

MEMORANDUM

Date: August 25, 2003.

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Device: Spectranetics CVX-300 Excimer Laser System

Subject: Summary of Clinical Review of PMA Supplement P910001/S022
Laser Angioplasty for Critical Limb Ischemia (LACI)

Device Description and Introduction

Marketing approval is sought for a catheter system delivering excimer laser energy for ablation or vaporization of thrombotic and/or atheromatous obstructions to lower extremity arteries. This is performed as a percutaneous endovascular procedure.

An initial feasibility study (LACI I) was completed using the device for treatment of ischemic gangrene in 25 limbs of 23 patients with lesions considered at high risk for surgical revascularization. The pivotal study (LACI II) for this application was subsequently conducted with an IDE approved protocol, G980199.

Study Protocol

The study was designed as a prospective observational trial of laser treatment compared to an historical control of medical therapy. The latter was the control arm of a multi-center European randomized trial of 1560 patients, with similar baseline demographics and clinical characteristics for CLI, conducted and reported by the Ischemia Cronca Critica degli Arti Inferiori (ICAI) Study Group. The control arm comprised patients receiving only conventional medical supportive therapy for limb ischemia. The sponsors of LACI did not have access to the raw data for this study, and relied entirely on the published article (Ann. Int. Med. 1999;130:412-421) for all comparison purposes. The 789 original control sample was reduced to 673 by censoring of 116 patients from 5 centers for protocol infringements. Seven additional patients were lost to follow-up.

The primary effectiveness endpoint in LACI was limb salvage, defined as freedom from amputation at or above the ankle, at 6 months. The primary safety endpoint was all cause mortality at 6 months. Secondary endpoints for safety and effectiveness were adapted from those recommended by the TransAtlantic Inter-Society Consensus (TASC) for management of Peripheral Vascular Disease (PAD) (J. Vasc. Surg. 2000;31:S285-6).

The Inclusion Criteria were intended to enroll a cohort of patients with CLI considered to be unsuitable candidates for surgical revascularization because of: i) American Society of Anesthesiologists physical class 4 or higher; or ii) absence of a suitable autogenous

venous conduit (SAV); or iii) the extent of vascular pathology. Patients recruited had lower extremity CLI defined as Rutherford Clinical Categories 4, 5, or 6, due to obstructive lesions in the Superficial Femoral Artery (SFA), Popliteal Artery (PA), and/or infra-genicular Tibio-Peroneal Arteries (TPA). Feasibility of endovascular revascularization was not an exclusion.

ICAI patients with CLI were defined by Fontaine Class 3 with rest pain and Class 4 with gangrenous ulceration or tissue loss; the Fontaine Class 4 patients in the Rutherford Classification are separated as minor and major tissue loss in categories 5 and 6.

Independent Clinical Events and Data Monitoring Committees monitored study performance.

Study Sample:

Based on what the sponsor reported as a 6-month limb survival for the ICAI trial (86%) and the LACI I feasibility study (70%), the LACI II sample size was calculated to reject equivalence to the control limb survival if LACI II 6-month limb salvage was $\leq 76.8\%$. The LACI sponsors justify this delta of 10 % on the entrance criteria requiring patients to be poor candidates for surgery. This was seen as resulting in patients with more comorbidity than the ICAI patients and consequently introducing a bias for worse outcomes.

One hundred forty-five (145) patients were enrolled at 14 sites; 58% of the enrollment occurred at 4 sites, and 52 patients were at centers outside the U.S. The control group was comprised originally of the 789 patients randomized to the control arm of the ICIA study of 1560 patients blocked to 56 Italian centers. This initial enrollment of ICAI patients was reduced by censoring 116 control patients enrolled at 5 centers for protocol infringements. The resulting reduction to 673 patients reported for a 6 month outcome is used in this review as the analysis denominator.

The control study evaluated outcomes on a per patient basis, not limbs. The LACI II analysis was performed by limb outcomes for treatment effect, and by patient status for patient effects. The LACI outcomes will be revised for this review to conform with the control assessment using the 145 patients studied as the denominator for determining rates of most variables; where the sponsor has provided information only on a per limb basis, these rates will be included as italicized percentages. This will facilitate comparisons between study and control arms and adheres to both TASC and Suggested Standards for Reports dealing with Lower Extremity Ischemia of the Society for Vascular Surgery/American Association of Vascular Surgeons (J. Vasc. Surg. 1997;26:517-38)

The primary objective of the study was to determine whether endovascular laser endarterectomy (ELA) prevented limb amputation and relieved CLI at 6 months. Secondary objectives included healing of limited amputations, preserving surgical options, and temporary relief of rest pain.

Study Outcome:

Entrance Criteria:

Sixty-six (46%) of patients were in ASA Class 4 and forty-six (32%) lacked SAV at enrollment into LACI. By contrast 30-34% of ICAI patients had some type of vascular surgical intervention on entrance to the study but apparently still remaining with CLI. In addition the ICAI report notes 35 major amputations in the control arm at admission to study. Without further information it is presumed that this condition, the primary endpoint, occurred in the limb contra-lateral to that for entrance to study.

Significantly higher history of tobacco use is recorded in the control arm. Demographic characteristics were in other respects similar at baseline between the LACI and ICAI control. Patients were also well balanced between control and LACI patients for severity of CLI, based on the ischemic clinical categories.

The extent of pathology was available for both vessels involved and extent of lesions for the LACI but not for ICAI patients. Seventy (45%) of the LACI cases had a combination of both stenotic and occlusive lesions, with a mean of 2.7 (+1.4) lesions per limb.

Procedural Success

Procedural success, defined as $\leq 50\%$ angiographic residual stenosis, was achieved in 132 (85%) LACI cases. Seventy patients required vascular stent placement. Procedural success rates were better in the stented cases (65/70, 93%) than in the non-stented cases (67/85, 79%). Adjunctive balloon angioplasty (PTA) was required in all of the cases in which procedural success was achieved.

Peripheral vascular endpoint

This secondary endpoint is defined as being alive but with major amputation or persistent CLI. A total of 287/673 (42.6%) of the control group was computed to be in this secondary endpoint category, 76 patients with amputations and 211 with CLI. The peripheral vascular endpoint was present in 52 (36%) LACI patients, 9 of these patients had had a major amputation and 43 persisted in CLI categories. The level of amputation was judged as diminished by the LACI process in 2 of the 14 (9%) LACI patients requiring a minor post-procedural amputation.

Surgical Revascularization

Two (2) LACI study patients underwent surgical by-pass and one had an endarterectomy reconstruction during the follow-up period. Successful ELA therapy is claimed to have provided target vessels for these procedures not available at study entrance.

Two hundred and seventy-two patients (34.8%) of the control patients underwent some type of revascularization intervention at entrance to the ICAI study, but apparently remained with CLI so as to meet the ICAI inclusion criteria. Thirty-three (21%) of the LACI patients had experienced interventions prior to enrollment. The ICAI control was not precluded from vascular surgical procedures at enrollment, as were the LACI patients judged as poor surgical candidates. This discrepancy was to be addressed in the equivalence study hypothesis delta.

Safety Endpoints:

The primary safety endpoint captured all cause mortality and occurred in 15 (11.2%) of 134 LACI patients (not including 11 patients lost to follow-up) during the 6 months of follow-up, compared to 96 deaths (14.4%) for the 666 ICAI patients. These rates were not statistically different.

Secondary safety was captured as 58 serious adverse events (SAEs) for the 155 limbs treated (40%), which were adjudicated by the LACI Clinical Events Committee to include 24 (15.5%) re-interventions and 11 (7%) major amputations. Two of the patients with major amputations later died within the 6-month follow-up period. Minor amputations, below the ankle, were performed in an additional 14 (9.6%/9%) cases.

SAEs were reported for 239 (35.9%) of the 666 control patients not lost to follow-up. Apart from myocardial infarction and neurologic events, these SAEs included 6 instances of hemorrhage which were classified as hematoma, re-interventions required in 34 (5%) cases, and major amputations in 76 (11.4%) patients.

Effectiveness Endpoints:

Mechanical crossing of the lesion with a guide wire is required for controlled delivery of laser energy. This was accomplished without requiring laser use in all but 26 (16.7%) cases. A step-wise laser procedure was used to cross the lesion successfully in 13 of the latter cases.

Primary Effectiveness: One hundred nineteen (82%) of the 145 LACI patients were available for evaluation at the 6 month study termination; 15 patients had died, and 11 patients were lost to follow-up. Nine (6.2%) of the surviving patients had required major amputations. Two of the patients included in mortality, died following major amputations. Seventy-six (11.4%) of the 666 control patients (not lost to follow-up) had major amputations performed during the six months follow-up. Ninety-six (96) controls had died and 7 patients were lost to follow-up. Thus, limb salvage had been achieved in 110 LACI patients alive at 6 months (76% of the original 145), and 494 (73%) of the 673 control patients at 6 months.

Treatment Effect: Ischemia was classified in the LACI study as CLI with Rutherford Clinical Categories (RCC) 4, 5, and 6. At 6 months, a single patient of the 11 patients in RCC 6 at admission remained in RCC 6, five were now in RCC 0-3, and information on

5 patients was not available. Data on twenty-seven (27) initial RCC 5 patients was unavailable while 4 had deteriorated to RCC 6; 6 patients improved to Category 4, and 37 to 0-3. Twenty-five (25) patients remained in RCC 5 at the 6-month follow-up. Data on five (5) patients with RCC 4 limbs on admission had no follow-up data. Thirty-three (33) Category 4 limbs improved, 6 remained in Category 4 with CLI, and 1 deteriorated to Category 5. In all, 37 patients lacked follow-up RCC due to death (15), loss to follow-up (11), or amputation (11).

Forty-three (39%) of 110 patients evaluated at the end of the LACI study continued to fall in Rutherford CLI categories, despite limb salvage, compared to 211 (43%) of the control patients.

The following table summarizes the study outcomes:

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%)
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%)
Peripheral Vascular Endpoint**	52 (35.9%)	287 (42.6%)
SAEs	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 percentage does not include patients lost to follow-up.

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

** Peripheral Vascular Endpoint: Living with amputation or CLI.

Review Conclusions:

This was a well conducted and rigorously monitored study with independent monitoring committees and a core laboratory. It suffers, however, from the choice of an historical control selected from a single published study for which original data were not accessible to the sponsor. The sponsor has consequently had to rely entirely on the published article to derive comparison data for control of their study.

The sponsor has supplemented the study report with an extensive post hoc review of recent peer-reviewed literature to support both the safety and effectiveness of ELA for

management of CLI. Comparisons have been made to treatment of CLI with PTA, surgical revascularization, primary amputation, and with a conservative medical management. The sponsor claims that these secondary analyses provide confirmatory evidence for their assessment that a risk/benefit advantage has been shown for ELA use compared to all these alternative therapies in CLI by the LACI study. However, this review process does not provide adequate data to assure case cohort comparability, and many of the claims for similar outcomes for LACI and the published studies are made based on widely dissimilar study variables, such as duration of follow-up, extent of disease, and co-morbidity.

The sponsor perceives the LACI patients to be at higher risk than the control group, based on entrance criteria, a perception they applied to the equivalence study design. However, only 46% of patients were in ASA Class 4 or higher, a classification that is in any event more a measure of prognosis for a systemic health problem than of risk for treatment outcome of a regional condition. Thirty-two percent of patients were lacking SAV, leaving the majority of patients as possible candidates for surgical revascularization procedures, e.g., pedal artery by-pass, for which excellent long-term results are published. The most significant co-morbidity factors influencing limb salvage in peripheral vascular disease are smoking and diabetes. A smoking history was statistically more prevalent in the control group.

The LACI study found that age was the only significant predictor for survival, and that Rutherford Category 6 was a predictor for limb amputation. Both of these predictors occurred with similar frequencies in LACI and ICAI.

All patients required balloon PTA for final achievement of LACI procedural success. This begs the question, given that guide-wire crossing of lesions was accomplished without laser therapy in 83% of cases, whether primary balloon PTA could not have been undertaken with the excellent outcomes reported in the literature reviews submitted. Re-intervention rates reported in the literature for PTA, while comparable to that for LACI, extend for periods beyond 6 months out to five years. The lack of a PTA control is particularly troublesome, as endovascular procedures were not an exclusion criteria for LACI entrance.

The incidence of SAEs, and in particular earlier re-interventions, were statistically significantly higher for LACI than for the ICAI control. This raises concerns regarding a possible injurious effect of laser energy on the vessel wall that could be resolved with a PTA control arm.

The sponsor's claim to have demonstrated a positive risk/benefit for ELA in CLI management is debatable. Forty-three (39%) of the 110 patients surviving without major amputations remained in CLI Categories. Fifteen (10.3%) of the original cohort had died, 2 having had major amputations, and 9 (6.2%) were alive after major amputations. In addition, re-hospitalization for adverse events were required in patients who had 58 (40%/37%) of the LACI treatments -- certainly a consideration for the quality of a life already generally severely compromised.

The deployment of stents in 70 (45%) of the LACI patients, 65% in SFA, adds a further uncontrolled confounding variable given the short-term assessment period and the complications seen with these devices long term, particularly in the SFA.