STATISTICAL REVIEW MEMO

I. Sponsor's Design and Summary Results

This was a prospective, active controlled, randomized multi-center study involving patients requiring conventional split thickness skin autografting for the management of burn injuries. The study incorporated a matched pairs design (i.e., each patient had two designated donor sites of equivalent surface area and depth). One of the patients two donor sites was randomized to receive a single treatment of either the control dressing or investigational device Composite Cultured Skin (CCS), the other donor site received the other treatment.

The primary efficacy variable was time to complete wound closure (complete re-epithelialization) as determined by photography. The sponsor states that the null hypothesis is time to complete wound closure is equal in the CCS treated sites and the control treated sites. The alternative hypothesis is that time to complete wound closure is different. Sponsor also states that efficacy of CCS will have been established if the null hypothesis is rejected, and the median healing times indicate that time to complete wound closure is shorter in the CCS treated sites compared to the control treated sites. The secondary efficacy variables were time to complete wound closure as determined by computerized planimetric assessment of unhealed wounds, time to complete wound closure as determined by investigator through clinical assessment, the rate of wound healing as determined by the percent change in wound area from baseline as determined by planimetric data, time to readiness for recropping as assessed by the investigator, and time to actual recropping of an original donor site.

Safety variables that were compared between the two treatments were: incidence of donor site specific adverse events, scar outcome, pain and itching scores, and incidence of donor site infection and breakdown, time to actual recropping, and recrop outcome. Adverse events were tabulated by preferred term, body system and severity (mild, moderate, severe, life-threatening or fatal).

A total of 82 patients were enrolled among 12 study sites. All 82 patients were included in the intent-to-treat and safety populations. The per-protocol population consisted of 74 patients (90.2%). Sixty patients (73%) completed the study, 22 patients (26.8%) discontinued study before the week 24 visit, and 8 patients were excluded from the per protocol analysis.

The sponsor claims statistical differences in 100% wound closure for both the intent-to-treat population and the population without protocol deviations for all evaluations of 100% wound closure (primary measure). Additional secondary efficiency measure presented also showed statistical significant difference compared to the control. The sponsor suggested that there was no adverse event differences between the device and the control for donor site involvement, and no severe adverse event occurred at the incidence of ≥ 5%.

II. Reviewer's Comments

1. The sponsor's sample size determination included in the protocol estimated 120 patients to be enrolled in order to complete 85 patients required in their determination of sample size requirement.

    (a) The sponsor's calculation used the proportional hazards assumption (Schoenfeld, 1983; Freedman, 1986; Friedman, Furburg, and DeMets, 1996). Estimate of hazard rates used reference by Donner, 1984. The reference section did not include where these references may be found. Please include the actual reference used in your sample size calculation.

(b) The sponsor's discussion of the investigational plan (Vol. 9, pg. 16) suggests the goal was to have 75 patients complete the trial and provide data for analysis. Please explain this discrepancy from the protocol where it was determined 85 patients are required to complete your trial.

(c) Sponsor's sample size calculation was calculated using two-sided assumptions. However, hypothesis for primary endpoint was superiority.

2. The primary effectiveness endpoint is time to complete healing. This is determined via 3 methods; physical exam, wound tracings, or photography, which is the gold standard, and the primary methodology suggested in the protocol. To help minimize the potential for observer bias via photography, the pictures were randomized and evaluated by two experts. If there was disagreement in the readings by the two experts, a third expert would break the tie.

   (a) It is my understanding that the device and the control look different, and the application procedures between the devices were different. The control device require staples. Thus, how could this be truly blinded?

   (b) How often did the third party evaluator need to break the tie? What were the findings?

   (c) Were the evaluator's familiar with either or both devices? Any financial interest? How were they selected?

3. The control used in this study, BioBrane, should be clinically acceptable. Note there are differences in this device and the control for placement and follow-up care. Note that the outer dressing wrap for CCS is to wrap every 48 – 72 hours. For BioBrane after the initial 24 – 48 hours, it is left open. Also, the protocol says that " in the event BioBrane requires premature removal and therefore, the exposed site is not completely epithelilialized, the entire open region will be traced". There is no similar statement for CCS. Why? Why not?

4. For patients with extensive surface area involvement who will require recropping, a total of 8 CCS devices may be allowed. Was time to complete healing for the 'other' areas different than the primary area used in the analysis? Could there be more than one primary area evaluated in a single patient? If so, what were the primary results for this population?

5. The study should have made sure all investigators were familiar with using both products. Were they? The sponsor should report primary effectiveness and safety variables by investigator (study site) and analyze for pooling.

6. The sponsor did several subgroup analysis including age, sex, Total Burn Surface Area (TBSA), and donor area size. All results presented appears to be consistent with the overall findings. I would suggest that the sponsor also analyze 'location' of burn site for completeness.

7. A total of sixty patients have completed the study. Twenty-two patients discontinued the study before week 24. Eight patients were excluded from the protocol analysis. Are there rates typical for this population? Was there any attempt to follow-up the 22 discontinued patients to assure they are not device failures? Please note that the sponsor has not met their proposed sample size requirement.

8. The statistical tests used to determine p-values for various endpoints appear to be appropriate. However, results are often reported without reporting numerator/denominator (actual numbers). Please include these values for completeness. For verification purposes we also would like the patient data be sent in electronic format (SAS readable).

9. The sponsor's claim that there were no severe, life threatening, or fatal adverse events that occurred at an incidence of ≥ 5% may not be complete. If we included 95% Confidence Intervals (CI) for these rates any reported event (n=1) would have an upper CI of ≥ 5%. Additionally, since infection may be of particular concern for the device, we suggest either post-market or other additional support be included. Note that the current design of this study may be excellent in evaluation effectiveness, but make safety determination more difficult to evaluate. Specifically, it may be difficult to determine immunological reactions, or other similar events to either the device or the control. Also note, 64 (78.0%) of the patients enrolled had at least one adverse event.