Investigator ITT	12.0	16.0	<0.0001	13.2	18.4	<0.0001
Investigator PP	12.0	16.0	<0.0001	12.9	17.9	<0.0001

* Kaplan-Meier estimates of the median days to 100% wound closure +Paired t-test

**Log-Rank test of the difference between median wound closure times

For the ITT population, the median days to 100% wound closure using photographic assessment for OrCel™ was seven days faster than the control (15 days vs. 22 days,

respectively; p=0.0006). For the ITT population, the mean days to 100% wound closure using photographic assessment for OrCel™ was four days faster than the control (18 days vs. 22 days, respectively; p<0.0001).

The mean and median times to 100% wound closure by photographic, planimetric, and investigator assessments were all significantly shorter (p<0.0006) for OrCel™ treated sites compared to the control dressing.

Results of ITT planimetric assessments support those obtained by photography, i.e., median and mean days to 100% wound closure for OrCel™ were 12 to 14 days, respectively, while those of the control treated sites were 17 and 19 days, respectively. These differences reflect a five-day shorter time to 100% wound closure with OrCel™ (p=<0.0001). Table 5 provides the median and mean days to 100% closure by planimetry in the ITT population, by investigational center..

Table 5**:** Median and Mean Days to 100% Closure by Planimetry, by Center**, ITT

Center	n	Median		Mean	
		OrCel™	Control	OrCel™	Control
1*	19	14.0	26.0	14.2	23.7
2	1	10.0	14.0	10.0	14.0
3*	9	14.0	28.0	15.3	25.6
4	16	11.0	11.5	11.3	12.8
5	3	9.0	11.0	16.0	17.3
7	7	12.0	15.0	11.3	18.4
8*	9	11.0	14.0	13.2	18.2
12	2	-	-	23.5	23.5
13	3	20.0	20.0	19.7	22.0
14	3	16.0	16.0	15.7	15.7
15*	10	11.0	16.0	12.9	18.2

*Sites with anabolic steroid use, predominately sites 1 and 15.
**Centers 6, and 9-11 did not enroll any patients.

Results of the ITT investigator assessment also support those obtained by photography, i.e., median and mean days to 100% closure for OrCel™ were 12 and 13 days, respectively, while those of the control treated sites were 16 and 18 days, respectively, reflecting a four to five day shorter time to 100% closure with OrCel™ (p<0.0001).

The Per Protocol (PP) population results obtained closely resemble those of the ITT population with statistically significant differences in time to wound closure for all three-assessment methods.

Incidence of 100% Wound Healing

All donor sites on the 82 patients were 100% closed by week 24. Table 6 displays the incidence of 100% wound closure in the study.

Table 6: Incidence of 100% Wound Healing

		OrCel™	Control
N		82	82
At 6 months:		82	82
At 32 days:	Photography	75	60
	Planimetry	79	71
	Investigator	81	71

Rate of Wound Closure

The rates of wound closure per day, as measured by planimetry, were observed during the 32-day post surgical period. For the ITT poplulation, the mean rate of wound closure for OrCel™ on days 6 through 16 was 61% faster than the control treated sites during the same period (6.1 vs 3.8 cm^2, respectively) and the mean closure time of OrCel™ during day 17-32 was 90% faster than that of the control treated sites (4.0 vs. 2.1 cm^2, respectively).

Time to Readiness for Re-Cropping

The time to readiness for re-cropping was assessed by the investigator. The median time to readiness for re-cropping in the ITT population for the OrCel™ treated site was 7 days less than the median time required for the control treated site; i.e., 14 days for OrCel™ vs. 21 days for control treated sites. Mean times to readiness for re-cropping were 5 days less for OrCel™ (i.e., 16 days for OrCel™ vs. 21 days for control treated sites).

Re-Cropping

Only 3 OrCel™ treated donor sites were recropped. The number of patients was insufficient to evaluate the results of recropping the treated study sites or the re-healing of recropped site.

Scarring Severity

Scarring severity was assessed by two methods. Investigator assessments were conducted at weeks 12 and 24 and at the follow-up visit using the Vancouver Scar Scale. Assessments were also conducted via blinded review of photographs utilizing the Hamilton Burn-Scar Rating Scale.

Table 7 depicts the mean Vancouver Scar Scores and Hamilton Burn-Scar Rating Scale scores for the Safety Population. The Vancouver Scar Scale is measured from a range of 0 to 15; 0 representing no scarring, 15 representing the most severe scarring. The Hamilton Burn-Scar Scale is measured from a range of 0 to 20; 0 representing no scarring, 20 representing the most severe scarring.

Table 7: Scar Outcome as Measured by Vancouver and Hamilton Scar Scales

	Vancouver Scar Scale			Hamilton Scar Scale	
	Week 12	Week 24	Week 52	Week 12	Week 24
OrCel™	2.26	2.56	3.10	3.89	2.96
Control	3.07	3.79	3.95	4.95	3.50

At week 12, mean scarring severity for OrCel™ was 2.26 (n=54) versus 3.07 (n=54) for control. At week 24, mean scarring severity for OrCel™ was 2.56 (n=55) versus 3.79 (n=56) for control. OrCel™ treatment resulted in statistically significant differences in scores at weeks 12 and 24 when compared to the control dressing, as measured by the Vancouver and Hamilton Scar Scales**.**

Signs of Infection and Breakdown

The percentage of OrCel™ donor sites exhibiting signs of infection was 1.2% (1/82) versus 3.7% (3/82) for the control treated sites. The percentage of OrCel™ donor sites exhibiting signs of breakdown or blistering was 5.0% (4/80) compared to 10.1% (8/79)for the control treated sites. No conclusions are drawn from these data due to the small number of patients with these adverse events.

Pain

Pain was assessed with the Wong-Baker Faces pain rating scale for patients more than three years old and visual analog scale with numeric markings for intensity (0 to 10: 0, no pain; 5, moderate pain; 10, worse possible pain). Pain associated with OrCel™ and the control sites were clinically comparable.

Itching

Severity and incidence of donor site itching was 72.2% for OrCel™ vs. 68.8% for control.

Baseline Status and 100% Wound Closure

The impact of baseline characteristic on 100% wound closure was analyzed for different subpopulations and is reported below as Table 8. The impact of a mild anabolic steroid[1] is included in this analysis because it was administered to a segment of the trial population (N=30).

Table 8: Baseline Status and Median Days to 100% Wound Closure

	N	Median Days (Photography)		Median Days (Physician Assessment)	
		OrCel™	Control	OrCel™	Control
Male	63	12.0	16.0	12.0	16.0
Female	19	12.0	19.0	12.0	21.0
<15 years	22	14.0	14.0	12.0	14.0
15-65 years	57	17.0	29.0	13.0	17.0
>65 years	3	14.0	29.0	16.0	29.0
White	44	15.0	20.0	12.0	16.0
Black	20	14.0	21.0	14.0	21.0
Other	18	17.5	22.0	12.0	15.5
TBSA <20%	21	14.0	14.0	11.0	14.0
TBSA 20-40%	47	17.0	29.0	12.0	16.0
TBSA >40%	14	21.0	32.0	16.0	25.0
Donor Area $\leq$ 45cm	20	14.0	21.0	12.0	17.5
Donor Area >45cm	62	17.0	28.0	13.0	16.0
Pts w/ anabolic steroid[1]	30	20.0	32.0	14.0	22.0
Pts w/o anabolic steroid[1]	52	14.0	19.0	12.0	14.5

[1] Indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infection, or severe trauma.

Safety Results

Adverse events are displayed in Section VI for both the pilot study and the pivotal study combined. All eight patients in the pilot study had at least one adverse event. Of the 82 patients enrolled in the study, 64 (78.0%) had at least one adverse event. In the pivotal study, most of the adverse events were mild to moderate in severity, however there were three fatalities not related to treatment of the donor site: sepsis, multiple organ system failure and dyspnea. Serious adverse events without donor site involvement were reported by 23 (28%) of the patients. There were no serious adverse events involving the donor sites. There were 12 mild to moderate adverse events involving the OrCel™ treated donor sites and 13 mild to moderate adverse events involving the control treated donor sites.

Deaths

A total of four patients died three during the pivotal study and one during the pilot study. Two patients had Adult Respiratory Distress Syndrome (ARDS). Both patients had predisposing respiratory conditions in their medical conditions prior to enrollment in the study. The third patient had bacterial sepsis secondary to burn injuries resulting in death. The fourth patient had septic shock and multi-system organ failure secondary to burn injuries resulting in death.

Immune Response

The impact of device application on patients' humoral and cellular immune responses to the allogeneic human cellular components of OrCel™, i.e., keratinocytes and fibroblasts, such as HLA antigens or potential blood group antigens, has not yet been evaluated. In

sera drawn from 90 patients treated in the donor site study, 2 patients exhibited elevations from baseline (8-9 Enzyme Immunoassay (EIA) units), 5 patients exhibited an indeterminate response (5-10 EIA units), and 8 patients exhibited a new positive antibody response (10-78 EIA units) to Type I collagen. Investigations with OrCel™, to date, have not revealed any clinical manifestations of product-related immune reactions. In the literature, studies of pretreatment serology show that approximately 8.4% of patients have pre-existing antibovine collagen antibodies.

X. CONCLUSIONS DRAWN FROM THE STUDIES

These studies provide reasonable assurance of the safety and effectiviness of OrCel™ for the treatment of fresh, clean split thickness donor site wounds in burn patients.

The preclinical safety studies demonstrate that the device is composed of biocompatible components. The animal studies also demonstrate that the collagen sponge component of the device is rapidly resorbed and does not interfere with wound repair.

The mean time to 100% wound closure in a large multicentered clinical evaluation of donor sites was significantly shorter for the OrCel™-treated donor sites than for the control-treated sites. The mean 100% wound closure times reported for the three methods of measurement were: 1) 18 days for OrCel™ compared to 22.4 days for the control by photographic analysis; 2) 13.7 days for OrCel™ compared to 19.3 days for the control by planimetric analysis; and, 3) 13.2 days for OrCel™ compared to 18.4 days for the control according to the investigator's evaluation. Median time to 100% wound closure by Kaplan-Meier estimate was also significantly different favoring OrCel™-treated donor sites.

There were no serious adverse events involving the donor sites in the large multicentered clinical trial. There were 12 mild to moderate adverse events involving the OrCel™ treated donor sites and 13 mild to moderate adverse events involving the control treated donor sites.

Clinical investigations to date have not revealed any significant clinical manifestations of product-related immunological reactions. In sera drawn from 90 patients treated in the donor site study, 2 patients exhibited elevations from baseline (8-9 Enzyme Immunoassay (EIA) units), 5 patients exhibited an indeterminate response (5-10 EIA units), and 8 patients exhibited a new positive antibody response (10-78 EIA units) to Type I collagen. Investigations with OrCel™, to date, have not revealed any clinical manifestations of product-related immune reactions. In the literature, studies of pretreatment serology show that approximately 8.4% of patients have pre-existing antibovine collagen antibodies

The sponsor has not determined the impact of device application on patients' humoral or cellular immune responses to the allogeneic human cellular components of OrCel™, i.e., keratinocytes and fibroblasts.

XI. PANEL RECOMMENDATION

The PMA was reviewed at the General and Plastic Surgery Devices Advisory Panel meeting held on July 17, 2001. The Panel unanimously recommended to the FDA that the application for OrCel™ was approvable on condition that the labeling contained the following:

1. The safety and effectiveness of OrCel™ (Bilayered Cellular Matrix) has not been studied on patients under 12 months of age.
2. The safety and effectiveness of OrCel™ has not been evaluated in split thickness donor sites in burn patients that have TBSA (total body surface area) larger than 288 cm^2.
3. The study exclusion criteria should be included in the labeling.
4. The labeling should include information about the possible effects of an anabolic steroid (indicated as adjunctive therapy to promote weight gain following exensive surgery, chronic infection, or severe trauma) administered to a segment of patients.
5. There should not be any claims about re-cropping or accelerated healing in the labeling.

XII. CDRH DECISION

Inspections of the sponsor's manufacturing facilities and sterilization sites were completed on September 27, 2000 and October 5, 2000, respectively, and were found to be in compliance with the device Good Manufacturing Practice regulations.

After the Panel meeting, FDA worked with the sponsor to finalize product labeling. The labeling was written to address the concerns discussed by the Advisory Panel.

FDA issued an approval order on August 31, 2001.

APPROVAL SPECIFICATIONS

Directions for Use: See product labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, and Adverse Reactions in the labeling.

Post Approval Requirements and Restrictions: See the Approval Order.