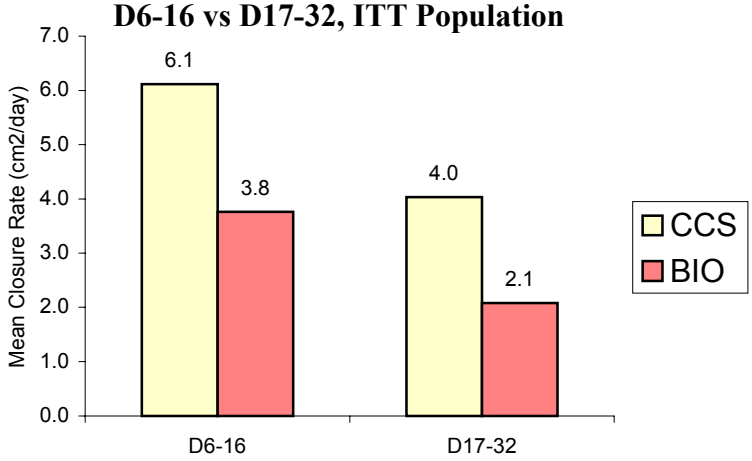
11.4.2 SECONDARY EFFICACY PARAMETERS

Rate of Wound Closure

Clinically meaningful and statistically significant differences in the rates of wound closure per day, as measured by planimetry, were observed during the 32-day post surgical period. Results of analyses indicate that CCS promoted a faster rate of healing than did Biobrane-L.

Figure 11.4.11: Rate of Wound Closure
D6-16 vs D17-32, ITT Population



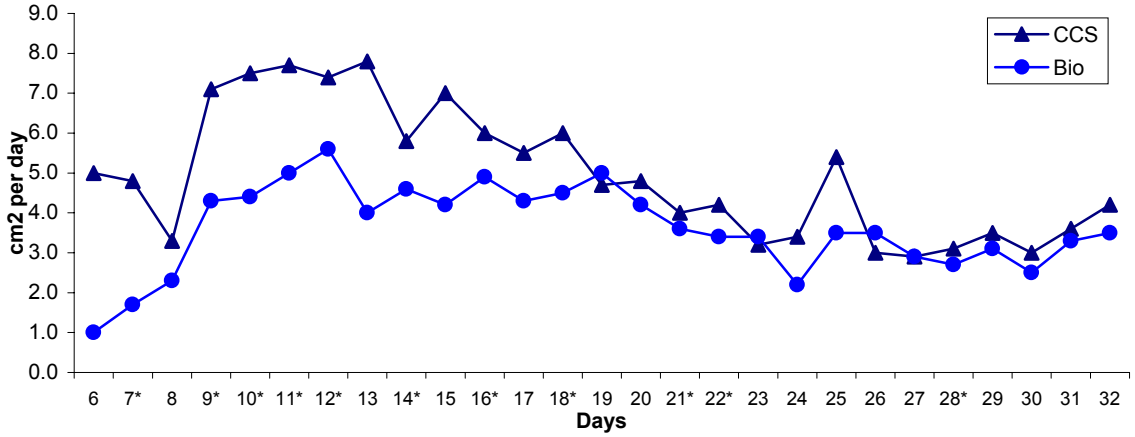
*Rate of wound closure, as measured by planimetry, days 6-16 and 17-32
p-values not determined
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table E.11, manual computation

The average mean wound closure rate for days 6-16 and 17-32 are depicted in Figure 11.4.11. The mean rate of wound closure for CCS on days 6 through 16 was 61% faster than Biobrane during the same time period (6.1 vs. 3.8 cm^2/day, respectively) and the mean closure time of CCS during days 17 - 32 was 90% faster than that of Biobrane-L (4.0 vs. 2.1 cm^2/day, respectively).

Statistically significant differences ($p < 0.05$) between the two treatments were observed on most days through day 16 (i.e., days 7, 9, 10, 11, 12, 14, and 16). After day 16, statistically significant differences between the two daily rates were not consistently

observed. Mean daily rates of wound closure for each treatment, as measured by planimetry, on days 6 through 32, are depicted for the ITT population in Figure 11.4.12.

Figure 11.4.12: Wound Closure, Daily Mean Rate
ITT Population

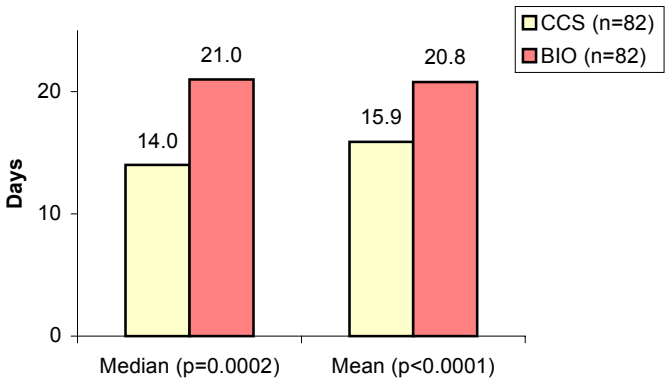


*Rate of wound closure, as measured by planimetry, is significantly greater for CCS ($p<0.05$), paired t-test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table E.11

Time to Readiness for Re-Cropping

The time to readiness for re-cropping, as assessed by the investigator, is depicted for the ITT population in Figure 11.4.13. The median time required for readiness to re-crop a CCS treated site was 7 days less than the median time required for the Biobrane-L treated site (i.e., 14 days CCS vs. 21 days Biobrane-L, [p=0.0002]). Mean times to readiness for re-cropping were 5 days less for CCS (i.e., 16 days CCS vs. 21 days Biobrane-L [p<0.0001]).

Figure 11.4.13: Time to Readiness for Re-Cropping
ITT Population



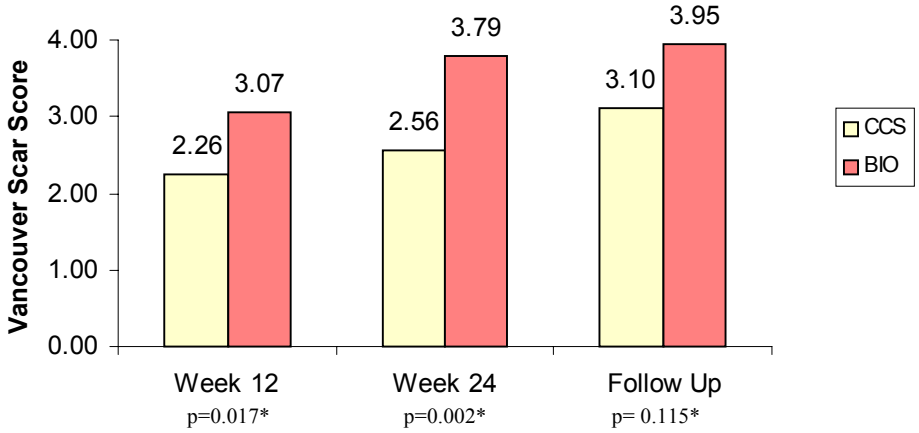
*Log-Rank test of the difference between median times, stratified by patient
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Tables E3.3 and E3.1

Scarring Severity

Scarring severity was assessed by two methods. Investigator assessments were conducted at weeks 12 and 24 and at the follow-up visit using the Vancouver Scar Scale. Assessments were also conducted via blinded review of photographs utilizing the Hamilton Burn-Scar Rating Scale. With both assessment methods, the total score for scarring severity at CCS treated sites was significantly lower ($p<0.05$) than Biobrane-L at weeks 12 and 24.

Figure 11.4.14 depicts the means of Vancouver total scores for the Safety Population, as assessed by the Investigator. At week 12, mean total scarring severity at CCS treated sites was nearly 30% less than Biobrane-L (2.26 versus 3.07, respectively, p=0.017). At week 24, mean total scarring severity for the CCS sites was more than 30% less than Biobrane-L (2.56 versus 3.79, respectively, p=0.002). At the follow up visit, no statistically significant difference was observed between the two treatments.

Figure 11.4.14: Vancouver Scar Scale
Investigator Assessment of Scarring Severity



*Paired t-test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table S23.3

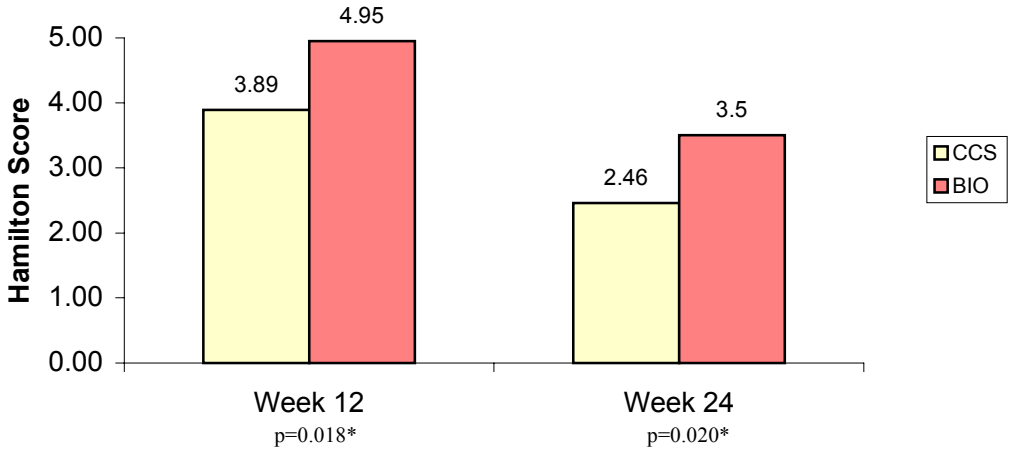
Table 11.4.15: Scar Assessments by Visit
Vancouver and Hamilton Scales

			CCS	BIO	P-value*
Vancouver Scar Score (Total) (Investigator Assessment)	Week 12	N	54	54	
		Mean (SD)	2.26 (2.19)	3.07 (3.13)	0.017
		Range	0-8	0-12	
	Week 24	N	55	56	
		Mean (SD)	2.56 (2.26)	3.79 (2.72)	0.002
		Range	0-8	0-11	
	Follow-Up	N	20	21	
		Mean (SD)	3.10 (2.40)	3.95 (2.78)	0.115
		Range	0-7	0-11	
Hamilton Scar Score (Total) (Blinded Photographic Review)	Week 12	N	55	55	
		Mean (SD)	3.89 (2.99)	4.95 (3.04)	0.018
		Range	0-11	0-12	
	Week 24	N	48	50	
		Mean (SD)	2.46 (2.21)	3.50 (2.74)	0.020
		Range	0-10	0-11	

*Paired t-test
Source: Section 14, Table S23.3

Scarring severity results obtained with the less sensitive blinded photographic review support those observed with the Investigator's assessment. Figure 11.4.16 depicts the mean Hamilton Burn Scar total severity scores for the Safety Population. At weeks 12 and 24, mean total scarring severity at CCS treated sites was nearly 30% lower than Biobrane-L. Statistical significance, in favor of CCS, was observed at both time points.

Figure 11.4.16: Hamilton Burn-Scar Scale
Blinded Photographic Review



* Paired t-test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table S23.3

Both of the scarring severity scales were composed of several parameters. The Vancouver Scar Scale, used by the investigator, scored pigmentation, vascularity, pliability and height of the donor site. The Hamilton Burn-Scar Rating Scale, used by the blinded reviewer when assessing photographs of the donor sites, contained similar elements (i.e., thickness/height, irregularity, vascularity, color/pigmentation, and overall appearance). Table 11.4.17, below, summarizes the number of donor sites with normal scores at week 24 for the individual parameters used in each of the assessment methods. These data indicate that the percentage of CCS sites appearing normal at week 24 was higher than the percentage of Biobrane-L sites across all parameters and both assessment methods with the exception of vascularity in the photographic method where they were nearly the same.

Table 11.4.17: Percentage of Donor Sites with Normal Scores All Scar Parameters, Week 24

Investigator Scar Assessments (Vancouver Score)		
	CCS N = 55	BIO N = 56
Vancouver	n (%)	n (%)
Normal Pigmentation	22 (40.0)	14 (25.0)
Normal Vascularity	31 (56.4)	23 (41.1)
Normal Pliability	36 (65.5)	29 (51.8)
Normal Height	41 (74.5)	35 (62.5)

Source: Section 14, Table S23.1

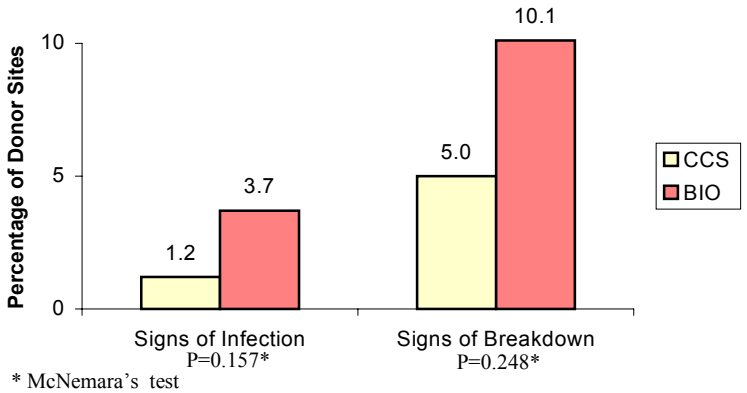
Photographic Scar Assessments (Hamilton Score)		
	CCS N = 48	BIO N = 50
Hamilton	n (%)	n (%)
Thickness (None)	39 (81.3)	34 (68.0)
Irregularity (None)	38 (79.2)	34 (68.0)
Vascularity (Normal/Mature)	26 (54.2)	28 (56.0)
Color (Normal to paler than normal skin)	17 (35.4)	13 (26.0)
Overall Appearance Acceptable	23 (47.9)	17 (34.0)

Source: Section 14, Table S23.2

Signs of Infection and Breakdown

Clinically meaningful differences were noted in signs of infection and site breakdown between the CCS and Biobrane-L sites, in favor of CCS. The percentage of CCS donor sites exhibiting signs of infection was 1.2% versus 3.7% for Biobrane-L. The percentage of CCS donor

Figure 11.4.18: Signs of Infection and Breakdown All Study Days, Safety Population



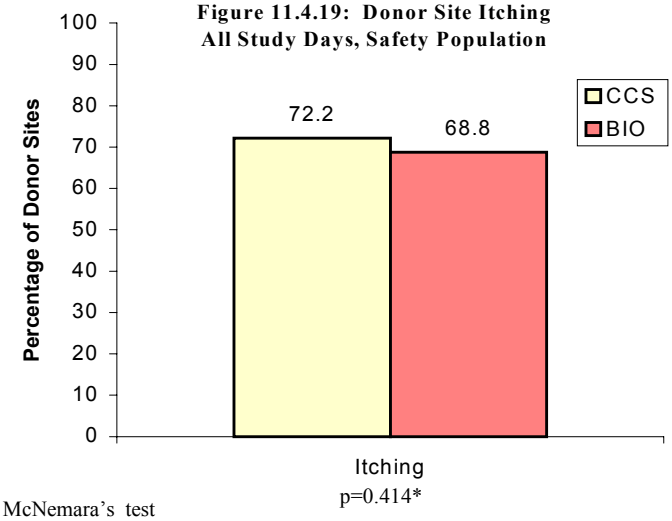
* McNemara's test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table S16

sites exhibiting signs of breakdown or blistering was 5.0% compared to 10.1% for Biobrane-L. Figure 11.4.18 depicts a summary of these data. Data are also displayed in Table 11.4.20.

Itching

Severity and incidence of donor site itching was similar for the two groups (72.2% vs. 68.8%, CCS vs. Biobrane, respectively), with no clinically meaningful or statistically significant increase in itching for the CCS group. A summary of donor site itching within the Safety Population is depicted in Figure 11.4.19 and presented in Table 11.4.20

Figure 11.4.19: Donor Site Itching
All Study Days, Safety Population



* McNemara's test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table S16

Table 11.4.20: Signs of Infection, Breakdown, and Itching

		CCS N (%)	BIO N (%)	P-value*
Signs of Infection	Absent	81 (98.8)	79 (96.3)	0.157
	Present	1 (1.2)	3 (3.7)	
	Total	82 (100.0)	82 (100.0)	
Signs of Breakdown/Blistering	Absent	76 (95.0)	71 (89.9)	0.248
	Present	4 (5.0)	8 (10.1)	
	Total	80 (100.0)	79 (100.0)	
Itching	None	22 (27.8)	25 (31.3)	0.414
	Mild	29 (36.7)	28 (35.0)	
	Moderate	21 (26.6)	21 (26.3)	
	Severe	7 (8.9)	6 (7.5)	
	Total	79 (100.0)	80 (100.0)	

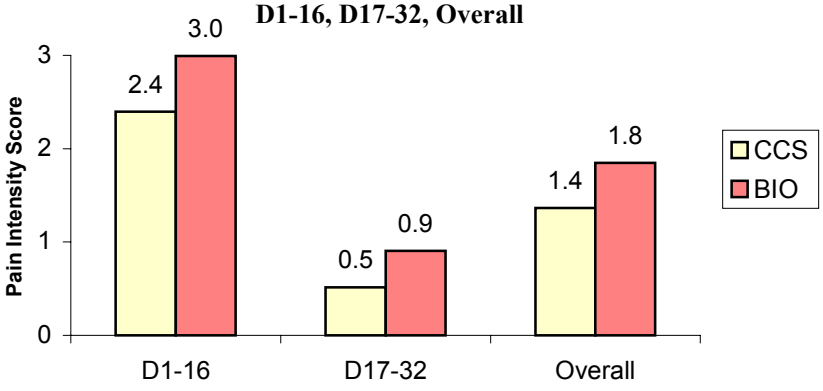
*McNemara's test
Present = symptom was present at one or more visits. Absent = symptom was absent at all visits
Events of itching were tallied once for each patient, at the highest reported severity.
Source: Section 14, Table S16

Pain

Donor site pain was assessed separately for three age groups (i.e., ≤ 8 years old, 3 to 7 years old, and < 3 years old).

Average mean pain intensity scores for Days 1-16, Days 17-32, and overall are depicted in Figure 11.4.21. Across all three "data cuts," the CCS sites exhibited lower average mean pain intensity scores than the Biobrane-L sites. When all days were considered, the average mean daily pain score for the Biobrane-L sites was 1.8 compared to 1.4 for CCS indicating, on average, nearly 30% more pain at the Biobrane-L sites. On the first 16 days of the study Biobrane-L sites exhibited approximately 25% more pain than did the CCS sites (3.0 vs. 2.4, respectively). On the last 16 days of the study, the average mean daily pain intensity for Biobrane-L sites was 0.9 compared to a CCS pain intensity of 0.5 indicating 80% more pain with Biobrane-L than with CCS. These data indicate that pain intensity for CCS treated sites was consistently lower than the pain intensity at Biobrane-L treated sites.

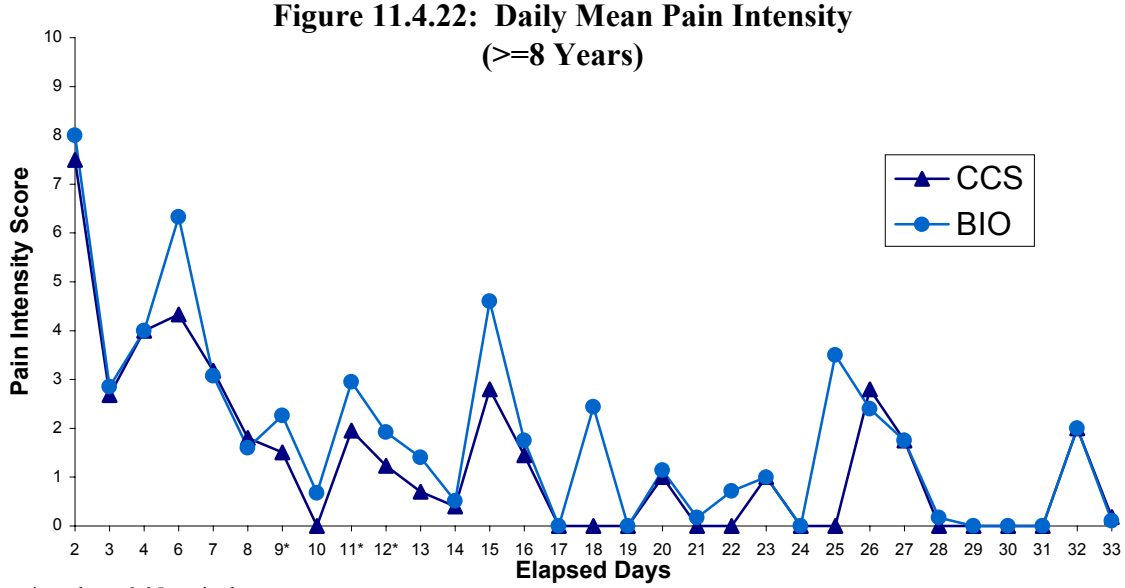
Figure 11.4.21: Average Mean Pain Intensity (>= 8 Years) D1-16, D17-32, Overall



CCS:Composite Cultured Skin, BIO:Biobrane-L
p-values not determined
Source: Section 14, Table S12.1, manual computation

Mean daily pain experienced at the CCS site for patients eight years and older (N=65) was lower than that experienced at the Biobrane-L sites on nearly all days and significantly lower pain intensities were noted on days 9, 11, and 12 for the CCS sites. These data are depicted in Figure 11.4.22.

Figure 11.4.22: Daily Mean Pain Intensity (>=8 Years)



*p-value < 0.05, paired t-test
CCS:Composite Cultured Skin, BIO:Biobrane-L
Source: Section 14, Table S12.1

The sample sizes for the 3 to 7 year old group (n=7) and the less than 3 year old group (n=10) were too small to make any valid comparisons between treatment groups in regards to pain. The number of assessments made on a daily basis for the 3 to 7 year olds was five or less. The number of assessments made on a daily basis for the less than 3 year old group was nine or less. Tables S12.2 and S12.3 in Section 14 display data for the 3 to 7 year old group. Tables S12.4 and S12.5 display data for the less than 3 year old group.

Time to Actual Re-Cropping

An insufficient number of patients underwent re-cropping to be able to accurately assess data for this parameter between the two products. Times to actual re-cropping are listed in Appendix 6.10, listing 16. Manual tabulation of these data indicates that of the 82 patients enrolled in the trial, 3 CCS sites were recropped (patient 01-009 on day 321,

patient 03-004 on day 30, and patient 08 005 on day 14) and one Biobrane-L site was recropped (patient 01-009 on day 321).

Functionality and Durability of Recropped Grafts

An insufficient number of patients underwent re-cropping to be able to accurately assess data for this parameter between the two products.

11.4.3 SUBPOPULATION ANALYSES

We conducted several subgroup analyses (gender, age, race, size of donor site, and percent body surface area burned) with all three assessment methods (i.e., photographic, planimetry, and investigator assessments) to evaluate whether one or more subpopulations were driving the observed superiority of CCS over Biobrane-L. In all subpopulations examined, there was a shorter mean time to 100% wound closure with CCS treated sites than with the Biobrane-L treated sites, indicating that no special populations were driving the observed superiority of CCS.

Table 11.4.23: Subpopulation Analyses
Mean Time to 100% Wound Closure, Planimetric Data, ITT Population

	Section 14 Source Table	N	CCS Mean (SD)	BIO Mean (SD)	BIO-CCS (delta)
Male	E1.5	63	13.7 (5.42)	19.4 (8.18)	5.7
Female	E1.5	19	13.9 (7.21)	19.2 (9.17)	5.3
<15 years	E1.5	22	12.2 (3.97)	15.3 (6.85)	3.1
15 - 65 years	E1.5	57	14.0 (6.16)	20.6 (8.42)	6.6
>65 years	E1.5	3	19.0 (8.89)	25.7 (8.50)	6.7
White	E1.5	44	13.1 (5.52)	17.6 (7.83)	4.5
Black	E1.5	20	15.0 (5.60)	22.4 (8.27)	7.4
Other	E1.5	18	13.9 (6.86)	20.1 (9.13)	6.2
TBSA <20%	P9-A	21	11.8 (2.94)	13.6 (4.14)	1.8
TBSA 20 - 40%	P9-A	47	14.1 (6.92)	20.6 (8.93)	6.5
TBSA >40%	P9-A	14	15.4 (4.45)	23.5 (7.06)	8.1
Donor Area <=45cm	P9-C	20	11.9 (3.80)	17.3 (8.02)	5.4
Donor Area >45cm	P9-C	62	14.3 (6.26)	20.0 (8.43)	5.7

Subpopulation data are presented in Table 11.4.23. The last column in this table (BIO-CCS [delta]) presents the difference between mean time to 100% wound closure for Biobrane-L and CCS. A positive delta indicates that CCS time to healing is shorter than Biobrane-L and the larger the delta, the larger the difference between the two treatment

groups. As is clearly indicated in Table 11.4.23 there were no negative data points (i.e., for all subgroups) the mean time to reach 100% wound closure for CCS treated sites was shorter than for the Biobrane-L treated sites.

Observed Trends

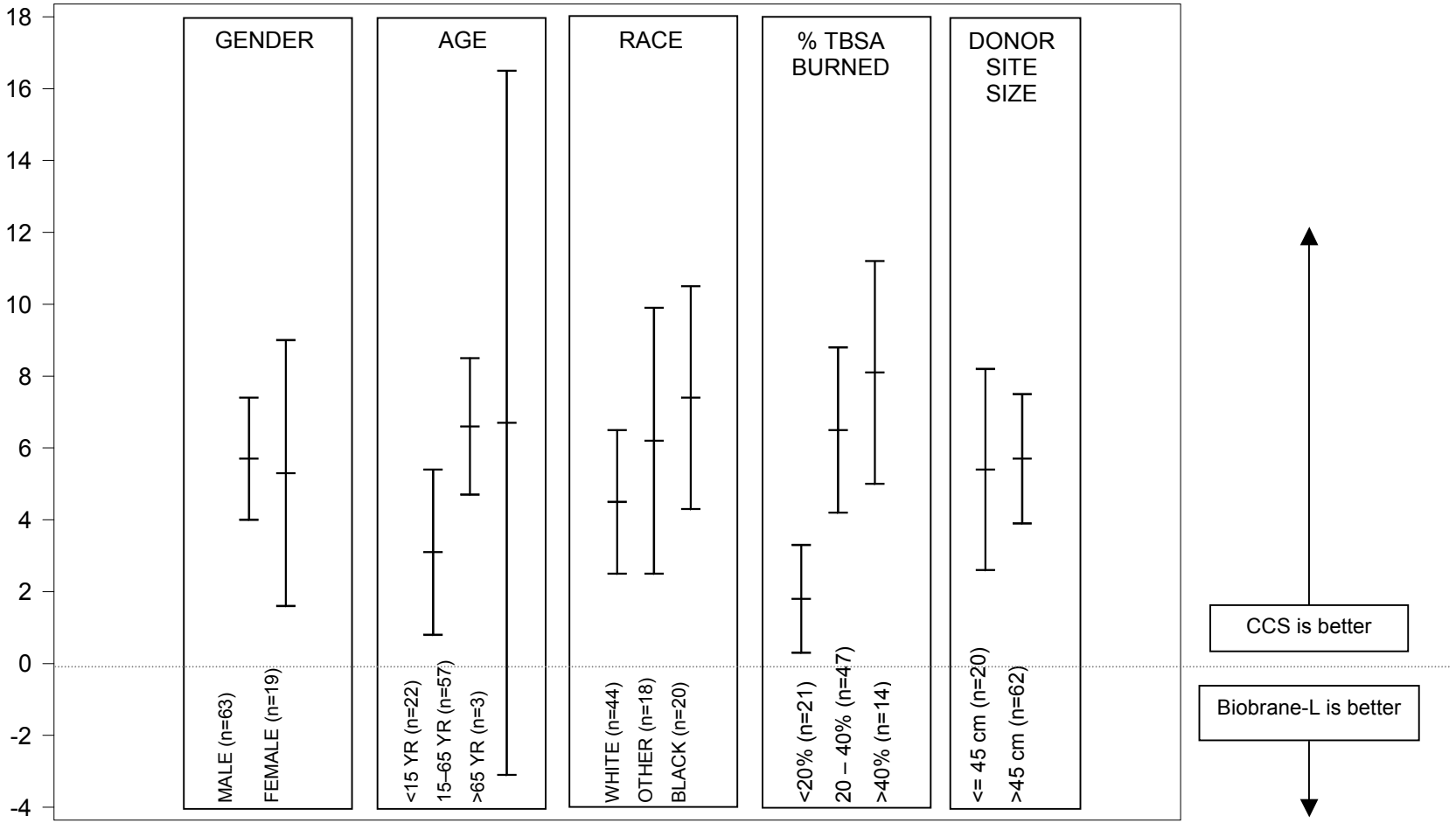
Planimetry data indicate that patients with burns encompassing larger percentages of their total body surface area had a greater difference between the CCS and Biobrane-L treated sites. For patients with burns less than 20% TBSA (n=21) there was a difference of 1.8 days between CCS and Biobrane-L (i.e.,11.8 days and 13.6 days, respectively). For patients with burns 20% - 40% TBSA (n=47) the difference was 6.5 days (14.1 and 20.6 days, respectively) and for patients with burns greater than 40% TBSA (n=14) the difference was 8.1 days (15.4 and 23.5 days, respectively).

Similar findings were observed for the age subgroups: for patients less than 15 years of age (n=22) the CCS treated sites healed 3.1 days faster than the Biobrane-L treated sites (CCS=12.2, Bio=15.3 days), for patients between 15 – 65 (n=57) the CCS treated sites healed 6.6 days faster than the Biobrane-L treated sites (CCS=14.0, Bio=20.6 days), and for patients older than 65 (n=3) the difference was 6.7 days (CCS=19.0, Bio=25.7 days).

Figure 11.4.24 depicts the mean differences between the healing times for CCS and Biobrane-L and their 95% confidence intervals (CI) for the subpopulations. Guidelines for reading the graph appear below the figure.

These data clearly demonstrate that for all subgroups with n >5 the mean time to 100% wound closure is statistically significantly shorter with CCS than with Biobrane-L. Furthermore, the data demonstrate consistency of the superiority of CCS in time to 100% wound closure and a trend toward faster healing times with CCS in more severely burned patients.

Figure 11.4.24: Subpopulation Analyses
Planimetric Results, ITT Population



For each subpopulation, the 95% CI is depicted as a vertical bar with 3 dashes. One dash appears at the top of each bar, one in the middle of each bar, and one at the bottom of each bar. The upper and lower dashes represent the 95% CI upper and lower limits, respectively, while the middle dash represents the point estimate or the mean difference between the two treatments.

Bars appearing above the zero line indicate that wound closure time with CCS treatment was statistically significantly shorter (i.e., better, than that of Biobrane-L). Bars appearing below the zero line indicate that wound closure time with Biobrane-L treatment was statistically significantly shorter than that of CCS. No statistically significant difference between the two treatments is indicated if the lower limits of any of the 95% CI cross the zero line

11.4.4 EFFICACY CONCLUSIONS

Results obtained from this study clearly demonstrate the superiority of CCS over Biobrane-L in time to complete wound closure, percentage of donor sites healed by day 32, rate of wound closure, time to readiness for re-cropping, and scarring severity. Furthermore, a clinically significant difference was noted, in favor of CCS, for rate of infection, donor site breakdown, and pain, and no significant increase in itching.

The primary efficacy outcome variable (i.e., time to complete wound closure) was measured by three separate methods, photography, planimetry, and investigator assessments. As discussed in Section 9.5.3 of this report, of the three assessment methods used in this study, the photographic method is the least sensitive. Nonetheless, all assessment methods provided clinically meaningful and statistically significant results ($p<0.05$) demonstrating the superiority of CCS over conventional treatment for skin graft donor sites. By photographic assessment, complete wound closure with CCS occurred 7 days earlier than with Biobrane-L. By planimetry, complete wound closure with CCS occurred 5 days earlier. And investigator assessment indicated that complete wound closure with CCS occurred 4 days earlier than with Biobrane-L. Additionally, the statistically significantly ($p<0.05$) shorter time to complete wound closure with CCS was consistent across the ITT and PP populations and persisted regardless of age, race, gender, size of donor site, or percent of total body surface area burned.

The percentage of CCS donor sites completely healed by day 32 was also statistically significantly higher than that of Biobrane-L with all three assessment methods. By photographic assessment, 24% more CCS donor sites were healed than Biobrane-L ($p=<0.0000$). By planimetry, CCS healed sites were 12% higher ($p=0.0039$); and by investigator assessment, CCS healed sites were nearly 10% higher ($p=0.0047$).

The accelerated time to 100% wound closure with CCS versus Biobrane-L is clearly reflected in the daily rate of wound closure. Planimetry data from this study indicate that during the first 16 days of treatment, CCS treated sites healed at a mean rate of 6.3 cm2/day while Biobrane-L treated sites healed at a mean rate of 3.8 cm2/day, demonstrating a statistically significant difference that translates into a CCS healing rate that is nearly 70% faster than Biobrane-L during the first 16 days of therapy. The rates of wound closure for both CCS and Biobrane-L appear to decrease after the 16th day,

however, the mean rate of wound closure for CCS during this time period remained greater than that of Biobrane-L by 16% (i.e., approximately 4.0 cm2/day vs. 3.5 cm2/day, respectively).

The significance observed in time to healing and rate of healing was supported by clinically meaningful and statistically significant differences in time to readiness for recropping. The median time required for readiness to re-crop a CCS treated site was 7 days less than the time required for a Biobrane-L treated site (i.e., 14 days vs. 21 days, respectively, p=0.0002). The difference in mean times was similar (i.e., 16 days for CCS sites vs. 21 days for Biobrane-L sites, p<0.0001).

Statistically significant and clinically meaningful results in scarring assessments were obtained at Weeks 12 and 24 by two separate assessment methods. The overall scarring severity scores as assessed by the investigator at Week 12 were 2.26 for CCS and 3.07 for Biobrane-L (p=0.017). At Week 24, investigator assessed scores were 2.56 for CCS and 3.79 for Biobrane-L (p=0.0002). A blinded photographic assessment yielded similar results (i.e., Week 12 CCS = 3.89, Biobrane-L=4.95 [p=0.018]; Week 24 CCS = 2.46, Biobrane-L = 3.50 [p=0.02]). Additionally, the numbers of CCS sites appearing normal in terms of individual scar parameters were consistently higher than Biobrane-L (i.e., pigmentation/color, pliability, height, thickness, irregularity, and overall appearance).

Clinically meaningful differences in the rate of infections, donor site breakdown, and pain intensity were noted. The percentage of CCS sites exhibiting signs of infection was 1.2% compared to 3.7% for Biobrane-L. CCS sites showing signs of breakdown or blistering was 5% compared to 10.1% for Biobrane-L. As for pain, when scores were averaged for the two sites across the 32 days of the study after surgery, the Biobrane-L sites elicited 30% more pain than did the CCS sites.

In summary, efficacy data demonstrate the consistent superiority of CCS over Biobrane-L in terms of time to complete wound closure, percentage of donor sites healed by day 32, rate of wound closure, time to readiness for re-cropping, scarring severity, rate of infection, donor site breakdown, and pain. Additionally, no significant increase in itching at the CCS sites was observed.