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MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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59TH MEETING

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TUESDAY,

JULY 17, 2001

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This transcript has not been edited and FDA makes no representation regarding its accuracy

The Panel met in Salons A and B, Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, at 10:30 a.m., Dr. Susan Galandiuk, Acting Panel Chairperson, presiding.

PRESENT:

SUSAN GALANDIUK, M.D., Acting Panel Chairperson

JOSEPH V. BOYKIN, JR., M.D., Voting Member

DEBERA M. BROWN, Industry Representative

PHYLLIS CHANG, M.D., Voting Member

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PRESENT (Continued):

ROBERT F. DIEGELMANN, Ph.D., Temporary Voting
Member

E. THOMAS GARMAN, D.Ed., Consumer Representative

MARY H. McGRATH, M.D., M.P.H., FACS, Temporary
Voting Member

DAVID KRAUSE, Ph.D., Executive Secretary

C-O-N-T-E-N-T-S

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P-R-O-C-E-E-D-I-N-G-S

(10:31 a.m.)

DR. KRAUSE: Good morning, everyone. We're ready to begin this, the 59th meeting of the General and Plastic Surgery Devices Panel.

My name is David Krause, and I'm the Executive Secretary of this panel, and I'm also a reviewer in the Plastic and Reconstructive Surgery Devices Branch.

I'd like to remind everyone that you are requested to sign in on the attendance sheets, which are available at the tables just outside the doors. Also, you may pick up an agenda, a Panel meeting roster, and information about today's meeting at the table. There also should be copies of the panel questions.

The information also includes how to find out about future meetings, future dates, and using the Advisory Panel phone line, and how to obtain meeting minutes or transcripts.

Before I turn the meeting over to Dr. Galandiuk, I'm required to read two statements into

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1 the record: deputization of temporary voting members'
2 statement and the conflict of interest statement.

3 I'm going to start by reading the conflict
4 of interest statement.

5 The following announcement addresses
6 conflict of interest issues associated with this
7 meeting and is made part of the record to preclude
8 even the appearance of any impropriety. To determine
9 if any conflict existed, the agency reviewed the
10 submitted agenda for this meeting and all financial
11 interests reported by the committee participants.

12 The conflict of interest statutes prohibit
13 special government employees from participating in
14 matters that could affect their or their employer's
15 financial interests. However, the agency has
16 determined that participation of certain members and
17 consultants the need for whose services outweighs the
18 potential conflict of interest involved is in the best
19 interest of the government.

20 Therefore, a waiver has been granted for
21 Dr. David DeMets and Joseph Boykin for their interest
22 in firms that could potentially be affected by the

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1 Panel's recommendations. The waiver allows these
2 individuals to participate fully in today's
3 deliberations.

4 Copies of this waiver may be obtained from
5 the agency's Freedom of Information Office in Room
6 12A-15 of the Parklawn Building.

7 We would also like to note for the record
8 that the agency also took into account consideration
9 of certain matters concerning Dr. DeMets and Boykin.
10 These panelists reported past and/or current financial
11 interests in firms at issue, but in matters not
12 related to today's agenda.

13 The agency has determined, therefore, that
14 they may participate fully in today's deliberations.

15 In the event that the discussions involve
16 any other products or firms not already on the agenda
17 for which an FDA participant has a financial interest,
18 the participant should excuse him or herself from such
19 involvement, and the exclusion will be noted for the
20 record.

21 With respect to all other participants, we
22 ask in the interest of fairness that all persons

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1 making statements or presentations disclose any
2 current or previous financial involvement with any
3 firm whose products they may wish to comment upon.

4 The second statement that I will read into
5 the record is the appointment to temporary voting
6 status.

7 Pursuant to the authority granted under
8 the Medical Devices Advisory Committee charter, dated
9 October 27th, 1990, and as amended August 18th, 1999,
10 I appoint Robert F. Diegelmann and Mary McGrath as
11 voting members of the General and Plastic Surgery
12 Devices Panel for this meeting on July 17th, 2001.

13 In addition, I appoint Susan Galandiuk to
14 act as temporary Chair for the duration of this
15 meeting.

16 For the record, these individuals are
17 special government employees and consultants to this
18 panel or other panels under the Medical Devices
19 Advisory Committee. They have undergone the customary
20 conflict of interest review and have reviewed the
21 material to be considered at this meeting.

22 And the memo is signed by Dr. David

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1 Feigal, Director, Center for Devices and Radiological
2 Health.

3 Before I turn the meeting over to Dr.
4 Galandiuk, this opportunity presents itself to do one
5 of the fun things that we get to do, which is present
6 one of our members with a little plaque in thanks for
7 their service.

8 Dr. Witten.

9 DR. WITTEN: Yes. I'd like to thank Dr.
10 Galandiuk for serving as a Panel member on our General
11 Plastic and Surgery Devices Panel for the past three
12 years. We really rely on our Panel members to
13 contribute their time and expertise to help us in
14 evaluation of new products and other new scientific
15 issues that we need advice on in the course of our
16 regulatory work.

17 And I also want to thank her for serving
18 as Acting Chairman for this meeting.

19 So I have a plaque and also a letter from
20 Dr. Suydam, our Senior Associate Commissioner,
21 expressing her thanks for your service.

22 ACTING CHAIRPERSON GALANDIUK: Thank you

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1 very much.

2 (Applause.)

3 DR. KRAUSE: Okay. At this time, I would
4 like to turn the meeting over to Dr. Galandiuk.

5 ACTING CHAIRPERSON GALANDIUK: Thank you.

6 A very nice way to start a meeting.

7 Good morning. My name is Susan Galandiuk.

8 I'm a colon and rectal surgeon and hold the rank of
9 Professor of Surgery and am a Program Director and
10 head of a section of colorectal surgery at the
11 University of Louisville.

12 Today the Panel will be making -- and I'm
13 Acting Chair for this meeting -- today the Panel will
14 be making recommendations to the Food and Drug
15 Administration on a pre-market approval application.

16 The next item of business is to introduce
17 the Panel members who are giving up their time to help
18 the FDA in these matters and the FDA staff here at
19 this table. I'm going to ask each person to introduce
20 him or herself, stating his or her specialty,
21 position, title, institution, and his or her status on
22 the panel, whether they are a voting member, industry

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1 or consumer representative, or deputized voting
2 member.

3 And I would like to start with Dr. Witten.

4 DR. WITTEN: Celia Witten, Division
5 Director of the Division of General Restorative and
6 Neurological Devices at FDA.

7 DR. DeMETS: I'm David DeMets. I'm a
8 statistician. I'm currently Professor and chair of
9 the Department of Biostatistics and Medical
10 Informatics at the University of Wisconsin in Madison.
11 And I'm a voting member on this Panel.

12 DR. BOYKIN: Dr. Joseph Boykin, a plastic
13 surgeon, currently the Medical Director of the HCA
14 Retreat Wound Healing Center and a Clinical Assistant
15 Professor of Plastic Surgery at the Medical College of
16 Virginia in Richmond, and I am a permanent voting
17 member.

18 DR. CHANG: I'm Phyllis Chang. I'm an
19 Associate Professor at the University of Iowa,
20 Division of Plastic Surgery, Department of Surgery,
21 and the section of hand and microsurgery, Department
22 of Orthopedic Surgery. I am a voting member of the

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1 FDA Panel.

2 DR. DIEGELMANN: I'm Robert Diegelmann.
3 I'm a Professor of Biochemistry and Anatomy at the
4 Medical College of Virginia, Virginia Commonwealth
5 University. My interests are in collagen metabolism
6 and tissue repair, and I'm a deputized voting member
7 for today.

8 DR. KRAUSE: My name is David Krause, and
9 I'm the Executive Secretary of the Panel.

10 DR. McGRATH: My name is Mary McGrath.
11 I'm a plastic surgeon, and I'm the Professor of
12 Surgery and Director of the Division of Plastic
13 Surgery at Loyola University Medical Center in
14 Chicago.

15 DR. GARMAN: I'm Tom Garman, a consumer
16 representative. I'm Professor Emeritus at Virginia
17 Tech. in consumer economics, and I direct research now
18 for the InCharge Institute of America in Orlando,
19 which is nonprofit credit counseling.

20 MS. BROWN: And I'm Debera Brown. I'm a
21 consultant to Fusion Medical Technologies, formerly
22 the Vice President of Regulatory Affairs and Quality

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1 Assurance for Fusion Medical Technologies.

2 ACTING CHAIRPERSON GALANDIUK: Dr. McGrath
3 is a deputized voting member for this panel.

4 MS. BROWN: Oh, and I'm the industry rep.
5 and a nonvoting member.

6 ACTING CHAIRPERSON GALANDIUK: To begin
7 with, we are going to be hearing from Mr. Stephen
8 Rhodes, who will give the Panel an update since the
9 last meeting of May 2000.

10 Mr. Rhodes.

11 MR. RHODES: Good morning, and thank you,
12 Dr. Galandiuk.

13 I am Stephen Rhodes. I'm the Branch Chief
14 of the Plastic and Reconstructive Surgery Devices
15 Branch.

16 The General and Plastic Surgery Panel last
17 met on May 8th, 2000, at which time it recommended
18 approval for Focal, Incorporated's FocalSeal
19 synthetic absorbable sealant for use as an adjunct to
20 standard closure of air leaks during elective
21 pulmonary resection.

22 The agency approved this application on

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1 May 26th, 2000.

2 At the last Panel meeting, the Panel also
3 recommended approval for Organogenesis, Incorporated's
4 Appligraf for use of full thickness, neuropathic,
5 diabetic foot ulcers of greater than three weeks'
6 duration.

7 The agency approved this application on
8 June 20th, 2000.

9 And at a previous Panel in March of 2000,
10 this Panel recommended approval of Mentor
11 Corporation's saline filled and spectrum filled breast
12 implants and McGhan Medical's saline filled breast
13 implants.

14 The agency approved both of these
15 applications on May 10th, 2000.

16 I'd like to make note of two personnel
17 moves since the last panel meeting last May. Jim
18 Dillard has moved to the directorship of the Division
19 of Cardiovascular and Respiratory Devices, and Mark
20 Melkerson is a new Deputy Director here in the
21 Division of General Restorative and Neurological
22 Devices.

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1 And lastly, the next meeting of the
2 General Plastic Surgery Panel is tentatively scheduled
3 for September 24 and 25.

4 And I want to thank you again for your
5 participation in today's meeting.

6 ACTING CHAIRPERSON GALANDIUK: Okay. We
7 will now proceed with the open hearing session of this
8 meeting.

9 All persons addressing the panel should
10 speak clearly into the microphone as the
11 transcriptionist is dependent on this means of
12 providing an accurate record of the meeting.

13 We are requesting that all persons making
14 statements during the open public hearing session
15 disclose whether or not they have financial interests
16 in any medical device company. Before making your
17 presentation to the panel, in addition to stating your
18 name and affiliation, please state the nature of your
19 financial interest, if any.

20 Since we have no formal requests to speak,
21 is there anyone who wishes to address the panel?

22 (No response.)

1 ACTING CHAIRPERSON GALANDIUK: Since there
2 are no requests to speak in the open public hearing,
3 we will now proceed to the open committee discussion.

4 We will now begin the review of the pre-
5 market approval application of OrCel Composite
6 Cultured Skin.

7 I would like to remind public observers at
8 this meeting that while this portion of the meeting is
9 open to public observation, public attendees may not
10 participate except at the specific request of the
11 panel. There will be a further opportunity for the
12 public to comment near the end of the meeting.

13 We are now ready to begin with the
14 sponsor's presentation.

15 DR. PAPASTEPHANOU: Good morning. I am
16 Costa Papastephanou, President of Ortec International.

17 And I would like to start by thanking the
18 FDA and the Panel for allowing us to present our data
19 today.

20 Ortec's mission is to discover, develop,
21 manufacture, and market innovative and superior
22 products for the repair, replacement, and regeneration

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1 of human tissues.

2 The study that we will talk about today is
3 the donor site pivotal, 82 patients in 12 centers.
4 Preceding this study were a number of other studies
5 for a total of 55 patients.

6 We have also engaged in venous stasis
7 ulcer studies and diabetic ulcers. So for a total as
8 of last week of 214 patients.

9 Before going into the presentation, I'd
10 like to give you a quick historical perspective of
11 Ortec and the product we're talking about. In 1971,
12 Dr. Eisenberg in Australia started research into
13 alleviating Epidermolysis Bullosa, which affected his
14 newborn son. Epidermolysis Bullosa, as some of you
15 may know, is a collagen disease. It is quite
16 debilitating.

17 In 1988, he was able to use CCS for the
18 first time on his son. In 1991, the company was
19 incorporated in the United States, and in February of
20 2001, we received an HDE for mitten hand deformity and
21 donor sites in recessive dystrophic Epidermolysis
22 Bullosa.

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1 Today we are seeking for approval for the
2 treatment of split thickness donor site wounds in burn
3 patients. The presentation goals for the next hour
4 will be an overview of the pivotal studies, and we
5 will also try to answer the FDA questions that we
6 received.

7 The agenda is in front of you, but I'll
8 very quickly go over it. We'll go over the product
9 description, followed by clinical needs in the
10 treatment of donor site wounds. We'll then go through
11 the protocol reviews, statistical analysis, talk about
12 clinical benefits of OrCel, and finally have some
13 concluding remarks.

14 At this point, I would like to introduce
15 our Vice President of R&D at Ortec, Dr. Melvin
16 Silberklang.

17 DR. SILBERKLANG: Thank you, Costa.

18 My name is Mel Silberklang. I am Vice
19 President of Research and Development at Ortec, and
20 I'd like to thank FDA and the Panel members for this
21 opportunity to present today.

22 By way of introduction, I am a molecular

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1 and cell biologist by training, and I have 20 years'
2 industrial experience in the pharmaceutical and
3 biotechnology industry and the production of
4 biologicals, vaccines, and cell based products.

5 This is the product we'll be describing
6 today, OrCel. We removed all of the backing so that
7 you can see the product here clearly. It's somewhat
8 translucent, very compliant. It's a thin sheath.

9 OrCel or a composite cultured skin is a
10 preformed bovine collagen sponge matrix. It's gel
11 coated on one side, and in the sponge we culture
12 normal human allogeneic skin cells, dermal fibroblasts
13 in the porous aspect of the sponge, and epidermal
14 keratinocytes on the gel coated, nonporous side of the
15 sponge.

16 OrCel is ready to use. It's delivered in
17 an insulated shipper with a three-day shelf life as
18 packaged. It requires no rinsing or preparation. It
19 adheres to the wound when applied, and it's
20 hemostatic.

21 This is what the package looks like. This
22 cassette arrives in a peelable sterile plastic pouch.

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1 It's delivered ready to use. When the cassette is
2 opened, nonadherent blue mesh is removed from the
3 fibroblast side of the sponge. The white, nonadherent
4 mesh remains with the sponge as it's applied to the
5 wound, and the fibroblast aspect is in direct contact
6 with the wound when it's applied.

7 This cartoon illustrates how we put the
8 product together. We begin with a collagen sponge,
9 which we coat on one side with collagen gel. Collagen
10 gel here is shown as an opaque layer. It's a very
11 thin layer.

12 We then, after this preparation step,
13 which takes several days, we seed with fibroblasts on
14 -- excuse me -- we seed with fibroblasts on the porous
15 aspect of the sponge and with keratinocytes on the
16 nonporous aspect of the sponge.

17 After nine days in culture, the product is
18 ready to ship with the fibroblast having penetrated
19 about one-third of the way into the sponge, and the
20 keratinocytes having stratified on the surface,
21 usually about one and a half layers to two layers
22 deep.

1 The biocompatibility of this collagen
2 matrix was tested through the normal tripartite
3 testing and was negative through all of these standard
4 tests.

5 This is a scanning electron micrograph
6 cross-section of the collagen sponge. Note the wide
7 open pores. You can see that there's a slight
8 asymmetry. The smaller pore side is the preferred
9 side for laminating with collagen gel, and the
10 fibroblasts are seeded on the more open side.

11 It's approximately 150 micron average pore
12 size in this open aspect.

13 We utilize the standard manufacturer
14 controls. We have extensive donor and cell line
15 safety testing. Safety testing of all biologically
16 sourced materials and media, including sterility,
17 mycoplasma, and testing for adventitious agents,
18 including relevant viruses.

19 We use validated processes under quality
20 systems, and we use extensive in-process and final
21 testing.

22 This is a brief summary of the safety

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1 testing of the donor's allogeneic cells. We first
2 test the donor, and since the donor is a neonate, we
3 use a surrogate of the mother, and we do blood tests
4 primarily for viruses as listed here, and then we also
5 test the cells when we make frozen cell banks, and the
6 cells are tested for many of the same viruses,
7 including sterility microplasma, carrier type,
8 tumorigenicity, et cetera. All of these tests are in
9 compliance with FDA guidelines.

10 Now, this is a brief description of the
11 manufacturing process, and it's in two colors because
12 we actually go through two different phases. The
13 first step is that we get neonatal foreskins, which we
14 separate enzymatically into an epidermal and dermal
15 layer, and then create two cell suspensions, which we
16 passage to passage 1 and cryopreserve.

17 So we have cryopreserved keratinocyte cell
18 line and the cryopreserved fibroblast cell line.
19 These are then further expanded to passage 3, and
20 passage 3 cells are the ones that are tested
21 extensively as I showed on the previous slide.

22 After the cells pass all of those tests

1 and after a six-month follow-up test on the mother,
2 blood tests, those cells are released for use in
3 production.

4 The actual production process is shown
5 here. Collagen sponges are first prepared by
6 lamination with collagen gel. This takes several
7 days. When the sponges are ready, they are inoculated
8 sequentially with the two cell types, fibroblast and
9 then keratinocytes, and then cultured for at least
10 nine days, and then we can ship the product anytime
11 between nine and 14 days of culture.

12 The final product is composite cultured
13 skin.

14 These are the release tests that are used
15 that were detailed in the PMA submission. We do an
16 extensive visual inspection for appearance. We check
17 dimensions. We recover the cells and check cell
18 density and viability. We look at fibroblast
19 morphology and keratinocyte morphology by carrying an
20 in-process test flask made from the same cells used to
21 see the product.

22 We check for pyrogenicity, sterility, and

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1 we check for histology.

2 In addition to the release testing, we've
3 also extensively characterized the product, and here
4 I show how we can do that and have done that with all
5 of the test samples shown in yellow and the tests
6 supplied to those samples shown in white.

7 The product, when it's cultured, we can
8 take the last spent culture medium and analyze it for
9 cytokine and other soluble factors. We also rinse the
10 product before we package it in a protein free rinse
11 that's suitable for pyrogenicity testing and an
12 additional sterility test.

13 We can directly punch sample using a
14 dermatology punch the product itself. We fix some of
15 those punches and use them for formalin histology.

16 We also can incubate those sponges and
17 have done so in Alamar Blue as a metabolic dye so that
18 we can measure metabolic activity.

19 And finally, we can hydrolyze the collagen
20 so that by hydrolyzing the matrix, we recover the
21 cells as a suspension. We can do a cell counsel for
22 viability, and we can also fix the cells in ethanol

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1 and use them for immunostaining and flow cytometric
2 analysis of the two populations, the keratinocytes and
3 the fibroblasts.

4 What we've learned by doing this type of
5 characterization is that OrCel cells are still in the
6 growth phase; that the cells demonstrate very high
7 viability. The cells are highly productive for wound
8 healing cytokines and growth factors, and that the co-
9 cultured compartmentalized cells produce more extra
10 cellular factors than either keratinocytes or
11 fibroblasts when cultured alone in the same collagen
12 sponge.

13 And I'd like to illustrate that in the
14 following slides. First, a histological cross-
15 section, this sustained with trichrome. You see that
16 the fibroblast in the lower aspect have penetrated
17 approximately 30 to 40 percent into the sponge in this
18 particular illustration.

19 On the surface are the keratinocytes about
20 one and a half layers deep, and below them, if you see
21 a thin blue line, that's the collagen gel layer.

22 When we stain the same type of cross-

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1 section with an antibody for KI-67, which stains
2 nuclei that are undergoing DNA synthesis, you see that
3 approximately 15 to 20 percent of the nuclei in this
4 particular cross-section, 15 percent overall were
5 measured of these fibroblasts that are actively
6 dividing.

7 On the keratinocyte side, it's usually one
8 to five percent.

9 When we looked at the cytokines, in this
10 case I'm showing an experimental approach where we
11 cultured fibroblasts only, shown in yellow;
12 keratinocytes only, shown in red; or the usual
13 product, the co-culture shown in blue. And we measure
14 the cytokines indicated here on the X axis.

15 You see that there's a much higher level
16 of productivity for many of the cytokines in the co-
17 culture than in the monoculture. The reason we have
18 two panels here is because there are two different Y
19 axes. These are produced in the nanogram level.
20 These are produced in the low picogram level.

21 But in all cases, you see that the co-
22 culture is more productive than the monoculture.

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1 When we saw these different levels of
2 production, we were interested in their biological
3 significance, and so in this slide I've compared our
4 levels of production to some publications on the
5 production of cytokines in wound fluid as studied
6 using wound cup technology, and we chose these papers
7 because they're very quantitative. So we could use
8 the same Y axis for both products. In this case it's
9 expressed as output per unit area and picogram per
10 centimeters squared per day.

11 And you see that in many cases, the light
12 gray from the literature is similar to our levels of
13 productivity overall, and I'll leave it at that
14 comparison.

15 Finally, in conclusion, what I'd like to
16 say is that we've shown that OrCel contains living,
17 dividing cells in an open collagen matrix. I hope
18 I've illustrated that the OrCel product has been well
19 characterized, and as we detailed in our PMA
20 submission, Ortec is manufactured under GMP/quality
21 system regulations using validated processes.

22 I'd now like to introduce our next

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1 speaker, Dr. John Griswold, who is Medical Director of
2 the Burn Center at Texas Tech. University Health
3 Sciences Center.

4 DR. GRISWOLD: Thank you.

5 Good morning. My name is John Griswold.
6 I'm Medical Director of a regionally designated burn
7 center and Medical Director of Trauma Services for a
8 Level I trauma center at Texas Tech. University in
9 Lubbock, Texas. I am Board certified in general
10 surgery and critical care.

11 In addition to doing a general surgery
12 residency at Texas Tech., I did a two-year burn
13 fellowship at the University of Washington. I have
14 about 15 years' experience taking care of burn
15 patients, and my research interests center around
16 infection and wound healing in burn patients,
17 especially donor sites, and I have been involved since
18 my fellowship in a large number of studies and
19 clinical trials related to dressing applications to
20 the healing aspects of donor sites.

21 My role this morning is to discuss briefly
22 the severity of burn injuries and the impact that

1 donor sites have on those burn injuries; to discuss a
2 little bit about the healing concerns of donor sites
3 and some of the dressing applications that have been
4 used.

5 There is no doubt that the burn injury is
6 the most severe and devastating insult the human body
7 can endure. It's a physiologic stress greater than
8 any trauma or illness that we know, and at the basis
9 of this physiologic stress is the marked increase in
10 metabolism, the hypermetabolism that these patients
11 suffer.

12 In addition, they have a diffuse immune
13 suppression that leads to a marked risk of infection,
14 with possible development of multi-organ system
15 dysfunction, failure, and possibly death.

16 Now, the duration and length of time of
17 this hypermetabolism strongly depends on how quickly
18 the wound is healed, and in addition, many of these
19 patients require excision and grafting, which
20 therefore leads to the development of another wound,
21 the donor site, that can add additional impact to this
22 hypermetabolism and ultimate outcome.

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1 Now, the technique for donor site harvest
2 is standardized. It's probably one of the most
3 standardized surgical techniques that we do in this
4 country, but once the donor site is developed, there
5 are several concerns that must be addressed.

6 First, the donor site is extremely
7 painful. The graft side is not painful. The nerve
8 endings in the dermis have been destroyed due to the
9 burn injury, but the donor site, those nerve endings
10 are irritated and so it is quite painful.

11 There's an infection concern. The skin
12 barrier has been disrupted in harvesting the skin so
13 that the donor site adds as another opportunity for
14 these patients to develop infection.

15 Healing speed or healing rate is of
16 concern. The rate of healing can impact the length of
17 hypermetabolism, can impact the length of painful
18 experiences for the patient, risk of infection, a
19 number of aspects.

20 And in patients who have a burn or burned
21 skin that's more than unburned skin, those patients
22 may need those donor sites recropped, reharvested, and

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1 therefore, healing time plays a major role in how
2 quickly we can get their wounds covered.

3 And finally, the cosmesis or appearance of
4 the donor site. The longer it takes to heal, the less
5 good cosmetic result, and this already impacts an
6 already devastating cosmetically disfiguring problem
7 as far as the burn injury.

8 One day difference in healing can make a
9 big difference in all of these issues and a difference
10 in outcome.

11 One of the ways that we can deal with
12 these concerns is the type of donor site dressing we
13 apply. So what would be that ideal donor site
14 dressing?

15 Well, first of all, as a clinician we
16 would want something that's easy to apply in the
17 operating room. These are very difficult, long
18 procedures, especially the major burns. We want
19 something that doesn't demand a lot of technical
20 effort or time to apply to the patient's donor site.

21 We would like a dressing that requires
22 minimal manipulation after the surgery. This would

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1 reduce their painful experience. Also it's important
2 in clinicians' time at the bedside.

3 We certainly would want a donor site
4 dressing that minimizes pain. The painful experience
5 not only is an issue for the patient, but also has
6 physiologic impact to their hypermetabolism.

7 We want a dressing that would speed the
8 healing process, and finally a dressing that gives the
9 best appearance, texture, function, and durability of
10 the donor site skin. Basically we would like a
11 dressing that would return the environment as closely
12 as possible to the patient's natural skin.

13 There have been a number of dressings that
14 have been used and are used in the care of donor
15 sites. First, the open technique has been used in the
16 past. Now, this would be just leaving the donor site
17 open to heal to its own devices. It desiccates and
18 scabs. It's very painful. It almost slows or stops
19 the healing process, and this dressing application or
20 approach to healing is probably not used anymore.

21 There are impregnated fine mesh gauzes,
22 such as Xeroform and Scarlet Red. They sting when

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1 they are applied to the donor site and shrink when
2 they dry. So they are quite painful, at least early
3 on in the healing process. The wound heals underneath
4 and the dressing peels off as the donor site heals.

5 There are occlusive and semi-occlusive
6 dressings that have been used, such as Opsite and
7 Duoderm. These certainly reduce the initial pain
8 experienced at the donor site, but the problem is that
9 fluid builds up underneath these dressings, often
10 causes them to fall off or to leak. They then need to
11 be patched or replaced. That can cause pain
12 experience as well as increase in infection risk.

13 And there are semi-biologic dressings
14 available, such as Biobrane or Biobrane-L. It also
15 adheres to the wound, yet does it in a less painful
16 way than the fine mesh gauze dressings, and it
17 provides a matrix or a template for keratinocytes to
18 migrate into and sheet over the donor site. It is
19 certainly one of the more common donor site dressings
20 available and appropriate for control as in this
21 study.

22 A little more about Biobrane-L. It's

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1 flexible synthetic silicone nylon sheet. It's coated
2 with collagen and binds to the wound surface as I
3 mentioned, helps to assist in hemostasis and provide
4 that matrix for that keratinocyte migration.

5 Biobrane-L is a modified version of
6 Biobrane, and in theory at least, it's supposed to be
7 a little bit easier to use and manage. It certainly
8 conforms to the body contour surface, making it easy
9 to apply. It adheres to the wound surface, causes
10 less pain than the impregnated gauze dressings. It is
11 semi-transparent so that the wound can be evaluated
12 without having to remove the dressing as the healing
13 process is ongoing, and it is porous so that there's
14 minimal fluid accumulation underneath the dressing.

15 OrCel, the product under discussion today,
16 I at my center had the opportunity to provide ten
17 patients for this study and have experience with those
18 ten patients. We noted a number of aspects related to
19 OrCel.

20 First of all, it is very easy to apply.
21 It's very quick, simple to do in the operating room
22 and requires very little time.

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1 It requires minimal dressing changes,
2 really no dressing change at the wound's surface while
3 the healing process is ongoing.

4 It provides for evaporative loss. We saw
5 no fluid accumulation under the dressing application.

6 It certainly minimizes wound pain. Our
7 patients tolerate and preferred the OrCel very much
8 during the study.

9 And probably the most dramatic aspect in
10 my experience is that it does speed the healing
11 process significantly better than the control Biobrane
12 as will be described later.

13 So in conclusion or concluding my remarks,
14 certainly the donor site is a significant clinical
15 problem in the care of burn patients. There are a
16 wide range of dressings that have been used and are
17 used for wound healing, but in my experience OrCel did
18 offer and does offer significant clinical benefit to
19 the treating of donor site wounds.

20 I will now turn this over to Stephen
21 Peltier, Vice President for Clinical and Regulatory
22 Affairs, to discuss the pivotal study donor site

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1 results.

2 MR. PELTIER: Thank you, John, and good
3 morning, Panel.

4 This morning I'm going to review for you
5 the protocol that was used in the pivotal clinical
6 trial. Before starting the pivotal clinical trial, we
7 conducted a single center matched pair, randomized
8 study in eight patients. Single applications of the
9 product were used.

10 The primary efficacy variable, as with the
11 pivotal protocol, was time to wound healing. One
12 hundred percent re-epithelialization was established
13 or the criteria was established using a very strict
14 protocol, and the initial results indicated
15 effectiveness and led to the development of the
16 pivotal trial.

17 The objective of the pivotal trial was to
18 examine the safety and effectiveness of OrCel in
19 facilitating timely wound closure of split thickness
20 donor sites in burn patients who were undergoing
21 excision and grafting, and it was compared to a
22 standard controlled dressing.

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1 This slide is presented to show you the
2 investigators who participated in the study and the
3 sites that participated in the study.

4 The next slide are the additional
5 investigators which add up to the 12 investigators in
6 the study.

7 The test device, as was described by Dr.
8 Silberklang, was forecell composite cultured skin, a
9 collagen matrix seeded with allogeneic skin cells and
10 cultured in two distinct layers.

11 During the course of the trial the product
12 was used as indicated for the treatment of donor
13 sites, and it was used by the clinical investigators
14 according to a strict protocol.

15 Biobrane was the control dressing. This
16 was already described by Dr. Griswold, a semi-
17 permeable silicone membrane. The product is indicated
18 for the treatment of donor sites, and it was used in
19 accordance with the package insert that was provided
20 by the manufacturer.

21 The selection of the control was based on
22 the information that you see on this slide here, and

1 as it was described by Dr. Griswold. Again, since the
2 product was indicated or recommended by the
3 manufacturer for use in the deeper split thickness
4 donor site, this is the one chosen for the study.

5 The study design was a matched pair
6 design, controlled, randomized, single treatment.
7 Eighty-five patients were originally planned in the
8 clinical trial. However, due to a very severe or
9 dramatic decrease in the patient population
10 availability due to the seasonal variance of being
11 able to obtain patients who have burn injuries, we
12 stopped at 82 patients.

13 Photography and plain imagery, along with
14 an investigator evaluation of wound healing were used
15 as the primary methods.

16 The schedule of visits are presented here
17 on day zero. The autograft was harvested, and the
18 donor site created. Following the creation of the
19 donor site, the patients were randomized to treatment
20 by utilizing a computer generated randomization scheme
21 that was provided in a sealed envelope.

22 Patients were then evaluated three days

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1 postoperatively, and then 48 hours thereafter until
2 healing was documented by the investigator's
3 assessment, at which time the study's schedule visits
4 were separated by one week until day 28.

5 Patients then underwent a three-month and
6 a six-month evaluation. Patients continued with a
7 biannual evaluation until the last patient enrolled in
8 the study completed a six-month evaluation.

9 In this study blinded photographic review
10 was used to evaluate the time to donor site healing as
11 the primary efficacy variable. Secondary endpoints in
12 the study included blinded planimetric evaluation for
13 donor site healing, investigator assessment for donor
14 site healing, and also the rate of donor site closure,
15 wound closure, and the time to readiness for
16 recropping.

17 I'd like to emphasize that a strict
18 definition for wound healing was adhered to in the
19 study at all time. Healing was defined as 100 percent
20 re-epithelialization, which was really characterized
21 by a continuous stratum corneum with no surface
22 moisture and no dressings required.

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1 Patients were not considered healed if
2 they were not 100 percent healed by this definition.

3 Safety endpoints included all adverse
4 events reported in the study. Donor site specific
5 adverse events were also evaluated. Infection pain,
6 itching, breakdown.

7 Scar outcome was evaluated by two methods.
8 The first method was a Vancouver Scar Scale, which
9 the clinical investigator assessed each patient's
10 wound at the clinical site. Photographic assessment
11 was also utilized utilizing the Hamilton Scar Scale.
12 Three blinded reviewers were used, and the results
13 were masked or the reviewers were masked.

14 Key inclusion criteria in the study
15 included patients who were 12 months or older with a
16 ten to 80 percent total body surface area injury.
17 There was a minimum and maximum donor site size as you
18 see up there. In the pediatric population, the
19 minimum size was kept at 45 square centimeters, which
20 would allow in a pediatric patient for the use of one
21 half of ACCS dressing.

22 All sites that were chosen were virgin

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1 donor site areas, and they were matched anatomically.
2 The donor site depth was controlled between .006 and
3 .014.

4 Key exclusion criteria included sepsis,
5 severe inhalation injury, and injury severity score or
6 pediatric trauma score that indicated that the patient
7 was severely injured or had a life threatening injury;
8 systemic corticosteroid treatment within 30 days and
9 insulin dependent diabetes.

10 Selection of the treatment site was based
11 on patients who were scheduled for undergoing excision
12 and autografting for treatment of their burns in the
13 routine practice of the investigator. They were
14 matched pairs so that each patient could serve as his
15 or her own control.

16 Two donor sites had to be of equivalent
17 size, surface area, depth, and they should be non-
18 articulating contiguous areas. In the event that one
19 single donor site was chosen and both dressings were
20 applied, the areas were separated by a .5 sonometer
21 distance utilizing a non-study donor site dressing
22 between them.

1 Randomization. As I indicated in the
2 beginning, the study was randomized. The patient
3 sites were designated as one or two by anatomic
4 position before surgical procedure, before harvesting
5 of the graft.

6 The donor sites were matched, the grafts
7 were harvested, and then the donor sites were randomly
8 assigned treatment based on a computer generated
9 scheme in a sealed envelope. The envelope was not
10 opened until the time that the dressings were to be
11 applied.

12 Evaluation methods included photography,
13 plain imagery, and an investigator's assessment not
14 only of wound healing, but of readiness for
15 recropping.

16 Photography was strictly controlled during
17 the study. Canfield Scientific of New Jersey provided
18 the sites with identical cameras that were set up for
19 fixed focal points, fixed distances, et cetera. A
20 single lot of film was purchased for the study. Each
21 investigator received training and operated according
22 to a standardized protocol.

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1 When the photographs were evaluated at the
2 end of the study, three masked independent reviewers
3 evaluated the photos. They were blinded as to the
4 treatment. They were blinded as to the sponsor of the
5 study, and they reviewed all photographs in random
6 order.

7 They also had to adhere to the strict
8 definition of 100 percent wound healing in order to
9 consider a wound healed, and the three reviewers were
10 set up so that the majority ruled. If two indicated
11 that a wound healed, it was scored as healed. If two
12 indicated that it wasn't healed, it was scored as not
13 healed.

14 Planometry was also tightly controlled
15 during the study. Again, Canfield Scientific provided
16 the control in this study for us. Acetate tracings
17 were taken on site by the clinical investigators.
18 They traced all of the open, unhealed regions of the
19 wound.

20 That was then sent to Canfield where
21 masked computerized quantitative planimetric analysis
22 was used to evaluate changes in size over time and

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1 from which we calculated a percent wound closure over
2 time.

3 Each of the staff at Canfield remained
4 blinded as to the treatment.

5 The investigators' assessment, as I
6 indicated, was twofold. The first one was to look at
7 wound healing. The investigator did this through a
8 physical examination of the wound, looking for 100
9 percent wound closure based on the definition that I
10 provided earlier.

11 The investigator also observed the wound
12 for readiness for recropping. So in addition, during
13 this physical exam, the investigator conducted a
14 tactile evaluation of the wound and tried to make a
15 determination for the ability of that particular site
16 to be able to produce a viable autograft.

17 At this point I'd like to introduce Dr.
18 Kazem Kazempour from Amarex Clinical Research, who
19 provided the data management and statistical analysis
20 for the pivotal study.

21 DR. KAZEMPOUR: Good morning, and thank
22 you, Steve.

1 My name is Kazem Kazempour. I'm President
2 of Amarex Clinical Research, a Maryland based
3 organization which was hired by Ortec International to
4 perform data quality control and statistical analyses
5 for the pivotal trial of this PMA in front of you.

6 In terms of background, I have been
7 working as a statistician in clinical research for the
8 last 25 years, first as a researcher, then as a
9 university professor working in or cooperating with
10 research institutions, such as Genentech Research
11 Institute, National Institutes of Health, and other
12 research based institutions.

13 I was a statistician and a statistical
14 reviewer in FDA for five years, since 1990 till 1995.
15 For the last six years, I've been working in the
16 private sector while remaining active in scholarly
17 activities related to clinical research.

18 Efficacy analyses were conducted on intent
19 to treat population, per protocol population, and it
20 was asked by FDA to look at week 24 completers
21 population.

22 We also conducted efficacy analyses on

1 several subpopulations, such as age, race, gender, and
2 percent total body surface area of burns.

3 The results we obtained are robust and
4 statistical methods independent. We have used
5 different statistical methods, such as time to event
6 analyses, Kaplan-Meier presentation of the data, log
7 rank tests, to analyze the median days to healing, and
8 we use paired T test, which is a mean based
9 statistics.

10 Regardless of the analysis method used and
11 the population tested, results are always in the same
12 direction, and statistically significant results
13 remain statistically significant.

14 Additionally, we conducted Cox regression
15 analyses as requested by the FDA statistician to see
16 if the covariates recommended by the agency can
17 explain away the treatment effect, and also we
18 conducted subpopulation analyses to see if individual
19 subpopulation results may be different than the
20 overall results.

21 The results of these analyses, the
22 covariates and subpopulation, are in agreement with

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1 the overall population.

2 Finally, we looked at Kappa statistics to
3 examine the agreement between assessment methods, that
4 is, planimetric, photographic, and investigator
5 assessment, and also to assess the agreement between
6 the three photographic reviewers.

7 An overview of the results from all of
8 these analyses will be presented in this session.

9 Here we have a Kaplan-Meier graph which
10 depicts the full range of days to healing for all
11 patients. As is clear from these curves, most of the
12 observed activity occurs in the first month. That's
13 right here. That means one event.

14 Some patients healed after the first
15 month. More of these cases are for the control
16 treated sites. As a result, the difference between
17 the two groups could be exaggerated if only mean based
18 statistics is used.

19 To avoid exploiting the difference, we
20 focused on median based statistics. Additionally, we
21 censored patients after their first month. Any days
22 after day 28, the last scheduled visit, could have

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1 been used. We chose day 32 to allow for weekends and
2 the fact that not all patients came on day 28.

3 Other days around day 28 would give
4 similar results.

5 You saw this slide earlier, but I'm going
6 to present it again because that has a major impact in
7 a statistical analyses when one used mean based
8 statistics.

9 At the design stage of this study, there
10 was an assumption that the wound would heal by day 28.
11 So several visits were planned for the first month,
12 and only two visits from month one to month six.

13 Given the primary endpoint of 100 percent
14 wound closure, the patient that is healed 98 percent,
15 their day 28 visits will not be used as the time of
16 healing because it was not 100 percent healed.

17 Although that patient would heal somewhere
18 between day 28 and the visits that come later, but
19 still we will not record that as a healed patient
20 because we need to see that patient when they reach
21 that, and we only use the data if we saw that patient.

22 Although we have limited patients with

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1 this type of scenario, but it did happen enough to
2 tell the mean to one site and, in particular, to the
3 site that the control was used.

4 Here, to be able to see the treatment
5 effects clear with the Kaplan-Meier, we present here
6 the same data that we saw, but we changed the X axis
7 to only 32 days.

8 This slide depicts the total number of
9 patients healed after day 32 for each assessment
10 method, and it confirms what we saw in the Kaplan-
11 Meier graph. There are more patients in the control
12 treated side that would all heal after day 32.

13 Therefore, our approach of censoring at
14 day 32 clearly benefitted the control arm when the
15 mean based statistics were used, nevertheless, and
16 since the data were analyzed and presented.

17 Here are the mean and median days to
18 healing using uncensored data. We present both mean
19 and median, but the median is the more robust
20 statistics as we discussed earlier.

21 With the uncensored data, the mean
22 difference between the OrCel and the control ranges

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1 from 11 to 24 days, depending on the methods of
2 assessment.

3 This slide presents results of our
4 original analyses using day 32 censored data for the
5 mean and median days to healing for the ITT
6 population. The mean censored data indicated that the
7 CCS-3, the site, heal an average of approximately four
8 to six days sooner than the control, depending on the
9 methods of assessment. This difference is not as
10 exaggerated as it was with the uncensored data with
11 respect to the mean. Median remains almost
12 unaffected.

13 The consistent message from these analyses
14 is that despite the methods used OrCel treated sites
15 continually provided fewer days to healing compared to
16 the control treated sites.

17 Now, I'm going to shift our attention to
18 subpopulation analyses to demonstrate that not only
19 are the results consistent across the statistical
20 methodology. They are consistent across subpopulation
21 as well.

22 This histogram presents median days to

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1 healing for several subpopulations: the male, female,
2 and three age groups, the race, and three total body
3 surface area variant categories.

4 I would like to bring your attention to
5 the age subgroup, the three age subgroups that we have
6 here. Notice that as age goes up, the media days to
7 healing increases for both treatment groups. However,
8 as patients' age increases, the difference in healing
9 time between the two treatment groups gets larger.

10 These results are from preliminary
11 assessment. Similar results were observed with
12 investigator and with photographic assessments.
13 Additionally, similar results were observed using mean
14 days, and the same pattern is reserved with the body
15 surface area burns.

16 The patient with larger total body surface
17 area burn took longer time to reach 100 percent wound
18 closure at the donor sites for both treatment groups.
19 The number of patients in each group, the n here
20 represents the number of patients in each group,
21 except age 65. We have only three patients.

22 It's large enough to make the results

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1 statistically meaningful. The only group that does
2 not have sufficient number of patients is this one,
3 and that's the only one that didn't come out to be
4 significant, although the difference appears to be
5 large, but that is only based on three observations.

6 Of note, this slide is the fact that OrCel
7 treated sites, number of days to healing remains under
8 15, except for when patients have more than 40 percent
9 total body burn and when we have ages greater than 65.

10 Our point is that the variability in
11 healing time for the control treatment group is very
12 important. As we go from one subgroup to another one,
13 the time to healing changes, and by the way, I'm using
14 median here, which is more robust.

15 Moving to other efficacy endpoints, here
16 we see the result of analyses for investigator
17 assessed time to readiness for recropping endpoint.
18 Treatment with OrCel resulted in a significantly
19 shorter time to readiness for recropping in the eyes
20 of the investigator. There are seven days fewer days
21 with respect to median and five days with respect to
22 mean.

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1 By the way, we have censored data here, as
2 well.

3 Depicted here are the results of rate of
4 wound closure endpoints. The slide shows the mean
5 rate of wound closure in terms of centimeter squared
6 per day with the study divided in two periods: day
7 six to 16 and day 17 to 32.

8 Points of interest in this slide are that,
9 first, the rate of wound closure for both OrCel and
10 control were faster in the first part of the study
11 than the last part. OrCel treated sites were six
12 centimeters square a day in the first part and four
13 centimeters square a day in the latter part, and the
14 control was four centimeters square a day in the first
15 part and two centimeters square a day in the latter
16 part, and two centimeter difference in each time
17 point.

18 These results strongly support the results
19 obtained for the primary endpoint, which was time to
20 healing.

21 Now I would like to bring your attention
22 to several statistical issues. These issues were

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1 presented to us by FDA statisticians. All have been
2 discussed in person or in writing with the FDA.

3 First and foremost is the issue of
4 treatment group independence, and using each patient
5 as its own control, the design was a matched pair
6 design. Using each patient as its own control reduces
7 the variability, which is a good thing, but with the
8 matched pair design, we'll lose the independence
9 between the treatment groups, which in general may not
10 be a good thing if the correlation is negative.

11 The assumption of independence between
12 treatment group is a fundamental element of a
13 statistical hypothesis tested. So are the treatment
14 groups in this study independent?

15 The answer is, no, these treatment groups
16 are not independent. Here we present correlation for
17 the two treatment groups. There is a large positive
18 correlation between the two treatment groups, time to
19 healing, for all three methods. In fact, the
20 correlation is more than 50 percent for the
21 investigator and planimetric assessments.

22 These correlations help to explain why we

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1 observe such a small p value in this study partly. At
2 the design stage of this study, the statistician
3 assumed a correlation of zero, although we are saying
4 it's larger than .5 in many cases.

5 A correlation of zero is very conservative
6 approach. Sample size calculation for the study was
7 based on the zero correlation assumption, and the
8 actual correlation is .5, that this may reduce the
9 variable by about 40 percent.

10 And the bottom line of this slide is that
11 the study was over powered because of the dependency
12 in the time to healing in both treatment sides using
13 matched pair design.

14 Next is the issue of covariates. In other
15 words, are there factors which can explain away the
16 difference between the two treatment groups?

17 The sponsor was asked to assess impact of
18 several prognostic factors, including age, race, donor
19 location, investigator, and we were asked to look at
20 the steroids. We looked at corticosteroid use, and we
21 have a limited number of patients on corticosteroid
22 use.

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1 Three factors, three prognostic factors,
2 age, race, and percent total body surface area burn,
3 came out to be statistically significant, are
4 presented here, but the treatment remained
5 statistically significant as well.

6 So these three factors, although they are
7 prognostic factors and important, but they did not
8 explain away the treatment effect. The investigator
9 also was there and was not statistically significant,
10 and corticosteroid use was not statistically
11 significant in the presence of other factors.

12 Here I'm presenting the subpopulation
13 analysis again for those three factors that were
14 statistically significant to show that that
15 significance are in the same direction, is not
16 flipping.

17 Okay. Based on our review of information
18 provided by the FDA regarding the steroid on
19 Oxandrolone usage, we would like to provide the Panel
20 with additional information, which is included in our
21 handouts.

22 Here I am presenting to you the control

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1 arm times to healing with respect to those patients
2 who had Oxandrolone and those who did not have
3 Oxandrolone. Please look at either the median or the
4 mean of them. Those patients who are on Oxandrolone,
5 they have larger time to healing compared to those who
6 did not have Oxandrolone. That is true in both
7 treatment groups, in OrCel as well as control.

8 The difference is larger when we look at
9 control treatment groups. When we looked at this
10 data, we wanted to see if there are other factors
11 involved here other than the Oxandrolone. So we
12 looked at age.

13 We have 30 patients or about 30 patients
14 in this group and about 50 patients in this group.
15 The age is larger in those patients who were using
16 Oxandrolone compared to those who did not, and the
17 total body surface area burn is larger in this group
18 compared to the other group. Obviously this is a
19 paired match design. Therefore, the results are the
20 same in both treatment groups.

21 We looked to see how much these steroids
22 impact the treatment effect. So we looked at the Cox

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1 model analysis. Yes, it is statistically significant,
2 but the p value for the treatment remained
3 statistically significant, and all the steroids now is
4 also statistically significant.

5 Here I'm presenting all of the steroids.
6 The previous slides was Oxandrolone alone.

7 When I brought into model age now, yes,
8 yes, the p value for steroids moved from .009 to .07.
9 The age is statistically significant. The treatment
10 remained significant.

11 When I brought total burn surface area
12 into model, it's significant, the age significant.
13 The p value moved away from .07 to .6 now. The
14 treatment remained significant.

15 Next, the issue of poolability. Efficacy
16 on safety analysis, pooled the results of 12 different
17 investigators from different parts of the United
18 States, each enrolling between one and 19 patients.

19 The sponsor was asked to provide evidence
20 that these data were, indeed, poolable. We conducted
21 two analyses to provide evidence of poolability. One
22 was the Cox model that you saw earlier, and additional

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1 analysis we did, and that was looking at the treatment
2 by investigator interaction, which in general no study
3 is powered to detect that interaction, but anyway, the
4 p value is between .10 to .2 regardless of methods of
5 assessment.

6 So we have concluded that the
7 investigators are poolable.

8 And next is the Kappa statistics, to
9 assess the agreement between the methods of assessment
10 and also the agreement between the three independent
11 photographic reviewers.

12 With Kappa statistics, obviously the
13 larger the Kappa, the greater the agreement. The
14 Kappa statistics for methods of assessment indicated
15 greater than 72 percent agreement across the three
16 methods of assessment, and the Kappa statistics for
17 photographic reviewer is more than 83 percent
18 agreement across the three reviewers.

19 Here I am presenting to you the Kappa
20 statistics, this column. That is more than 72
21 percent, regardless of which method of assessment we
22 look at, and here is it 95 percent confidence lower

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1 limit and 95 percent upper limit.

2 As I mentioned, there's more than 72
3 percent agreement, which is the lowest one
4 photographically.

5 And here the Kappa statistics across the
6 three photo reviewers. There is large agreement
7 between photo reviewer two and three, but in general,
8 we have more than 83 percent agreement. The 95
9 percent lower limit, the 95 percent upper limit.

10 Looking at completers by week 24, the
11 sponsor was asked to perform time to healing analysis
12 using data from only those patients that completed
13 week 24 of the study, although most of the patients
14 healed by the first month.

15 We have 60 patients who had week 24
16 assessment completed. Here are the mean and median
17 times to healing for patients that completed week 24.
18 Again, the both medians and mean indicate that the
19 time to healing for OrCel treated side was
20 significantly shorter than that of control sites.
21 Regardless of methods of assessment.

22 Also, please note that data are uncensored

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1 here, as was requested to present to the agency.

2 Now, we will present a few slides on
3 safety parameters. The safety --

4 ACTING CHAIRPERSON GALANDIUK: I'd like to
5 ask the sponsor to wrap up within the next five
6 minutes.

7 Thank you.

8 DR. PAPASTEPHANOU: Thank you

9 DR. KAZEMPOUR: The safety profile of
10 OrCel and control were similar.

11 We used two methods of assessment to
12 assess the scar, the Vancouver Scar Scale as well as
13 Hamilton. We do see difference between the three time
14 points that we assessed that, and two of them being
15 statistically significant, and the follow-up was not.

16 The second was the Hamilton Scar Scale.
17 The same pattern was observed.

18 Signs of donor site infection, again, we
19 see the same pattern was we saw. We do see less sign
20 in the OrCel treated site versus the control treated
21 site.

22 With respect to adverse events, both

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1 treatment sides have very limited number of adverse
2 events. No serious adverse events reported, 12 AE in
3 OrCel treated sites and 13 AE in control treated
4 sites. The event and frequency and their severity are
5 presented in this table.

6 Conclusion. Shorter time to healing with
7 respect to OrCel; consistent results across the
8 populations and the statistical methodology.
9 Subpopulations were in agreement with the overall
10 population with respect to recropping. OrCel treated
11 sites were shorter than the control sites.

12 The conclusion with respect to safety,
13 with respect to scar, significantly better scar
14 outcome with OrCel treated sites compared to control
15 using Vancouver and Hamilton, and other safety
16 endpoints were similar.

17 Thank you.

18 DR. PAPASTEPHANOU: With your permission,
19 we'll go directly to the conclusion and skip the next
20 speaker.

21 DR. WITTEN: Actually we are ahead of
22 schedule. So it's up to the Panel chair, but --

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1 ACTING CHAIRPERSON GALANDIUK: Would you
2 conclude, please?

3 DR. WITTEN: -- we do have time. I think
4 we have time available for the other speaker.

5 MR. PELTIER: Just bear with me for one
6 moment.

7 Just a quick wrap-up then. Everyone, I'd
8 like to thank you for your attention. What we believe
9 we've shown is that in preclinical safety demonstrates
10 that OrCel composite cultured skin is safe and
11 biocompatible. Few adverse events were seen during
12 the clinical trial and were comparable for both
13 groups.

14 Pain and infection rates were low and
15 comparable in both treatment groups.

16 The median time to 100 percent wound
17 healing in a large, multi-center trial was
18 statistically shorter for the OrCel product than the
19 control products, and in the subgroups, the same trend
20 was seen.

21 Median healing times for the three methods
22 are presented again on the slide for you.

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1 In the efficacy evaluation, we showed
2 significantly faster healing rates, significantly
3 faster readiness for recropping, and significantly
4 better scar outcome.

5 OrCel composite cultured skin has been
6 demonstrated to be safe and effective for the
7 treatment of split thickness donor sites in burn
8 patients.

9 That concludes our presentation, and thank
10 you again.

11 DR. WITTEN: I just want to mention that
12 we do have -- in terms of time, it's up to the Panel
13 chair, but we do have time for the case presentations.

14 ACTING CHAIRPERSON GALANDIUK: Would you
15 like to present one of your case studies?

16 DR. PELTIER: Dr. Glat, would you present
17 one of the case studies then?

18 DR. GLAT: Thank you.

19 My name is Paul Glat, and I'm the Director
20 of the Burn Unit and the Director of the Division of
21 Plastic Surgery at St. Christopher's Hospital for
22 Children in Philadelphia. I'm an Assistant Professor

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1 of Surgery at MCP Hahnemann University and Board
2 certified in general and plastic surgery.

3 I was one of the principal investigators
4 in this study, and I enrolled 16 patients in this
5 study.

6 Let me go back. Excuse me.

7 I've been asked to present one of the two
8 patients I prepared, and the first patient is a 75
9 year old African American male who had a 25 percent
10 total body surface area burn. He was enrolled in the
11 Augusta Medical Center by Dr. Joseph Still. This
12 patient had thermal burns to the neck, chest, right
13 flank, right anterior leg, the upper bilateral arms.

14 The autograft thickness was taken at
15 12/1,000 of an inch, and the surface area of the donor
16 sites was 144 squared centimeters for both sites.

17 The location of the donor sites was on the
18 left thigh for both patients.

19 This is this patient at day zero. This
20 was upon application of both the OrCel and the control
21 in the operating room. You'll note that the OrCel has
22 the white, nonstick backing overlying the pink

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1 collagen sponge, which was placed in unison at this
2 time in the operating room.

3 Staples were used in this particular
4 patient, which was also at the discretion of the
5 individual investigators.

6 On the right you see the control patient
7 at the same time. On the left you see the OrCel site
8 at day number seven. Here the white backing has been
9 removed.

10 When looking at this slide, the pink areas
11 are re-epithelialized while the red areas remain open.

12 At this point I wanted to briefly discuss
13 the concept of take. This is a terminology often
14 associated with skin grafting or other tissue
15 engineered wound care products.

16 OrCel works by the process of tissue
17 regeneration. In this particular product, the sponge
18 itself actually dissolves after three to five days
19 post application, and this is after it has delivered
20 the living keratinocytes and fibroblasts into the
21 wound. In this way the OrCel doesn't actually take,
22 but actually promotes accelerated tissue regeneration.

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1 Here you see it on day say again on the
2 left, that the pink sponge is actually completely
3 gone. It has been completely resorbed, and the
4 patient's own skin has begun to re-epithelialize
5 diffusely in this particular wound.

6 On the right you see the control dressing
7 at day seven without any signs of healing. On the
8 left is the OrCel site at day 11. The patient is
9 completely re-epithelialized, except for this small
10 area of punctate bleeding on the upper left.

11 Due to the strict criteria of the study,
12 this was rated as not completely healed, and this did
13 go on to be completely healed at day 12. For a
14 patient in this particular age group, 75 years, I
15 would consider this a good result.

16 Here on day 14 we see complete healing on
17 the OrCel side on the left, and of note, you notice
18 that the pigment of the patient is coming back into
19 this wound on the left already at day 14. Again, we
20 see the control dressing on the right.

21 On the left at the OrCel site all wound
22 dressings were discontinued at this time.

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1 Finally, this is the week 24 follow-up,
2 six months. I just wanted to note the improved
3 cosmesis in the donor site and the OrCel site when
4 compared to the control.

5 Should I conclude at this point?

6 Thank you.

7 DR. PAPASTEPHANOU: Thank you, Dr.
8 Galandiuk.

9 ACTING CHAIRPERSON GALANDIUK: We will now
10 proceed with questions of the Panel members of the
11 sponsor. Dr. DeMets and Dr. Boykin will be the lead
12 panel reviewers and make presentations later, but, Dr.
13 DeMets, since many of the June 19th letter points
14 focus on statistics, would you have any questions for
15 the sponsor?

16 DR. DEMETS: Yes. Some of them have been
17 answered, but I still have some I'd like some more
18 clarification of.

19 Could you elaborate a little more on the
20 process at which the study was terminated, the
21 decision to stop at I guess it was 82 patients? There
22 was a goal to go further, and then you stopped at 82.

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1 Could you just elaborate on that for me a bit?

2 MR. PELTIER: That's correct. We stopped
3 at 82 patients because we had reached the seasonal
4 time when burn patients were no longer being
5 identified in the institutions that we were working
6 at, and according to their previous records, it would
7 take us another six months to really begin enrollment.
8 So we felt that stopping at 82 patients was justified
9 at that point.

10 DR. DeMETS: And I guess the question is
11 who knew what when.

12 MR. PELTIER: Well, we certainly didn't
13 open any blinds or do any statistical analysis or
14 recalculations of any type. We made a business
15 decision at that point to stop the study.

16 DR. DeMETS: Okay. Was there a monitoring
17 committee or an ongoing statistical analysis process?

18 MR. PELTIER: There was not an ongoing
19 statistical analysis. We certainly did capture data
20 in terms of recording the size of each of the wounds.
21 So we could see by casual observation changes over
22 time, but we conducted no analyses. No blinds were

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1 broken at that point, and it was strictly a business
2 decision.

3 DR. DeMETS: Okay. The next question was
4 alluded to, and it's the fact that you had a matched
5 pair design, which means there's an internal inter-
6 patient correlation, and you approached that a bit.
7 My question to you is: did you try any of the
8 statistical methods which take into consideration the
9 fact that you have a within patient correlation?

10 DR. KAZEMPOUR: Yes, we did. One of the
11 analyses that we conducted was paired T tests, which
12 takes into account the correlation. The results were
13 very similar to results that we observed by non-paired
14 T tests.

15 DR. DeMETS: So the pairing was on median
16 time to closure?

17 DR. KAZEMPOUR: No. The pair T tests that
18 we conducted was on the mean basis statistics.

19 DR. DeMETS: Okay.

20 DR. KAZEMPOUR: And because we knew that
21 median are less impacted, but the mean are heavily
22 impacted and influenced by off-liers. Therefore, we

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1 conducted a paired T test, and that was statistically
2 significant, and the results were similar to what we
3 saw in the median.

4 The approach of using median would be more
5 robust statistics because the design was not planned
6 to capture every event at the moment it occurred.

7 DR. DeMETS: So the test statistics that
8 you show in your Slide 64, which I'm not sure you have
9 reference to, but it has to do with your mean and
10 median for the treatment control with a few of those.
11 Those are based on paired T tests or log ranked tests
12 or what is the p valuation?

13 DR. KAZEMPOUR: All of the p values that
14 I presented for the median were based on log ranked
15 tests. All the p values I presented were are based on
16 log ranked tests.

17 For paired T tests, we saw similar
18 results, but I did not present them here. They were
19 the ones that were submitted to the agency as well.

20 DR. DeMETS: Okay. This is getting
21 probably too technical, but what's the impact of the
22 discreteness of the time at which you can determine

1 whether a wound is healed 100 percent?

2 You have weekly or very frequent at the
3 beginning, and then you have large gaps. Can you give
4 some sense of how the log rank test is affected sine
5 that's what you're testing your overall comparisons
6 with?

7 DR. KAZEMPOUR: That is very solid point.
8 Obviously when we look at log ranked tests, log ranked
9 is going to be impacted by larger data points, but for
10 example, with Wilcoxon rank tests in general was in
11 agreement with log ranked tests because Wilcoxon is
12 not as influenced by the outliers out there as log
13 rank is. We could use any one of them. I used log
14 ranked tests because it is very common in survivor
15 analyses.

16 DR. DeMETS: It would have been helpful to
17 specify which test you're using and which p values.
18 I was not sure when I went through your presentation
19 or your reading.

20 You've talked about the Kappa statistic in
21 comparing the three reviewers. Could you give us some
22 sense of what you think a good Kappa is and why?

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1 DR. DeMETS: Usually in FDA presentation,
2 when Kappa is larger than 70 percent, people think it
3 is a good Kappa.

4 DR. DeMETS: And why? For the panelists,
5 a Kappa is sort of like a correlation coefficient, but
6 not quite. So if you square it, you don't get the
7 usual interpretation, which is why I'm asking the
8 question. It's a nasty question, but you presented
9 it.

10 So you think that 70 percent is good
11 enough from your experience?

12 DR. KAZEMPOUR: That has been my
13 experience with the FDA panels, yes.

14 DR. DeMETS: The last question I have is
15 the new information you presented. Without getting
16 into the discussion that we probably will have this
17 afternoon, you didn't present us in the analysis where
18 you focused just on -- I lost the name of the drug,
19 but at any rate -- Oxandrolone, I guess.

20 DR. KAZEMPOUR: Oxandrolone.

21 DR. DeMETS: You lumped steroids. Now,
22 for me I don't know whether that is -- is that a

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1 bushel basket of steroids or is it just the one? I'd
2 be curious if that same analysis were done just with
3 Oxandrolone.

4 DR. KAZEMPOUR: I do conduct similar --
5 first of all, the analysis that I presented to you was
6 on all steroids.

7 DR. DeMETS: Yes.

8 DR. KAZEMPOUR: But when I brought and
9 present them to our physicians, they stated, no, you
10 have to do it only on Oxandrolone.

11 DR. DeMETS: Okay.

12 DR. KAZEMPOUR: And the p values that came
13 up for that are very much in agreement with when we
14 did for all methods of all steroids. I can read the
15 p values for you if you want me.

16 The p value was .0001 for treatment, and
17 for Oxandrolone alone, it was .0036. When I
18 introduced age, the p value for the treatment remained
19 the same. For the Oxandrolone, it became .0476, and
20 for age it became .018, and when I brought in total
21 body surface area burn, the p value for treatment
22 remained .0001. For Oxandrolone, it became .3538,

1 lost its significance. Age became .0053, and total
2 body surface area burn became .0373.

3 So whatever it was significant when I
4 looked at all steroids, it was also significant when
5 I looked at the Oxandrolone alone.

6 DR. DeMETS: Would it be possible for
7 those tables to be copied and presented to us for
8 something?

9 DR. KAZEMPOUR: The last one was done
10 about an hour ago.

11 DR. DeMETS: Okay.

12 MR. PELTIER: And, yes, we'll provide
13 copies to the Panel.

14 DR. DeMETS: The question I have with that
15 analysis is did you do an interaction test, although
16 I recognize they're not necessarily the most powerful
17 thing one can do. Did you do it, and if so, what
18 happened?

19 DR. KAZEMPOUR: Yes, I did do interaction
20 analysis only on -- I only conducted interaction
21 analysis for the investigators, but not for every
22 other ones, no.

1 DR. DeMETS: I'm just asking about this
2 particular drug. The treatment effect in the presence
3 of this drug.

4 DR. KAZEMPOUR: No, I did not do
5 interaction between this drug and the treatment, no.
6 Just I used this drug as a factor in the model.

7 DR. DeMETS: Okay. I think that takes
8 care of my questions for now.

9 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin.

10 DR. BOYKIN: Thank you.

11 I just have a few clinical questions.
12 Actually one is preclinical. I'd like to know if
13 there was any information on preclinical testing of
14 cellular retention for the device.

15 MR. PELTIER: Okay. Dr. Silberklang.

16 DR. SILBERKLANG: By preclinical, which
17 type of animal model do you have in mind?

18 DR. BOYKIN: Whatever you have.

19 DR. SILBERKLANG: Most of the work that
20 we've done in animals was done in skid mice and nude
21 mice. In nude mice, we have some early time points
22 where we looked at the device in day one or day three

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1 after application, and the full cellular complement
2 was there 24 hours later, and the keratinocytes were
3 sinking down to the sponge as it dissolved by three
4 days.

5 So at this point, that's about all I can
6 say. We also do have and was submitted with the PMA
7 evidence on two patients where biopsies were taken at
8 day 15 and 19 and that were used for PCR analysis for
9 the presence of the allogeneic donor cells at 15 days
10 or 19 days in the case of the other patient post
11 treatment, and in both cases there were no donor cells
12 detected.

13 DR. BOYKIN: Okay. You have a very
14 complete -- well, as complete as it could be --
15 analysis of the different groups of patients that were
16 treated with regards to the age of the patients, the
17 total body surface area of the burns. Would I get
18 correct in stating that it appears that for patients
19 less than 12 years of age and for patients with burns
20 less than 20 percent, there is not a significant
21 difference between the control population and the CCS
22 population?

1 DR. KAZEMPOUR: With the 12 years of age,
2 yes, you are right. We had limited number of patients
3 in those. The difference was there, but it was not
4 statistically significant I do believe due to lack of
5 enough patients there. I do believe we have less than
6 20 patients, even less, yeah, in the age less than 12,
7 but with the total body surface area burn, I believe
8 the statistical significant for the 20 percenter is
9 there.

10 DR. BOYKIN: Yeah.

11 DR. KAZEMPOUR: The reason for that is
12 although the number is small, but the variability is
13 less when we looked at that group. Therefore, p value
14 could show itself.

15 DR. BOYKIN: So the burns that were less
16 than 20 percent were not significantly different?

17 DR. KAZEMPOUR: Burns with less than 20
18 percent were significantly different.

19 DR. BOYKIN: They were?

20 DR. KAZEMPOUR: They were significantly
21 different. But the age was not. The age less than 12
22 was not statistically significantly different.

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1 DR. BOYKIN: All right. Well, we'll get
2 back to that a little bit later.

3 The other question I had was more involved
4 with the clinical treatment of the patients. Do we
5 have any information on what time after the burn these
6 grafts were harvested? In other words, how many days
7 after the patient admission were the grafts taken, and
8 if there was a protocol addressing that or data?

9 MR. PELTIER: There's not a protocol
10 addressing that, and I don't believe the case report
11 forms in all cases had that information. Let me just
12 check for one moment.

13 No, just confirmed that that data was not
14 recorded. Some of these burns were initial, and some
15 of them were older burns undergoing excision and
16 grafting.

17 DR. BOYKIN: Right. Well, you know, the
18 other things, the timing after burn injury for
19 grafting was and still is a very interesting topic for
20 debate. I mean, you have some fairly well divided
21 camps on how soon grafts should be harvested, if
22 aggressive grafting is better, and of course, you're

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1 not really interested in that aspect of it.

2 MR. PELTIER: Right.

3 DR. BOYKIN: You're looking at the donor
4 site, but I think that plays into another part of it,
5 and the other issue is that of fluid resuscitation
6 because I would assume that patients with burns
7 greater than about 20 or 25 percent are all going to
8 need some fluid resuscitation. They are going to be
9 displaying some signs of burn shock. They may need
10 variable amounts of resuscitation.

11 Was that aspect of the clinical treatment
12 standardized in any way? And do we have information
13 on that particular part of their therapy?

14 MR. PELTIER: I'm going to let Dr.
15 Grossman (phonetic) and Dr. Glat try to address that
16 information for us.

17 DR. BOYKIN: Okay.

18 DR. GRISWOLD: All I can do is respond to
19 out groups of patients, the ten that we provided, and
20 compare them to our standard treatment resuscitation
21 is at our burn center, and that is that we use the
22 Parkin (phonetic) formula. The lactated ringers

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1 (phonetic) is our fluid of choice. We use three to
2 four cc's per kilogram for percent body surface burn
3 for the first 24 hours. All of our patients are
4 resuscitated pretty much the same. We use urine
5 output of 30 to 50 cc's an hour for adults and one to
6 two cc's per hour, kilogram per hour, for children,
7 and that's very standard. We don't vary from that.

8 So in our group, that's how our patients
9 were resuscitated. I don't have any total volume of
10 fluid that they received or how they compared to what
11 their calculations were though.

12 MR. PELTIER: It would be unlikely that
13 anybody still receiving the fluid resuscitation at the
14 time of this treatment anyway.

15 DR. GRISWOLD: Very rare, yes. Very rare.

16 DR. BOYKIN: Well, let me ask you another
17 question while you're there. The backing on the CCS
18 dressing was removed at day seven.

19 DR. GRISWOLD: That's correct.

20 DR. BOYKIN: Now, after day seven, how do
21 you treat that site?

22 DR. GRISWOLD: What we did is we applied

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1 a nonstick dressing, like Adaptek, and then just
2 followed the dressing daily looking for heal time, the
3 re-epithelialization.

4 DR. BOYKIN: So you covered it completely?

5 DR. GRISWOLD: Yes.

6 DR. BOYKIN: And how did you treat the --
7 you treated the control site similarly?

8 DR. GRISWOLD: Well, the Biobrane adheres
9 to the wound and peels off similar to the fine mesh
10 gauze dressings like Xeroform or Scarlet Red. So that
11 was as the dressing peeled off, and it looked like
12 epithelialization underneath.

13 DR. BOYKIN: No, but did you cover the
14 Biobrane dressed area?

15 DR. GRISWOLD: No, sir.

16 DR. BOYKIN: Okay. The many places in
17 which we would put Adaptek four-by-fours and ABD pads
18 over that to reduce the amount of evaporation. If that
19 area becomes very dry and desiccated, of course, the
20 healing is going to be slowed down significantly.

21 I'm not saying that's an issue with what
22 you did, but is everybody on the same wave length?

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1 Were all of the investigators leaving the Biobrane
2 open?

3 DR. GRISWOLD: I'd have to bow to the
4 study coordinators.

5 MR. PELTIER: Yes. All of the study
6 investigators treated the sites the same. So at day
7 seven, the backing from the CCS site was removed, and
8 the Biobrane once any drainage or exudate stopped,
9 then the Biobrane was left open, but as long as the
10 wounds were exudate -- exudate was present, then the
11 wounds were covered with an absorbent dressing.

12 DR. BOYKIN: Okay. That's all I have for
13 right now.

14 ACTING CHAIRPERSON GALANDIUK: Dr. Chang.

15 DR. CHANG: One of the exclusions was use
16 of corticosteroids within 30 days of initiating the
17 treatment. Can you amplify the rationale for
18 including some patients, I believe 30 within the group
19 who did receive steroids?

20 MR. PELTIER: Right. I will give you a
21 brief explanation and then perhaps a little bit more
22 information on the Oxandrolone group.

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1 The corticosteroids, both the prednisone
2 and dexamethasone patients, were excluded, were to be
3 excluded and were excluded from the analysis. We
4 didn't consider the same corticosteroid effect for the
5 Oxandrolone patients, and so they were not excluded
6 from the study nor from the analysis until we received
7 information from Dr. Boykin where we then did the
8 analysis that way.

9 But I would like to have Dr. Grossman --
10 Dr. Griswold respond to that question from a clinical
11 perspective as well.

12 DR. GRISWOLD: Again, I'm John Griswold
13 from Texas Tech. University in Lubbock, Texas.

14 The Oxandran or Oxandrolone patients, the
15 Oxandrolone is something that we do use more from a
16 nutritional support, anabolic protein, anabolism
17 standpoint. We did not feel that that would
18 negatively impact the study, and it's very routine for
19 us to put patients who are older or larger burns on
20 Oxandrolone and didn't feel that that was a deterrent
21 to wound healing or the dressing aspect.

22 I can't respond to any of the

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1 dexamethasone or prednisilone (phonetic) patients. We
2 don't use that routinely in our unit.

3 MR. PELTIER: Okay, and again, just to add
4 to that, it was a matched pair design. So if there
5 were any impact, it would have been seen across both
6 treatment groups.

7 ACTING CHAIRPERSON GALANDIUK: Dr. Chang,
8 do you have any other questions?

9 DR. CHANG: No.

10 ACTING CHAIRPERSON GALANDIUK: No? Dr.
11 Diegelmann.

12 DR. DIEGELMANN: A couple of technical
13 questions. During the production of the OrCel,
14 presumably it's cultured in the presence of serum when
15 the cells are seeded there. What tests were done to
16 see how much the serum cytokines, TGF beta, PPGF, are
17 carried onto the product when it's placed on the donor
18 site?

19 MR. PELTIER: Okay. I'm going to ask Dr.
20 Silberklang to address that.

21 DR. SILBERKLANG: I'm Mel Silberklang,
22 Vice President of Research and Development, and I'm

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1 the one who presented those slide on cytokine
2 production.

3 All of the data that you saw subtracted
4 out with serum effect since we'll be using condition
5 medium, in fact, the serum contribution is fairly
6 small, and our serum is diluted out by a protein free
7 rinse which has been validated as the last step prior
8 to packaging.

9 So whatever we measured initially, which
10 is a few percent of the total that is diluted out,
11 another ten to 100-fold during that final rinse. So
12 it's a very low level contributed by the serum.

13 DR. DIEGELMANN: That's the level that you
14 can extract out of the matrix. Were any tests done to
15 see what stuck to the collagen matrix because collagen
16 has an affinity to bind to these materials?

17 DR. SILBERKLANG: No. At this point we
18 have not directly looked at cytokines bound to the
19 collagen matrix or proteins bound to the collagen
20 matrix. We've only seen what we can wash out by
21 extensive washing of the collagen matrix.

22 DR. DIEGELMANN: In the slide that

1 describes the cytokine production by the co-cultured
2 cells did you also examine prone planitory mediators,
3 such as IL-1, IL-8, TNF?

4 DR. SILBERKLANG: Yes. We looked at IL-1.
5 We looked at TNF. We did not look at IL-8. We looked
6 at IL-6. All that produced the level of IL-1 alpha is
7 in approximately the range of normal wound healing.
8 Less than 100 picogram per mL is what we harvest from
9 the median. The TNF alpha is essentially the
10 detection limit. So there's almost none. The IL-6 is
11 in a moderate level approaching an nanogram per mL in
12 harvested media toward the end of the culture period.

13 DR. DIEGELMANN: Okay. Thank you.

14 ACTING CHAIRPERSON GALANDIUK: Dr.
15 McGrath.

16 DR. McGRATH: I have a couple of
17 questions, and they're not very sophisticated
18 actually. I need you to walk me through how you use
19 this product. In other words, you put it on and you
20 chose seven days as the day when you would take off
21 the film covering.

22 Why seven days?

1 DR. SILBERKLANG: Most of the decisions
2 that were made for this pivotal trial, if you noticed,
3 when we put up -- when Dr. Papastephanou, our
4 President, put up the slide of the history of the
5 product. There were previous clinical trials. For
6 the most part, small cohorts of patients were tested,
7 and over the experience both with Epidermolysis
8 Bullosa patients, burn patients, and the first cohort
9 of donor site patients, it was found that that's an
10 appropriate time for addressing change.

11 And since it was an appropriate time for
12 addressing change, and since it was an appropriate
13 time for addressing change, it became the first
14 observation point.

15 DR. McGRATH: So it just happened de
16 facto. There's no --

17 MR. PELTIER: Let me add to it. During
18 the earlier studies, we did find that when you
19 attempted to remove the dressings, and we looked at
20 attempting to remove the dressings beginning earlier
21 than seven days, that the backing would not just peel
22 off because there had not been a sufficient amount of

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1 re-epithelialization.

2 When we conducted this trial, we began
3 looking at 72 hours postoperatively and then every 48
4 hours after that to determine whether the wounds had
5 100 percent re-epithelialized. If the backing easily
6 came off before day seven, it would have just come
7 off.

8 So at day seven if it had not already slid
9 off because you had good re-epithelialization under
10 the backing, then at day seven we attempted to remove
11 it. In some cases at day seven, it may not have been
12 ready to come off because there was not complete
13 healing. So then it would be removed after that.

14 DR. McGRATH: Now, this re-
15 epithelialization at that point, you're talking under
16 the backing. Do you have any histology? What's re-
17 epithelialized? Which set of cells? A donor or
18 recipient?

19 DR. SILBERKLANG: If I could make a
20 comment, again, we do not have a lot of histology on
21 the donor side trial that you see before you, but we
22 did have a lot of histology on a burn patient trial

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1 that we did in the past, and that epithelialization is
2 the burn patient's own cells to the best of our
3 ability to interpret those results.

4 DR. McGRATH: Okay. Now, absent the fact
5 that we don't have it for this study, what's the
6 purpose of the keratinocytes if by five or seven days
7 it's the patient's own donor cells? Why are you
8 seeding it with keratinocytes?

9 DR. SILBERKLANG: The best comment that I
10 could make to that is that in the development of the
11 product initially other forms of product were
12 considered like keratinocyte only, fibroblast only by
13 Dr. Eisenberg, which didn't work for his indication.
14 they weren't potent, and the most potent was the co-
15 cultured product.

16 I tried by showing cytokine profiles of
17 co-cultured versus monocultured product to indicate
18 that they are different and that they're not the same
19 and that what they contribute to a wound bed is going
20 to be different, and so we believe that this is the
21 most potent form of the product, and that's why we
22 produced it that way.

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1 DR. McGRATH: But you don't even really
2 know how long those donor keratinocytes last. There's
3 no histology on that?

4 DR. SILBERKLANG: At this point we do not
5 have specific data to say how many days the donor
6 keratinocytes last other than what I responded
7 previously to a previous question, which is that in
8 animal studies we know that they're still there for
9 three days. We do not know in this particular human
10 indication how long they last.

11 DR. McGRATH: Tell me a little bit about
12 the handling of the Biobrane because it's just a
13 different kind of product. You chose to remove the
14 biobrane at a certain date. How did you decide about
15 when the Biobrane came off?

16 MR. PELTIER: We actually followed the
17 manufacturer's recommendation in clinical practice.
18 I think this was presented a little bit earlier by Dr.
19 Griswold. What happens is the Biobrane forms an
20 attachment at the surface area, and as healing takes
21 place, as tissue is re-epithelialized, the Biobrane
22 sheds off. So it doesn't come off by peeling it off

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1 in one piece. As epithelial islands or as migration
2 of epithelial cells move towards the center, pieces of
3 the dressing are able to be peeled off. So that's
4 generally how it's done.

5 DR. McGRATH: So when you were doing your
6 study and you were measuring how much healing was
7 going on on the control side, what were you looking
8 at? Were you looking through the Biobrane that was on
9 there or under the Biobrane or at the Biobrane that
10 had peeled off?

11 Very specifically, because it's such a
12 different way to remove it.

13 MR. PELTIER: Right, and I think you
14 touched on all three areas. What the investigators
15 were doing was looking at those areas that still
16 appeared unhealed by looking through the dressing and
17 looking at those areas that appeared healed by peeling
18 up the dressing where they could or where the dressing
19 had already been removed or sloughed off.

20 And the only area measured as unhealed was
21 what was observed through the dressing as unhealed.

22 DR. McGRATH: And the assumption was made

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1 that what was still stuck was still unhealed?

2 MR. PELTIER: I think, again, it's more of
3 a clinical observation, and I'm going to have Dr. Glat
4 respond to that.

5 DR. GLAT: We attempted to --

6 MR. PELTIER: Just introduce yourself.

7 DR. GLAT: I'm sorry. Paul Glat again.
8 I'm one of the investigators in this study from MCP
9 Hahnemann University in Philadelphia.

10 We attempted every two days after the
11 seven day to attempt to determine complete healing and
12 how that was done is the edges of the Biobrane would
13 be peeled up and trimmed until they would no longer
14 peel off, and those areas were considered unhealed.

15 At times you were able to actually peel
16 off some areas, and you would cause some bleeding or
17 you would find that that area was not unhealed, and
18 that was also determined to be unhealed in those
19 locations as well. So it was either areas where it
20 was seen not to be healed when it was removed or where
21 it was adherent.

22 DR. McGRATH: You made a differentiation

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1 in your protocol about a difference between readiness
2 for recropping and actual recropping. Readiness
3 for -- what was the difference here?

4 MR. PELTIER: Again, readiness for
5 recropping was a clinical evaluation by each
6 investigator, and I'd like to have Dr. Glat address
7 that one again for you.

8 DR. GLAT: Basically we were just asked to
9 determine if we felt that the area could be recropped
10 if needed, and that was when at that point we would
11 say, yes, it is ready for recropping.

12 I never personally recropped any patients
13 and did not need to reuse that, and I'm not sure of
14 the total number in the study, but it was very few, I
15 believe may be two that were actually recropped.

16 DR. McGRATH: What is your definition
17 though of readiness for recropping?

18 DR. GLAT: It was a clinical decision
19 based on the pliability and the thickness of the skin
20 and whether you felt that that area could be reused to
21 be as another split thickness skin draft in another
22 area of burn. It was relatively subjective.

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1 DR. McGRATH: Subjective. Okay. Thank
2 you. I didn't understand that.

3 I do have another question that's a little
4 odd. I'm curious about the neonatal foreskin. How do
5 you harvest that? What's the consent process on it?
6 Do you pay the mothers who do this and then have the
7 blood test afterwards and so forth?

8 DR. SILBERKLANG: Yes, we do pay the
9 donor. It's a nominal amount. We have a formal
10 consent form where the donor consents to what would
11 have normally been a discarded tissue to be used for
12 this application, and the mother consents to have
13 blood tests done, and we pay an additional amount at
14 the end of six months if all tests have passed and the
15 cell lines are cleared for use in production. And
16 that's just the format that we've devised.

17 MR. PELTIER: Right, and that additional
18 payment at the end of six months is to do an
19 additional evaluation of blood. So the mother gets
20 tested at zero time and at six months following the
21 harvesting of the foreskin.

22 DR. McGRATH: Thank you.

1 ACTING CHAIRPERSON GALANDIUK: Ms. Brown,
2 do you have any questions?

3 MS. BROWN: I have no questions.

4 ACTING CHAIRPERSON GALANDIUK: I have one
5 question for the sponsor. Initially it was stated, I
6 think, under the safety portion that one of the
7 advantages would be that the healed area would be
8 ready for recropping and would be durable as such.

9 Why were only three patients recropped?
10 Were that many smaller burns included in the study?
11 That seemed a very low number.

12 MR. PELTIER: It wasn't based on the size
13 of the burns per se. It was a clinical judgment made
14 by each investigator. So even in those areas where
15 there were large burn surface areas, those
16 investigators chosen not to reuse the donor site or
17 not to reuse the treated site as a new autograft site.

18 ACTING CHAIRPERSON GALANDIUK: And
19 secondly, there was one patient who had a rash for two
20 months in the vicinity where this was applied, and it
21 was initially said to be due to the compression
22 garment that was applied to the patient, but it was

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1 initially treated with antibiotic ointment.

2 Were any cultures or any other assessment
3 made of that site?

4 MR. PELTIER: I believe we have the
5 investigator here who had that patient. So I think
6 Dr. Glat can present that to us.

7 DR. GLAT: That particular trial had what
8 we thought was a pustular rash underneath the pressure
9 garment, which we now feel was probably just something
10 like a heat rash. It was initially treated in the
11 clinic, but with topical antibiotics, and then just
12 once it resolved relatively quickly, just with a
13 moisturizing ointment, but we never did culture
14 anything at all, no.

15 ACTING CHAIRPERSON GALANDIUK: But it
16 persisted for two months?

17 DR. GLAT: I believe it was just a very
18 mild -- as it was resolving over time, it wasn't a
19 significant clinical problem for the child over that
20 time.

21 ACTING CHAIRPERSON GALANDIUK: Do any of
22 the panel members have a question? Dr. DeMets.

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1 I have a follow-up question to the
2 evaluation by the three panel members that reviewed
3 things. It would be my guess that it would not be
4 blinded. I mean, these look different. I presume
5 when they were scoring, reviewing, they could make a
6 pretty good guess as to whether this was your product
7 or the control.

8 Can you sort of walk me through how this
9 process took place and what bias might or how the bias
10 might have been eliminated, I guess, is my question.

11 MR. PELTIER: Okay. Well, let me talk to
12 you about the three masked evaluators. As we
13 indicated, they were hired by a third party. There
14 was no knowledge as to who the sponsor of the project
15 was, nor what dressings were being studied.

16 When the photographs were presented to the
17 blinded reviewers, they were independently presented
18 to each reviewer separately, and they were not given
19 the photographs that demonstrated the product in
20 place, in other words, at the zero time.

21 Photographs were then presented from day
22 seven forward. So it would have been somewhat

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1 difficult, yet not impossible, to say that the two
2 sides were different, but not knowing really which
3 dressing was which because we didn't provide that
4 information.

5 ACTING CHAIRPERSON GALANDIUK: Well, if
6 you thought these were Biobranes stuck on one, you'd
7 think it was the --

8 MR. PELTIER: Yes, and I would think that
9 if someone were very familiar with Biobrane, that they
10 could tell. But, again, they didn't know they were
11 doing an evaluation for a clinical study to approve a
12 new product. They weren't given information about the
13 sponsor or the other product. They were just
14 reviewing wound healing slides in random order.

15 ACTING CHAIRPERSON GALANDIUK: Dr. Chang.

16 DR. CHANG: Can you -- this is a simple
17 question. Is it known whether or not the eight
18 patients in the initial pilot study received
19 Oxandrolone or any steroid?

20 MR. PELTIER: The same exclusion criteria
21 was there in the study. I don't have knowledge off
22 the top of my head if they received Oxandrolone or

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1 not.

2 ACTING CHAIRPERSON GALANDIUK: Dr.
3 Diegelmann, do you have any last questions?

4 DR. DIEGELMANN: Yes. One of your
5 efficacy endpoints is that there was no moisture
6 detected. How was that pursued?

7 MR. PELTIER: Clinical observation by the
8 investigator looking at the wound surface during his
9 examination, as well as looking at the absorbent
10 dressings that were initially applied over the top of
11 the product.

12 So if you had a nice, dry, opalescent
13 layer indicative of a stratum corneum that had
14 continuity across the wound and there was no surface
15 moisture present, it was a clinical evaluation.

16 DR. DIEGELMANN: Was there ever any
17 testing in using instruments that could detect vapor
18 evaporation?

19 MR. PELTIER: There was no MVTR type
20 testing done.

21 ACTING CHAIRPERSON GALANDIUK: Dr.
22 McGrath, any other questions?

1 DR. McGRATH: No.

2 ACTING CHAIRPERSON GALANDIUK: No. Well,
3 then we will now break for lunch, and we will
4 reconvene at 1:30.

5 (Whereupon, at 12:19 p.m., the meeting was
6 recessed for lunch, to reconvene at 1:30 p.m., the
7 same day.)

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