



**Title: Evaluation of WIRION™ EPS in Lower Extremities Arteries**

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**WISE LE Study protocol synopsis dated July 20 2016  
NCT02780349**

Title:	WISE LE: Evaluation of WIRION™ EPS in Lower Extremities Arteries
Study Objective	Demonstrate the safety and performance of the WIRION™ EPS in subjects undergoing lower extremity atherectomy for the treatment of Peripheral Arterial Disease (PAD).
Study Design	Prospective, multi-center, non-randomized, open label, single arm study. Up to 153 consented subjects who undergo atherectomy due to lower limb PAD will be enrolled. All subjects will undergo baseline assessment, intervention (atherectomy in conjunction with WIRION™ EPS) and post procedure follow up. All subjects will have a follow up visit at 30±7 days post procedure. Results will be compared to a performance goal based on an analysis of previous trials that studied atherectomy with an embolic protection filter in similar patient cohorts.
Study Population:	<p>Both male and female subjects who meet all the eligibility criteria and give written informed consent will be enrolled in the study.</p> <p><b>Inclusion Criteria</b></p> <ol style="list-style-type: none"> <li>1) Subject is at least 18 years of age</li> <li>2) Subject or authorized representative, signed a written Informed Consent form to participate in the study, prior to any study related procedures</li> <li>3) Subject is willing to comply with the protocol requirements and return to the treatment center for all required clinical evaluations</li> <li>4) Rutherford classification 2-4</li> <li>5) Has moderate to severe calcification visualized on angiogram in the femoropopliteal arteries</li> <li>6) Planned atherectomy of the native femoropopliteal arteries</li> <li>7) Reference vessel diameter for intended filter location must be visually estimated to be ≥3.5mm and ≤6.0mm</li> <li>8) An adequate “landing zone” for placement of the WIRION™ device distal to the target lesion of at least 30mm</li> <li>9) A female subject is eligible if not of child bearing potential or has a negative pregnancy test within the previous 7 days and agrees to remain on birth control throughout the study</li> </ol> <p><b>Exclusion Criteria</b></p> <ol style="list-style-type: none"> <li>1) Any planned surgical or endovascular intervention within 30 days before or after the index procedure</li> <li>2) A lesion deemed not accessible by the WIRION™ EPS</li> <li>3) Inability to take aspirin or ADP receptor antagonists</li> <li>4) History of bleeding diathesis or coagulopathy or will refuse blood transfusion if deemed necessary</li> </ol>



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	<ul style="list-style-type: none"> <li>5) Has perforation, dissection, or other injury of the access or target vessel requiring additional stenting or surgical intervention before enrollment</li> <li>6) Subject is enrolled in another drug or device study protocol that has not reached its primary endpoint (participating in registry studies is not excluded)</li> <li>7) Life expectancy less than 12 months</li> <li>8) Known severe renal insufficiency (eGFR &lt;30 ml/min/1.72m<sup>2</sup>).</li> <li>9) ≤1-vessel tibial run-off status</li> </ul>
Number of subjects:	Up to 153 with an interim analysis after 100 subjects
Clinical sites:	Up to 10 sites; up to 1/3 of the study patients at OUS sites
Investigational Product:	WIRION™ Embolic Protection System (Gardia Medical Ltd.)
Primary end point	<p>Freedom from major adverse events (MAE) to 30 days post procedure.</p> <p>MAE defined as a serious adverse event that results in death, acute myocardial infarction, thrombosis, pseudo-aneurysm, dissection (grade C or greater) or clinical perforation at the filter location, distal embolism (clinically relevant), unplanned amputation, or clinically-driven target vessel revascularization (TVR), through 30 days post-procedure, as adjudicated by the Clinical Events Committee (CEC).</p>
Secondary end points	<ul style="list-style-type: none"> <li>• <u>Device success</u> Defined as: <ul style="list-style-type: none"> <li>- A successful delivery and deployment of WIRION™ distal to the intervention site without complications, AND</li> <li>- Successful retrieval of WIRION™ following completion of the stenting procedure, without complications</li> </ul> </li> <li>• <u>Clinical success</u> Defined as: Device success with freedom from procedure related serious adverse events ascribed to the WIRION</li> <li>• <u>Technical success</u> Defined as: Freedom from device malfunctioning causing the procedure to be aborted</li> <li>• <u>Percent of filters with visible debris</u></li> </ul>
Assessment Schedule:	<p><b>Baseline Visit:</b></p> <ul style="list-style-type: none"> <li>a) Eligibility according to inclusion and exclusion criteria</li> <li>b) Obtaining signed Informed Consent Form (ICF)</li> <li>c) Demographics (sex, year of birth, smoking status)</li> <li>d) Risk factors &amp; medical history</li> <li>e) Concomitant medications</li> <li>f) Disease oriented physical examination including vital signs (weight, height, BMI, heart rate, blood pressure) and ABI (except in cases</li> </ul>



	<p>where blood pressure cuff occlusion of the extremity is contraindicated)</p> <ul style="list-style-type: none"> <li>g) Blood test including: RBC, Hemoglobin, WBC, Platelet count, PT, aPTT, INR, serum creatine-kinase isoform MB (CK-MB) and serum creatinine</li> <li>h) Pregnancy test, if applicable</li> <li>i) Safety evaluation (AE/SAE evaluation)</li> </ul> <p><b>Intervention (Use of WIRION™):</b></p> <ul style="list-style-type: none"> <li>a) Investigational procedure &amp; materials (atherectomy device, EPS, guide wires and contrast medium)</li> <li>b) Intervention details (investigator name, procedure duration and fluoroscopy time)</li> <li>c) Angiography of target lesion</li> <li>d) Dilation after atherectomy</li> <li>e) Stent placement after atherectomy</li> <li>f) Angiographic assessment of visible distal embolization, as evidenced by new angiographic filling defect, slow flow, and/or loss of distal tibial runoff</li> <li>g) AE/SAE</li> <li>h) Usability questionnaire</li> <li>i) Visual assessment of debris in the filter</li> <li>j) Concomitant medications</li> </ul> <p><b>Pre-Discharge Follow-up:</b></p> <ul style="list-style-type: none"> <li>a) Disease oriented physical exam including vital signs (heart rate and blood pressure) and ABI (except in cases where blood pressure cuff occlusion of the extremity is contraindicated)</li> <li>b) AE/SAE evaluation</li> <li>c) Blood test including: RBC, Hemoglobin, WBC, Platelet count, PT, aPTT, INR and serum creatine-kinase isoform MB (CK-MB) and serum creatinine</li> <li>d) Concomitant medications</li> </ul> <p><b>End-of-Study Follow-up Visit (30±7 days post procedure):</b></p> <ul style="list-style-type: none"> <li>a) AE/SAE evaluation</li> <li>b) Disease oriented physical exam including vital signs (heart rate and blood pressure) and ABI (except in cases where blood pressure cuff occlusion of the extremity is contraindicated)</li> </ul>
<p>Statistical Considerations:</p>	<p>A performance goal group sequential design with a maximum of two stages with rejection boundaries according to Lan-DeMets alpha spending function with O’Brien- Fleming boundaries. The expected proportion of subjects who would meet the primary endpoint if treated according to current clinical practice is 10.7%. This performance goal is based on the DEFINITVE LE and DEFINITVE Ca++ trials.</p> <p>The study is designed to test the primary null hypothesis that the 30-day MAE outcome using the WIRION™ EPS in conjunction with atherectomy is equal to or higher than the PG of 19.26%, as opposed to the alternative hypothesis that the MAE is less than this PG. An interim analysis will be carried out when</p>



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	<p>100 (68.5%) of the originally planned subjects have reached the 30-day follow-up. Using an Exact Binomial Test and under the following assumptions:</p> <p>Alpha (one-sided) = 0.025 <math>\beta</math>= 0.20 PE= 10.7% Performance goal= 19.26%</p> <p>An estimated 145 evaluable subjects will be required for 80% power if the study reaches the final analysis. With an anticipated combined loss-to-follow-up of up to 5%, 153 patients will be enrolled in the study.</p> <p>An interim analysis will be performed when 100 subjects (approximately 68.5% of the 145 evaluable subjects) have completed the study; two potential options will be pursued:</p> <p>The study will be stopped for efficacy if the primary null hypothesis is rejected at one sided alpha = 0.0068 based on the Lan-DeMets alpha spending function with O'Brien - Fleming boundaries.</p> <p>If based on the interim analysis the primary null hypothesis cannot be rejected, then the trial will continue to a total sample size of 153 enrolled subjects (i.e., 145 evaluable subjects). This test will be conducted at one-sided alpha = 0.0229, in order to control the overall Type I error at 2.5%.</p> <p>Study success is defined as rejecting the null hypothesis.</p>
Duration of Study	The estimated study duration is ten months, including a recruitment phase and follow up period of 30±7 days