

## A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:29 p.m.)

1  
2  
3 ACTING CHAIRPERSON GALANDIUK: I would  
4 like to reconvene the FDA Panel meeting, and now we  
5 will proceed with the FDA Panel presentations, the  
6 preclinical and technical aspect will be covered by  
7 Dr. Sam Arepalli, and to follow him, Dr. Roxolana  
8 Horbowyj will discuss the clinical aspect.

9 Dr. Arepalli.

10 DR. AREPALLI: All right. Good afternoon.

11 The product under consideration is  
12 composite cultured skin indicated by use in  
13 (unintelligible) autograft downsize in burn patients.

14 My name is Sam Arepalli, and I'm the lead  
15 reviewer for this PMA, and the first of the three FDA  
16 presenters this afternoon. I will be presenting the  
17 administrative preclinical and manufacturing aspects  
18 of the product from FDA point of view.

19 Subsequently Dr. Roxy Horbowyj and Mr. Mel  
20 Seidman will review the clinical studies and  
21 statistical issues. Dr. Charles Durfor will review  
22 the manufacturing section of this PMA, and he's in the

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1 audience in case you don't have any questions. He'll  
2 be happy to answer them.

3 Composite cultured skin measures six  
4 centimeters by six centimeters and consists of a  
5 bovine collagen matrix on (unintelligible) human  
6 neonatal fibroblast cells and keratinocyte cells and  
7 culture.

8 The final product is tested for  
9 morphology, survivability, cell attachment, epidermal  
10 college (phonetic), sterility, mycoplasma, and  
11 physical container integrity.

12 The product has a shelf life of 72 hours  
13 when stored inside a temperature maintained shipping  
14 container. The device was approved in February 2001  
15 for the treatment of recessive dystrophic  
16 Epidermolysis Bullosa patients as humanitarian device  
17 exemption, and it is not approved for any other  
18 indication yet.

19 This slide shows the indications for use  
20 of the device. This device is indicated for the  
21 management of (unintelligible) autograft dermicides  
22 (phonetic) in burn patients.

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1 Both the current matrix and cellular  
2 components of the device were thoroughly tested for  
3 the biocompatibility and sterility, and this slide  
4 shows the biocompatibility testing of collagen metrics  
5 and all tested -- all tests past the biocompatibility  
6 test.

7 This slide shows the biocompatibility and  
8 toxicology testing of cellular components, and the  
9 tests are listed there. All of them passed the test.

10 In summary, CCS used in this clinical  
11 study was manufactured under aseptic conditions from  
12 a single human neonatal donor. The fibroblast and  
13 keratinocyte cells, cell banks which are the source of  
14 the cells from which CCS is derived are tested for  
15 human and animal viruses, retroviruses, bacteria,  
16 fungi, yeast, mycoplasma, karyology, isoenzymes, and  
17 tumorigenicity.

18 The safety of the cell components was  
19 tested and several points of the device manufacturing.  
20 Product manufacturing also includes (unintelligible)  
21 from animal materials. All animal derived materials  
22 are tested for viruses, retroviruses, bacteria, fungi,

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1 yeast, and mycoplasma before used, and all bovine  
2 material is obtained from countries free of bovine  
3 spongiform encephalopathy.

4 The sponsor has concluded all the  
5 biocompatibility and toxicology test in a cognitive  
6 ISO 10993 and FDA guidance documents (unintelligible)  
7 satisfactory.

8 Roxy.

9 DR. HORBOWYJ: Thank you.

10 Good afternoon. My name is Roxy Horbowyj.  
11 I'm a general critical care surgeon, and as a clinical  
12 reviewer for this PMA, I represent the FDA perspective  
13 in OrCel composite cultured skin use in the treatment  
14 of split thickness skin graft donor sites in burn  
15 patients.

16 I will go over a brief introduction, the  
17 produce indication for use, in the pilot study design  
18 and outcome, as well as the pivotal study design and  
19 outcome, and a brief summary.

20 Burn patients, as you know, can have two  
21 wounds, the burn wound, if deep and partial or a full  
22 thickness, is commonly treated with split thickness

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1 skin autograft, and therefore, there is the second  
2 wound to be treated.

3 Treatments, as you have heard, can include  
4 impregnated fine mesh gauze and hydrocolloid  
5 dressings, as well as temporary wound dressings.

6 Time to 100 percent wound healing with  
7 dressings such as this is multi factorial and known to  
8 vary. Commonly with fine mesh gauze and hydrocolloid  
9 dressings, literature will report healing, 100 percent  
10 healing at the donor sites in ten to 14 days.

11 Literature for Biobrane can report or has  
12 reported time to 100 percent wound healing with donor  
13 sites ranging from nine to 19 days. The OrCel  
14 composite cultured skin product is proposed to be  
15 indicated for use in accelerating closure of split  
16 thickness donor site wounds in burn patients, and the  
17 basis of this are G990063 pilot and pivotal studies.

18 The split thickness autograft donor site  
19 pilot study was a single center safety and preliminary  
20 efficacy study in which eight burn patients who were  
21 undergoing graft work included in treatment. Study  
22 data is reported for five of these eight burn patients.

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1 In the pilot study, treatment and control  
2 sites were as has been described by the sponsor within  
3 patient matched pair sites, which were randomized to  
4 CCS or Biobrane-L. The sites were treated with a one  
5 time application of the randomized device. In  
6 patients over three years old up to two CCS devices  
7 could be applied. A control would be applied in an  
8 equivalent area since the sites were matched.

9 And for patients under three years old up  
10 to one CCS device could be applied. Control of an  
11 equivalent area was applied for a matched site.

12 Outcomes for the pilot study for efficacy  
13 were evaluated by photography, planimetry, and  
14 investigator assessment. For this study, the means  
15 were typically -- the difference in the means between  
16 CCS and control were typically comparable from method  
17 analysis to method analysis about six. The medians,  
18 however, varied.

19 As I said before, eight patients were  
20 studied. Five were reported for the three control  
21 sites of CCS and three control sites were censored due  
22 to either non-healing or blistering.

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1           The pivotal study was designed to be a 15  
2 center safety and efficacy study based on the pilot  
3 study, as there were no gross safety concerns  
4 otherwise with the pilot study. Twelve centers did  
5 participate. Three did not enroll any patients.

6           The design was similar in that treatment  
7 and control were within patient patched pair sites,  
8 and the patients were patients with split thickness  
9 autograft donor sites.

10           The study was designed to enroll 100  
11 intent to treat patients and 85 evaluable patients,  
12 and again, the treated sites in patients over three  
13 years old at this time could have up to four donor  
14 sites, four CCS devices applied with a comparable  
15 control area, and patients under three years old up to  
16 two CCS devices could be applied with a comparable  
17 control area.

18           The objectives in this study were to  
19 evaluate CCS and control for safety and efficacy and  
20 facilitated timely wound closure of split thickness  
21 skin donor site in burn patients. Other objectives  
22 included the function and durability of recropped skin

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1 serving as an autograft, as well as the time to  
2 complete 100 percent re-epithelialization or healing  
3 of the recropped and retreated donor site in a subset  
4 of burn patients with massive surface area of  
5 involvement.

6 This submission and our discussion focus  
7 on objective number one. There were three CCS sites  
8 and one Biobrane site that were recropped. Data is  
9 very limited on these sites, and so we're addressing  
10 objective number one.

11 Efficacy was evaluated by time to healing,  
12 as you have heard. The primary efficacy endpoints was  
13 determined by photography evaluated by three  
14 independent reviewers, and the final score being two  
15 of three agreeing scores by these reviewers.

16 Secondary objectives were time 100 percent  
17 wound healing by planimetry, which was performed by an  
18 unmasked investigator and analyzed at a central  
19 laboratory, masked to treatment as well as tied to 100  
20 percent wound healing by the unmasked investigator,  
21 incidence of 100 percent wound healing and time to  
22 recropping.

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1 Safety was assessed by profiles of adverse  
2 events, treated site pain, infection and itching, and  
3 scar outcomes as assessed by the investigator at 12  
4 and 24 weeks using the Vancouver Burn Scar and as  
5 assessed by photo evaluation, again two or three  
6 agreement scores, at 12 and 24 weeks, and that photo  
7 evaluation was by the Hamilton Burn Scar Scale.

8 Pivotal study outcome, patient accounting.  
9 The total enrolled number of patients was 82. The  
10 proposed number had been 100 patients. Sixty patients  
11 completed the study out to six months. Twenty-two had  
12 been discontinued.

13 Originally as presented in the PMA, the  
14 safety cohort was presented for 82 patients, and the  
15 efficacy cohort was presented for 74 patients.

16 The sponsor today has presented their data  
17 for safety and for efficacy based on 82 patients, in  
18 addition, efficacy presented for the per protocol 74  
19 patient cohort.

20 As I have said, the recrops cohort  
21 consisted only of three CCS sites and one control  
22 site.

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1 A pivotal study was conducted primarily in  
2 patients who were male, in the age range of 15 to 65  
3 years, primarily Caucasian, with total body surface  
4 area burn of 20 to 40 percent, and with donor site  
5 area of greater than 45 centimeters squared.

6 Efficacy as determined by the three  
7 different measurements of assessment is presented  
8 here. Time to wound, 100 percent wound healing. The  
9 column here represents the differences between CCS and  
10 control.

11 The trends, the direction is consistently  
12 showing that CCS wounds healed faster than control  
13 wounds. However, there are differences depending on  
14 the method of use and also whether the mean or median  
15 are evaluated.

16 Variation was noted to occur depending on  
17 the sites that -- by sites, by investigational sites,  
18 and these differences are not based strictly on the  
19 number of patients that were enrolled because the  
20 differences between CCS and Biobrane-L are most  
21 prominent at Centers 1 and 3, who enrolled 19 and nine  
22 patients, respectively.

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1                   However, in a comparable site with 16  
2 patients, sites number four, the differences are not  
3 comparable really to the differences seen in the prior  
4 two sites, and also in site number eight, which  
5 enrolled nine patients, the differences are not the  
6 same as in Sites 1 and 3, also in Site No. 15, which  
7 enrolled ten patients. So there are some site  
8 variations.

9                   The sponsor presented today a covariate  
10 analysis with p values which are new really as of  
11 today. However, looking clinically at some of the  
12 covariates as the sponsor did present them, again, I'm  
13 going to really look at differences because I think  
14 that just makes it easier to look at.

15                   You can see that as patients were older,  
16 the difference between Biobrane and control increased.  
17 Specifically, there was a question about patients with  
18 age less than 12. In the PMA in Volume 9 for patients  
19 12 years old and less or less than 12 years old, there  
20 are no differences, and it is not statistically  
21 significant for CCS compared to control. The  
22 differences are presented for planimetry and

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1 photography and particularly for photography I believe  
2 it's 12 days for both CCS and control.

3 And the same for donor sites. While the  
4 differences here broken out for less than 45 square  
5 sonometers and greater than 45 square sonometers,  
6 differences are somewhat comparable. The differences  
7 were not statistically significant for patients with  
8 donor sites smaller than 20 square centimeters, and  
9 that is in the PMA Volume 9.

10 Continuing through this list, you can see  
11 that there were differences due to race. African  
12 American patients had a greater difference than  
13 Caucasian patients and patients of other race, and  
14 there were differences in patients with varying total  
15 body surface area burned, the difference being smaller  
16 as of the total body surface area burned is smaller  
17 and becoming greater as the body surface area burned  
18 increases.

19 Comparing data with Oxandrolone, when the  
20 overall population is presented the n is 82. CCS  
21 tied to wound closure is a median of 12 days and  
22 control is a median of 17 days, and this data is based

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1 on planimetry.

2 When looking at patients who were also  
3 treated with Oxandrolone, the median time to 100  
4 percent wound healing for patients treated with CCS is  
5 comparable to the overall populations, 13 days  
6 compared to 12.

7 However, for control patients also treated  
8 with Oxandrolone, the median time to 100 percent wound  
9 healing is 22 compared to 17. For patients with  
10 Oxandrolone and also treated with CCS, again, the time  
11 to 100 percent wound closure is comparable to the  
12 other patients, being 12 days for this cohort, and for  
13 control the time to 100 percent wound healing without  
14 Oxandrolone is 14 days. So there are differences that  
15 are observed here, particularly in the control group.

16 Incidence of 100 percent wound healing.  
17 All patients healed by the end of the study at six  
18 months. The sponsor has presented to you the number  
19 of patients who didn't heal by 32 days. The numbers  
20 presented here represent patients who did heal by 32  
21 days, and being that there is a difference in the  
22 overall cohort for time to would closure, that is why

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1 we get these differences.

2 Time to readiness for recropping is  
3 presented for the overall patient population, and the  
4 median -- the difference in the median time to  
5 readiness for recropping is seven days, and the mean  
6 is 4.9 days. Again, the negative number here is  
7 adjusting that.

8 The readiness to recropping was achieved  
9 faster for sites treated with CCS than with control.

10 Safety. In the PMA, again, in Volume 9  
11 and as well as in Amendment 2 to the PMA, there is  
12 report of one patient having infection at both of the  
13 donor sites. So there was report of infection at one  
14 CCS treated site and one control treated site, and  
15 these are both in the same patient. So there's really  
16 no difference between the cohorts.

17 Signs of infection were reported in three  
18 controlled treated sites and one CCS treated site, and  
19 signs of blistering and breakdown were reported in  
20 eight controlled treated sites and four CCS treated  
21 donor sites.

22 Itching was recorded as none, mild

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1 moderate and severe. Again, looking at the difference  
2 between CCS and controls, so a negative number would  
3 suggest that there is less itching reported in  
4 controls in the case of none. However, this would  
5 suggest that more patients reported no itching at  
6 their controlled treated site than in their CCS  
7 treated site, and then more patients reported itching  
8 at their CCS treated site compared to control, but  
9 these numbers are quite small.

10 Pain. Pain was reported using different  
11 skills depending on the patient's age. Pain is  
12 reported for children less than or equal to three  
13 years old as to whether or not they're able to use  
14 their treated sites, and eight out of ten patients are  
15 reported to have been able to use their treated sites.

16 Pain reported for ages four to seven and  
17 patients greater than eight years old reported on the  
18 basis of a scale of ten, and the differences here  
19 between CCS control suggest that for the patients of  
20 age four to seven, they reported a .3 of ten  
21 difference in means, with CCS being reported slightly  
22 higher than control and the median is in the same

1 direction.

2 For patients greater than ten, the  
3 direction was opposite, being lower in the CCS treated  
4 sites for both the mean and the median, but again,  
5 this is .4, .3 on a scale of ten. So I think the  
6 differences are very small.

7 The Vancouver Burn Scar and the Hamilton  
8 Burn Scar were evaluated both at 12 weeks and at 24  
9 weeks. The Vancouver Burn Scar score ranges from zero  
10 to 15. So the maximum score that can be assigned is  
11 15. The Hamilton Burn Scar score can be up to 20.

12 And looking again at the differences, the  
13 differences between CCS and control was .81 of 15, and  
14 the differences, the median, there was no difference  
15 in the median at 12 weeks for the Vancouver Burn Scar  
16 score as evaluated by the investigators.

17 The Hamilton Burn Scar score, the mean and  
18 the difference between the means was 1.06, and the  
19 difference between the medians was two. Again, this  
20 was out of 20.

21 The reason I focus on this and on the  
22 range is that there is a Panel question that addresses

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1 this.

2           These differences were statistically  
3 significant, but we will ask that the comment on the  
4 clinical significance of these differences  
5 considering the range of scores that is possible.

6           Also then looking at data from week 24, we  
7 see that the Vancouver Burn Scar score has increased.  
8 However, the Hamilton Burn Scar score compared to what  
9 it was at 12 weeks has decreased. Now, the median  
10 difference here is zero.

11           In summary, effectiveness was evaluated by  
12 time to 100 percent wound healing, and the median for  
13 CCS was 12 days. The median for control was 16 days.  
14 The mean was 13. Point, two days for CCS treated  
15 sites, and the means for control treated donor sites  
16 was 18.4.

17           The incidence of 100 percent wound healing  
18 was 100 percent. All donor sites healed while they  
19 were on study.

20           A comment as to recropped wounds. It is  
21 very limited because only three sites treated with CCS  
22 were recropped, and one site treated with Biobrane was

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1 recropped. Safety outcomes are clinically comparable  
2 for CCS and control.

3 And now I'll introduce Mel Seidman to give  
4 you the statistical presentation.

5 MR. SEIDMAN: I don't have any overheads,  
6 but you do have my handout.

7 Mel Seidman. I'm a statistician with OSB,  
8 and I was the statistician assigned to review this  
9 application.

10 I have several statistical comments or  
11 basically three issues for your consideration.

12 One, the statistical test used to  
13 determine P values for various endpoints did appear to  
14 be appropriate. However the results were often  
15 reported without numerator or denominator, and  
16 sometimes without the statistical test reference.  
17 This made it difficult to verify the sponsor's  
18 findings.

19 I did receive a disk that included patient  
20 data from all 82 patients last week, and from this  
21 disk I have verified primary effectiveness results  
22 using all 82 patients not censored, and my conclusions

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1 are the same as the sponsor's, that the CCS device was  
2 statistically better than the Biobrane-L for 100  
3 percent wound closure.

4 Two, the sponsors claim that there were no  
5 severe, life threatening, or adverse events that  
6 occurred at an incidence of greater than five percent  
7 may not be complete. This is because if we included  
8 95 percent confidence intervals for these rates any  
9 reported event would have an upper confidence level of  
10 greater than five percent.

11 Note that 64 or 78 percent of the patients  
12 enrolled had at least one severe event. The  
13 confidence intervals are directly related to the  
14 sample size.

15 Three, the primary effectiveness endpoint  
16 is time to complete healing. This is determined by  
17 three methods: physical exam, wound tracing, or  
18 photography, which is the gold standard and the  
19 primary methodology suggested in the protocol.

20 To help minimize the potential for  
21 observer bias via the photography, pictures were  
22 randomized and evaluated by experts. The methodology

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1 used appears to be acceptable.

2           However, it is my understanding that the  
3 device and the control look different, and the  
4 application and removal procedures of the devices were  
5 different.

6           For example, the control device required  
7 staples. So how could this truly be a blinded study?

8           Four, pooling by investigator. The  
9 sponsor states that the data is poolable across  
10 centers despite differences among investigators and  
11 between methods that are greater than differences  
12 between treatment cohorts. This was true when  
13 typically we look at each center for acceptance when  
14 this is true.

15           The sponsor did do this. Please note that  
16 the sponsor's trend analysis is true. At no case did  
17 the control perform better than the device by  
18 investigator.

19           However, you should also note that if we  
20 excluded investigator number one, the findings do not  
21 show statistical difference between the device and the  
22 control based on 100 percent wound healing evaluated

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1 by photography.

2 Five, at a June 11th meeting with the  
3 sponsor and FDA, I asked the sponsor why such a big  
4 difference between the mean and median time, why they  
5 thought such a big difference occurred.

6 The sponsor explained this by saying once  
7 the investigator said there was 100 percent wound  
8 closure, the follow-up then was changed to 30 days.  
9 This appears to be a potential deviation from the  
10 protocol and seems to me could possibly influence the  
11 photography conclusion.

12 Six, the study was stopped before  
13 completion. The sponsor states at the time the  
14 decision was reached to stop the study due to  
15 decreased enrollment rate where approximately 90  
16 percent of the patients had to achieve wound healing,  
17 and that the sample size of between 75 to 80 patients  
18 would be sufficient to achieve statistical  
19 significance.

20 Therefore, the trial was stopped early in  
21 May of 2000.

22 The sponsor addressed this issue with a

1 post hoc power calculation based on primary endpoints  
2 prespecified in the protocol. The sponsor's reported  
3 results are correct based on their assumptions.  
4 However, the claim of a conservative standard  
5 deviation of 8.5 used in the calculations may not be  
6 conservative as claimed. This is primarily due to  
7 censoring the patient if after 32 days 100 percent  
8 wound healing was not achieved.

9 Please note that a slightly larger  
10 standard deviation of only greater than ten would lead  
11 to inadequate power based on the same assumptions  
12 used.

13 Also, note that the sponsor originally  
14 estimated 120 patients would be enrolled in order to  
15 complete 85 patients.

16 Seven, the sponsor used the last  
17 observation carried forward assumption in their  
18 analysis. If there is a worsening trend, this type of  
19 analysis may miss the trend. The potential for  
20 missing data can be an enormous problem, and the  
21 sponsor's assumption is that all patients with missing  
22 data are not failures.

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1                   There were 22 of 82 patients who  
2 discontinued the study before week 24.

3                   And finally, I just wanted to mention that  
4 the steroid information and some other information was  
5 presented today and has not been reviewed by our  
6 staff.

7                   Thank you.

8                   ACTING CHAIRPERSON GALANDIUK: Thank you,  
9 Dr. Seidman.

10                  I will now ask Dr. Sam Arepalli to read  
11 the FDA questions.

12                  DR. AREPALLI: Okay. Panel Question No.  
13 1: adverse events, such as pain, infection, and  
14 itching, are similar in the clinical study for both  
15 the CCS and the Biobrane control. Please discuss  
16 whether the safety data for CCS provides a reasonable  
17 assurance that CCS itself (unintelligible) autograft  
18 donor sites in burn patients.

19                  Panel Question No. 2: the primary  
20 effectiveness endpoint in the protocol was time to  
21 complete wound closure as measured by photographic  
22 assessment. The study was designed to demonstrate a

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1 9.5 day improvement in time to wound closure. The  
2 primary effectiveness results are provided in this  
3 table as shown here, and I don't want to read all  
4 this, but as you can see from the p values they are  
5 reaching statistical significance for both mean and  
6 median as to wound closure.

7 Do these data demonstrate that there is a  
8 reasonable assurance that in a significant portion of  
9 the target population the use of CCS will provide  
10 clinically significant results?

11 Panel Question No. 3 regarding safety  
12 again. This is regarding the scar score. What  
13 Hamilton and Vanguard scale scores are provided here,  
14 they are displayed in the slide, on the slide, and  
15 this is Vancouver burn scale at 12 and 24 weeks. The  
16 previous one was Hamilton burn scar score for 12 and  
17 24 weeks, and the question is: the difference between  
18 CCS in Vancouver burn scar score and Hamilton burn  
19 scar score at 12 weeks and 24 weeks is statistically  
20 significant. Please discuss the clinical significance  
21 of these differences for Vancouver burn scars at 12  
22 weeks, Vancouver burn scar at 24 weeks, Hamilton burn

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1 scar at 12 weeks, Hamilton burn scar at 24 weeks.

2 Finally, Panel Question No. 4, do you have  
3 any recommendations regarding the proper labeling,  
4 including indications, contraindications, warnings,  
5 precautions, instructions for use, et cetera.

6 Thank you.

7 ACTING CHAIRPERSON GALANDIUK: thank you  
8 very much.

9 We will now have the panel deliberations  
10 and comments. Before we start the panel  
11 deliberations, we would like to call on two panel  
12 members to comment on this PMA application. We'll  
13 start with Dr. Joseph Boykin, who will give us a  
14 critical overview of the study, and then proceed with  
15 Dr. DeMets who will comment on the statistics of the  
16 submission.

17 Dr. Boykin.

18 DR. BOYKIN: Thank you.

19 I was asked to comment on the study  
20 concerning the pivotal review of data provided by the  
21 sponsor. We'll try to highlight some of the subjects  
22 or the areas that we had questioned earlier. Some of

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1 the questions I may have later have already been  
2 answered.

3 In summarizing the CCS, we understand is  
4 a bilayer skin substitute. I think everybody  
5 understands that.

6 The pivotal study from 12 sites with one  
7 investigator per site, pooled data presented. The  
8 study design for 100 patients, and essentially 60  
9 followed through for the entire 28-week period, with  
10 control group consisting of patients receiving  
11 Biobrane treatment as outlined.

12 I'm doing it wrong now.

13 ACTING CHAIRPERSON GALANDIUK: Following  
14 these presentations, panel members will have an  
15 additional opportunity to ask the sponsor questions.

16 DR. BOYKIN: All right. The modes of  
17 action as described by the sponsor are those of the  
18 device acting as a temporary absorbable hemostatic and  
19 protective wound dressing, which is biocompatible with  
20 a tissue regeneration matrix, and that the device acts  
21 as a source of biologically active extra cellular  
22 matrix components, cytokines and growth factors, and

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1 I believe this has been well documented, you know.

2 The hypothesis stated by the sponsors, the  
3 application enriches the growth factor environment of  
4 an acute wound bed, in this case a donor site, and  
5 contributes as a net positive influence on the wound  
6 healing process.

7 The benefits as stated are that there is  
8 an early opportunity for recropping, early donor site  
9 healing, low incidence of infection, decreased pain  
10 and discomfort, and improvement in scar formation,  
11 which we have just reviewed the last few minutes.

12 These are the data that you've seen for  
13 several previous slides, and I'm not going to review  
14 that in detail.

15 I'll go on to the next one.

16 The critique at this time of the study has  
17 a few points that we have discussed along the way.  
18 First of all, the indications for efficacy, I believe,  
19 need to be more focused with the device as we  
20 understand it.

21 Dr. Horbowyj and even the data supplied by  
22 the sponsor have pointed to the fact that the data

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1 indicates a fairly significant role for efficacy with  
2 healing, earlier healing of the donor site with  
3 patients over the age of 12 and for burns that are  
4 greater than 20 percent total body surface area, and  
5 I believe that the indications in terms of labeling  
6 should be considered along these guidelines.

7 The grafts were not monitored in terms of  
8 the timing after the burn injury. This variable,  
9 along with the thickness of the wound and also the  
10 clinical condition of the patients, is somewhat of a  
11 debate, but I think not an issue that would present a  
12 hard challenge for the evaluation of the device.

13 There appear to be an absence of  
14 instructions, however, for the care of the infected  
15 donor site with the device in place. I believe this  
16 needs to be addressed. Precautions for the patients  
17 that have been excluded from the pivotal study should  
18 also be placed in the labeling of the device so that  
19 individuals who are being treated for burns who fall  
20 into this category are not treated with the device as  
21 it has been studied.

22 I would also add that it would be

1 important to place a precaution that the device not be  
2 used on the burn wound as I'm certain that would be a  
3 temptation by many clinicians who are into high tech  
4 devices.

5 There were no clear, adequate preclinical  
6 studies of sale or retention or the survival of the  
7 donor cells in the patient population. This, I  
8 believe, needs to be addressed. I absolutely don't  
9 feel that there's a fear on the public sector that  
10 there may be retention, but I think the risk of this  
11 needs to be clearly outlined.

12 Now, in terms of the stand alone  
13 treatment, we've been kicking this drug back and  
14 forth. It came to my attention that 30 of the  
15 patients in the study were about 37 percent had  
16 received this drug. I thought it would be beneficial  
17 to try to review this situation in terms of what it  
18 really means.

19 So I'm going to, if you'll just bear with  
20 me through this slide, review very clinically the  
21 significance of Oxandrolone and human growth hormone  
22 in the treatment of burn patients, and this will give

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1 you a little historical perspective of why we've been  
2 concerned about this.

3 In the burn treatment experience, human  
4 growth hormone was initially looked at as an agent to  
5 promote anabolic metabolism enhancing the acute  
6 chronic phases of recovery and the amelioration of the  
7 catabolic response to burn injury in severe burn  
8 patients, and the human growth hormone was looked at  
9 following experimental studies in early clinical  
10 trials by Pruden, Wilmore and Herndon up until 1990.

11 This subsequently led to clinical trials  
12 which basically showed that there was increased whole  
13 body protein recovery by more than 25 percent, a  
14 reduction in the hospital length of stay by 25  
15 percent, and also improvement in the healing rate of  
16 skin graft donor sites by 30 percent in patients  
17 treated with human growth hormone.

18 Now, the problems with that hormone  
19 therapy is there was associated hyperglycemia which  
20 required insulin therapy and accentuated  
21 hypermetabolism in the patients being treated.

22 So research continued into methodologies

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1 that would render the same types of results, but  
2 without the complications. And in 1999, Dr. Demling  
3 reported his comparison of the anabolic effects and  
4 complications of human growth hormone and the  
5 testosterone analog Oxandrolone after severe burn  
6 injury.

7 Now, Oxandrolone has been approved by the  
8 FDA for involuntary weight loss. It is clinically  
9 used for severe burn patients on a regular basis, as  
10 has already been discussed, but the concern, again,  
11 that we've had is what effect might this drug have on  
12 a study on donor site healing.

13 As seen by Dr. Demling in his study  
14 comparing Oxandrolone to human growth hormone, he  
15 found that Oxandrolone could achieve an identical  
16 reduction in net wet loss, nitrogen loss, and  
17 significantly decrease donor site healing time after  
18 burn injury as that observed with human growth hormone  
19 treatment.

20 He also went on to show that there was not  
21 the same hyperglycemia or hypermetabolic response with  
22 the Oxandrolone as there was with human growth

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1 hormone, and how it is commonly used in place of this.

2 So we seem to have a problem. The  
3 research summary on the data with Oxandrolone looking  
4 at Oxandrolone versus placebo patients who have seen  
5 donor site healing decrease in 13 plus or minus three  
6 days in the placebo group; the nine days plus or minus  
7 two days in the study published in the Journal of  
8 Critical Care last year. He showed no significant  
9 difference when Oxandrolone was compared to  
10 recombinant human growth hormone, and in a fairly  
11 recent study reported in Wound Repair and  
12 Regeneration, Dr. Demling went on to demonstrate that  
13 the anabolic steroid Oxandrolone significantly  
14 enhanced wound healing unrelated to any generalized  
15 increase in protein mass as would be reflected in body  
16 weight.

17 Now, the discussion that goes along with  
18 this particular report alludes to the fact that there  
19 is probably synergy with axis factors stimulated by  
20 Oxandrolone to include insulin growth factor 1 that  
21 may somehow stabilize or enhance the effect of growth  
22 factors at the site of injury.

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1 This, of course, would lead one to believe  
2 that perhaps there may be issues related to different  
3 types of wounds, especially ones that might be treated  
4 with additional growth factor types of devices and how  
5 they might respond.

6 This has essentially led to these two  
7 questions, and I would certainly like to hear the  
8 Panel discuss. First of all, having made the  
9 statements that we have just reviewed and  
10 understanding the data as we've tried to break it down  
11 into the different cohorts: does the presence of  
12 Oxandrolone treatment in 30 of the 82 patients  
13 randomized for this study of donor site wound healing  
14 allow an unbiased determination of the efficacy of CCS  
15 in the treatment of burn patient donor sites.

16 And lastly, assuming that all patients  
17 receiving Oxandrolone were removed from the study,  
18 would the remaining cohort receiving CCS achieve  
19 statistical significance with skin graft donor site  
20 healing?

21 Thank you very much.

22 ACTING CHAIRPERSON GALANDIUK: Thank you.

1 Dr. DeMets, would you?

2 DR. DeMETS: For obvious reasons, I'm  
3 going to try a lower tech approach.

4 (Laughter.)

5 DR. DeMETS: And while we're waiting, I  
6 just want to make a comment which I don't have a  
7 transparency on, but there was some discussion in the  
8 material presented about sample size discussion and  
9 noncompliance and power which was alluded to earlier.  
10 My own feeling is that I don't think the sample size  
11 adjustment that's necessary was fully appreciated  
12 because if you have a 30 percent noncompliance, for  
13 example, in the treatment group, the sample size  
14 adjustment is actually multiplied by a factor of one  
15 over .7 squared. So you also have to double the  
16 sample size.

17 So I would say that the sponsor was  
18 probably lucky in a sense that with the noncompliance  
19 you had, you should have had a lot bigger sample size  
20 going into it, but at any rate, it turned out in your  
21 favor at least as far as we can tell so far.

22 And I want to point out and draw the

1 panel's attention to a few statistical issues that I  
2 think are relevant. The material that was presented  
3 had lots of different analyses based on intention to  
4 treat per protocol and so forth and son on.

5 By intention to treat, by the way, we mean  
6 all patients. That means all patients and all events  
7 as best we can find, and if you have some kind of  
8 noncompliance and you start fiddling around, you can,  
9 in fact, get some bias which I'll show.

10 I know it's popular and sometimes asked  
11 for, a per protocol analysis, but I am consistent in  
12 my campaign to speak against the per protocol analysis  
13 because I think it's hard to interpret and it's  
14 extremely vulnerable to bias.

15 Next transparency. That's fine right  
16 there. Actually put up -- that's fine. That's fine.

17 So when we think about a trial, there are  
18 lots of biases we want to eliminate. Patient  
19 allocation, while this was a randomized trial, that's  
20 good. The issue of concomitant therapy, we just had  
21 some discussion about Oxandrolone. We're going to  
22 come back to that in a minute, but you want to have

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1 concomitant therapy.

2 The issue of patient evaluation. Well,  
3 device trials are challenging because they're tough to  
4 blind, as we all know. So you have to work especially  
5 hard at trying to minimize the bias that can creep  
6 into patient evaluation, and I think that this study  
7 has done a pretty good job of trying to address that.  
8 I wouldn't say it's perfect or it's eliminated it, but  
9 it's a pretty good approach and one that I've  
10 experienced in other studies.

11 The issue of the analysis, intent to  
12 treat, I'll come to in a second, but that's another  
13 area which I want to focus on. The matched pair  
14 design I raise in my questions, and while I think a  
15 conservative analysis as far as I can figure out was  
16 used, nevertheless, probably in future trials of this  
17 and perhaps even in reexamining this, that it would be  
18 worthwhile at least looking into the statistical  
19 methodology that takes in the fact that you're looking  
20 at the treatment and the control in the same patient.

21 So I don't think it's going to matter to  
22 our interpretation one bit as far as I can tell, but

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1 it would probably be more correct.

2 Now, let me show you why -- the next  
3 transparency -- I think this intention to treat issue  
4 is so important and why I don't like per protocol  
5 analysis. I've given this lecture to this panel  
6 before. So I apologize for redundancy.

7 This is an example that comes from the  
8 cancer world, and I recognize it's cancer therapy and  
9 not device therapy, but you can find these examples  
10 all over the literature.

11 This is a study of disease free survival  
12 in a cancer patient population, and the therapy, I've  
13 even forgotten all of the details of, but it's post  
14 surgery, post mastectomy, and what's depicted here is  
15 compliance, disease free survival and compliance.

16 The top line is the Kaplan-Meier curve for  
17 the patients who had better than 85 percent  
18 compliance, and the middle curve is those in the 65 to  
19 84, and the bottom is less than 65.

20 And by compliance here, it is the amount  
21 of dose you took over the dose that the protocol  
22 specified that you should have taken if you complied

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1 the whole way perfectly.

2 So you can see that the good compliers do  
3 better and the poor compliers do worse. So what's the  
4 big deal. Well, the big deal here, this is the  
5 placebo arm of the trial. So dividing patients up by  
6 compliance is tricky business.

7 Furthermore, I didn't bring the  
8 transparency, but I can reorder these any way you want  
9 by tinkering in appealing ways to the definition of  
10 compliance. So the minute you start horsing around  
11 with compliance in a per protocol analysis, you tell  
12 me what result you want and I'll get it for you. I'll  
13 just be creative enough.

14 And I can even make arguments that sound  
15 pretty appealing. So for that reason we really need  
16 to rely on the intention to treat analysis. It's the  
17 safest ground. Now, I know that it's not a perfect  
18 approach. It has its problems, but it's where you  
19 start, and so I would ask the panel to focus their  
20 attention on the intention to treat analysis in this  
21 study. As far as we can tell, it doesn't seem to  
22 matter.

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1 Let's move on.

2 Now, the issue of missing data, which is  
3 an issue if you believe in the intention to treat  
4 principle. If you don't believe in that, then missing  
5 data is easy. You just get rid of the patients with  
6 missing data and you move on.

7 If you believe in intention to treat,  
8 which is all patients and all events, then missing  
9 data is a problem. The trouble with that is that you  
10 assume that the data is missing at random, and that's  
11 probably not true because as patients get lost to  
12 follow-up, it could, for example, be the sickest  
13 patient. So there were patients who said, "I don't  
14 like the toxicity. I'm getting out of here."

15 So the fact that it's not missing at  
16 random makes the missing data a problem, and here we  
17 use, I guess, the last observation carried forward  
18 rather than last value carried forward.

19 That's the traditional approach. It's the  
20 one we always use or at least always used to use, and  
21 it's not a perfect analysis. It is not immune to  
22 introducing biases because you make certain

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1 assumptions about that. You assume that what would  
2 happen is what happened in the past.

3 So it's not a perfect analysis. I don't  
4 have an answer to tell you what they should have done  
5 instead of that, but just remember it has some basis  
6 that you had to sort of put in the back of your mind  
7 when you interpret the data.

8 Next.

9 One nice thing about transparencies is you  
10 can make up your talk at the last minute, and I was  
11 struck by several of the reviewers, their curiosity at  
12 least about subgroups, and I had to say, "Be very  
13 cautious about subgroups, especially in a study that  
14 has a total of 82 patients.

15 The small numbers is really at work here,  
16 and it's clinically almost compelling to look because  
17 you want to understand it better.

18 Well, a study this size, explaining this  
19 data too fine is really asking for trouble. If it's  
20 consistent, that's comforting, but you see  
21 differences. Hard to know what to make of them. It  
22 could be just random noise. It could be real. This

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1 trial is not going to sort that out.

2 We have multiple analyses, and my only  
3 point about that is that these are not sort of  
4 independent confirmations, but these are just  
5 variations of the same theme. So it's nice that these  
6 analyses are robust. It doesn't matter which test,  
7 but you're still looking at the same outcome by and  
8 large or variations of it.

9 So it's great. I'm glad it works that  
10 way, but it's not as though we're stacking up more and  
11 more data in argument that this is good.

12 I wanted to focus some comments on this  
13 issue which Dr. Boykin raised, which is what I call  
14 treatment by treatment interaction. Maybe if you  
15 could just move that up a bit.

16 What I've tried to graph here is sort of  
17 what's going on. If you look at the -- this is a  
18 response. We have a response. I guess it was days  
19 till wound healing, as was shown. I've got the  
20 control arm and the treatment arm, and I've got these  
21 numbers are roughly in the right order, I think.

22 If you look at the control arm and the

1 days, it's like 22 and 14 or something like that, and  
2 over on treatment it's the smaller numbers, and I have  
3 them in front of me here, like 13 and a half and 12.

4 So what you can see here is depending on  
5 whether you're on the drug or not, you get a different  
6 response. It's what we would call a quantitative  
7 interaction. In other words, it's in the same  
8 direction. It just modifies the size of the effect.  
9 So if you were to just do the overall, you're going to  
10 get some kind of average. So the red dot here and  
11 comparing the red dot here to the red dot there.

12 But if you were to break it down as we've  
13 already seen, you have different effects. So I do not  
14 personally believe that one should be breaking these  
15 analyses down too fine because of the number of  
16 patients. This could be chance. It could be real.  
17 Again, this study won't by itself prove it, except for  
18 the external information which was just presented.

19 So the real question for us is I don't  
20 think it changes the idea that this treatment is  
21 probably effective and beneficial, but the size of the  
22 effect in general depends on what mix of population.

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1 I mean, if all of the patients are going to start  
2 getting this drug, that tells us one kind of response.  
3 If half or more than half are not, then we get  
4 something else.

5 So that's a clinical interpretation as to  
6 how we might see the size of the effect relative to  
7 the standard. It clearly indicates that this is  
8 certainly as good as, if not better than the standard  
9 class life.

10 On the bottom there are some issues raised  
11 about poolability. Well, I think because of the  
12 design this was this was randomized within the center.  
13 I don't view this as an issue because I expect some  
14 variation across centers, even only 12 centers.

15 At the worst, you could stratify your  
16 analysis by center, but if you flip to the next  
17 transparency, I'll show you why I believe in this.  
18 This is a trial, and I apologize for presenting drug  
19 results to you. It's where I've spent most of my  
20 life, working in drug trials, but this is an old  
21 study, 20 years ago, of beta blockers and treating  
22 heart attack patients, a trial called BHAT, beta

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1 blocker heart attack trial, 32 centers.

2 This is the odds ratio plotted up here.  
3 So one means there's no effect. To the left means  
4 there's a beneficial effect. To the right means  
5 there's a harmful effect.

6 Well, this was a highly statistically  
7 significant trial with a 20-some percent reduction in  
8 mortality, but you'll notice there's a few sites  
9 that's in the wrong direction.

10 Does that mean we should throw those sites  
11 out or the therapy isn't effective in North Dakota or  
12 in Southwest Texas? I don't know. I don't think so.  
13 You expect variation. A statistical theory would tell  
14 you there's some variation.

15 So while you look for sites to be out of  
16 line and say, "What could possibly be going on there?"  
17 one must be very cautious about kicking those sites  
18 out. That's certainly my advice to ourselves.

19 And so we expect some variation, and  
20 sometimes when you check out, you find out  
21 unfortunately the problem, you know. There was  
22 something wrong going on at that site. But we have

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1 got to be cautious about it.

2 I think that's the end of the my formal  
3 comments. So I think the issues that have been  
4 raised, this trial has many strong features, and I  
5 think many of the issues that needed to be addressed  
6 were addressed, but nevertheless, we're left with a  
7 few questions to discuss.

8 Thanks.

9 ACTING CHAIRPERSON GALANDIUK: Before we  
10 go on to the Panel questions, I'd like to ask if any  
11 of the Panel members have comments to make right now  
12 or questions to sponsor. Dr. McGrath, any questions  
13 of the sponsor that you want to address at this time?

14 DR. McGRATH: You mean just to add to the  
15 ones that have already been raised? Oh, yeah.

16 I was just going to ask the sponsors to  
17 comment on why they think there's a racial difference.

18 And I was also going to ask have they  
19 looked at the Oxandrolone effect by center. Does it  
20 correlate with Centers 1 and 3?

21 MR. PELTIER: Since we just received that  
22 question or issue in the last --

1                   ACTING CHAIRPERSON GALANDIUK:       Mr.  
2           Peltier, could you please come to the podium and also  
3           identify yourself, please.

4                   MR. PELTIER:   Yes, thank you.

5                   Stephen Peltier with Ortec International.

6                   We just received that information or that  
7           issue in the past 24 hours.   So we haven't done a  
8           detailed analysis by center, but certainly we tried to  
9           present to you the information that we did in these  
10          couple of slides that demonstrated that it didn't  
11          appear that there was any negative effect.

12                   And certainly although there were  
13          differences both in the control and the treatment  
14          group, directionally the information or the healing  
15          times are still the same.

16                   DR. McGRATH:   Racial?

17                   MR. PELTIER:   And racial, I don't know  
18          that I can give you an explanation for that.   It was  
19          a matched pair design, random analysis, a random  
20          effect in the analysis, and I don't really have an  
21          explanation for it.

22                   Kazem, do you have any?   Dr. Kazempour

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1 from Amarex.

2 DR. KAZEMPOUR: Kazem Kazempour from  
3 Amarex.

4 No, I do not have any reasoning for  
5 explaining the racial differences, but after I found  
6 that race being a factor, being statistically  
7 significant, I discussed that with our clinical  
8 people. They said it's possible, but that possibly  
9 can be just by chance.

10 DR. McGRATH: I understand that, but I  
11 guess the reason I bring it up is that do you think it  
12 can be real or is it perceptual? In other words, is  
13 it a real difference related to race or is it a  
14 perceptual difference because of the difference when  
15 you do your evaluative process that it might be more  
16 difficult to make a determination about healing under  
17 the Biobrane in people with different colored skin?

18 DR. GRISWOLD: John Griswold from Texas  
19 Tech. in Lubbock.

20 I appreciate the concern, although I think  
21 at least from an experience standpoint, a pigmentation  
22 doesn't seem to make a big impact on how we decide

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1 whether a donor site is healed because it had a lot to  
2 do with the moisture aspects of it.

3 And also, as far as the Biobrane is  
4 concerned, it really has to do with whether the  
5 Biobrane has adhered to the donor site wound. In my  
6 experience, once the wound is healed, the Biobrane  
7 comes off. If it's not healed, it stays adherent.

8 So I haven't in my experience noticed a  
9 difficulty in determining difference based on skin  
10 pigment color.

11 ACTING CHAIRPERSON GALANDIUK: Ms. Brown,  
12 do you have any questions of the sponsor?

13 MS. BROWN: Yes. Did I hear correctly  
14 that Oxandrolone is used fairly typically in burn  
15 patients?

16 MR. PELTIER: I think that --

17 DR. GRISWOLD: Again, John Griswold.

18 I can't respond if it's used typically in  
19 a wide range of burn patients. I can respond to our  
20 experience, and that is that we feel confident and  
21 comfortable with the data available that it helps in  
22 large burns and in patients who have maybe a little

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1 more difficulty to heal, like older patients.

2 So our practice is to use it in patients  
3 who have large burns and in older patients.

4 MS. BROWN: Thank you.

5 ACTING CHAIRPERSON GALANDIUK: Dr.  
6 Diegelmann, do you have any questions?

7 DR. DIEGELMANN: I also have some concerns  
8 about the way the control site was treated. In the  
9 introduction here, we heard that Biobrane is expected  
10 to cause re-epithelialization within nine to 19 days,  
11 and on page 21 of this Volume 2, you cite a study  
12 where Biobrane typically heals within 13 and eight  
13 days, yet in this study the time to healing for the  
14 control sites seem to be so much larger.

15 Do you have any explanation of why this  
16 might be?

17 MR. PELTIER: I think there may be two  
18 types of explanations to look at. The first is trying  
19 to compare information from the literature when you  
20 don't know the measurement tools that were used,  
21 photography, planimetric analysis, et cetera, and what  
22 the definition of 100 percent wound healing was.

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1 As you note in this study, we had a very  
2 tightly controlled definition of 100 percent wound  
3 healing standardized across all of the centers and  
4 utilized in each evaluation method.

5 So it's very hard to compare ourselves or  
6 to compare this to the literature. However, it was a  
7 matched pair design in the same patient being their  
8 own control. So I think it gives a fair  
9 representation of the expected healing time that one  
10 might expect with Biobrane.

11 I also wonder if Dr. Griswold could come  
12 up and probably give you a more clinical  
13 interpretation of his experience in using Biobrane and  
14 the variation in healing time.

15 ACTING CHAIRPERSON GALANDIUK: If I might  
16 request that we use the podium for this portion and  
17 not the table. Thank you.

18 MR. PELTIER: Thank you.

19 DR. GRISWOLD: The way I would respond is  
20 as Mr. Peltier described, I have been involved with  
21 previous studies, including some of the previous  
22 Biobrane studies. The difference that sets this study

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1 site is the several ways that healing was determined  
2 in investigator, planimetry, and photography, where in  
3 most of the other studies it's a single investigator,  
4 somewhat more subjective determination.

5 Also there was a variance in those studies  
6 between whether it was 100 percent, 95 percent, 90  
7 percent healed. And so I think it puts this study  
8 into a little bit different category and may explain  
9 why the heal time was different.

10 DR. DIEGELMANN: Also, the control sites,  
11 I presume, 100 percent of them the Biobrane was held  
12 in place by staples. What percent of the treated  
13 sites were held in place by staples? Did that have an  
14 impact on the healing rates?

15 DR. GRISWOLD: I can respond from our  
16 experience. We used staples on all of our patients,  
17 the ten patients that we contributed to the study in  
18 both the Biobrane and the CCS. So I don't feel it  
19 contributed any difference.

20 So I'm not sure about the other sites.

21 MR. PELTIER: Let me just add. It's Steve  
22 Peltier from Ortec again.

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1 That same experience that Dr. Griswold  
2 just presented in terms of whether or not to use  
3 staples was our experience at all of the other sites.  
4 Although it was left up to the investigator whether to  
5 use staples or not in the CCS treated group, most of  
6 the investigators stapled it in place the same as they  
7 did with the Biobrane treated patients.

8 ACTING CHAIRPERSON GALANDIUK: Dr. Chang,  
9 do you have any questions to add?

10 DR. CHANG: Using the Vancouver score, as  
11 I recall it uses several elements, such as height of  
12 the scar, pliability, the vascularity, and the  
13 pigmentation, and I can't recall the fifth element.

14 Was there any thought of having more than  
15 one person evaluate that so that there was -- since  
16 some of these measurements or evaluations are  
17 subjective, was there any thought to having more than  
18 one investigator give you that score?

19 MR. PELTIER: Steve Peltier from Ortec  
20 again.

21 I think if you look at if that was the  
22 reason, but we also chose to use the Hamilton Scar

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1 Scale. So the Vancouver was performed on site by the  
2 clinical investigators and, as you point out, has some  
3 subjectivity to it. We then took the photographs and  
4 had those evaluated by masked evaluators, again,  
5 randomly, and I think both scores at least show the  
6 same direction.

7 DR. CHANG: Thank you.

8 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin  
9 or Dr. DeMets, any additional comments?

10 No. Then one last question to Dr. McGrath  
11 before we proceed to the questions.

12 DR. McGRATH: This just flared from  
13 something that Dr. Diegelmann just said. I again just  
14 want to understand the groups a little better. All of  
15 the Biobranes were stapled on. So all of the controls  
16 were stapled, but investigators had discretion about  
17 stapling the product under investigation; is that  
18 correct?

19 MR. PELTIER: Steve Peltier from Ortec.

20 Yes, that is correct, but as I reported,  
21 in most of the cases the control product, I mean the  
22 CCS product, was also stapled.

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1 DR. McGRATH: But it seems as though some  
2 of the Biobrane evaluation issues were subjective  
3 because in some cases it had to do, as you said  
4 earlier, with when it came off. So was there a set  
5 protocol about when you took the staples out of the  
6 Biobrane?

7 MR. PELTIER: I'm going to have it  
8 answered in two ways. The protocol was established to  
9 use the product based on the manufacturer's package  
10 insert. The package insert doesn't put a time frame  
11 on when to take the staples out. So that, again,  
12 became a clinical judgment by the investigator based  
13 on healing, and if Dr. Griswold could come up, I think  
14 he can give you a little more insight into how that's  
15 established.

16 DR. GRISWOLD: John Griswold.

17 Again, just reporting on our center, we  
18 remove all the staples both on graft sites and donor  
19 sites, depending upon what the dressing is or  
20 irrespective of the dressing at three days. So at day  
21 three, all of the staples were removed at our center.

22 DR. McGRATH: But that wasn't set in the

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1 protocol. So the Biobrane separation issue could be  
2 partially dependent on when the staples were removed  
3 if they weren't removed in three days?

4 DR. GRISWOLD: I suppose it may have some  
5 impact, although what I believe most centers did was  
6 that they did more than just observe the Biobrane and  
7 whether it would come off. The Biobrane edges were  
8 manipulated. The Biobrane was tested with a Q-tip or  
9 some type of touching aspect to see if it was still  
10 adherent.

11 So although I guess that would have to be  
12 done in and around the staples because the staples  
13 were still there, I think more than just observing if  
14 it was ready to fall off was done.

15 ACTING CHAIRPERSON GALANDIUK: I'd like to  
16 as Mr. Stephen Rhodes now to put the first Panel  
17 question on the screen.

18 While we're waiting for this to come up,  
19 I'll just read the first Panel question. Adverse  
20 events such as pain, infection and itching are similar  
21 in the clinical study for both the CCS and the  
22 Biobrane-L control. Please discuss whether the safety

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1 data for CCS provides a reasonable assurance that it  
2 is safe for the management of the split autograft  
3 donor sites in burn patients.

4 Dr. Diegelmann, can we have you start?  
5 How would you like to answer that?

6 DR. DIEGELMANN: In respect to this  
7 question, I still have some concerns that Dr. Boykin  
8 raised about the persistence of the cells and the  
9 absorption of the materials there. So I still have  
10 some concerns about that safety issue.

11 ACTING CHAIRPERSON GALANDIUK: Dr. Chang?

12 DR. CHANG: I plan to address the question  
13 very literally in terms of pain, infection, and  
14 itching. Clinically I believe they are similar  
15 between the two groups and so they are safe regarding  
16 those clinical issues.

17 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin?

18 DR. BOYKIN: I think that in terms of  
19 clinical safety, that the device provides reasonable  
20 assurance that it is safe for the management of the  
21 donor site.

22 ACTING CHAIRPERSON GALANDIUK: Dr. DeMets?

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1 DR. DeMETS: From a statistical  
2 perspective, I would agree with Dr. Boykin.

3 ACTING CHAIRPERSON GALANDIUK: Ms. Brown?

4 MS. BROWN: I thought the two groups  
5 appeared to be similar with respect to their safety  
6 profiles and were acceptable because the adverse  
7 events were fairly minimal.

8 ACTING CHAIRPERSON GALANDIUK: And Dr.  
9 McGrath?

10 DR. McGRATH: I agree. From a clinical  
11 sense, the control group and the experimental group  
12 appear to be similar and, therefore, the product  
13 assumed to be clinically safe.

14 But, frankly, I would like to see  
15 histology.

16 ACTING CHAIRPERSON GALANDIUK: At this  
17 time does the sponsor want to address either the  
18 concerns of Dr. McGrath regarding histology or the  
19 concerns that Dr. Diegelmann had regarding the  
20 persistence of cells?

21 MR. PELTIER: Steve Peltier from Ortec  
22 International.

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1                   Again, we recognize that that data is not  
2                   there, and we certainly have plans to do that kind of  
3                   work in the future. So we recognize the Panel's  
4                   concern for cell retention.

5                   ACTING CHAIRPERSON GALANDIUK: Dr. Witten,  
6                   from our panel members, other than Dr. Diegelmann's  
7                   concern regarding the persistence of cell and Dr.  
8                   McGrath's desire for more histology, I think it's the  
9                   consensus of the panel that this is safe.

10                   Is the FDA satisfied with that response  
11                   and have we addressed that adequately?

12                   DR. WITTEN: Thank you, yes.

13                   ACTING CHAIRPERSON GALANDIUK: We'll  
14                   proceed to the second question.

15                   And, again, in the absence of the screen,  
16                   I will reread it. Panel Question No. 2: the primary  
17                   effectiveness endpoint in the protocol was time to  
18                   complete wound closure as measures by photographic  
19                   assessment. The study was designed to demonstrate a  
20                   9.5 day improvement in time to wound closure. The  
21                   primary effective results were show before by Dr.  
22                   Arepalli during his presentation. Do these data

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1 demonstrate that there is reasonable assurance that in  
2 a significant portion of the target population the use  
3 of CCS will provide clinically significant results?

4 Dr. Chang, would you like to begin?

5 DR. CHANG: With the comments by the  
6 statisticians and looking at the data, the numbers  
7 show a difference, but I have to express very grave  
8 reservations about the potential that the differences  
9 that we see are not solely due to the efficacy of the  
10 combination of keratinocytes and fibroblasts in this  
11 product.

12 And in light of comments by Dr. Boykin and  
13 citing the literature, those are my major concerns.  
14 So looking at the statistics and the data presented,  
15 the answer is a qualified yes, but I have significant  
16 reservations regarding the action of Oxandrolone in  
17 terms of enhancing the donor site healing.

18 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin?

19 DR. BOYKIN: I'll agree with Dr. Chang  
20 that we see the difference, and of course, the  
21 questions -- and I've obviously raised this earlier --  
22 is that we're curious about another effect or another

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1 effector, if you will, that may have a substantial  
2 impact on the outcome of the study.

3 ACTING CHAIRPERSON GALANDIUK: Dr. DeMets.

4 DR. DeMETS: Well, as I indicated, I think  
5 that the effectiveness data suggest that there's an  
6 improvement. The question is we didn't -- at least  
7 the estimate didn't make the 9.5 day goal, but perhaps  
8 to bring some confidence intervals on that, our  
9 observed differences would help address that, but I  
10 think the fundamental question is still is the  
11 estimate that we have the right estimate, given the  
12 other factors that Dr. Boykin raised.

13 I do believe that this is evidence of  
14 effectiveness. It's just the question of the site.

15 ACTING CHAIRPERSON GALANDIUK: Ms. Brown?

16 MS. BROWN: I'm not a statistician. So I  
17 or I'm sorry. I'm not a clinician. So I can't  
18 comment on the clinical significance of the results,  
19 but it appeared to me that the sponsor did meet its  
20 statistical criteria for demonstrating that the  
21 product was superior to Biobrane. So I would say that  
22 it's statistically effective.

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1 ACTING CHAIRPERSON GALANDIUK: Dr.

2 McGrath?

3 DR. McGRATH: Well, I'm struggling with  
4 this because the effectiveness data really rides on  
5 visual observation, and it seems that using Biobrane  
6 without better standardizing perhaps the handling of  
7 the Biobrane certainly tends to prejudice in favor of  
8 the CCS because of issues with the way Biobrane raises  
9 up and so forth.

10 I perhaps would feel better if we had some  
11 way to be more confident that the Biobrane had been  
12 given, you know, an equal playing field in terms of  
13 the way it was secured and so forth.

14 I also have some questions that arise  
15 really out of the racial and the center differences,  
16 cognizant of what you said, Dr. DeMets, about how you  
17 can't look too much at differences within small  
18 numbers. But still those two centers really do stand  
19 out, and the racial issue really stands out, and I'd  
20 like to just have some thoughts about why those are so  
21 different.

22 And I guess the third thing that I'm still

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1 struggling with is for this product the effectiveness  
2 of adding the cellular component, the keratinocytes,  
3 is really based on cytokine data rather than any  
4 knowledge of where, when, how those keratinocytes are  
5 behaving.

6 And I'd just like to know more about that  
7 before I feel confident that we're dealing with  
8 something that is a validly more effective product.

9 ACTING CHAIRPERSON GALANDIUK: Dr.  
10 Diegelmann?

11 DR. DIEGELMANN: I would answer the  
12 Question 2 with a qualified yes, but I'm also  
13 concerned about the subgroups that Dr. Boykin pointed  
14 out with the stand alone treatments, and also the way  
15 the Biobrane was handled and maybe not provided a  
16 proper moisture environment that would potentiate its  
17 effectiveness.

18 But overall I think the answer to this  
19 question would be a qualified yes.

20 ACTING CHAIRPERSON GALANDIUK: Does the  
21 sponsor wish to make a comment at this time?

22 DR. GRISWOLD: John Griswold, again.

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1 Just in response to the Biobrane question,  
2 especially about moisture, in the early studies one of  
3 the things that seemed to slow the Biobrane take and  
4 actually slow healing was keeping the Biobrane in an  
5 occlusive covering or keep it covered, and it was  
6 found that if it was uncovered fairly quickly, within  
7 the first 24 to 48 hours, that it actually had an  
8 improved healing rate; that keeping it moist prevented  
9 its adherence to the wound, providing that matrix.

10 So covering the Biobrane actually at least  
11 in early study showed the detriment to the healing  
12 process.

13 As far as the Biobrane overall and how it  
14 was handled, I guess from my standpoint and at least  
15 from talking with some of the other principal  
16 investigators felt fairly comfortably that it was  
17 handled pretty standard, that the staples were removed  
18 fairly quickly, that it was just allowed to remove or  
19 fall off or come off as the epithelialization occurred  
20 underneath.

21 So I think the Biobrane was handled pretty  
22 standardly as far as the package insert and the

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1 recommendations for healing the Biobrane.

2 ACTING CHAIRPERSON GALANDIUK: Dr. Witten,  
3 I believe the consensus of the panel is that the  
4 answer to this question would be yes, with  
5 reservations specifically regarding the possibility of  
6 combining subgroups, the perhaps inequality of  
7 treatment of patients that underwent Biobrane  
8 application, as well as the use of Oxandrolone in some  
9 patients.

10 Is that adequately answered for the FDA?

11 DR. WITTEN: Yes. Thank you.

12 ACTING CHAIRPERSON GALANDIUK: In the  
13 meantime we should have Question No. 3 on the screen.  
14 If we could go to the last page for Question No. 3  
15 regarding the difference in the Vancouver burn scar.

16 Can I start with Dr. Boykin? Can you  
17 discuss the clinical significance of these  
18 differences?

19 DR. BOYKIN: Well, I'm glad you said  
20 "clinical." I think there's questionable significance  
21 really between the two. When you look at the scales  
22 that are used, I know statistically the numbers are

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1 showing up, but my clinical instinct would be that  
2 looking at a patient on a scale of 20 who went from  
3 two to three wouldn't really cause me to make a  
4 notation in the chart.

5 So I would say there's questionable  
6 clinical significance.

7 ACTING CHAIRPERSON GALANDIUK: Dr. DeMets?

8 DR. DeMETS: Well, I have no particular  
9 expertise. In fact, I have no expertise in these  
10 particular measures. So my comments would be similar  
11 to Dr. Boykin's looking at a scale with that range and  
12 the size of the effect. While it's probably a real  
13 statistical difference there, its clinical impact to  
14 me seems to be marginal at best.

15 ACTING CHAIRPERSON GALANDIUK: Ms. Brown?

16 MS. BROWN: I just had one question with  
17 the Vancouver Scar Scale, that there were  
18 statistically significant differences at week 12 and  
19 week 24, but then at, quote, follow-up there's not a  
20 difference.

21 What is "follow-up"?

22 MR. PELTIER: Steve Peltier from Ortec.

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1 The patients who were enrolled in this  
2 study early had a biannual follow-up until the last  
3 patient in the study completed the six-month follow-  
4 up. So that information was what is there.

5 MS. BROWN: So by the very, very, very end  
6 there weren't differences?

7 MR. PELTIER: When you went out beyond a  
8 year, you began not to see the same differences; is  
9 that correct?

10 MS. BROWN: I had that question, but I  
11 don't really have other comments about the scars.

12 ACTING CHAIRPERSON GALANDIUK: Dr.  
13 McGrath?

14 DR. McGRATH: Just that the differences  
15 seem modest between CCS and the control, but that  
16 clinically it's reflective of safe results.

17 ACTING CHAIRPERSON GALANDIUK: Dr.  
18 Diegelmann?

19 DR. DIEGELMANN: My response to Panel  
20 Question 3 would be that there's probably a marginal  
21 clinical significance between the two.

22 ACTING CHAIRPERSON GALANDIUK: And Dr.

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1 Chang?

2 DR. CHANG: To put it in English or to  
3 translate clinically, in using the Vancouver burn  
4 scar, in week two if one looked at the median, there  
5 was no difference. If one looked at the mean between  
6 CCS and control, it was an improvement of .81 out of  
7 a scale of 15. By week 24, looking at the median,  
8 there was a difference of two for the median and the  
9 difference of 1.23 out of 15.

10 That would mean clinically that if one  
11 looked at the color, it might be more pink or if we  
12 felt the scar, it might be a little bit firmer or  
13 there might be a little more hyper or hypo darker or  
14 lighter color. I mean, one out of the five was a  
15 grade better.

16 But as mentioned before, going out beyond  
17 the six months, if you gave it enough time, then there  
18 would be from the numbers that were filed the  
19 suggestion that given time scars will even out in  
20 terms of how they look.

21 And so clinically, statistically the  
22 numbers are there, but clinically I don't believe that

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1 there is a difference in the outcome.

2 ACTING CHAIRPERSON GALANDIUK: Does the  
3 sponsor wish to make any additional comments?

4 DR. GLAT: Paul Glat from Philadelphia.

5 I don't disagree that the numbers are not  
6 highly remarkable. However, I think especially in my  
7 patient population, I do all pediatric burns. I think  
8 scarring is quite a significant problem for my  
9 patients. They tend to scar worse, especially in the  
10 beginning. They tend to be prone to the need for  
11 pressure garment and occupational therapy in their  
12 donor site scars, and the possibility for eliminating  
13 this is a potential great benefit to my patients. the  
14 expense, the time lost from work or school for the  
15 families is quite significant.

16 I also have a fair amount of experience  
17 actually having to operate on donor sites  
18 unfortunately. So I think the potential to eliminate  
19 some of those is a significant benefit to this.

20 Thank you.

21 ACTING CHAIRPERSON GALANDIUK: Dr. Witten,  
22 the consensus of the panel regarding Question No. 3 is

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1 that the difference in these scores is not clinically  
2 significant. Is the FDA satisfied with the  
3 discussion?

4 DR. WITTEN: Yes. Thank you.

5 ACTING CHAIRPERSON GALANDIUK: Then  
6 proceeding on to the last question, which we'll start  
7 here about the labeling, Dr. DeMets, do you wish to  
8 make any comments on this?

9 DR. DeMETS: I probably do, but I can't  
10 quite formulate them.

11 It would have to do with the issue around  
12 the use of this drug whose name I keep forgetting,  
13 Oxandrolone. I don't quite know how to formulate it,  
14 but I'm still troubled by how to sort that out, and I  
15 don't think we have enough data probably to do that,  
16 but that's really the issue that I would put on the  
17 table.

18 ACTING CHAIRPERSON GALANDIUK: Ms. Brown.

19 MS. BROWN: I had the same comment, that  
20 it might be useful in the clinical section to simply  
21 have some, if it would be statistically legitimate, to  
22 simply have some description about the results with

1 Oxandrolone versus not with Oxandrolone just so that  
2 clinicians have the benefit of that information.

3 ACTING CHAIRPERSON GALANDIUK: Dr.  
4 McGrath, do you have any recommendations?

5 DR. McGRATH: I'm sorry. I sort of  
6 haven't had time to put this together very clearly,  
7 but I would be troubled if the recommendations or, in  
8 other words, if the labeling suggested significant  
9 differences from the control product.

10 I don't think that we have any evidence to  
11 support any claims about readiness for reharvesting or  
12 retaking the skin graft at this time with what we  
13 have. So I don't think that can really be used as an  
14 indication.

15 And I know that at the outset the initial  
16 presentation said that the hope was that CCS showed  
17 improved function and durability of the donor site,  
18 and I don't think that evidence exists yet about  
19 function and durability of the donor site.

20 ACTING CHAIRPERSON GALANDIUK: Dr.  
21 Diegelmann?

22 DR. DIEGELMANN: To add to that, perhaps

1 some indications regarding the age of the patient and  
2 percent of total body surface area.

3 ACTING CHAIRPERSON GALANDIUK: Can you  
4 elaborate on that?

5 DR. DIEGELMANN: Just based on the  
6 indications as presented, patients under 12 years of  
7 age and 20 percent total body surface area.

8 ACTING CHAIRPERSON GALANDIUK: So it  
9 should not be utilized in patients?

10 DR. DIEGELMANN: Perhaps just a comment  
11 about the efficacy of those.

12 ACTING CHAIRPERSON GALANDIUK: And not in  
13 burns less than 20 percent body surface area. Okay.

14 Dr. Chang.

15 DR. CHANG: I would just echo sentiments  
16 by Dr. Diegelmann that I'm not convinced that the  
17 product is superior for less than 20 percent body  
18 surface area burns or the younger patient population,  
19 less than 12 years, from looking at the results I have  
20 here.

21 I would like to see on the label for the  
22 clinician what are signs that there's an infection

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1 brewing in that donor site with the application of the  
2 product and for the clinician recommendations for  
3 that.

4 Obviously it's not your job to dictate  
5 practice, but just suggestions for management of signs  
6 of infection.

7 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin?

8 DR. BOYKIN: I would agree with Dr. Chang  
9 that the statement just describing the absence of  
10 clear efficacy for the use of the product in the group  
11 less than 12 and less than 20 percent be made; that  
12 instructions be outlined for the treatment of the  
13 infected donor area that received CCS.

14 And also I noticed in the labeling that  
15 the exclusion criteria for the study were not  
16 reflected in the labeling, and I think that there  
17 should be a statement which indicates that patients  
18 with the following conditions -- and basically list  
19 the exclusion criteria -- have not been clinically  
20 evaluated with this device so that these individuals  
21 won't accidentally wind up being treated and have some  
22 condition that couldn't be defined in the earlier

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1 study.

2 I also think that it would be beneficial  
3 to describe the difference in the populations with and  
4 without Oxandrolone. I think that's an important note  
5 to add to the labeling.

6 I think that's all I have at this time.

7 ACTING CHAIRPERSON GALANDIUK: Does the  
8 sponsor wish to make any comments at this time perhaps  
9 regarding how one can tell if there's an infection  
10 here or any of the other things that were mentioned?

11 MR. PELTIER: Steve Peltier from Ortec.

12 In terms of the precaution about how to  
13 evaluate an infection or some recommendations on how  
14 to handle an infection in the donor site, we agree  
15 that we should have something in the label.

16 DR. KAZEMPOUR: Kazem Kazempour from  
17 Amarex.

18 In terms of patients with age less than  
19 12, the time to healing was shorter for both treatment  
20 groups, but for patients with total body surface area  
21 burns, less than 20 percent, the median difference was  
22 two days. Again, it was a small.

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1 It just happened accidentally. I was  
2 looking at the confidence interval, trying to produce  
3 that, and statistically it was significant when we  
4 used T tests, but the p value that is reported, it is  
5 log ranked as looking at median. And, yes, the median  
6 was not significant.

7 We have reported both of them to the  
8 agency, and when we conduct a confidence interval  
9 around them, that's my favorite. It statistically was  
10 significant, and the difference was only 1.8 days, but  
11 because both of the variables it was so low in  
12 patients with total body surface area burn less than  
13 20 percent, was statistically significant using T  
14 tests.

15 And the rate of healing for patients for  
16 less than 12 years was a lot faster within the first  
17 14 days, again, all of them being statistically  
18 significant.

19 Thank you.

20 ACTING CHAIRPERSON GALANDIUK: Thank you.

21 MR. PELTIER: I'm sorry. We still have a  
22 couple more comments if you would allow us.

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1                   ACTING CHAIRPERSON GALANDIUK:     Yes,  
2     please.

3                   MR. PELTIER:    Thank you.

4                   DR. GLAT:    Paul Glat from Philadelphia.

5                   Again, I do strictly pediatric burns. To  
6     me I just wanted to comment on the fact even though  
7     the days are not statistically significant, there does  
8     seem to be a trend towards earlier healing and  
9     specifically to faster healing rates, which I think  
10    were demonstrated earlier to be about two square  
11    centimeters a day faster.

12                   So even if we're not getting 100 percent  
13    healed at a faster rate, I think we're getting some  
14    benefits from the faster rates of healing. In my  
15    population I found a lower incidence of pain as we  
16    went out in the treatment group. That was my  
17    anecdotal experience with that.

18                   And this to me seems to be beneficial in  
19    allowing my patients to get a little bit earlier  
20    mobilization, earlier rehab, possibly an earlier  
21    discharge from the hospital.

22                   So I think there are some benefits other

1 than the primary directive, which is to get complete  
2 closure. I think we do see some benefits in the  
3 pediatric population.

4 ACTING CHAIRPERSON GALANDIUK: There was  
5 no mention in the protocol though of time to rehab in  
6 any of these evaluations, was there?

7 DR. GLAT: No, there was not.

8 DR. GRISWOLD: John Griswold.

9 And just to comment about the Oxandrolone  
10 usage and just something for the panel to consider,  
11 currently I utilize Oxandrolone in my patient  
12 population, at least in the ones we describe, larger  
13 burns and older patients.

14 But as far as the heal time, I think it's  
15 important to realize that there are currently, as far  
16 as I'm aware of in the literature, only two single  
17 site studies, one that was blinded and one that was  
18 not, to show the improved healing, and in our  
19 experience, we have not experienced any wound healing  
20 improvement. It has only been weight maintenance or  
21 weight gain and protein anabolism.

22 We have not seen any impact in the

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1 Oxandrolone usage in donor site or graph site healing.

2 Thank you.

3 ACTING CHAIRPERSON GALANDIUK: Does the  
4 sponsor have any other comments? No.

5 Dr. Witten, summarizing the responses from  
6 the panel regarding the recommendations for proposed  
7 labeling, the Panel feels that the label should  
8 contain a statement saying that there's no significant  
9 improvement in healing in patients who have burns --  
10 in burn patients that are less than 12 years of age  
11 and also in patients with burns that comprise less  
12 than 20 percent of their total body surface area.

13 In addition, the Panel feels that the  
14 exclusion criteria for the current study should be  
15 listed so that people who use this product could  
16 evaluate which patients the product has not been  
17 tested on.

18 Several Panel members felt strongly that  
19 the possible effect of Oxandrolone use on wound  
20 healing should be addressed in the package labeling.

21 There also should be no claim regarding  
22 the ability of increased recropping of donor sites,

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1 nor on their increased function or their ability sine  
2 the study did not provide such data.

3 And lastly, the Panel felt that there  
4 should be an instruction on the labeling telling  
5 clinicians when they -- how they could detect  
6 infection in these donor wound sites.

7 Is the FDA satisfied with that response?

8 DR. WITTEN: Yes. Thank you.

9 ACTING CHAIRPERSON GALANDIUK: Now we will  
10 proceed to any additional public comments that there  
11 are. If there are any members of the audience that  
12 wish to address the Panel at this time, please raise  
13 your hand to be recognized.

14 (No response.)

15 ACTING CHAIRPERSON GALANDIUK: Okay.  
16 Good. Now, does the FDA have any final comments at  
17 this point?

18 DR. WITTEN: No.

19 ACTING CHAIRPERSON GALANDIUK: No. Okay.  
20 Does the sponsor have any final comments they wish to  
21 make? Okay.

22 Mr. Krause will now read the voting

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1 instructions for the Panel.

2 DR. KRAUSE: The medical device amendments  
3 to the Federal Food, Drug, and Cosmetic Act, as  
4 amended by the Safe Medical Devices Act of 1990,  
5 allows the Food and Drug Administration to obtain a  
6 recommendation from an expert Advisory Panel on  
7 designated medical device pre-market approval  
8 applications that are filed with the agency.

9 The PMA must stand on its own merits, and  
10 your recommendation must be supported by safety and  
11 effectiveness data in the application or by applicable  
12 publicly available information.

13 Safety is defined in the act as reasonable  
14 assurance, based on valid scientific evidence, that  
15 the probable benefits to health under conditions on  
16 intended use outweigh any probable risks.

17 Effectiveness is defined as reasonable  
18 assurance that in a significant portion of the  
19 population the use of the device for its intended uses  
20 and conditions of use when labeled will provide  
21 clinically significant results.

22 The recommendations of the panel are as

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1 follows. You may recommend approval if there are no  
2 conditions attached.

3 You may recommend approvable with  
4 conditions. The Panel may recommend that the PMA be  
5 found approvable subject to specified conditions, such  
6 as physician or patient education, labeling changes,  
7 or a further analysis of existing data.

8 Prior to voting, all of the conditions  
9 should be discussed by the panel.

10 You may recommend not approvable. The  
11 Panel may recommend that the PMA is not approvable if  
12 the data do not provide a reasonable assurance that  
13 the device is safe or if a reasonable assurance has  
14 not been given that the device is effective under the  
15 conditions of use prescribed, recommended or suggested  
16 in the proposed labeling.

17 Following the voting, the Chair will ask  
18 each Panel member to present a brief statement  
19 outlining the reasons for their vote.

20 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin,  
21 as the clinical reviewer for the panel, would you like  
22 to make a motion?

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1 DR. BOYKIN: I'd like to make a comment  
2 first. I believe that this is a safe device. I  
3 actually am excited about the technology. I think  
4 that there's always room for improvement.

5 I really appreciate Dr. Griswold's  
6 comments because he has put some important clinical  
7 perspective on the problems that I've had in  
8 evaluating this.

9 We only have three or four studies on  
10 Oxandrolone, but they all point to a certain effect  
11 which you haven't shown in this study. As a matter of  
12 fact, it has been just the opposite. And that  
13 confounded it even more. So there's something there  
14 that needs to be sorted out.

15 And if we're going to continue to use  
16 Oxandrolone in patients who are burned, then we need  
17 to understand what's going on there.

18 Having said that, I would vote that we  
19 approve the product with the condition which I would  
20 love to discuss with the other Panel members in the  
21 form of some follow-up study after a set period of  
22 time with which the public, the other clinicians in

1 this country have had a chance to use the product so  
2 that we can review the data and be at least more  
3 comfortable about the questions that we've raised.

4 So I believe that it is approvable with  
5 some specified conditions.

6 ACTING CHAIRPERSON GALANDIUK:  
7 Specifically what type of follow-up?

8 Actually, okay. Do I have a second for  
9 the motion?

10 DR. DIEGELMANN: Second.

11 ACTING CHAIRPERSON GALANDIUK: Okay. Dr.  
12 Diegelmann seconds it.

13 Okay. It has been moved and seconded that  
14 the pre-market approval application -- discussion?  
15 Okay. It has been moved and seconded that the pre-  
16 market approval application for the OrCel composite  
17 cultured skin from Ortec International be recommended  
18 for approval with conditions.

19 And if we can now have the Panel discuss  
20 what conditions. Dr. Chang?

21 DR. CHANG: My comment to answer this is  
22 that in my mind the sponsor has demonstrated that this

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1 is safe and, by and large, shown that there is an  
2 improvement in the results in comparing the product  
3 with their control.

4 But there were reservations that we  
5 mentioned might be put on product labeling specific to  
6 Oxandrolone.

7 I recognize that at clinical trial or any  
8 trial involving patients will be, I think, extremely  
9 expensive, and so I believe clinical trials, the data  
10 should stand in terms of approval or not on what we've  
11 seen today and not put the burden of another clinical  
12 trial as a condition for approval.

13 However, that being said, I do agree that  
14 there are enough questions about cell survival and  
15 histology that that is not as daunting a project and  
16 commitment to be made as a condition for approval.

17 So in discussion, I would say I think  
18 clinical trials are going to be inordinately  
19 expensive, and given the data that we've had I'm  
20 satisfied in terms of patient population, but provided  
21 the question of Oxandrolone is mentioned in the  
22 labeling. That would be the condition that I would

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1 feel would be important.

2 And I do think histological studies are  
3 being planned. I think that that is doable and a  
4 reasonable request.

5 ACTING CHAIRPERSON GALANDIUK: Dr.  
6 Diegelmann.

7 DR. DIEGELMANN: Also I reflect the same  
8 comments. I feel like the data we reviewed today I  
9 feel reasonably confident that the product is safe.  
10 I do think it has some effectiveness, but perhaps not  
11 as significant as we may see statistically, but  
12 clinically it may be more marginal.

13 And then I believe that the comments you  
14 made about the conditions and indications in the  
15 labeling should be followed through.

16 ACTING CHAIRPERSON GALANDIUK: Dr.  
17 McGrath?

18 DR. CHANG: And the specifics of labeling,  
19 I believe, have been laid out, and they certainly  
20 would be worked out between FDA staff and the sponsor.

21 ACTING CHAIRPERSON GALANDIUK: Dr.  
22 McGrath.

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1 DR. McGRATH: As far -- agree with  
2 approval with conditions, and my thinking would be  
3 that safety has been addressed sufficiently in these  
4 clinical trials, but I don't think these clinical  
5 trials have established that this product is more  
6 effective than existing products that are on the  
7 market, and therefore, I think any claims in this area  
8 would have to be very modest about benefits relative  
9 to currently available products until those have been  
10 demonstrated.

11 I agree with the comments that have  
12 already been made about the specific items that would  
13 be put in the labeling with regard to the things that  
14 we outlined in our last comments and that were just  
15 brought out again by Dr. Chang and Boykin.

16 ACTING CHAIRPERSON GALANDIUK: Dr. DeMets.

17 DR. DeMETS: Well, I share some of the  
18 concerns of my colleagues. I think that my own guess  
19 is that the issue of the Oxandrolone drug is chance.  
20 It's small numbers. It goes in the opposite  
21 direction, if I understand this previous data, but  
22 nevertheless, I think it should be mentioned and until

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1 further clarification.

2 A question though. If we were to approve  
3 this with no reservations, does that wipe out what we  
4 just did in the Question 3 or in the Question 4 where  
5 we talked about all of the labeling changes? I'm  
6 asking do we have to -- we've already made our  
7 comments about labeling suggestions, and now does that  
8 mean if we believe that, do we have to vote approval  
9 with conditions?

10 ACTING CHAIRPERSON GALANDIUK: I believe  
11 they're independent of each other, but let me ask Dr.  
12 Witten to answer that question.

13 DR. WITTEN: Well, I'm not sure I  
14 understand the question, but let me just say if you  
15 think it should be approvable with the condition of  
16 the labeling recommendations that you made in response  
17 to the previous question, you could say that, and then  
18 that would be the condition.

19 DR. DeMETS: Okay, okay. I was just  
20 trying to understand.

21 Anyway, I think that the conditions I'm  
22 most interested in is the Oxandrolone question.

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1                   ACTING CHAIRPERSON GALANDIUK: Okay, and  
2                   Dr. Boykin, can I just ask you to elaborate a bit on  
3                   the clinical trial you mentioned with respect to  
4                   specific endpoints you would evaluate? Briefly.

5                   DR. BOYKIN: How many years have I been on  
6                   this Panel now?

7                   Quickly, I can certainly support  
8                   histological follow-up of patients who are treated  
9                   with this device, and I will be quite happy with a  
10                  statement concerning Oxandrolone as part of the  
11                  labeling, and I believe that new studies specific to  
12                  that area, as I've mentioned, are probably not  
13                  necessary.

14                  DR. WITTEN: Just some clarification would  
15                  be helpful, and that is if you all are recommending  
16                  histological studies, it would be helpful for us at  
17                  FDA if you could tell us histologic studies to answer  
18                  what question.

19                  ACTING CHAIRPERSON GALANDIUK: Dr. Boykin  
20                  or Dr. McGrath, would you?

21                  DR. BOYKIN: Well, the earlier protocols  
22                  discussed histology of the donor site with regards to

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1 DNA fingerprinting, which would help us with the  
2 question of cellular retention and morphology, and I  
3 believe that this could be done perhaps within a time  
4 frame of a year after the device has been applied and  
5 the donor site is healed.

6 We would simply like to see a sample of  
7 the patients who have been successfully treated with  
8 the device and look at the histology and the DNA  
9 fingerprinting and have a level of comfort about  
10 what's happening there.

11 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin,  
12 do I understand you correctly saying you would like  
13 histology to determine which cells are growing in,  
14 whether it's cells of the product in question or the  
15 patient's own cells?

16 DR. BOYKIN: Right.

17 ACTING CHAIRPERSON GALANDIUK: Is that  
18 correct?

19 DR. BOYKIN: Un-huh.

20 ACTING CHAIRPERSON GALANDIUK: Dr.  
21 McGrath?

22 DR. McGRATH: I agree with that, although

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1 I heard it said today that on the basis of the two  
2 biopsies that were done, it was the belief that it was  
3 the donor cells that was responsible for the re-  
4 epithelialization, and that the -- I'm sorry --- the  
5 recipient cells that were responsible, the person's  
6 own, for the re-epithelialization and not the ones in  
7 the product.

8 But I would like to know more about the  
9 true life span of the ones that are in the product and  
10 when they really disappear, and then I'd like to see  
11 some of that correlated with the conclusion that  
12 cytokines produced by those cells in a mixture with  
13 cytokines produced by the fibroblasts in this product  
14 are what are responsible for the potential improvement  
15 and rapidity with which the recipient can re-  
16 epithelialize the surface.

17 DR. SILBERKLANG: Can I ask a question?

18 ACTING CHAIRPERSON GALANDIUK: Dr. Witten,  
19 is the sponsor allowed to make comments at this time?

20 DR. WITTEN: It's up to you.

21 ACTING CHAIRPERSON GALANDIUK: Okay.

22 Please.

1 DR. SILBERKLANG: Mel Silberklang from  
2 Ortec International.

3 The reason I got up is because there's a  
4 proposal for follow-up of patients, and so I wanted to  
5 make it more concrete and specific.

6 There are ongoing studies by other product  
7 producers that make products with live cells as to  
8 cell retention. Cell retention goes down with time.  
9 So what would be an appropriate time point if we were  
10 to pick one to take a histological sample? That's one  
11 question.

12 And the second -- post treatment -- the  
13 second question is whether it would be acceptable to  
14 the Panel members, and this is just a suggestion, if  
15 we were to look, for example, at female patients where  
16 we can stain for male chromosomes since we have  
17 exclusively male cells. Then we could actually  
18 histologically see whether there are any remaining  
19 male cells.

20 That's a doable study in addition to a DNA  
21 study. A DNA study would only say that there's  
22 persistent DNA, not necessarily that it's actually the

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1 cell that's persistent.

2 And having once worked on DNA vaccines  
3 when I was at Merck, I can tell you DNA can persist  
4 for a very long time as DNA, as a depot effect under  
5 the skin.

6 ACTING CHAIRPERSON GALANDIUK: Okay. Dr.  
7 Witten, I would like to sum up the motion so far. We  
8 have a motion to approve the product with conditions,  
9 and it was the following conditions: that the answers  
10 to Question No. 4, those labeling specific items be  
11 added to the labeling, and that there also be a  
12 histology follow-up study with conditions that will be  
13 determined by the FDA at a later point.

14 I would now like to -- and that includes  
15 the claims of no more -- in the labeling there should  
16 also be a statement that the device does not  
17 necessarily provide more rapid healing than other  
18 products currently available.

19 I would like to ask all of those in favor  
20 of this motion to raise their hands, please.

21 (Show of hands.)

22 ACTING CHAIRPERSON GALANDIUK: Okay. The

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1 recommendation of the panel is unanimous in that the  
2 pre-market approval application for OrCel composite  
3 cultured skin from Ortec International be recommended  
4 for approval with conditions as outlined previously.

5 DR. WITTEN: Thank you.

6 Do they need to go around the room and  
7 state the names of who voted yes? No.

8 DR. KRAUSE: If it's unanimous, it's not  
9 necessary, but everyone should be polled as to why  
10 they voted the way they did.

11 ACTING CHAIRPERSON GALANDIUK: Yeah. And  
12 I would like to go through the panel members and ask  
13 everybody why they voted like they did.

14 Dr. McGrath?

15 DR. McGRATH: Oh, I voted for approval  
16 because the product appears to be a safe one that's  
17 reasonably effective, probably as effective as others  
18 that are already available. I put the conditions on  
19 it because I think the claims can't yet be made about  
20 improved effectiveness until these are established in  
21 clinical trials and in greater numbers.

22 ACTING CHAIRPERSON GALANDIUK: Dr. DeMets.

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1 DR. DeMETS: I voted in favor because I  
2 believe that the product has been demonstrated to be  
3 safe. It certainly seems to be no worse than the  
4 standard and in all likelihood is better than for the  
5 outcomes we have, and there is a need for some further  
6 clarification, but it didn't prevent me from feeling  
7 it was safe and effective.

8 ACTING CHAIRPERSON GALANDIUK: Dr. Boykin.

9 DR. BOYKIN: Yes. I vote as I did because  
10 I believe it's a safe product. Obviously there were  
11 some issues that clouded the determination, but  
12 looking back upon it, even at that point it still  
13 appeared to be fairly safe, and there seemed to be  
14 enough of a difference to support its use.

15 And I also feel strongly that the future  
16 clinical use of this in other reports by the centers  
17 will help us in the future.

18 ACTING CHAIRPERSON GALANDIUK: Dr. Chang.

19 DR. CHANG: I vote as I did, first,  
20 because of safety data and because we do need products  
21 that will accelerate wound healing. We are in need of  
22 that, and I feel that given the data that was

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1 presented today, it's deserving of a chance for  
2 patients to accelerate wound healing, given the  
3 reservations stated in our previous discussions.

4 ACTING CHAIRPERSON GALANDIUK: Dr.  
5 Diegelmann.

6 DR. DIEGELMANN: I voted the way I did  
7 because I think the product is safe. I think it is  
8 another important element that needs to be added to  
9 the treatment of these patients, and I also feel very  
10 strongly that this area of technology needs to be  
11 developed further.

12 ACTING CHAIRPERSON GALANDIUK: I would  
13 like to thank all of the Panel members for their time  
14 and attending the meeting, and also thank the FDA  
15 personnel and the audience for your attendance.

16 The meeting is adjourned.

17 (Whereupon, at 3:25 p.m., the Panel  
18 meeting in the above-entitled matter was concluded.)

19

20

21

22

CERTIFICATE

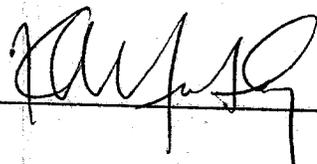
This is to certify that the foregoing transcript in the  
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                                  59th Meeting

Before:                       DHHS/FDA/CDRH

Date:                         July 17, 2001

Place:                        Gaithersburg, MD

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.



A handwritten signature in black ink, appearing to be "R. J. [unclear]", is written over a horizontal line.