MEMORANDUM

Date: May 19, 2003

From: R. Murty Ponnapalli, Mathematical Statistician, OSB/DBS
Revised (09/02/03) by Barbara Krasnicka, Mathematical Statistician, OSB/DBS

Device: Spectranetics CVX-300 Excimer Laser System

Subject: Statistical Review of P910001/S22, a laser treatment for Critical Limb Ischemia submitted by Spectranetics Corporation

Through: Dr. Gregory Campbell
Director, Division of Biostatistics

In this submission, the sponsor seeks approval for the use of its Excimer Laser System in peripheral arteries. A nonrandomized trial using prospective and retrospective (historical control) studies was used to demonstrate the evidence of safety and effectiveness of excimer laser ablation of target vascular obstructions. The laser angioplasty in critical limb ischemia (LACI) group enrolled 155 limbs of 145 patients from14 sites (US and German). All patients were poor surgical candidates with critical limb ischemia (CLI). The treatment in the LACI group was laser atherectomy plus balloon angioplasty (PTA) and optional stenting in superficial femoral artery (SFA).

It was agreed at the IDE stage that the study control would be the control arm of an Italian study published in the Annals of Internal Medicine, Vol.130, pp 412-421, 1999, by the ICAI study group; the publication title is "Prostanoids for Chronic Critical Leg Ischemia."

The treatment for patients in the control arm was standard medications for blockage of arteries and/or surgical interventions at the time of randomization. Number of patients in the control group was originally 789; however, 116 patients were withdrawn because of some irregularities in reporting at 5 centers. Therefore, only 673 patients were left in the control group. The following is the description given by the ICAI group about the irregularities: "A cross-check of follow-up data through census offices or the patients themselves or their relatives revealed incorrect reporting of outcome events for 18 patients followed by five centers. In the absence of source documents against which to check individual clinical record forms and in agreement with the International External Safety and Efficacy Monitoring Committee, all 226 patients recruited by those centers were excluded from the efficacy evaluation at 6 months."

The following baseline differences in characteristics of legs (observed in the treatment and control arms) were found to be statistically insignificant: Rutherford categories 4 and 5 or 6, ulcers or gangrene, and previous interventions. The baseline

characteristics found to be statistically significantly different were rest pain, previous minor and major amputation.

According to the clinical protocol of the study under review, the primary effectiveness endpoint is the percentage of alive patients without amputations at 6 months and the primary safety endpoint is the percentage of deaths during the 6-month follow-up period. The summary of events in the treatment and control arms are given in the following table.

Table 1.

Patient Status	LACI Group Patients	LACI Group Limbs	Control Group Patients	Control Group Mortality Data Patients
At the baseline	145	155	789	789
Withdrawn			116	
In the analysis	145	155	673	789
Lost to follow-up	11(7.6%)	11(7.1%)	7(1%)	5
Completed the study	134	144	666	
Death	15	17	96	113
Major Amputation	9*	9*	76	
Limb Salvage	110	118	494	

* Two additional major amputations occurred in patients who subsequently died within the 6-month follow-up (for a total of 11 major amputations).

The percentage of patients in the present study who were alive without major amputation at 6 months was 110/145 = 75.9% and the percentage in the control was 494/673 = 73.4%. The approximate 95% confidence interval for the difference (treatment-control) turns out to be (-5.3%, 10.2%). Since this interval includes 0, the two percentages are not statistically significantly different at 5% level of significance.

The percentage of deaths with the Excimer Laser System was 15/134 = 11.2% and the percentage of deaths in the control was 96/666 = 14.4% (or 113/784 =14.4%, mortality data was available for 784 patients). The exact 95% confidence interval for the difference in the true percentages in the treatment and the control is (-11.6%, 4.4%). Again we see that there is no statistically significant difference in the percentages of deaths.

The sponsor defines a serious adverse event (SAE) as death, myocardial infarction, stroke, reintervention of treatment site during concurrent hospitalization, major perforation necessitating surgical repair, acute limb ischemia necessitating intravascular intervention or thrombolytic drugs, amputation due to distal thrombosis, hematoma or false aneurysm necessitating surgical intervention, nerve injury, or major amputation. According to this definition, there were SAEs (35.8%) in 48 patients in the treatment group and in 239 (35.9%) patients in the control group. These rates were not

statistically different. When calculated on a limb basis, however, the SAEs in the treatment group were 58/144 (40.3%). One of the SAEs, reintervention, was more frequently observed in the LACI group (24/134 or 18%) than in the control group (34/666 or 5%) ($p<0.001$). Approximate 95% confidence interval for the difference in the probabilities of occurrence of reintervention SAE in the LACI and control groups is (0.061, 0.1951). Since this interval does not include zero, the estimated difference 0.1281 between two probabilities is significant at the level 5%.

A survival type analysis was performed in order to evaluate the differences between the LACI and control groups with respect to times of occurrence of major amputation and death during 6 months. To compare freedom from major amputation times for LACI and control groups, the Wilcoxon and Log-rank tests were applied. The values of the chi-squared statistics were 1.14 and 1.43, respectively, and the corresponding P-values were 0.28 and 0.23. There is no difference between the freedom from major amputation times for the two groups. Again, for evaluations of the difference of survival times between the two groups, the Wilcoxon test was used. The value of the chi-squared statistics was 1.86 and the corresponding P-value was 0.1728. The difference between the two groups is not significant at the 5% level.

The following predictors for major amputation/death were investigated using the univariate Cox proportional hazard model: Rutherford category 6, age, previous minor amputation, diabetes, Rutherford category 5-6, gender, procedure success, straight line flow established, and stented leg. The significant univariate predictor for major amputation turned out to be Rutherford category 6. Age was only a predictor of death within 6 months after randomization. These two variables, age and Rutherford Category 6, occurred with similar frequencies in LACI and control group.

Comments

1. The control (historical) data and LACI group data may not be pool-able. These two studies were carried out in different countries, and hospitals that are different with respect to patient care and other country/hospital characteristics.

2. The LACI and control patients are not comparable. For example, the following baseline characteristics were found to be statistically significantly different: rest pain, previous minor amputation, and previous major amputation. Additionally, the control group is a historical one, based on the published paper. This means that detailed information, including raw data at the patient level, are not available. The statistical analysis of this kind of the study has serious limitations. For example, it is impossible to use the propensity scores to remove possible bias due to Rutherford category 5-6, history of CAD, and gender in comparison of the death rates at 6 months.

3. Point estimates, test and confidence intervals for the differences between the treatment and the control may not be accurate due to the following reasons:

a. the study is not a randomized one (historical control)
b. there is considerable missing information (e.g., 8% was lost in the follow-up for LACI group)
c. multiple imbalanced covariates (e.g., history of major amputation at the baseline) could not be considered in the covariate adjusted treatment comparisons, because of the character of the study (see comment 2)
d. in the LACI group, some patients (7% of 145 patients) received treatment for two legs, meaning that the primary events are not statistically independent (the same patient)
e. there is no information on how many legs were 'treated' in the control group.

4. All analyses should be interpreted with caution. The sponsor's suggestion that statistical results support the statement that the primary efficacy and safety endpoints of the LACI and the control group are to be statistically at least equivalent ("LACI provides benefit and reduced risk in all outcomes" on page 69 of the Clinical Summary) may be not correct.

5. In the LACI group, treatment was the laser atherectomy plus balloon angioplasty and optional stenting in SFA. In the control group, the treatment was standard medications for blockage of arteries (although sometimes the treatment included the bypass surgery and/or others procedures). It is very difficult to evaluate in this study the effectiveness of laser device because of the concomitant procedures which were not included in the control group treatment. For that reason, the statistical consideration given by sponsor does not evaluate the excimer laser therapy.

6. According to the Transatlantic Inter-Society Consensus (TASC) published in the Journal of Vascular Surgery, Vol. 31, 1, Part 2, Jan. 2000, the primary endpoint for peripheral artery disease should consist of nonfatal events that include major amputation, nonhealing of ischemic ulcers, ischemic pain, myocardial infarction, and ischemic stroke. In the present study, only major amputation is taken as the primary efficacy variable and the other components recommended by TASC are taken as the secondary endpoints.

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