

	Safety and Effectiveness Evaluation of Eximo Medical's B-Laser™ atherectomy Device, in Subjects Affected with Infrainguinal PAD	Date: 02 Oct 2017
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Protocol Number	EX-PAD-03
Title	Safety and Effectiveness Evaluation of Eximo Medical's B-Laser™, an Atherectomy Device, in Subjects Affected with Infrainguinal PAD
Objective(s)	The primary objective of the study is to assess the safety and efficacy of the Eximo Medical's B-Laser™ catheter in subjects with infrainguinal peripheral artery disease (PAD)
Study Design	This is a prospective, single-arm, multi-center, open-label study.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Subject is ≥ 18 years old. 2. Subject is a candidate for atherectomy for infrainguinal peripheral artery disease. 3. Documented symptomatic atherosclerotic peripheral artery disease Rutherford Classification 2-4. 4. Subject has an infrainguinal target lesion(s) with any type of stenosis (naïve recurrent, or in-stent) estimated to be ≥70% based on CT angiogram or any other imaging modality. 5. Subject is capable and willing to comply with the scheduled follow up 6. Subject or appropriate legal surrogate is able and willing to sign a written Informed Consent Form (ICF). <p>Intraoperative inclusion criteria (by fluoroscopy angiogram):</p> <ol style="list-style-type: none"> 1. Target lesion has a stenosis estimated to be ≥70%. 2. In ATK subjects - at least one patent tibial run-off vessel into the foot
Exclusion Criteria	<ol style="list-style-type: none"> 1. Target lesion is in a vessel graft or synthetic graft. 2. Target lesion length <1cm and >15 cm (in ISR cases could be >25cm). 3. Endovascular or surgical procedure in the target limb performed less than or equal to 30 days prior to the index procedure OR Planned endovascular or surgical procedure 30 days after the index procedure. 4. Intent to use other atherectomy device in the same procedure. 5. Evidence or history of intracranial or gastrointestinal bleeding, intracranial aneurysm, myocardial infarction or stroke within the past 2 months. 6. Evidence or history of aneurysm in the target vessel within the past 2 months. 7. History of bleeding diathesis, coagulopathy or inability to accept blood transfusions. 8. History of heparin-induced thrombocytopenia (HIT) or inability to tolerate antiplatelet medication(s), anticoagulation, or thrombolytic therapy. 9. Subjects requiring dialysis. 10. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 11. Serious illness that may affect subject compliance to protocol and 30-day follow-up. 12. Participating in another clinical study 13. Subject is pregnant or planning to become pregnant during the study


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	<p>period.</p> <p>14. Life expectancy < 12 months</p> <p>15. Any planned amputation above the ankle.</p> <p>Intraoperative exclusion criteria (by fluoroscopy angiogram):</p> <ol style="list-style-type: none"> 1. Inability to intraluminally cross and secure a 0.014" wire across the target lesion. 2. Target lesion length <1cm and >15 cm (in ISR cases >25cm). 3. Reference vessel lumen diameter proximal to target lesion is <150% of the outer diameter of the B-Laser™. 4. Any clinical and/or angiographic complication prior to the planed insertion of B-laser™.
Primary Effectiveness Endpoint	<p>Acute technical success:</p> <p>Reduction from baseline in residual diameter stenosis (measured in percent), prior to any adjunctive therapy, achieved by the B-Laser™ catheter, as assessed quantitatively by the core laboratory based upon the procedure angiograms. This study's primary endpoint will be met if the mean reduction in residual diameter stenosis is greater than 20%, prior to any adjunctive therapy.</p>
Primary Safety Endpoint	<p>Freedom from the following Major Adverse Events (MAEs) through a 30-day follow-up period, as adjudicated by the Clinical Event Committee (CEC):</p> <p>Unplanned target limb amputation above the ankle</p> <p>Clinically Driven Target Lesion Revascularization (CD-TLR)</p> <p>Cardiovascular related deaths</p> <p>This endpoint will be met if the freedom from MAE rate is greater than 85%</p>
Secondary Safety Endpoints	<p>Freedom from the following <u>Clinically Significant</u> Device Related Adverse Events requiring intervention in the target vessel, as adjudicated by the CEC for up to 30 days:</p> <ul style="list-style-type: none"> • Perforation • Dissection • Distal embolization or <i>in situ</i> thrombus • Pseudoaneurysm <p>Freedom from <u>non-Clinically Significant</u> Device Related Adverse Events in the target vessel, as adjudicated by the CEC for up to 30 days:</p> <ul style="list-style-type: none"> • Perforation • Dissection • Distal embolization or <i>in situ</i> thrombus • Pseudoaneurysm
Secondary Effectiveness Endpoints	<p>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.</p>


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	<p>PAD measurements at the 30-day visit post-procedure compared to baseline:</p> <ul style="list-style-type: none"> • Ankle-Brachial Index (ABI) • Rutherford Classification • Walking Impairment Questionnaire (WIQ) <p>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 is < 2.5. ¹</p>
Statistical Methodology	
Primary Effectiveness	<p>The primary effectiveness endpoint is the reduction from baseline in residual diameter stenosis (measured in percent), prior to any adjunctive therapy, achieved by the B-Laser™ catheter, as assessed quantitatively by the core laboratory based upon the procedure angiograms. This study's primary effectiveness endpoint will be met if the mean reduction in residual diameter stenosis is greater than 20%, prior to any adjunctive therapy.</p>
Statistical Hypothesis	<p>The primary effectiveness hypothesis to be tested is:</p> $H_0: \mu_{DS} \leq 20\% \text{ vs. } H_1: \mu_{DS} > 20\%$ <p>where μ_{DS} is the mean reduction from baseline in residual diameter stenosis.</p>
Statistical Test	<p>The hypothesis will be tested using Analysis of Covariance (ANCOVA)</p>
Minimum Sample Size	<p>97 treated subjects (assuming one lesion per subject)</p>
Primary Safety	<p>The primary safety endpoint is the percent of subjects free of MAEs throughout the 30-day follow-up period, as adjudicated by the CEC.</p>
Statistical Hypothesis	<p>The primary safety hypothesis to be tested is:</p> $H_0: \pi_{MAEF} \leq 85\% \text{ vs. } H_1: \pi_{MAEF} > 85\%$ <p>where π_{MAEF} is the proportion of subjects free of MAEs throughout the 30-day follow-up period.</p>
Statistical Test	<p>The hypothesis will be tested via the lower limit of a one-sided exact binomial confidence interval.</p>
Study Population	<p>The trial population will consist of male and female subjects eighteen (18) years of age or older, with symptomatic infrainguinal PAD, scheduled for endovascular intervention. Subjects must also meet all other inclusion criteria and not meet any of the exclusion criteria described in Sections 5.3.1 and 5.3.2 of the Study Protocol.</p>

¹ Per FDA request, PSVR will be presented for any subject that underwent DUS. Yet, in cases when a reference PSV is unreliable, an asterisk will be added, and the meaning of this asterisk is that true PSVR could not be calculated by the core lab and rather the core is presenting a PSVR that is using the best PSV that could be taken. The company will keep in house the records of the alternative determination of patency by the core lab in such cases that are based on correlating factors that will be used to determine stenosis (further information can be found in section 3.1 of the study protocol, PAD diagnosis, Duplex ultrasonography (DUS)).

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6-Month Outcomes Analysis (from Day 36 to the end of study)	<p>The follow-up duration for each subject is 30-days post procedure for the primary and secondary endpoints, however subjects will be followed for 6-months post procedure.</p> <p>At follow up visits the following parameters will be collected and recorded:</p> <ul style="list-style-type: none">6-Month Patency (per Lesion): Duplex Ultrasonography for core lab assessment of PSVR< 2.5.6-Month Clinical Presentation (per Subject): Clinical performance by Rutherford Class, ABI and WIQ6-Month Site-Reported Adverse Events & Serious Adverse Events6-Month CEC-Adjudicated Adverse Events6-Month Protocol Deviations <p>All parameters measured after the 30-day follow-up (from Day 36 after procedure) will be summarized via descriptive statistics by data type.</p>				
Visit schedule	Visit, Number, (Time point)	Screening Visit 1 (<2m pre-procedure)	B-Laser™ procedure Visit 2 (to discharge)	Follow up Visit 3 (30d ± 5d post procedure)	Follow up Visit 4 (6m ± 2w post procedure)
	Informed consent	X			
	Assess eligibility	X			
	Medical history & demographic	X			
	Blood Tests	X			
	Con-meds	X	X	X	X
	Baseline lesion evaluation	X	X		
	Short Physical examination	X			
	Ankle-Brachial Index	X		X	X
	Rutherford Classification	X		X	X
	WIQ	X		X	X
	& Confirm eligibility per intraoperative inclusion/exclusion		X		
	PAD Intervention including B-Laser™ Atherectomy		X		
	Safety- AE, SAE, MAE, ADE		X	X	X

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Results	<p>Primary Effectiveness Results</p> <p>At baseline, the mean (SD) percent stenosis at the target lesion was 85.7% (12.2%). Post B-Laser™ prior to adjunctive therapy, the mean (SD) percent stenosis at the target lesion was 52.1% (14.9%). This resulted in a crude mean (SD) reduction from baseline to post B-Laser™ of 33.6% (14.2%).</p> <p>Primary Safety Results</p> <p>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%, so the success criteria for this endpoint is met.</p>
Discussion and Conclusions	<p>The aim of the study was to assess the safety and efficacy of the use of the Eximo Medical's B-Laser™ catheter in subjects affected with infrainguinal PAD. The study was designed to assess both safety and effectiveness of the device, and there were two hypotheses in this study.</p> <p>The primary effectiveness endpoint was the mean reduction from baseline in residual diameter stenosis (measured in percent), prior to any adjunctive therapy, achieved by the B-Laser™ catheter, as assessed quantitatively by the core laboratory based upon the procedure angiograms. Because the lower limit of the one-sided 97.5% confidence interval was greater than 20%, we conclude that the mean reduction from baseline in diameter stenosis is > 20% prior to any adjunctive therapy, and the success criterion for this endpoint is met.</p> <p>The primary safety endpoint is the percent of subjects free of MAEs throughout the 30-day follow-up period, as adjudicated by the Clinical Events Committee (CEC). This hypothesis was tested via the lower limit of the one-sided 97.5% exact binomial confidence interval. Because the lower limit of the confidence interval was greater than 85%, this endpoint is met.</p> <p>Thus, the study is deemed successful as both null hypotheses (primary efficacy and primary safety endpoints) were rejected and the acceptance criteria were met. It can be claimed that Eximo Medical's B-Laser™ device is safe and effective according to its intended use.</p> <p>The results found were quite robust. There did not appear to be statistically significant differences in the primary effectiveness endpoint across centers (p=0.3071) and there was only 1 non-device related MAE though 30 days, suggesting a very strong safety profile.</p> <p>The 6-month observational outcomes showed a global improvement of the peripheral artery disease symptoms.</p> <p>An independent Data and Safety Monitoring Board has also reviewed and evaluated the results and affirmed that based on the information that the committee was provided, the device is safe for its intended use.</p>