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«Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

Διπλωματική Εργασία

«Protocol development of a randomized clinical trial for the evaluation of efficacy and safety of Superficial Femoral Artery Angioplasty with Paclitaxel-eluting absorbable Magnesium-based Stent»

«Ανάπτυξη πρωτοκόλλου τυχαιοποιημένης κλινικής μελέτης για την αξιολόγηση της αποτελεσματικότητας και της ασφάλειας Αγγειοπλαστικής Επιπολής Μηριαίας Αρτηρίας με Στεντ από Μαγνήσιο και έκλυση Πακλιταξέλης»

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1. Abstract/Περίληψη

Writing a protocol is mandatory for the success of a randomized clinical trial (RCT). The aim of this phase-II trial is to show the non-inferiority of the Mg-based paclitaxel-eluting stent at treating superficial femoral artery (SFA) lesions from the aspect of effectiveness and safety.

The protocol is developed according to the principles of the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements. It describes the background of peripheral artery disease (PAD) and the evolution of stent technology and bioabsorbable scaffolds. Also, it presents the trial design of non-inferiority with statistical methods and endpoints. It includes the inclusion and exclusion criteria for the subjects, the information about the device interventions and the safety assessments and procedures according to a schedule of activities. All the regulatory and operational considerations are taken into account in order to ensure the rights, safety, well-being of the participants and the strict compliance with the protocol.

Magnesium-based stent and paclitaxel-eluting antiproliferative agent in combination are considered a novel and promising technique for the treatment of SFA lesions in PAD and an organized protocol for RCT is a requirement for reliable results of efficacy and safety.

Key words: Magnesium, Non-inferiority, Protocol design, RCT, SFA lesions

Η συγγραφή πρωτοκόλλου είναι υποχρεωτική για την επιτυχία μίας τυχαιοποιημένης κλινικής μελέτης. Ο στόχος της παρούσας φάσης ΙΙ μελέτης είναι να δείξει την μη-κατωτερότητα της ενδοπρόθεσης από μαγνήσιο μαζί με την έκλυση Πακλιταξέλης στην θεραπεία αλλοιώσεων επιπολής μηριαίας αρτηρίας από την πλευρά αποτελεσματικότητας και ασφάλειας.

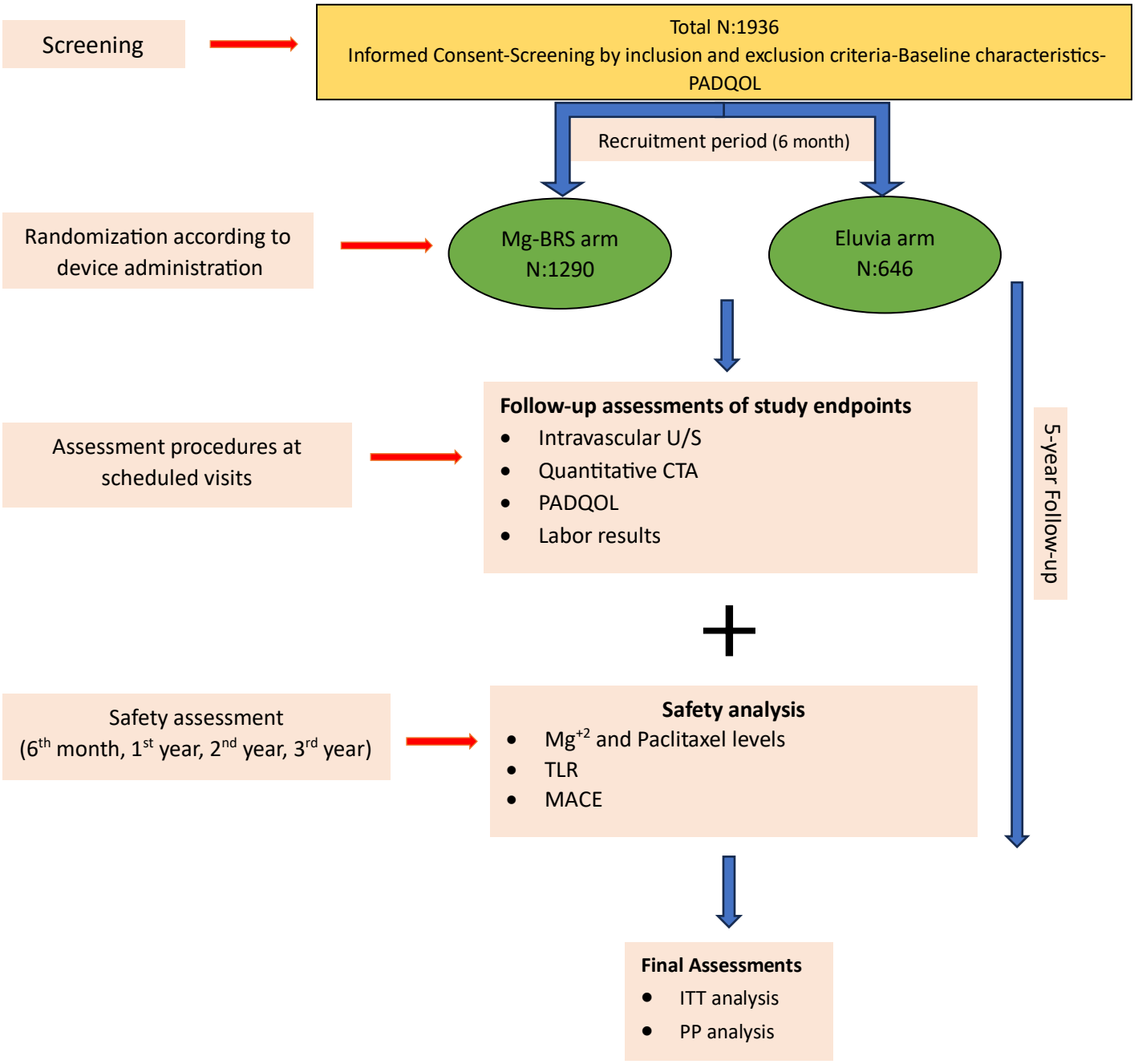
Το πρωτόκολλο αναπτύσσεται βασιζόμενο στις αρχές της Διεθνούς Συνεδρίασης Εναρμόνισης για Καλή Κλινική Πρακτική και στις ισχύουσες ρυθμιστικές αρχές. Περιγράφει το πλαίσιο της περιφερικής αρτηριακής νόσου και την εξέλιξη της τεχνολογίας ενδοπρόθεσης και την απορρόφηση του ικριώματος. Επίσης, παρουσιάζει τον σχεδιασμό της μη-κατωτερότητας με στατιστικές μεθόδους και τα τελικά σημεία. Περιλαμβάνει τα κριτήρια εισαγωγής και αποκλεισμού των ασθενών, τις πληροφορίες για τις συσκευές επέμβασης και τις αξιολογήσεις και διαδικασίες ασφάλειας σύμφωνα με ένα πρόγραμμα δραστηριοτήτων. Όλες οι ρυθμιστικές και λειτουργικές εκτιμήσεις λαμβάνονται υπόψιν ώστε να εξασφαλιστούν τα δικαιώματα, η ασφάλεια, η ευημερία των συμμετεχόντων και η αυστηρή συμμόρφωση με το πρωτόκολλο.

Οι ενδοπροθέσεις από μαγνήσιο σε συνδυασμό με την έκλυση του αντί-πολλαπλασιαστικού παράγοντα Πακλιταξέλης θεωρούνται μία καινοτόμα και υποσχόμενη τεχνική για την θεραπεία αλλοιώσεων επιπολής μηριαίας αρτηρίας στην περιφερική αρτηριακή νόσο και ένα οργανωμένο πρωτόκολλο για τυχαιοποιημένη κλινική μελέτη είναι προϋπόθεση για αξιόπιστα αποτελέσματα αποτελεσματικότητας και ασφάλειας.

Λέξεις κλειδιά: Αλλοιώσεις Επιπολής Μηριαίας Αρτηρίας, Μαγνήσιο, Μη-κατωτερότητα, Σχεδιασμός πρωτοκόλλου, Τυχαιοποιημένη Κλινική Μελέτη

2. Schema

The total number of patients will be 1936 after a 10% attrition rate



3. Schedule of activities (SOA)

Procedures	Screening/ Baseline	Enrollment/ Administration (6 month)	Study treatment Period (weeks)									
			1	3	6	12	18	24	30	36	48	60
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-	-	-	-
Administer study intervention	-	X	-	-	-	-	-	-	-	-	-	-
Concomitant medication review	X	-	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-	-
Weight	X	-	X	-	X	X	-	X	-	X	-	X
Performance status (PADQOL)	X	-	X	-	X	X	-	X	-	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-
EKG	X	-	X	-	-	X	-	X	-	X	-	X
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Mg^{+2} and Paclitaxel concentration	-	-	X	X	X	X	-	X	-	X	X	X
Quantitative Angiography assessment	X	-	X	-	-	X	-	X	-	X	X	X
IV Ultrasound assessment	-	-	X	-	-	X	-	X	-	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X

4. Introduction and Study Rationale

Peripheral artery disease (PAD)

PAD is the narrowing or blockade of the artery vessels in the lower extremities (most common site of the human body) and it is caused by the building of fatty plaque, a process known as atherosclerosis. Every individual can be affected by PAD but is more common in men and in the African-American race. Hispanic-White race has a similar or slightly higher impact of PAD comparably to non-Hispanic-White race. It is estimated that in the US, around 6.5 million people have PAD and the age-standardized mortality is 1.01 per 100,000 globally with the highest mortality in Eastern Europe. There are many symptoms and signs of PAD, such as the symptom of

pain, aches, or cramps at buttock, hip, thigh or calf with exercise that is relieved after resting (claudication) and the physical signs of muscle atrophy, hair loss, cool and shiny skin, ulcers non-healing, asleep toes and decreased or absent pulses. PAD is diagnosed using the ankle brachial index (ABI), a noninvasive technique which measures the systolic blood pressure of the ankles in comparison with the SBP of the arm and it is defined as an ABI <0.9 or imaging tests, for instance, U/S, MRA and CTA with an auxiliary precision. Age plays a major role in developing PDA, with patients >40 years old having an increased risk and people >60-70 years old having a greater risk. Others risk factors are smoking, diabetes mellitus, hypertension, dyslipidemia, renal failure, sedentary lifestyle and genetic variants background.[1,2]

1. Chronic Limb Ischemia

It is an expression of PAD that refers to all the patients with typical chronic ischemic rest pain according to Rutherford classification or ischemic skin lesions such as ulcer or gangrene for more than two weeks. It must be distinguished from acute limb ischemia.

2. Intermittent claudication

It's a classic manifestation of PAD and it is characterized as limited walking and exercise ability affecting quality of life. Symptoms are muscle fatigue, aching or cramping which are occurred with physical activity, they are relieved by rest in less than 10 minutes and the most common location is the calf, but it can also affect the thigh and the buttocks. Occlusion lesion leads to lower arterial supply of the lower extremities and imbalanced oxygen–metabolic demand.

Medical management for chronic atherosclerotic peripheral occlusive disease:

PAD is connected systematically with the atherosclerotic process in other vascular beds (coronary, carotid and cerebral arteries). Thus, there is an increased risk of cardiovascular mortality. The two main therapeutic goals of treating PAD are the diminution of fatal cardiovascular events and the management of the limbs' symptoms (improvement of walking distance, tissue loss, etc.). Modification of the typical cardiovascular risk factors should be treated aggressively. A beneficial non-pharmacological intervention is a supervised exercise program in addition with pharmacotherapy. Other pharmacological agents aiming the risk factors are statins, ACEIs, prostaglandins and various supplements. Pharmacotherapy strategy with FDA approval for IC consists of two drugs, cilostazol (first-line agent) and pentoxifylline (second-line agent).[3]

TASC II:[4,5]

Revascularization

The best method of revascularization is based on the underlying arterial tree (adequate inflow and outflow, size and length of the diseased segment), the severity of co-morbid conditions and the type of procedure. The location and morphology of the lesion must be characterized prior the intervention. There are endovascular (balloon angioplasty, stents, stent-grafts and plaque debulking procedures) and surgery techniques (autogenous or synthetic bypass, endarterectomy or an intra-operative hybrid procedure). Anatomic factors (severity in run off arteries, length of the stenosis and number of lesions treated) and clinical/systematic variables affect the results of revascularization. Between these two techniques, when there is well-matched short-term and long-term improvement, endovascular method is preferable.

Classification of lesions

Guidelines for suggest that TASC A and B lesions have excellent and sufficiently good results with endovascular method respectively, but for B lesions, patient's overall assessment and medical history should be considered. TASC C lesions are handled with the open method, but for good-risk patients an endovascular technique could be deployed and for D lesions the treatment of choice is surgery. In general, PAD management is complicated while more than one lesion and a variety of severity are involved (Figure 1).

For SFA occlusive disease, the above classification is the same. Results from multicenter RCTs show endovascular approach is the preferred choice in limited disease. A normal vessel above and below the lesion is the key for permitted access. When PTA fails, stent placement is indicated for better primary patency rates. Nitinol self-expanding stents coated with an antiproliferative agent are superior for endovascular method and balloon PTA coated with the same agents is promising.

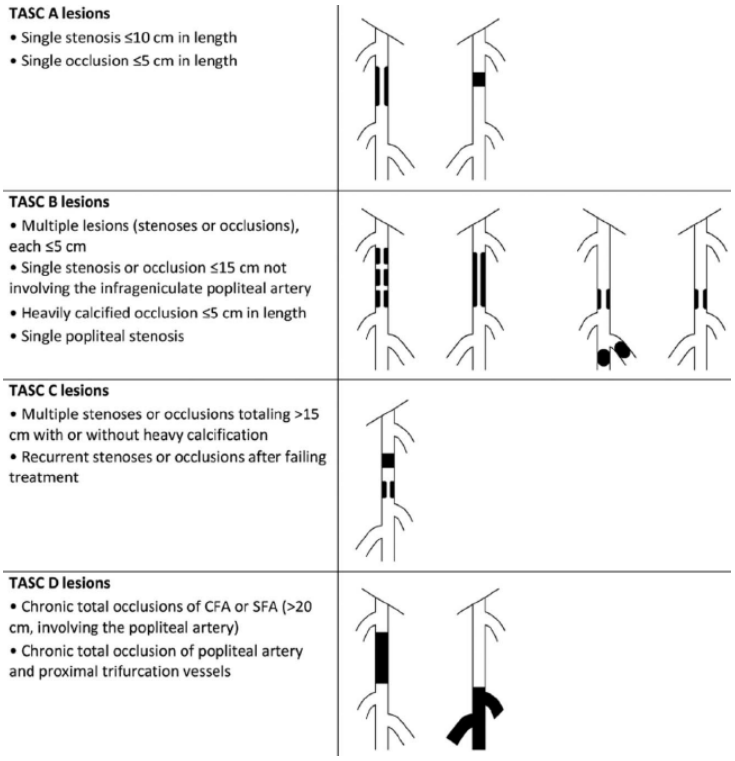


Figure 1: Classification of femoral popliteal lesions (TASC II). CFA – common femoral artery, SFA – superficial femoral artery

Antiplatelet and anticoagulant therapy

The risk of thrombosis at the site of intervention is the major problem of revascularization. Thus, intra-intervention heparinization and after the intervention the adjuvant of a life-long medication with antiplatelets (ASA, clopidogrel, etc.) are recommended. According to the guidelines of TASC II, 60 days are required with post-procedure dual antiplatelet therapy. Adding or continuing anticoagulant drugs should be investigated according to patient's medical history, contraindications and especially the risk of bleeding.

Stenting

Stenting is a medical procedure for treating the occlusion of arteries (coronary, cerebral, renal, upper-lower extremities, etc.) and other parts of the body which have a cylinder shape (bile duct, ureter) and restore the unworried blood or other liquid flow. It is a minimally invasive technique through a hardly any incision of derma (percutaneous) and via the femoral artery that is the most preferred site (transluminal). Using a guidewire, a sheath, a balloon or a stent wire with the associate of live angiography for imaging the vessels, the targeted lesion is opened and the flow is undisturbed.[6] Stent expansion denude the endothelium and expose its extracellular matrix to the environment causing an inflammatory response, leukocyte and platelet deployment resulting in neointimal tissue growth. Excessive and abnormal reendothelization induce unfavorable outcomes such as restenosis of the stent and rise of atherosclerotic plaque. Smooth muscle cell hyperplasia is the leading cause.[7]

DES

Drug-eluting stent (DES) are developed by covering a bare metal stent (BMS). It consists of a three parts structure: 1) strut, 2) polymer coating and 3) antiproliferative agent. The platform is made by a durable material like SS, CoCr, PtCr. The polymer coating can be made by a durable material like SIBS, PEVA, PBMA, PVDF-HFP, MPC, LMA, HPMA, 3-MPMA, PVP, PHMA, PVA or a bioabsorbable material like PLGA, PLLA, PDLA, PDLLA. Tested antiproliferative drugs are Sirolimus, Everolimus, Zotarolimus, Novolimus and Paclitaxel. The Their innovation was remarkable and they improved the clinical outcomes of coronary artery disease by reducing the risk of repeat revascularization and in-stent thrombosis compared to BMS.[8] Further investigation showed some limitations of DES, such as very late stent thrombosis, late expansive and adaptive vessel remodeling, issue with surgical revascularization, weakness of computer tomography imaging. The idea of a stent that will disappear after a period of time and will display similar functionality with DES is ideal.

BRS

Bioresorbable scaffold (BRS) is a fully bioresorbable stent made by biodegradable polymers or metals which will degrade, setting free the vessel from the permanent metallic strus of bare metal stents (BMS) or drug-eluting stents (DES) and reducing long-term stent complications. In other words, total resorption has many advantages allowing restoration of vasomotor response, expansive remodeling and maintenance of shear stress.

After the temporary support, endothelium returns on its previous function and physical properties. The inflammation time reduces and healing process is faster. Vasomotion (systolic and diastolic) of the vessel wall is restored and covering of side branches is transient. Necessity for long-term dual-antiplatelet therapy seems to be minimized. Also, a significant benefit is the safer and more unhampered from a metal matter approach if surgical revascularization is necessary.[9] Success of bioresorbable technology is hidden in the ability to control assimilation at a desirable level.

The majority of BRS has a backbone composed of poly-L-lactide (PLLA) polymer which needs 2-3 years to be absorbed. Final products of the chemical degradation are H_2O which is regulated by the renal system and CO_2 which is emitted by the pulmonary system (Kreb's cycle is the main

biochemical pathway). PLLA hydrolysis is slow and in a such case it increases the duration of the vessel's mechanical support. The outermost layer is coated with a thin layer of another polymer with other properties and it reabsorbed at a faster rate from the scaffold's alloy, within several months, contributing to controlled release of the antiproliferative drug.[10]
However, PLLA misses of the mechanicals properties of a durable material such as cobalt-chromium (CoCr) and lacks of stiffness and plasticity. In order to support a vessel's wall with appropriate radial strength and tensile, thicker backbone is mandatory. Strus is thicker than the conventional DES leading to larger endothelial cell coverage area and migration distance and inadequate endothelization. Moreover, the protrusion of the thick scaffold causes local flow loss and shear stress promoting platelet activation and thrombotic environment. In addition, occurrence of structural damage reveals its poor mechanicals capabilities and reveals a hurdle of using post-expansion technology and avoiding malapposition.[11] In vivo studies have highlighted that dynamic blood flow has a major role in the behavior of BRS and that degradation rate is slower if the stents are inserted in the arterial lumen in comparison with the arterial wall.

Other current technologies for the scaffold are the non-toxic metal alloys like magnesium and iron. Magnesium is mixed with other elements giving a bioabsorbable metal with radial strength and durability comparable with that of aluminum alloys and producing a thinner strus. Iron-based stents have good mechanical properties, radiopacity and thinner strus but a slow degradation rate.
Implantation procedure is important, too. The PSP guideline (Preparing the lesion, Sizing appropriately and Post-dilation) should be adopted and followed strictly, a way to ensure lower rate of thrombosis, misplacement and to-end clinical outcomes.[10,12]

The first biodegradable stent was used for coronary arteries and it was Igaki-Tamai stent (Kyoto Medical Planning Co, Kyoto, Japan) in 2000. Its scaffold was made by PLLA polymer, with no drug coating, a strut thickness of 0.17mm, various diameters, 12mm length and two radiopaque gold markers set at 2mm from each end. A follow-up of >10 years showed a 3-year disappearance of the stent, major adverse cardiac events at acceptable rates and similar to a bare metal stent and eventually a long-term safety.[13]
The REMEDY stent (Kyoto Medical Planning Co, Kyoto, Japan) is the successor of the Igaki-Tamai stent and it is commercially available for peripheral arteries lesions since 2009 when received a Conformité Européene (CE) mark. It is also made by PLLA and it is not drug eluting. Its radial strength is maintained for 6-9 months and it is absorbed fully in 3 years.[14] First report of using the REMEDY stent was published by the GAIA-Study in purpose of evaluating efficacy and safety in treatment of SFA lesions. It achieved favorable acute angiographic results, improved in WIQ, good mechanical properties with a low vessel recoil, but high patency rates compared to nitinol stents.[15]

5. Objectives and Endpoints

5.1. Primary efficacy endpoints

To evaluate if BRS could maintain the vessel patency of a previous stenotic SFA (>50%) with in de novo atherosclerotic lesion, a) after 2 years of follow-up (approximately one year after stent's full absorption) for efficacy and safety success and b) after 5 years of follow-up period, as benchmark time points.

The primary endpoints are:

- Absence of binary restenosis rate or alternatively primary patency rate (PPr) (Defined as no evidence of restenosis (>50% of vessel diameter) or occlusion within the target lesion, based on intravenous ultrasound (IVUS) or quantitative angiography (QA) and in the absence of TLR. Restenosis and occlusion are defined also as no color flow with Triplex test by an increase in peak systolic velocity > 2.0)

5.2. Secondary efficacy endpoints

Further information to assess the effectiveness of our biodegradable stent could give secondary endpoints which are:

- Parameters for the severity of obstruction obtained by Quantitative Angiography, all measured in mm
    - Lesion length
    - Diameter stenosis = (reference diameter − minimal lumen diameter)/reference diameter
    - Acute gain = post-stenting minimal lumen diameter − baseline minimal lumen diameter
    - Late Lumen Loss = post-stenting minimal lumen diameter − follow-up minimal lumen diameter
- Change in Rutherford category for the treated limb
  (Rutherford classification system for CLI assesses clinical presentation with objective findings including ABI, Doppler and pulse volume data.[16]
- Change in ABI for the treated limb
  (Defined as ratio of the highest ankle systolic blood pressure in one leg and using a continuous wave Doppler to detect return of blood flow in the anterior tibial and posterior tibial arteries, to the highest of either arm systolic blood pressure. Performed at rest with subject in supine position.
  0.9-1.3: Normal range
  <0.9: PAD, <0.8: moderate disease, <0.5: severe disease
  >1.3: calcification of arteries' walls/noncompressible arteries)
- Change in Quality-of-Life score for PAD (PADQOL)

    - Walking Impairment Questionnaire (WIQ) which assesses the degree of walking impairment
    - SF-36 which assesses the health status
    - Profile of Mood States (POMS) that evaluates the mood status
- Target Lesion Failure (TLF)
- Stent fracture
- Device performance
    - Technical success per segment (successful access and ≤ 30% diameter residual stenosis after revascularization
    - Device success per patient (exact deployment of the device according to the manufacturer's instructions)
    - Procedural success per patient (combination of technical success and device success and absence of procedural complications)

5.3. Primary safety endpoints

- Freedom from Target Lesion Revascularization (TLR)
  (Defined as any repeat percutaneous intervention with or without evidence of stenosis ≥ 50% to improve blood flow or within 5 mm proximally or distally of the treated target lesion.)
    - Clinically-driven TLR
      (Defined as revascularization performed on a patient who returns with clinical symptoms)
    - Angiographically-driven TLR
      (Defined as angiographic detection of significant restenosis in a patient who is clinically asymptomatic)
- Freedom from major amputation (above the knee)

5.4. Secondary safety endpoints

- Major adverse cardiovascular events (MACE)
    - Peri-procedural complications
    - In-hospital mortality
    - Mortality during follow-up
- Freedom from all cause-death

6. Study Design

6.1. Overall Design

This is a phase-II, non-inferiority (NI), randomized, single-blind, multicenter trial and the same protocol is applied for every clinical site. Its parallel design consists of two arms. The first one is the test device, Mg-based paclitaxel-eluting stent and the second arm is the control device, Eluvia DES. Purpose of the study is to show NI effectiveness of the experimental device in contrast to

standard intervention. The duration of the study is 5 years and the 2rd year is a landmark for efficacy and safety success. Recruitment and screening period will last 6 months. A stratification will be included based on the clinical site and the status of diabetes (existing or not). Interim analysis will be performed for baseline characteristics, for the time when the last patient has enrolled in the study and for safety assessment at 6-month, 1 -year, 2-year and 3-year.

6.2. Measures to Minimize Bias: Randomization and Blinding

Randomization:

After the screening procedure and the fulfillment of the eligibility requirements, participants will randomly be assigned with a ratio of 2:1 to two groups (experimental device: Mg^{+2} bioabsorbable scaffold paclitaxel-eluting stent, reference device: Eluvia DES). The subject will be considered randomized and registered after successful treatment of the target SFA lesion. Crossover is not permitted and ITT analysis will be used, regardless of the actual device the subject received. If a complication occurs in both of the study groups, whichever rescue approach should be followed by the clinician for the individual's best outcome. Randomization will be stratified for clinical site and diabetes mellitus as a known risk. Every study site will be noted for the randomization number.

Blinding:

This trial is single-blinded and it means that the subjects are unaware of the treatment-device they will receive, but the physician and the assistants who perform the stent implantation procedure are not blinded. The angiographic and in general, the imaging core laboratories are not-blinded, too. Staff will have the necessary training not to disclose the treatment assignment to the subjects and a restricted access to the clinical database will be granded. Also, follow-up visits and interviews will be recorded by personnel that did not take part in the intervention procedure in order to minimize bias. Data Safety Monitoring Board (DSMB) will be blinded, unless safety issues are emerged.

7. Study population

7.1. Inclusion criteria

General and angiographic requirements must have a subject in order to participate in this study:

- Age > 18 years old
- Male or Female
- Patient must provide signed and dated informed consent form (ICF)
- Patient must state willingly participation in the study and compliance with all procedures and follow-up demands
- Eligible for the standard surgical repair, if necessary
- Patient must belong clinically to Rutherford category 2 to 6
- Resting ABI ≤ 0.9 or TBI ≤ 0.7
- Total occlusion or > 50% stenosis of a single SFA lesion
- Target lesion must be successful crossed with a guide wire

- One long or multiple serial lesions (stenotic or occluded) within the same vessel with a 4cm ≤ length ≤ 14cm
- 4mm ≤ Reference vessel diameter ≤ 6mm
- Lesions must be located at least 3cm above the knee joint, defined as the distal end of the femur and at least 2cm below the origin of the profunda artery
- Patent infra-popliteal and popliteal artery
- Poor inflow (defined as > 50% stenosis angiographically) of the aortoiliac and common femoral artery must be corrected for adequate support of femoropopliteal bypass graft if necessary. It can be done prior to treatment of the target lesion and success means < 30% stenosis and gradient pressure ≥ 20mmHg
- Bilateral obstructive SFA is accepted based on the above criteria and an interval period for the other limb intervention must be 30 day.

7.2. Exclusion criteria

General and angiographic exclusion criteria are:

- Patient's participation in another clinical trial
- Renal impairment (creatinine level, urea)
- Dialysis dependent
- Active systematic or local infection
- Paclitaxel intolerance
- Immunocompromised
- ABI > 1.3
- Aneurysm at target SFA vessel
- Implanted stents at target SFA lesion previously (defined as need for stent-in-stent replacement, such as in-stent-restenosis)
- Thrombolysis of target vessel within 72 hours and incomplete resolution of the thrombus
- Acute thrombus at target SFA vessel
- Parameters that prohibit access to the target lesion or 90^{o} tortuosity preventing delivery of the stent device
- Need for stent placement within 1cm of a previous stent
- Allergy to contrast media for angiography, heparin, aspirin, nitinol and clopidogrel or ticlopidine or prasugrel
- Life expectancy < 1 year
- Breast feeding or pregnancy or intention for a woman to get pregnant within 1 year
- Bleeding disorders
- Hypercoagulability disorders
- Significant anemia
- MI within 3 months
- Stroke within 3 months
- Atrial fibrillation uncontrolled with medication

8. Study Intervention

8.1. Study Intervention Description

Mg-based Bioresorbable Scaffold Paclitaxel-Eluting Stent System:

It is a device/drug combination product. The bioresorbable scaffold backbone is made of Magnesium (Mg) and the coating is made of the bioresorbable polylactide (PDLLA) which includes the active pharmaceutical ingredient paclitaxel. Nominal concentration of paclitaxel is 0.167μg/mm^2. There are two embedded platinum markers at both proximal and distal ends of the scaffold for radiodensity assistant. The delivery system consists of 3 shafts with rapid exchange capability. This vascular stent system is produced for various diameters and lengths and it is compatible with 0.035in guidewires.

Rationale of Magnesium alloy for stent fabrication:

Magnesium is one of the essential elements in human physiology and thus it is safe for vascular stent construction. The advantages of Mg stents are good biocompatibility, biodegradation and biomechanical properties. In vitro studies provided knowledge about the addition of rare earth elements for the improvement of corrosion resistant and mechanical strength, especially radial strength. The thin strus thickness, approaching the standard stainless steel, and the high elastic modulus provide some cons. Moreover, a double-layer coating is used to control biocorrosion and drug release with the appropriate hemocompatibility. In animal studies, signs of bio-resorption of Mg occurs between 1 to 12 months. Finals products of this process are magnesium oxide (MgO), different salts, hydrogen and hydroxyapatite which is ingested be the macrophages.

The disadvantages of Mg stents are firstly, the rapid and local degradation rate which lead to decline of mechanical support and increment of arterial recoil prior to the vascular remodeling and secondly, the production of a high concentration of Mg ions that could induce problems with coagulation and inflammation. Also, there are some concerns about the hydrogen releasing from the corrosion process, but the is no evidence so far. Low plastic deformation and high brittleness because of thin strus, make them prone to fracture.

The Triune Principle for a biodegradable Mg alloy design and therefore for a perfect stent is the precondition of biosafety, the basis of strength and ductility balance and the clinical goal of degradation controllability.[17–20]

An example of Mg-based market launch stent is Magmaris device (CE Mark approved) which is manufactured by Biotronik and it is a Magnesium-based scaffold with sirolimus eluting drug component and a strus size of 120-150 mm.

The Boston Scientific ELUVIA™ Drug-Eluting Vascular Stent System:

Eluvia is a device/drug combination product. The device-stent component is composed of the delivery system and the stent. The stent is a laser cut self-expanding stent made of nickel-titanium alloy (nitinol)and it is available in various diameters (6mm and 7mm) and lengths (40mm, 60mm, 80mm, 100mm, 120mm). Radiopaque markers, made of tantalum, are found on both the proximal and distal ends of the stent for implantation assistant. The delivery system is 6F, it is designed with 3 shafts for technical success reasons, it is offered in two working lengths (75cm, 130cm) and it is compatible with 0.035in guidewires. The drug component consists of the coating which is composed of the dual-layer coating polymers PBMA, PVDF-HPF and an anti-proliferative drug, paclitaxel (active drug). Nominal concentration of paclitaxel is 0.167μg/mm^2. CE mark was received in 2016 for commercial distribution.

Paclitaxel

Paclitaxel is an antineoplastic agent and it is mostly administered to patients with breast and ovarian cancers. Its biochemical function is to bind reversible to microtubules promoting polymerization of tubulin and forming stable microtubules. This interaction effects the mitotic cellular functions (arrests cell-cycle in the G2/M phase). Signal transduction for proliferation and migration is impeded. Paclitaxel actions are dose-dependent and lower doses have cytostatic results, on the other higher doses have mitotic arrest/apoptosis results. Potential adverse events of paclitaxel include but are not limited to allergic reactions, hematologic dyscrasia, peripheral neuropathy, alopecia and myalgia/arthralgia.

Preclinical studies have shown that paclitaxel can also be delivered via an eluting stent and utilized as an antiproliferative drug aiming to reduce the smooth muscle proliferation and the restenosis rates. It is released progressively, with higher rate in the first hours, from a polymer matrix which covers the stent. Its lipophilic characteristic helps to rapid absorption into the arterial wall and to a low plasma dispersion and systematic absorption. The load onto the stent device is 400 lower than the oncological application and interactions are not detectable.[21,22]

FDA gathered so far data from numerous trials and meta-analysis studies which refer to paclitaxel-coated devices. New vital status information and long-term follow-up with at least 5 years indicate that these devices are not associated with a late mortality risk.

8.2. Preparation/Handling/Storage/Accountability

Strict guidance must be followed according to manufacture's instructions for the handling, the storage and the operation of the device. The package must not be used if it is opened or damaged and if the labeling in incomplete or illegible. Proper preparation includes inspection prior to use, patient's and facility preparation, delivery procedures and stent deployment procedure. Enmeshed staff is mandatory to be familiar with current medical practice on stent implantation.

9. Study Intervention, Participant Discontinuation/Withdrawal and Lost to Follow-up

Participants are free to decide whether they remain or not in the study at any time after requesting. Discontinuation does not mean that the data will be destroyed but they will be stored under restricted supervision for further investigation, especially for the safety and efficacy endpoints. If a participant misses a visit, immediate contact will be attempted and a new visit will be arranged. If the contact is impossible by all means, the subject will be written down as lost-to-follow-up. Also, the investigator may withdraw a participant if it is necessary. For example, the investigator could terminate a subject because of protocol requirements violation or risk possibility. Every possible withdrawal will be recorded on the case report form and if it is related to an adverse event, it should be pointed out. There will not be replacement of a subject and the investigator must report to the sponsor and the IRB/IEC for discontinuation issues. 5-year follow-up is the landmark for subject's successful completion of the study.

10. Study assessments and procedures

10.1. Screening procedures

Screenings procedures are defined according to the SOA.

10.2. Adverse Events/Serious Adverse Events/Device Deficiency

- Device Deficiency (DD) is considered the inadequacy of a medical device related to its identity, durability, quality, reliability, safety and performance. In general, the medical device fails to meet its performance specifications based on the labeling of the device.
- Adverse Event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. In our study the intervention is both the stent types.
- Serious Adverse Event (SAE) is considered any unwanted medical occurrence if it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when they might put the participant in risk and might require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Suspected Unexpected Serious Adverse Reaction (SUSAR) is any adverse reaction that is classed as serious and is suspected to be caused by the investigational product and is not consistent with the information about it in the investigators protocol.

Every clinician who participates in the trial must be aware of any AE, serious or not and its possible relationship to study's design. Causality is examined and established by investigator's clinical judgment with a degree of certainty which is graded using a binary assessment. The investigational device must always be suspected. Binary assessment is presented as:

Related:

The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related:

There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

10.2.1. AE/SAE/DD/ SUSAR Reporting

Investigator and sub-investigators must record any AE/SAE/DD/SUSAR that may occur during the study and fill correctly the case report form (CRF) for every participant at every scheduled visit. An extra document must be completed for events which are possible related to the peripheral artery lesion itself. Sponsor and Data and Safety Monitoring Board (DSMB) must be informed for the adverse events according to the protocol's timetable by the investigators. Sponsor's duty is to evaluate the received information and report the results to the Food and Drug Administration (FDA), the Institutional Review Board (IRB) and all the others investigators of the study. All the reports must be accomplished within 5 days.

10.2.2. Reporting of Pregnancy

Investigator must consult a female patient not to get pregnant, if applicable, until 1 year has rolled by. If she becomes pregnant within the whole period of the study, investigator must inform her about the possible effects of a foreign material inside the body to the fetus and the inverted condition because of the changes in physiology experience a woman bearing a child. Sponsor and IRB/IEC will receive immediately from investigator a report for a possible pregnancy. Pregnant women will have to be checked periodically by a gynecologist and the follow-up for them will be as it stands according to scheduled activity.

11. Statistical Considerations

11.1. Statistical Hypothesis and Sample Size Determination

The trial's non-inferiority (NI) design aims to show that the experimental device is sufficiently close to the results of the reference device. According to FDA's guidance for establishing non-inferiority effectiveness, a null and alternative hypothesis for inferiority and non-inferiority are formed, respectively. General schema is the following:

The effect of the test device (T) is not inferior to the effect of the control device (C) by a specific amount, called the non-inferiority margin or Δ. The lower bound of the 95% two-sided confidence

interval of this NI comparison must be smaller than Δ corresponding to a one-sided test size of 0.025 (alpha = 0.025).

H_0: C – T ≥ Δ (T is inferior to the C by Δ or more)
H_a: C – T < Δ (T is inferior to the C by less than Δ)

Primary efficacy endpoint of primary patency rate is used for defining the hypothesis test for NI of Mg-BRS paclitaxel-eluting stent and Eluvia DES and for calculating the sample size of the trial. One-sided alpha of 0.05 and the 2-year primary patency rate are taken into account.

H_0: $PPr_{Mg} - PPr_{Eluvia} \geq \Delta_{PPr}$
H_a: $PPr_{Mg} - PPr_{Eluvia} < \Delta_{PPr}$

PPr_{Mg} and PPr_{Eluvia} are the 2-year primary patency rate in the Mg-BRS and Eluvia groups, respectively. Δ_{PPr} is the non-inferiority margin for this primary endpoint.

a) Power = 90%
b) Alpha = 0.05
c) $\Delta_{PPr} = 0.1$
d) PPr_{Eluvia} = 83% (literature review)
e) PPr_{Mg} = 80% (clinically important)
f) Randomization ratio of 2:1

An effective sample size of 1936 participants, at 2-year primary patency rate, is needed to demonstrate non inferiority success. According to ordered ratio, 1290 subjects will be assigned to the Mg-BRS arm and 646 subjects to the Eluvia DES arm.[23]

11.2. Populations for Analyses

Intention-to-Treat (ITT) population:

ITT analysis is defined as the subjects enrolled in the study at the point of randomization and they will be analyzed based on the initial group assignment, regardless of the treatment they actually received. Individuals who enrolled but did not randomize will not be included in the ITT analysis.

Per-Protocol (PP) population:

PP analysis is defined as the subjects who fulfill the eligibility criteria and complied with the protocol's terms sufficiently. Outcomes of this analysis is restricted to a selected population, representing the effect of intervention under optimal conditions.

11.3. Statistical Analysis

Continuous variables will be presented as mean/standard deviation or median/interquartile ranges, while categorical variables will be presented as counts/percentages. Intergroup differences for continuous variables will be assessed by the parametric Student's t-test for normal

distributed data and the non-parametric Mann-Whitney U test for non-normal distributed data and for dichotomous or polytomous variables, Pearson's Chi-Square test or Fisher's exact test will be used as appropriate. Survival analysis will be performed using the Kaplan-Meier method. Survival curves and cumulative event rates will be constructed and log-rank test will be used for the differences between the groups. Statistical tests will be two-sided, a = 0.05 is used as a level of significance and 95% confidence of intervals is calculated. Statistical analysis is performed using statistical software packages (SPSS, version 2023, IBM, Armonk, New York).

12. Regulatory and Operational Considerations

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The trial's conduction will conform to International Council on Harmonization Good Clinical Practice (ICH GCP) requirements and national regulations/judiciary of every participant country.

An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be constituted by members qualified to examine the trial's matters, according to national laws. They will ensure the safety, well-being and rights of all trial subjects and they will comply with GCP. Relevant data and documents to the study (recruitment procedures, written informed consents, Investigators Brochure (IB), the protocol, etc.) or any modifications required must have a written approval. No deviations from the protocol are permitted without prior written IRB/IEC favorable opinion of an alteration, except when it is essential to secure safety for the participants or when only logistical issues exist. Investigator should report to IRB/IEC on time the following:

1. Deviations from the protocol to efface jeopardy to the participants or modifications that increase the risk of the subjects and affect the trial's progress.
2. Serious and unexpected adverse events
3. New information about hazards and trial's impairments

12.2. Informed Consent/Assent Procedures and Documentation

A written Informed Consent Form (ICF) must be provided to the subjects prior to the enrollment. Meaning of the informed consent is to explain to the subject the nature and the scope of the trial, the procedures that will be followed, the expected benefits and risks, the voluntary aspect, the confidential of its information, the granted access to the medical records of the subject from monitor, audit and IRB/IEC staff and the compensation in the event of an injury. The ICF or any other written information will have already the IRB/IEC's approval. Also, every modification or important for the subject attachment will receive favorable opinion in advance. Trial's trained staff will fully inform the person or its legally representative, if the individual is unable to provide informed consent. The language of the ICF will be non-technical, plain and understandable, plenty of time will be provided and subject will have the right to inquire details about the study so as to come to a decision. None unduly influence for participation by the personnel is acceptable. Original document will be stashed together with all the other important subject's medical records

and a copy of the signed written informed consent will be handed over to the subject or its legally representative.

12.3. Study Discontinuation and Closure

If an arguable reason shows up suspending or prematurely terminating the trial, the investigator will procced to written notification presenting essential information about the suspension or the termination of the study. Recipients are the participants, the IRB and the sponsor. Conceivable circumstances are:

- Significant jeopardy for the participants
- Efficacy outcomes not corresponding to the desirable
- A Protocol deviation to a great extent
- Not sufficient/evaluable data
- The primary endpoints have been met

12.4. Confidentiality and Privacy

All the information that is related to the participants and the trial will be under restricted control and only authorized personnel will have access. All source documents will be held under strict confidence and the staff will be trained for this purpose. Unauthorized third party must take a written approval from the sponsor in order to get legal access. Inspection of the participants' private documents is permitted to monitors, IRB and national regulatory agencies. Data will be used only for statistical analysis and safety evaluation during the study's period. After the end of the study, all records will be kept for a determined time period and therefore they will be destroyed.

12.5. Safety Oversight by Data Safety Monitoring Board (DSMB)

A DSMB is formed and it has under its direction the collection of cumulative safety data from the study. The Board is independent and its primary role is to ensure the well-being and safety of the participants. The Board may advise and recommend any alterations or a possible termination based on its review of the safety data. A safety oversight documentation will be printed by the board, including all adverse, expected or unexpected, events. The reports will be published to IRB/IEC and the Sponsor.

12.6. Clinical Monitoring

Sponsor will recruit at the beginning of the study trained and qualified monitors to oversee the trial's progress. Purpose of the visits is to ensure that all the participants are protected regarding their rights and well-being and all information is accurate and complete. Monitor personnel will ensure at 1st visit, prior to the initiation of the trial, that some criteria pertaining to Investigator, staff and clinical site are met:

- Investigator and staff are obligated to comply with International Council on Harmonization Good Clinical Practice (ICH GCP), with applicable regulatory requirements and with trial's protocol and amendments,
- There is sufficient time, fully equipped facilities and enough number of subjects to conduct the study,
- The source documentation with the all the proper information for all the parts of the study is available (such as ICF, eCRF, reporting of adverse events, etc.),
- Sponsor's monitors will verify the documents unhampered and with a comfort working environment.

There will be appointed four (4) on-site visits: before onset-(1^{st}), at 1 year-(2^{nd}), at 2 years-(3^{rd}) and at 5 years-(4^{th}) and they will be conducted in comprehensive extent for 100% data verification. Any problems with the study should be discussed. Reporting to sponsor must be completed within 15 days for every visit.

Independent auditing will be conducted by sponsor's auditors between the intervals of the monitoring visits with a view to secure consistent practice across all clinical sites.

12.7. Quality Assurance (QA) and Quality Control (QC)

Each clinical site, with the supervision of the investigator, will conduct a quality management plan for data collection, documentation and completion. Staff will be trained for an accurate QC in order avoid missing data. Every data anomaly that appears will be reported to the investigator for resolution. Monitors, auditors and regulatory authorities will have direct access in the trial's related archive so as to assure compliance with protocol, ICH GCP and GLP, based on written Standard Operating Procedures (SOP).

12.8. Data Handling and Record Keeping

12.8.1. Data Collection and Management Responsibilities

Source documents are all information, original records and observations in clinical trial. Each clinical site will have trained staff on the protocol and CRF filling-in and it will be responsible for the collection of participants' source data such as signed ICF, previous examinations documentation, hospital records from previous admissions, concomitant medication, laboratory data, adverse events report, etc. Primary data capture will take place at first on paper form, when it is possible and later it will be redirected into an electronic CRF in consistence. The data system will be a secure web software and password will be provided only to authorized people. Recording must be accurate and plain for an easy interpretation. Within the software, a validation checklist will aid investigator for troubleshooting inconsistent and missing data and monitor is responsible corroborating the investigator's handling.

12.8.2. Study Records Retention

Source documents will be archived for at least 5 years after the 5 years follow-up period. Any modification needed for maintaining the records pertaining to the trial is determined by the sponsor. Also, sponsor is liable to indicate to the investigator the time of destruction of all the records with a written consent and investigator have to take permission from the sponsor for writing purposes.

12.9. Protocol Deviations and Non-Compliance

It is the investigator's responsibility to track done, record and report every deviation from the protocol and non-compliance to IRB and Sponsor.

12.10. Publication policy

Investigators from each involved in the trial clinical center have the right to perform sub-studies and publish the results (as single-experienced center) after getting the written approval of the sponsor. Multi-center data and outcomes generated by the trial are accessible to the sponsor and it has the only right to use them as publication material. Registration to clinicals.gov is mandatory and it is sponsor's responsibility. Public will have free and unlimited access to the results of the study regardless of positive or negative impact.

12.11. Insurance

Subjects enrolled in the trial will be informed about the insurance policy at the time of the ICF completion and they will be insured according to national laws. They will receive a copy of the insurance.

13. Abbreviations

AE	Adverse Event	ICH	International Council on Harmonization
CE	Conformité Européene	IRB	Institutional Review Board
(e)CRF	(Electronic) Case Report Form	ITT	Intention-To-Treat
DD	Device Deficiency	PP	Per Protocol
DSMB	Data Safety Monitoring Board	QA	Quality Assurance
IEC	Independent Ethics Committee	QC	Quality Control
FDA	Food and Drug Administration	SAE	Serious Adverse Event
GCP	Good Clinical Practice	SOA	Schedule of Activities
GLP	Good Laboratory Practices	SOP	Standard Operating Procedure
IB	Investigator's Brochure	SUSAR	Suspected Unexpected Serious Adverse Reaction

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