

Circulatory System Devices Panel Questions

October 2, 2003

P910001/S022

Spectranetics Corporation

CVX-300 Excimer Laser System

Introduction:

Effectiveness and safety of endovascular laser atherectomy (ELA) to treat critical limb ischemia (CLI) were evaluated in a multi-center single-arm study referred to as the Laser Angioplasty for Critical Ischemia (LACI) trial. An historical control was selected for comparison, taken from the non-treatment arm of a randomized trial studying a drug treatment of CLI in 1560 patients. This latter study was conducted by Ischemia Cronica Critica degli Arta Inferiori (ICAI). In the LACI trial, 155 limbs in 145 patients were treated; 11 patients (8%) were lost to follow-up during the 6-month follow-up period.

Study Design:

The sponsor of LACI predicated the sample size on demonstrating that freedom from major limb amputation at six months (the primary endpoint) was not more than 10% worse than the control. Entrance criteria for the LACI trial were intended to ensure that LACI patients are at greater risk from co-morbidities than the control, justifying the 10% difference.

LACI intended to enroll a cohort of patients that were not candidates for surgical revascularization, based on the inclusion criteria of: ASA risk of Class 4 or higher; or absence of suitable autogenous vein (SAV) for conduit; or the extent of vascular disease. (Patients were not excluded if they were candidates for endovascular procedures.)

Sixty-six (46%) of the 145 LACI patients were classified as being in ASA 4 anesthesia risk status.

Forty-six (32%) of the 145 patients were described as lacking SAV.

Univariate analysis established that only Rutherford Class 6 was a predictor for major amputation in the LACI study, and occurred with similar incidence in the treatment and control groups at baseline.

- 1. Please comment on the following aspects of the study design:**
 - a. Please comment on whether or not the characteristics of patients in the LACI trial and the control group demonstrate an increased risk for limb loss in LACI, sufficient to justify the 10% difference for the primary effectiveness endpoint.**

- b. An active intervention for limb salvage in LACI is compared to a control arm of non-intervention. Please comment on whether the outcomes for this endovascular procedure can be satisfactorily assessed without comparison to balloon percutaneous transluminal angioplasty (PTA).**

Safety:

The primary safety endpoint was death within 6 months. This occurred in 15/134 (11.2%) patients in the LACI study, and was not significantly different from the 113/782 (14.5%) patient deaths in the enrolled control group. Patient age was the sole predictor for this outcome, and was similar at baseline for both study arms.

Secondary safety endpoints were serious adverse events (SAEs) as adjudicated by an independent Clinical Events Committee. SAEs occurred in 48/134 (36%) patients and 58/144 (40%) limbs in LACI (not including patients lost to follow-up); these SAEs included 24/134 (18%) re-interventions and 11/134 (8%) major amputations. The SAE rate in the control group was 239/666 (36%), with 10/666 (1%) re-interventions and 76/666 (11%) major amputations. To put these results in context, the sponsor noted that the rate of adverse events at 6 months is comparable to the rates reported for PTA for periods that extend to five years.

- 2. Re-interventions were significantly higher in the LACI study than the control group. Please comment on whether the adverse event data from the LACI study provide reasonable assurance of the safety of ELA used to treat CLI.**

Effectiveness:

The primary effectiveness endpoint of the LACI II study was limb salvage (absence of major amputation) at six (6) months. In the LACI II study, documented limb salvage at six months was achieved in 110 patients (75.9% of 145 patients enrolled); of the other 35 patients, 15 died, 11 were lost to follow-up, and 9 had major amputations. (Two other major amputations were performed on patients who subsequently died.) By comparison, limb salvage at six months in the control group was achieved in 494 of 673 patients (73.4%); of the other 179 patients, 96 died, 7 were lost to follow-up, and 76 had amputations. Rutherford Class 6 was the only significant univariate predictor for this effectiveness endpoint; eleven (7.5%) LACI patients were in this class at baseline. By comparison, 60 (7.6%) control patients were listed at enrollment as being in Fontaine Class 5, which includes both gangrenous ulceration and tissue loss.

Of the 110 LACI patients who were evaluated at 6 months and were free of major amputation, forty-three (39%) continued to be classified with CLI. This is compared to 211 (43%) cases of persistent CLI in the control group reported by ICAI.

Outcomes for LACI Study

Variable	LACI	ICAI
Patients enrolled	145	789
Censored (withdrawn from analysis)	--	[116] ¹
Number of patients for analysis	145	673
Lost to follow-up	11 (7.6%)	7 (1.0%)
Patients not lost to follow-up	134	666
Deaths ²	15 (11.2%)	96 (14.4%)
Alive with Major Amputations at 6 months	9 (7.6%)	76 (13.3%)
Primary Effectiveness Endpoint*	110 (75.9%)	494 (73.4%)
Persisting CLI	43 (29.7%)	211 (31.4%)
Serious AEs	58 (40.0%)	239 (35.5%)
Re-interventions ²	24 (17.9%)	34 (5.1%)

1 All 226 patients at five centers (116 from control arm) were excluded by the monitoring committee due to reporting inaccuracies for 18 patients.

2 Calculation of these percentages does not include patients lost to follow-up.

* Primary Effectiveness Endpoint: Alive without amputation, and not lost to follow-up.

- 3. The clinical objectives of the study were stated as: (i) protection from acute amputation; (ii) limb salvage; (iii) resolution of CLI; and (iv) preservation of surgical options. Please comment on whether the outcomes for the LACI study demonstrate that these objectives have been achieved.**

Laser ablation requires crossing of the culprit lesions with a guidewire for control of energy delivery. Where standard guidewire crossing cannot be achieved, "step-wise" use of the laser can assist in achieving guidewire crossing. In LACI, the guidewire negotiated the lesion without need of laser in all but 26/155 (16.7%) limbs. Following the use laser energy, balloon angioplasty was required in all cases for the final reduction of lesion obstruction to <50% angiographically. This Procedural Success was attained in 132/155 limbs (85%).

- 4. Please comment on the added value provided by the laser therapy, which is used as an adjunct prior to the PTA required for final resolution of the lesion obstruction.**

Risk/Benefit:

Co-morbidity associated with CLI has accounted for mortality greater than 50-60% in patients out to five years, and as high as 40% at two years in some reports. Primary amputation has been recommended as an acceptable alternative to revascularization attempts in some cases. While freedom from amputation was obtained in 110 of the 155 limbs in this study, 15 patients died and 43 patients remained in Rutherford classifications for CLI. In addition, re-hospitalization for SAEs was necessary for 48 (36%) patients.

- 5. Please comment on whether the benefit demonstrated in this study, particularly with respect to quality of life-years, outweighs the adverse events that occurred and the persistence of CLI documented.**

Labeling:

6. Labeling for a new device should indicate which patients are appropriate for treatment, identify potential device-related adverse events, and explain how the device should be used to optimize its risk/benefit profile. If you recommend device approval, please address the following:

- a. Do the Indications for Use, as stated below, adequately define the patient population and procedural use for which the device will be marketed?

The Spectranetics CVX-300[®] Excimer Laser System is indicated for facilitation of limb salvage in patients with critical limb ischemia (associated with Rutherford Categories 4, 5 and 6) who have angiographically evident culprit stenoses and/or occlusions in the SFA, popliteal and/or infrapopliteal arteries, who are poor surgical candidates, and who are acceptable candidates for revascularization.

- b. Based on the study results, please discuss whether the proposed warnings, precautions, and contraindications are acceptable.
- c. Please discuss whether the instructions for use adequately describe how the device should be used.

7. Please indicate if the following findings are sufficiently robust to warrant incorporation in the label:

- a. The 110 LACI patients in Rutherford Clinical Categories 5 and 6 experienced 15% mortality and an amputation rate of 7%. This contrasted with 1% mortality and 2% amputation rate in 45 Category 4 patients.
- b. Seventy limbs in the LACI study also required stent placement. Stents were placed in 56 superficial femoral arteries (SFAs) in the 104 limbs with SFA lesions. Forty-nine (87.5%) of the SFAs with stents remained amputation-free at 6 months.

8. The sponsor has proposed the following training requirements in the draft Instructions for Use:

The use of the CVX-300[®] Excimer Laser System is restricted to physicians who are trained in atherectomy, Percutaneous Transluminal Coronary Angioplasty (PTCA) and who meet the training requirements listed below. These requirements include, but are not limited to:

- 1. Training of laser safety and physics.*
- 2. Review of patient films of lesions that meet the indications for use.*
- 3. A review of cases demonstrating the CLiRpath catheters in lesions that meet the indications for use.*

4. *A review of laser operation followed by a demonstration of the CVX-300[®] Excimer Laser System.*
5. *Hands on training with the CVX-300[®] Excimer Laser System and appropriate model.*
6. *A fully trained Spectranetics representative will be present to assist for a minimum of the first three cases.*
7. *Following the formal training session, Spectranetics will make available additional training if so requested by the physician, support personnel, the institution or Spectranetics.*

Please comment on whether these training requirements are adequate.