Acute and 30-Day Safety and Effectiveness Evaluation of Eximo Medical's B-LaserTM, a novel atherectomy Device, in Subjects Affected with Infrainguinal Peripheral Arterial Disease: Results of the EX-PAD-03 Trial

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Acute and 30-Day Safety and Effectiveness Evaluation of Eximo Medical's B-Laser™, a novel atherectomy Device, in Subjects Affected with Infrainguinal Peripheral Arterial Disease: Results of the EX-PAD-03 Trial

Short title: EXIMO B-Laser™ in the treatment of symptomatic infrainguinal peripheral arterial disease

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Conflict of Interest: Dr Shammas receives educational and research grants from Boston Scientific, Bard and Intact Vascular and is on the Speaker Bureau of Janssen, Boehringer Ingelheim and Novartis. Dr Rundback is the National Principal Investigator and receives fees from EXIMO Medical. Drs Chandra, Palena and Cawich have nothing to disclose. Dr Lee is a consultant to CSI and BD and a trainer to Cook Medical.

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Abstract

Background. B-Laser™ is a novel atherectomy device that uses a solid-state third harmonic pulsed Nd:YAG laser with an output of 355nm. Early data showed that the B-Laser™ is safe in treating a broad range of infrainguinal arterial lesions. We present the results of the EX-PAD-03 U.S. pivotal trial of the EXIMO B-Laser™.

Methods. EX-PAD-03 is a prospective, single-arm, multi-center, international, open-label, clinical study. The study enrolled patients in the United States and Europe. The primary efficacy endpoint was the average reduction in residual diameter stenosis of greater than 20% from baseline prior to any adjunctive therapy achieved by the B-Laser™ catheter alone. The primary safety endpoint was freedom from major adverse events (MAEs) defined as: unplanned target limb amputation above the ankle, clinically driven target lesion revascularization (CD-TLR) and cardiovascular related death.

Results. A total of 97 subjects (107 lesions) were enrolled. Mean age was 70.5 years and 51% were males. Diabetes mellitus was present in 42.3%. Mean lesion length was 53.96 ± 43.18 mm and 26.2% had severe calcification. Lesions were *de novo* (79.4%), followed by in-stent restenosis (ISR) (15.9%) and non in-stent restenosis (4.7%). The mean percent stenosis at the target lesion as assessed by the Core lab was 85.7% ± 12.2 (femoro-popliteal 85.6 ± 12.8%; tibials 86.0 ± 9.6%). Post B-Laser™ and prior to adjunctive therapy, the mean percent stenosis at the target lesion was 52.1%. This resulted in a mean reduction from baseline to post B-Laser™ of 33.6% ± 14.2% meeting the primary efficacy endpoint goal. The freedom from MAE through the 30-day follow-up period after intervention was 98.9%. Per Core lab, there was no device-related distal embolization, dissections that required additional therapy, perforation, or

pseudoaneurysm. Bailout stenting was 0.9%. A significant improvement from baseline in ABI (0.24 ± 0.18), Rutherford category (-1.79 ± 1.22) and WIQ (0.26 ± 0.28) were noted at 1 month. There was no target lesion revascularization and the patency was 96.8% by duplex ultrasound criteria at 30-day follow up.

Conclusion. The Eximo B-Laser™ is effective and safe in ablating atherosclerotic and restenotic tissue for both above and below the knee obstructive arterial disease. The device has a high safety profile including a low risk of distal embolization.

Introduction

Atherectomy is an established technique to treat denovo obstructive disease in infrainguinal arteries. There are several atherectomy devices on the market including *rotational* (Jetstream [Boston Scientific, Marlborough, MA], Rotablator [Boston Scientific, Marlborough, MA], Phoenix [Phillips, Andover, MA]), *ablative* (Excimer laser [Phillips, Colorado Springs, Co]), *directional* (SilverHawk/TurboHawk [Medtronic, Minneapolis, MN]) and *orbital* (Diamondback [CSI, St Paul, MN]). These debulking devices improve vessel compliance and therefore reduce dissections and bail out stenting (1). The use of Excimer laser has also been shown to improve patency and target lesion revascularization at 1 year in treating in-stent restenosis when compared to balloon angioplasty (2).

The "B-Laser™" (Eximo Medical, Israel) is a novel atherectomy device that was investigated in the United States (Figure 1) and that was cleared by FDA following the results of this study. The" B-Laser™ Atherectomy System" is based on a solid-state third harmonic pulsed Nd:YAG laser with an output of 355nm and short pulses at 40Hz (3,4). Characteristics are displayed in Table 1. It is a single use catheter made of an array of optic fibers for laser energy transmission, surrounded by a circumferential blunt blade. The B-Laser™ is provided in several sizes: 0.9mm, 1.5mm, 2.0mm and 2.35mm. In addition, the 2.0mm and 2.35mm B-Laser™ catheters have an aspiration feature, and the 2.35mm B-Laser™ catheter includes an off-center feature (a gradual shift of the catheter shaft that is parallel to the vessel axis). All B-Laser™ catheters work over a standard 0.014" guide wire placed in the artery's lumen. The B-Laser™ fluence is 50

and 60 mJ/mm^2. Preclinical data have shown that the B-Laser™ ablates calcified (4) or fibrotic atherosclerotic plaque (5) and restenotic tissue.

We present the primary effectiveness and safety endpoints of the EX-PAD-03, assessing the B-Laser™™ in infrainguinal arterial occlusive disease, conducted to gain Food and Drug Administration clearance for the EXIMO B-Laser™ in the United States.

Methods

The EX-PAD-03 is a prospective, single-arm, multi-center, international, open-label, clinical study assessing the safety and efficacy of the Eximo Medical's B-Laser™ in subjects with symptomatic infrainguinal peripheral artery disease (PAD). This study was performed under an Investigational Device Exemption application and was approved by the Western Institutional Review Board (for 7 US sites) and the respective IRBs for additional US sites and the 3 European sites, and registered on clinicaltrials.gov NC# 03157531. All patients signed an informed consent prior to enrollment. The study enrolled 97 patients at 8 sites in the United States and 3 sites in Europe (2 in Italy and 1 in Austria) from September 2017 to March 2018. Inclusion and exclusion criteria are listed in Table 2.

The primary efficacy endpoint was an average reduction (for the entire cohort) in residual diameter stenosis of greater than 20% from baseline prior to any adjunctive therapy achieved by the B-Laser™ catheter alone, as assessed quantitatively by an angiographic core laboratory. The 20% threshold was a conservative estimate based on preclinical work done with the device, and this primary endpoint was approved by the FDA.

The primary safety endpoint was freedom from the following major adverse events (MAEs) through a 30-day follow-up period, as adjudicated by a Clinical Event Committee (CEC): unplanned target limb amputation above the ankle, clinically driven target lesion revascularization (CD-TLR) and cardiovascular related death.

Secondary efficacy endpoints and additional analyses are shown in Table 3.

The degree of calcium in the vessel wall was assessed by the Core lab. The following grading scale was used:

Grade 0 – No Calcification. No visual calcification is present along the arterial wall of the artery.

Grade 1 – Mild Calcification. Calcium is visible along one side of the arterial wall in the area of the target lesion. The calcium present encompasses < 50% of the total target lesion treatment area and/or the calcium is not circumferential (360°) in nature (i.e. on both sides of the vessel lumen). No impedance of blood flow in the vessel.

Grade 2 – Moderate Calcification. Calcium is visible along one side of the arterial wall >50% of the total target lesion treatment area or both sides of the arterial wall <50% in the area of the target lesion treatment area, and/or the calcium is not circumferential (360°) in nature (i.e. on both sides of the vessel lumen on a single AP view) for more than 2 cm and/or does not impede blood flow by more than 50%.

Grade 3 – Severe Calcification. Calcium is visible along both sides of the arterial wall ≥ 50% of the total target lesion treatment area by visual estimate and/or the

calcium is circumferential (360°) in nature (i.e. on both sides of the vessel lumen on a single AP view) for more than 2cm and/or significantly impedes blood flow in the vessel.

Procedure

After obtaining an informed consent, patients that met the general eligibility criteria underwent a baseline clinical status evaluation documenting their Rutherford category, ABI and WIQ. Angiography was then performed and if all inclusion criteria and none of the exclusion criteria are met, patients were enrolled in the study. Angiographic images were obtained as per angiographic Core laboratory procedures. The angulation that was deemed by the operator to represent the worst lesion severity was used, and kept as such throughout the procedure to evaluate angiographically after each procedural step. Patients were considered to be a screen failure if they did not meet angiographic eligibility criteria.

The size and type of B-Laser™ catheter was selected based on a prespecified matrix in the protocol using reference vessel diameter (RVD) and stenosis severity by operator's visual estimation. Subjects then underwent atherectomy in the target lesion with B-Laser™ at 1 mm per second as per Instructions for Use (IFU), followed by any other adjunctive therapy per operators' choice including regular (n=28) or drug coated balloons (DCB) (n=50), or bare metal (BMS) (n=20) or drug eluting stents (DES) (n=6). Stenting was considered bailout if it was performed to treat a flow limiting dissection otherwise it was considered primary stenting. No other atherectomy devices were

allowed in the study. Up to 3 lesions could be treated in one limb (both above the knee (ATK) and below the knee (BTK)). Stenting was left to operator's choice. All cine images were assessed by the core lab for dissection/ perforation/ distal embolization and any other procedural related complications after each step of the intervention (baseline, after atherectomy and after adjunctive therapy). Angiograms to the foot were obtained to evaluate for distal embolization. Procedural anticoagulation followed local practice. During device activation, a heparinized saline solution was flushed via the access sheath. Embolic protection device use was performed in 2 cases at the discretion of the operators.

Primary patency was evaluated at 30-day post index procedure by Core lab (Vascore, Boston, MA). Peak systolic velocity gradient (PSVR) of < 2.5 indicated patency.

The CEC committee evaluated all complications identified by the investigator or the Core lab as potentially related to the index procedure and/or underlying disease, whether or not related to the B-Laser™ and any complication that was defined as "event" by the CEC charter. These complications were adjudicated for their relationship to the device and procedure and to whether they are serious or non-serious adverse events or met study endpoints.

The Data and Safety Monitoring Board (DSMB) reviewed all clinically significant adverse events related to B-Laser™ and any MAE's in this study. There was no prespecified stopping point but the DSMB committee had the authority to request more data and ask for stopping or modifying the study based on submitted information.

Statistical analysis

The sample size has been calculated to test the null hypothesis of a mean reduction from baseline ≤ 20% against the alternative hypothesis of a mean reduction from baseline > 20% with a one-sample two-sided t-test, at a one-sided 2.5% level of significance, and 90% power. Based on preclinical data, it is assumed that the mean reduction in percent stenosis would be 25% and its standard deviation 15%, a total number of 97 subjects would be required. Also, a sample size is calculated to test the null hypothesis of percent of subjects free from MAEs ≤ 85% against the alternative hypothesis of percent of subjects free from MAEs > 85% via the lower limit of the one-sided 97.5% exact binomial confidence interval of the percent of subjects free from MAE. Assuming that in the study the percent of subjects free from MAE = 94%, a total number of 75 subjects are required for the lower limit to be greater than 85% with a conditional probability >0.999. The conditional probability represented the probability that the half width of the confidence interval is at most the target value, which in our study was 9% since the point estimate of the no MAE rate was 94% and the required lower limit 85% (94%-85%= 9%). Based on the above sample size calculations for efficacy and for safety endpoints, the higher sample size is for efficacy, and therefore the required sample size was 97 subjects. The hypothesis was tested using Analysis of Covariance (ANCOVA) with center and subject as a categorical covariate.

Statistical analyses were performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA). The required significance level of findings is 5%. All statistical tests were two-sided unless otherwise stated. Where confidence limits are appropriate, a two-sided 95% confidence interval were constructed. For comparison of means

between subgroups, the two-sample t-test or the Wilcoxon rank sum test were used as appropriate. For comparison of proportions between subgroups, the Chi-squared test or Fisher's exact test were used as appropriate.

Results

A total of 97 subjects were enrolled in an intention-to-treat (ITT) population. Of those, 94 subjects comprise the per protocol (PP) population (2 subjects were lost to follow-up before their 30-day visit and 1 subject died before the 30-day visit). There were 44 subjects from Office Based Lab (OBL) and 33 subjects from hospitals in the US and additional 20 from hospitals in EU.

Demographics and clinical variables

Table 4 shows the baseline demographics and clinical variables. Mean age was 70.5 ± 9.9 years, with a range of 46 to 86 years. There were slightly more males than females (53% vs. 47%) with 85.6% of subjects were Caucasian, 13.4% African American or Black and 1% other. Former smokers comprise 45.4% of the cohort, followed by current smokers at 35.1% and 19.6% have never smoked. Of the 97 subjects, 82 (84.5%) have had a past peripheral arterial procedure. Hypertension was present in 91.8% of subjects; 85.6% had a history of hyperlipidemia and 42.3% had diabetes mellitus. The mean ABI was 0.7 ± 0.2, with a range of 0.3 to 1.2. The mean Rutherford was 2.80 ± 0.6. The mean WIQ was 0.23 ± 0.22 with a range of 0 to 1.

Baseline angiographic variables

Table 5 shows the baseline angiographic variable. A total of 107 lesions were included. The mean lesion length was 53.96 ± 43.18 mm, with a range of 10.27 to 236.79 mm; 24 (22.4%) lesions had no calcification, 55 (51.4%) had mild or moderate calcification and 28 (26.2%) had severe calcification, as assessed by the Core Lab. The mean percent stenosis, as assessed by the sites, was 92.5% ± 7.4%) with a range of 70 to 100%. The most common stenosis type was *de novo* (79.4%), followed by in-stent restenosis (ISR) (15.9%) and then non in-stent restenosis (4.7%).

Primary effectiveness endpoint

Table 6 displays the index and 30-day outcomes post B-Laser™ treatment. At baseline, the mean percent stenosis at the target lesion as assessed by the Core lab was 85.7% ± 12.2% (range of 53 to 100%). Post B-Laser™ and prior to adjunctive therapy, the mean percent stenosis at the target lesion was 52.1% ± 14.9%, with a range of 12 to 83%. This resulted in a mean reduction from baseline to post B-Laser of 33.6% ± 14.2% with a range of 9 to 81%. Based on the ANCOVA model, which adjusted for within-subject correlation and site correlation, the mean reduction from baseline in residual diameter stenosis was 33.5%, with a lower limit of the one-sided 97.5% confidence limit of 30.8%, which is greater than the pre-specified threshold of 20%. The p-value for center was 0.3071, which suggests that the mean reduction from baseline in residual diameter stenosis did not vary significantly by center. The presence and degree of calcification, in-stent restenosis or above/below the knee treatment as well as lesion length had no impact on the primary effectiveness endpoint.

Primary Safety endpoint

The freedom from MAE through the 30-day follow-up period after intervention was 98.9%, with a lower limit of the one-sided 97.5% exact binomial confidence interval of 94.2%, which is greater than the pre-specified threshold of 85%. The Kaplan-Meier analysis of MAE through the 30-day follow-up period is presented in Figure 2. There was no clinically significant device related adverse events. Embolic filter protection was left up to the operator but was used in only in 2 cases by one operator (in the first case performed and in a second case for a thrombotic lesion), 1 ISR and 1 full thrombus within a stent. Per core lab there were no noted device related distal embolization, dissections that required additional therapy, perforation, amputation or pseudoaneurysm. One case of mild cholesterol emboli to the toe was noted on routine 1-month follow-up that was deemed only possibly related to the device but resolved with no consequences and did not require additional therapy. Post B-Laser™ alone there were a total of 16/109 (14.7%) dissections (type A [n=11], B [n=5]). CEC adjudicated serious adverse events included 1 pseudoaneurysm, 1 target limb pain, 1 cardiovascular related death, all adjudicated as not device related. The one death was due to a myocardial infarction post procedure during index hospitalization.

Secondary endpoints

Bailout stenting was 0.9% and was not device related. An improvement from baseline in ABI (0.24 ± 0.18), Rutherford category (-1.79 ± 1.22) and WIQ (0.26 ± 0.28)

were noted at 1 month. Freedom from MAE through a 30-day follow-up was 98.9%. There was no target lesion revascularization and the primary patency was 96.8% by duplex ultrasound criteria at 30-day follow up.

Discussion

In this pivotal clinical trial, the EXIMO B-Laser™ met its primary safety and effectiveness endpoints. B-Laser™ using a novel atherectomy technology, was able to reduce stenosis severity by a mean of 33.6% from baseline and with a freedom from MAE of 98.9% at 30 days. No differences in the primary endpoints were seen across centers, gender, lesion types, lesion length or lesion level of calcification.

Data from this study support early feasibility findings (EX-PAD-01) with the B-Laser™. EX-PAD-01 was conducted in Europe (Poland) at 2 investigational sites (7). Fifty (50) symptomatic PAD patients were enrolled and treated with the B-Laser™ with 100% success rate in crossing the target lesion. At 30-day follow up, there were no device-related clinically significant adverse events and no MAEs. No MAEs were noted in any of the 50 subjects at 6 months and only 2 MAEs (both CD-TLR) were at 12-month follow-up (2/46). Although EX-PAD-03 enrolled relatively shorter lesions, severe calcification and CTO were present in 26.2% and 21.5% of treated lesions respectively. There was no difference in device safety or effectiveness when analysis was conducted per lesion type or length. The B-Laser™ effectiveness in severe calcified disease is likely related to its short pulse duration (~10 nanoseconds) within the UV spectrum allowing the delivery of sufficient fluence for ablation of calcified disease. Although the

device was effective in a small number of chronic total occlusions and calcified lesions, more imaging data are needed to demonstrate actual changes in the actual calcification ablation.

The EXIMO B-Laser™ has also been shown to be effective in reducing stenosis of in-stent restenotic tissue with no adverse events. Currently the Excimer laser (Spectranetics) is approved in the US for in-stent restenosis (ISR) treatment (2) and early data suggest that the Jetstream can also be effective in cutting and removing restenotic tissue (8). In contrast to other atherectomy devices in ISR, there has been no reported clinically significant distal embolization definitely related to the B-Laser™, in part due to the aspiration capability incorporated into the larger 2.0 mm and 2.35 m devices. Both Excimer laser (Spectranetics) and the Jetstream had reported distal embolization in treating ISR (2,8-10). In the EX-PAD-03, embolic filter protection was left up to the operator but was used in only in 2 cases, 1 ISR and 1 with thrombosed stent. One case of distal cholesterol embolization was noted one-month post procedure and was judged as possibly related to the device by the CEC but resolved with no consequences. This distal embolization did not become apparent until the next routine patient visit at 1-month post index procedure. Patient noted a minor discomfort in her toe and micro-embolization was identified on physical exam. This resolved spontaneously. The timing of discovery of this embolization could not be adjudicated as directly related to the B-Laser™ as other possibilities may have caused the embolization including wire crossing the lesion, adjunctive angioplasty or spontaneous embolization days after the procedure. This finding is in contrast to all atherectomy devices including the Excimer laser that are known to have a significant distal

embolization potential which could be partially related to the built in aspiration mechanism in the EXIMO B-Laser™. The lack of distal embolization may reduce procedure time and contrast use, which need to be evaluated in future studies.

One advantage to atherectomy is reducing dissection and bail out stenting (11-13). The bailout stent varies considerably with devices and is dependent on lesion length, presence of moderate to severe calcification and total occlusions (14). In the EX-PAD-03, bailout stenting was minimal at 0.9% despite a significant number of CTO and moderate to severe calcification. This is supported by core lab analysis of dissections that were type A and B, generally not severe enough to stent. This can probably arise from the previously reported selectivity feature of the B-Laser™, for which the B-Laser™ was shown to ablate fibrotic atherosclerotic plaque by having higher affinity to fibrotic tissue than the vessel endothelium (5). The B-Laser™ reduced lesion severity by 33.6%. This is in line with orbital, Jetstream and Excimer laser atherectomy where lesion reduction was 46% (12), 40.6% (15) and 34.7% (16) respectively.

In this study, there was no 30-day serious event rates that were definitely or otherwise related to the device. Also patency and freedom from TLR were high and correlated with an improvement in clinical symptoms and ABI. The long term durability of these results remain unknown at this time and will likely be affected by the use of drug coated balloons or drug eluting stents post B-Laser™.

One of the advantages of the B-Laser™ using nanosecond pulses at a wavelength of 355 nm is the minor disruption effect of the contrast media (3). On the other hand, contrast is significantly disruptive on the Excimer laser effects. In addition, the console of the B-Laser™ is small, generates no noise during treatment, easily

mobile in the cath lab and does not require catheter calibration. Furthermore, there is no downtime in waiting for the console machine to warm up prior to use and no calibration is needed prior to connecting the catheter. These features along with the ability to ablate thru severe calcium, lack of distal embolization and no toxic gases utilized make the B-Laser™ a highly appealing novel atherectomy device. Following the results of this study as part of a 510(k) submission, the B-Laser™ is now cleared by the FDA.

We conclude that the B-Laser™ is effective and safe in ablating atherosclerotic and restenotic tissue including ISR, calcium and CTO for both above and below the knee obstructive arterial disease. The device carries no clinically significant distal embolization despite a low use of embolic filter protection.

Limitations

The study is not randomized and operator selection bias cannot be excluded. However, this bias has been reduced by the multicenter design of the study and the lack of statistical difference between sites. The data also indicate that this device is equally effective in a variety of complex disease including severe calcification and CTO. Also, this is a short term follow up protocol with both primary and secondary endpoints at 1-month follow-up intended to generate safety data for regulatory approval. Additional studies are needed to determine the long-term outcomes with the B-Laser™. Furthermore, although no distal embolization was reported by the core lab as definitely or probably related to the device, the nature of the debris generated by this device was

not analyzed as filter use was very low and pathology data was not collected. Finally, no comparative data can be made with other atherectomy devices and this should await data analysis from large registries and randomized trials.

References

1. Shammas NW, Coiner D, Shammas GA, et al. Percutaneous lower-extremity arterial interventions with primary balloon angioplasty versus Silverhawk atherectomy and adjunctive balloon angioplasty: randomized trial. J Vasc Interv Radiol. 2011; 22:1223-8.
2. Dippel EJ, Makam P, Kovach R, et al; EXCITE ISR Investigators. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE ISR trial (EXCImer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis). JACC Cardiovasc Interv. 2015;8(1 Pt A):92-101
3. Herzog A, Steinberg I, Gaisenberg E, Nomberg R, Ishaaya AA. A route to laser angioplasty in the presence of fluoroscopy contrast media, using a nanosecond-pulsed 355-nm laser. IEEE Journal of Selected Topics in Quantum Electronics 22 (3), May-June 2016. DOI: 10.1109/JSTQE.2015.2487889
4. Herzog A, Oszkinis G, Planer D, Ziaja K, Kruszyna Ł, Stanisic´ MG, Ziaja D, Ishaaya AA, Kuczmik W. Atherectomy using a solid-state laser at 355 nm wavelength. J. Biophotonics 2017; 1–8. DOI 10.1002/jbio.201600209
5. Herzog A, Bogdan S, Glikson M, Ishaaya AA, Love C. Selective tissue ablation using laser radiation at 355nmin lead extraction by a hybrid catheter; a preliminary report. Lasers Surg Med 2015;1-7 Published online in Wiley Online Library (DOI 10.1002/lsm.22451)
6. Nicolaï SP, Kruidenier LM, Rouwet EV, et al. The Walking Impairment Questionnaire: An effective tool to assess the effect of treatment in patients with intermittent claudication. J Vasc Surg 2009; 50:89-94.
7. Laird J. Abstract. VEITH 2016, Podium session 5. First Clinical Experience with The B-Laser™ Hybrid Laser Atherectomy Catheter for Infrainguinal Lesions. http://www.veithsymposium.org/viewposter2016.php?site=veith&sid=3&KeepThis=true&TB_iframe=true&height=515&width=707 . Accessed 08/22/2018
8. Shammas NW, Shammas GA, Banerjee S, Popma JJ, Mohammad A, Jerin M. JetStream Rotational and Aspiration Atherectomy in Treating In-Stent Restenosis of the Femoropopliteal Arteries: Results of the JETSTREAM-ISR Feasibility Study. J Endovasc Ther. 2016; 23:339-46.
9. Shammas NW, Coiner D, Shammas GA, Christensen L, Dippel EJ, Jerin M. Distal embolic event protection using excimer laser ablation in peripheral vascular interventions: results of the DEEP EMBOLI registry. J Endovasc Ther. 2009; 16:197-202.

10. Banerjee A, Sarode K, Mohammad A, Brilakis ES, Banerjee S, Shammas GA, Shammas NW. Safety and Effectiveness of the Nav-6 Filter in Preventing Distal Embolization During Jetstream Atherectomy of Infrainguinal Peripheral Artery Lesions. J Invasive Cardiol. 2016; 28:330-3.
11. Shammas NW, Lam R, Mustapha J, Ellichman J, Aggarwala G, Rivera E, Niazi K, Balar N. Comparison of orbital atherectomy plus balloon angioplasty vs. balloon angioplasty alone in patients with critical limb ischemia: results of the CALCIUM 360 randomized pilot trial. J Endovasc Ther. 2012; 19:480-8.
12. Dattilo R, Himmelstein SI, Cuff RF. The COMPLIANCE 360° Trial: a randomized, prospective, multicenter, pilot study comparing acute and long-term results of orbital atherectomy to balloon angioplasty for calcified femoropopliteal disease. J Invasive Cardiol. 2014; 26:355-60.
13. McKinsey JF, Zeller T, Rocha-Singh KJ, Jaff MR, Garcia LA; DEFINITIVE LE Investigators. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. JACC Cardiovasc Interv. 2014; 7:923-33.
14. Shammas NW, Coiner D, Shammas G, Jerin M. Predictors of provisional stenting in patients undergoing lower extremity arterial interventions. Int J Angiol. 2011; 20:95-100.
15. Shammas NW, Shammas GA, Jones-Miller S et al. Long term outcomes with Jetstream atherectomy with or without drug coated balloons in treating femoropopliteal arteries: a single center experience (JET-SCE). Cardiovascular Revascularization Medicine 2018; https://doi.org/10.1016/j.carrev.2018.02.003 (In press)
16. Dave R, Patlola R, Kollmeyer K, et al. Excimer Laser Recanalization of Femoropopliteal Lesions and 1-Year Patency: Results of the CELLO Registry. J Endovasc Ther. 2009; 16:665–675

Figures

Figure 1. The EXIMO B-Laser™™ device (future commercial system design)
Figure 2. Kaplan-Meier analysis of major adverse events at 30 days. MAE=major adverse event

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16. Dr. Paolo Sbarzaglia (site 11, SUB-I and user)
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18. Dr. Kareem Oshoala (site 11, SUB-I and user)
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21. Dr. Robert Ambruster (site 13, SUB-I and user)
22. Dr. Gil Vardi (site 13, SUB-I and user)
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24. Dr. Sanjaya Saheta (site 13, SUB-I) and user
25. Dr. Usman Qayyum (site 13, SUB-I and user)
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Site 1. Holy Name Medical Center, Teaneck, USA

Site 2. Orlando Heart Specialists, Orlando, FL, USA

Site 3. Cardiovascular Solutions Institute, Bradenton, USA

Site 4. North Florida Regional Medical Center, Gainesville, FL, USA

Site 5. No site 5 was part of the study

Site 6. Wellmont CVA Heart Institute, Kingsport, USA

Site 7. Arkansas Heart Hospital, Little Rock, AR, USA

Site 8. Midwest Cardiovascular Research Foundation, Davenport, IA, USA

Site 9. Division of Angiology, Medical University of Graz, Graz, Austria

Site 10. No site 10 was part of the study

Site 11. Maria Cecilia Hospital, Cotignola, Italy

Site 12. Policlinico Abano Terme, Abano Terme, Italy

Site 13. St. Louis Heart and Vascular, St Louis, MO, USA

Table 1. Main characteristics of the B-laser™ system

Active medium	Nd:YAG
Wavelength	355 nm
Catheter output fluence	50-60 mJ/mm2
Pulse repetition rate	40 Hz
Energy at the catheter tip at 60 mJ/mm2	30.6 mJ/Pulse
Averaged power at the catheter tip at 60 mJ/mm2	1.2 Watt
Pulse width (duration)	10-25ns, FWHM
Console	
Weight	85 kg / 187.4 lbs
Main body volume:	
Length	74 cm / 29.13 in
Height	95 cm / 37.4 in
Width	33 cm / 13 in
Blocking volume:	
	Length 91.2 cm / 35.9 in Height 125.2 cm / 49.3 in Width 40 cm / 15.75 in
Control touch panel	10.1" diagonal

(All dimensions are approximate)

Table 2. Inclusion and exclusion criteria for the EXIMO™ B-Laser EX-PAD-03 trial

General inclusion criteria	
	Subject is ≥ 18 years old.
	Subject is a candidate for atherectomy for infrainguinal peripheral artery disease.
	Documented symptomatic atherosclerotic peripheral artery disease Rutherford Classification 2-4.
	Subject has an infrainguinal target lesion(s) ≥70% based on CT angiogram or any other imaging modality.
	Subject is capable and willing to comply with the scheduled follow up
	Subject or appropriate legal surrogate is able and willing to sign a written Informed Consent Form (ICF).
Intraoperative inclusion criteria	
	Target lesion has a stenosis estimated to be ≥70%.
	In above the knee interventions, subjects should have at least one patent tibial run-off vessel into the foot
General exclusion criteria	
	Target lesion is in a vessel graft or synthetic graft.
	Target lesion length <1cm and >15 cm (in ISR cases could be >25cm).
	Endovascular or surgical procedure in the target limb performed ≤ 30 days prior to the index procedure .
	Endovascular or surgical procedure planned endovascular or surgical procedure 30 days after the index procedure.
	Intent to use other atherectomy device in the same procedure.
	Evidence or history of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stroke within the past 2 months.
	Evidence or history of aneurysm in the target vessel within the past 2 months.
	History of bleeding diathesis, coagulopathy or inability to accept blood transfusions.
	History of heparin-induced thrombocytopenia (HIT) or inability to tolerate antiplatelet medication(s), anticoagulation, or thrombolytic therapy
	Subjects requiring dialysis.
	Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
	Serious illness that may affect subject compliance to protocol and 30-day follow-up.
	Participating in another clinical study

Subject is pregnant or planning to become pregnant during the study period.
Life expectancy < 12 months
Any planned amputation above the ankle.

Intraoperative exclusion criteria

Inability to intraluminally cross and secure a 0.014" wire across the target lesion.
Target lesion length <1cm and >15 cm (in ISR cases >25cm).
Reference vessel lumen diameter proximal to target lesion is <150% of the outer diameter of the B-Laser.
Any clinical and/or angiographic complication prior to the planed insertion of B-laser.

Table 3. Secondary efficacy endpoints

Percent of subjects with residual stenosis by angiography of <30% post procedure including any adjunctive therapy, with no flow limiting dissection, as adjudicated by the core laboratory.

30-day secondary endpoints

Changes in in ankle-brachial index (ABI), Rutherford classification and Walking Impairment Questionnaire (WIQ) (6) when compared to baseline

Clinical success at 30 days defined as <50% stenosis at the treated lesion, as assessed quantitatively
by duplex ultrasound by the core laboratory when the peak systolic velocity ratio (PSVR) is <2.5.

Freedom from the following clinically significant device-related adverse events requiring intervention
in the target vessel, as adjudicated by the CEC committee for up to 30 days:

a. Perforation
b. Dissection
c. Distal embolization or in-situ thrombus
d. Pseudo-aneurysm

Freedom from the following non-clinically significant device related adverse events in the target vessel,
as adjudicated by the CEC committee for up to 30 days:

a. Perforation
b. Dissection
c. Distal embolization or in-situ thrombus
d. Pseudo-aneurysm

Table 4. Baseline demographics and Clinical characteristics

Variable		n	mean ± SD
Age (years)		97	70.5 ± 9.9
Body Mass Index (Kg/m2)		97	27.6 ± 5.6
Ankle Brachial Index		88	0.7 ± 0.2
Rutherford Category		97	2.8 ± 0.6
Walking Impairment Questionnaire		93	0.23 ± 0.22
		n/n'	Percentage
Males		51/97	52.6
Race			
	White	83/97	85.6
	Black or African American	13/97	13.4
	Other	1/97	1
Smoker			
	Current	34/97	35.1
	Former	44/97	45.4
Coronary artery disease		53/97	54.6
Hyperlipidemia		83/97	85.6
Hypertension		89/97	91.8
Diabetes		41/97	42.3

Table 5. Baseline angiographic characteristics

Variable		n	mean ± SD
Baseline stenosis per core lab (%)		107	85.7 ± 12.2
	Non in-stent restenosis lesions	90	85.7 ± 12.1
	in-stent restenosis lesions	17	85.8 ± 13.2
	Above the knee	87	85.6 ± 12.8
	Below the knee	20	86.0 ± 9.6
Lesion length (mm)		107	53.96 ± 43.18
		n/n'	Percentage
Calcification level			
	No	24/107	22.4

	Mild/Moderate	55/107	51.4
	Severe	28/107	26.2
Chronic total occlusion (stenosis 100%)		23/107	21.5
Stenosis type			
	Denovo	85/107	79.4
	Restenosis	5/107	4.7
	In-stent restenosis	17/107	15.9

Table 6. Procedural and 30-day outcome post B-laser treatment

Variable		n	mean ± SD
Post B-laser stenosis with no adjunctive treatment (%)		107	52.1 ± 14.9
In-stent vs non in-stent restenosis			
	non in-stent restenosis	90	52.0 ± 15.4
	in-stent restenosis	17	52.9 ± 12.1
Above vs below the knee			
	Above the knee	87	53.7 ± 13.7
	Below the knee	20	45.3 ± 18.1
Calcium severity			
	Calcium: none	24	51.6 ± 17.3
	Calcium: mild to moderate	55	51.7 ± 14.6
	Calcium: severe	28	53.4 ± 13.5
	Chronic total occlusion	23	61.9 ± 14.2
Reduction from baseline in residual diameter stenosis (%)		107	33.6 ± 14.2
In-stent vs non in-stent restenosis			
	non in-stent restenosis	90	33.7 ± 14.3
	in-stent restenosis	17	32.9 ± 14.0
Above vs below the knee			
	Above the knee	87	32.0 ± 12.8
	Below the knee	20	40.7 ± 17.8
Calcium severity			
	Calcium: none	24	34.3 ± 17.3
	Calcium: mild to moderate	55	32.8 ± 12.8
	Calcium: severe	28	34.5 ± 14.2
Chronic total occlusion		23	38.1 ± 14.2
ABI at 30-day visit post-procedure		88	0.95 ± 0.15
ABI difference (post-procedure - baseline)		82	0.24 ± 0.18
Rutherford Category at 30-day post procedure		94	0.98 ± 1.01
Rutherford category difference (post-procedure - baseline)		94	-1.79 ± 1.22
WIQ at 30-day visit post-procedure		84	0.50 ± 0.32
WIQ difference (post-procedure - baseline)		81	0.26 ± 0.28

	n/n'	Percentage
Reduction from baseline in residual diameter stenosis of > 20%	94/107	87.9
Percent of lesions with residual stenosis by angiography of ≤30% post-procedure	95/107	88.8
Freedom from MAE through a 30-day follow-up	92/93	98.9
Clinical success at 30 days defined as < 50% stenosis (< 2.5 PSVR) at the treated lesion	90/93	96.8

Bailout stent*	1/107	0.9

*patient had chronic total occlusion and severe calcification. This was not B-laser related.

Figure 1

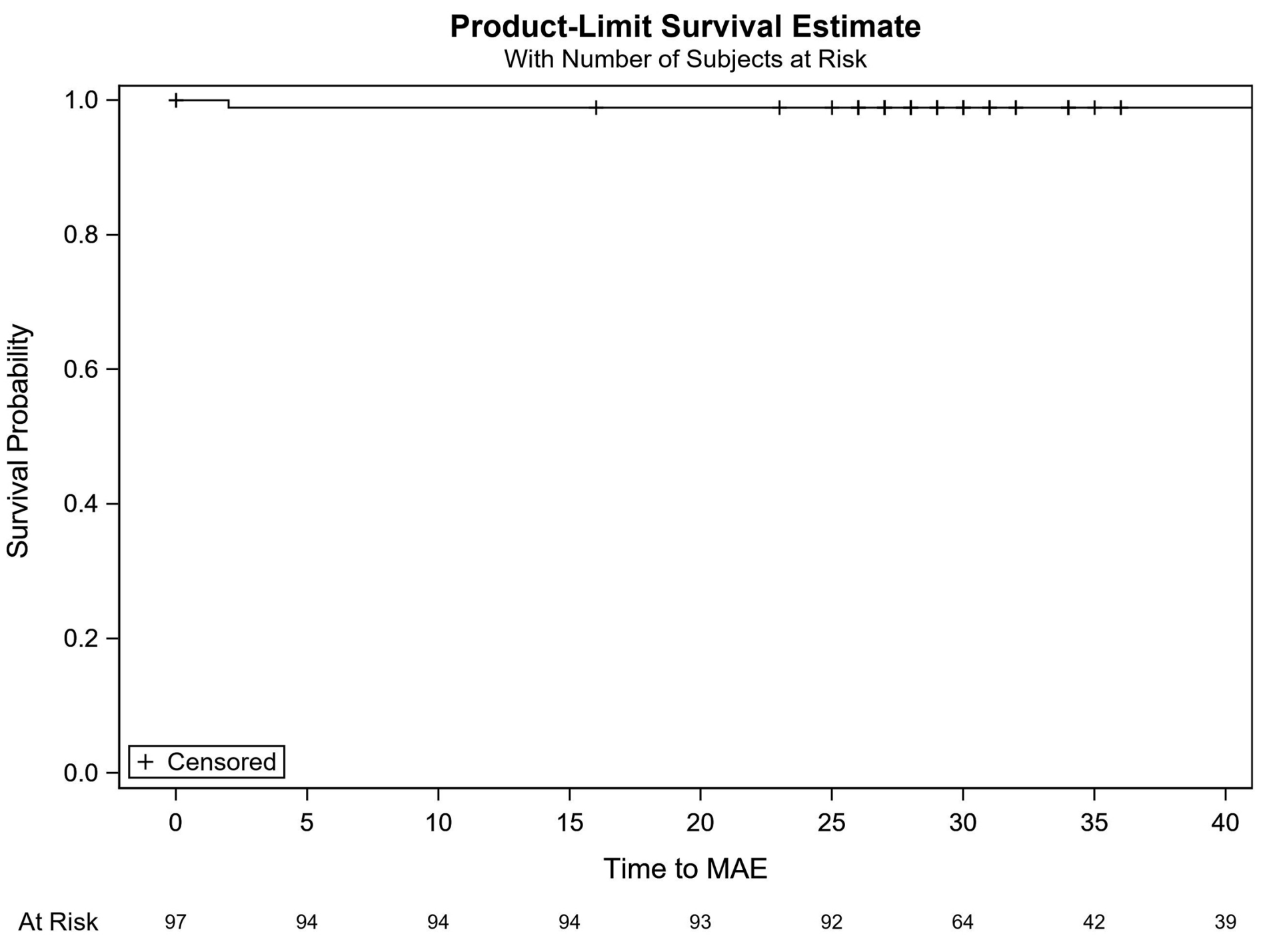
Product-Limit Survival Estimate
With Number of Subjects at Risk
1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
+ Censored
0
5
10
15
20
25
30
35
40
Time to MAE
At Risk
97
94
94
94
93
92
64
42
39

Figure 2