Clinical Investigation Plan

STREAMLINER STUDY

EVALUATION OF SAFETY AND EFFICACY OF THE BIFURCATED MULTILAYER FLOW MODULATOR (BMFM®).

Protocol N° 12-2013
Version 5.0 (3/05/2017)

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Study Centers	Up to 12 centers in Europe, Israel, Morocco, Turkey and Bahrain
Date of Issue	Version 5.0 (3/05/2017)

Date(s) of Amendment(s)	V2.0 (12/12/2014): • New center and new PI added: Elytis Hospital Hope Iasi, Romania, Dr. Mihai-Christian Rotar • Principal Investigators contact information updated (point 1.2.) • Interim analysis will be performed after the 10 first enrolled patients will complete their 6 months follow-up (point 7.6.) • Addition of 6 months mortality in the endpoints (point 5.2.) • Adverse Event definition – update (point 12.1.1.).
	V3.0 (06/11/2015): • New center and PI added: Mohammed Bin Khalifa Bin Sulman Al Khalifa Cardiac Centre, Dr. Husam Noor • Principal Investigators contact information updated (point 1.2.) • New references of the BMFM® kit added (point 3.) • Enrollment period extended to 24 months (point 5.2.)
	V4.0 (25/08/2016) • Enrollment period extended to 36 months (point 5.2)
	V5.0 (3/05/2017) • Enrollement period extended to 38 months (point 5.2)

Investigator's Signature Page

STUDY NAME **STREAMLINER**

STUDY TITLE **Evaluation of Safety and Efficacy of the bifurcated multilayer flow modulator** (BMFM®).

STUDY CENTER

_____
(Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the ICH Guidelines for Good Clinical Practice (GCP); the International Standard ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects); ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country laws and regulations. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____
Principal Investigator (Print Name)

Principal Investigator (Signature) Date

STREAMLINER STUDY
PROTOCOL SUMMARY

STREAMLINER Study is designed to evaluate the safety and efficacy of the Bifurcated Multilayer Flow Modulator (BMFM®).

Study Reference:
12-2013

Device:
Cardiatis, S.A. Bifurcated Multilayer Flow Modulator (BMFM® kit).

Study Design:
STREAMLINER is an international, multicenter, prospective, non-randomized study. It is designed to evaluate safety and efficacy of the BMFM® kit use. About 40 patients in up to 12 centers in EU, Israel, Morocco and Turkey will be enrolled and screened per the protocol-required inclusion, exclusion criteria, in order to obtain 30 completed patients**.** For early demonstration of efficacy and safety an interim analysis will be performed after the 10 first enrolled patients will complete their 6 months follow-up.

Start Date:
April 2014

Study Purpose:
The study purpose is to determine the safety and efficacy of the BMFM® kit in the use for the endovascular treatment of aortic aneurysm involving iliac arteries. The BMFM® body is an adaptation of the aortic MFM® to the aortoiliac bifurcation anatomy. It should be noted that the aortic MFM® has CE mark approval for the aortic aneurysm treatment.

Patient Population:
Patients with aortic aneurysm involving iliac arteries and morphology suitable for endovascular repair.

Sample Size:
40 subjects will be enrolled in the study.

Follow-up:
All patients will have clinical follow-up prior to hospital discharge, at 1, 6 months, 1 year and annually within the 4 subsequent years.

Number of Institutions:
Up to 12 centres will participate in Europe, Israel, Morocco, Bahrein and Turkey.

Primary Endpoint:
- Prevent aneurysm rupture, in stabilizing it;

- Mortality 30 days, 6 months and 1 year aneurysm-related.

Secondary Endpoints:

- Branch and collaterals permeability maintained;
- Mortality 30 days, 6 months and 1year not aneurysm-related;
- Major Adverse Events;
- Technical success (successful delivery and deployment of the BMFM® kit);
- Procedural/in-hospital evaluations (Anesthesia time, procedure time; fluoroscopy time; contrast volume; estimated blood loss; time to hospital discharge).

Inclusion criteria

For this study all subjects will be eligible to participate in the study if they fit with all the inclusion criteria and they don't have any exclusion criteria mentioned below.

Patients must meet **ALL** of the following criteria:

- Age over 18
- Life expectancy > 12 months
- Aortic aneurysm involving iliac arteries
- Healthy proximal and distal landing zone
- Adequate arterial access
- Healthy branches and collaterals (no stenosis or previously treated by angioplasty)
- Informed consent understood, signed and patient agrees to all follow-up visits

Exclusion criteria

Patients will be excluded if **ANY** of the following conditions apply:

- Aneurysm rupture, impending or contained rupture
- Aortic dissection
- Aortic root aneurysm
- Pleural effusion
- Prior all surgical procedure within 30 days unless procedure is in preparation for device implantation or planned within 30 days post stent deployment
- Myocardial infarction or cerebral vascular accident within 6 weeks of treatment
- Presence/suspicion of connective tissue disorders, for example, Marfan or Ehlers-Danlos etc.
- Contraindications to the anticoagulant or/ and antiplatelet medications
- Allergic reaction to a contrast agent
- Patient with undergoing or planned chemotherapy
- History of bleeding disorder (coagulopathy) or thrombophilia
- Shaggy aorta
- Takayasu's arteritis
- Presence/suspicion of infection (for example: mycotic aorta)
- The use of the MFM® with stent-grafts or previously implanted stent-grafts
- Pregnant or breastfeeding woman
- Patients included in another clinical study

It should be noted that the contrast agent must be used with precautions when patient with renal insufficiency and/or creatinaemia > 200 micromol/l before injection of contrast agent.

Statistical method

Primary descriptive statistical techniques and a method based on the survival table will be used to evaluate the results of the study.

List of Abbreviations:

AAA: Abdomino Aortic Aneurysm
ACT: Activated Clotting Time
AE: Adverse Event
ADE: Adverse Device Effect
APTT: Activated ProThrombin Time
ASA: American Society of Anesthesiologists
ASADE: Anticipated Serious Adverse Device Effect
ASTM: American Society for Testing and Materials
b/f EVAR: Branched / Fenestrated Endovascular Aneurysm Repair
BMFM®: Bifurcated Multilayer flow Modulator
CEC: Clinical Events Committee
CG: Chimney Graft
CIA: Common Iliac Artery
COPD: Chronic Obstructive Pulmonary Disease
CT: Computed tomography
DMC: Data Monitoring Committee
DVT: Deep Vein Thrombosis
EC: Ethics Committee
e-CRF: electronic Case report forms
EDC: Electronic Data Capture.
e**GFR:** Estimated Glomerular Filtration Rate
EIA: External Iliac Artery
EVAR: Endovascular Aneurysm Repair
GCP: Good Clinical Practice
IB: Investigator Brochure
ICF: Informed Consent Form
ICH: International Conference on Harmonisation
IFU: Instructions For Use
IIA: Internal Iliac Artery
IP: Intellectual Property
LAR: Legal Authorized Representative
MFM®: Multilayer Flow Modulator
MRI: Magnetic resonance imaging
PWSS: Peak Wall Shear Stress
SADE: Serious adverse device effect
SAE: Serious adverse event
SMA: Superior Mesenteric Artery
TAA: Thoracic Aorta Aneurysm
TAAAs: Thoraco Abdomino Aortic Aneurysm
TT: Thrombin Time
UI: Unit International
USADE: Unanticipated Serious Adverse Device Event

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1 Study contact information

1.1 Study sponsor

The Sponsor of the STREAMLINER Study is Cardiatis S.A.

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2 Introduction and Rationale

An aortic aneurysm is a permanent and localized dilatation of the aorta wall, resulting from an irreversible loss of integrity of the artery wall. The infrarenal segment of the abdominal aorta is the most common site for the development of aneurysms, however, both the ascending aortic arch and the descending thoracic portion of the aorta can be the site of aneurysms (1,2). Most Thoracic Aortic Aneurysms (TAAs) can be found in the aortic root and/or ascending aorta (60%), followed by the descending aorta (40%), the aortic arch only (10%) and the thoracoabdominal aorta (10%), with some involving more than one aortic segment (1,2). Aortic aneurysm may be identified incidentally or due to the present of secondary symptoms from aneurysm expansion.

Fann argued that the incidence of thoracic aneurysms was 6 cases per 100,000 people per year. Merk reports that the distribution of thoracic aortic aneurysms (TAAs) is: 40% in the ascending aorta, 10% in the arch, 35% in the descending aorta and 15% in the thoracoabdominal aorta (3). If the frequency of Crawford types I to IV comprises approximately half the cases, this would equate to 3 cases per 100,000 people per year for thoracoabdominal aortic aneurysm (TAAA) [2]. Webb *et al.,* estimated that the incidence of TAAA was around 2.2 per 100,000 people per year (5). Globally, in the spectrum of aneurysmal disease, TAAs account for only 3% of diagnosed aneurysms in the United States (6).

The initial classification schema for TAAAs was described in 1986 by Crawford and Coselli (7). TAAAs are classified into 4 subtypes of varying extent of the thoracic and abdominal aorta (Figure 6). In 1999, Safi and Miller (8) modified the initial classification by adding a fifth subtype.

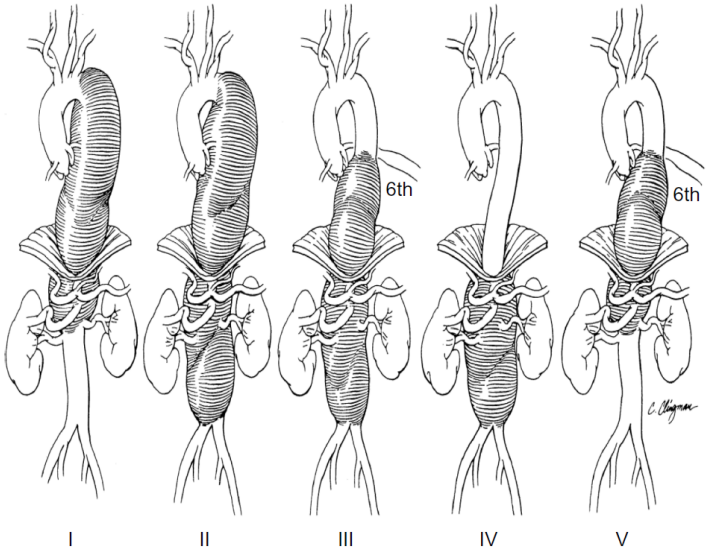


Figure 1: Thoracoabdominal aneurysm classification (58)

The mortality from untreated aneurysm rupture is high (46% to 74%) (9). Eventually, among patients with TAAAs greater than 7 cm, 43% will progress to dissection or rupture (10). Both female sex and the presence of Chronic Obstructive Pulmonary disease (COPD) have been associated with aneurysm rupture, while the female sex is associated with delayed time to aneurysm formation. However, the absolute risk of rupture is increased in size for size match cohort (2). COPD represents a major comorbidity associated with rupture, with a 3.6 fold higher risk of rupture. Also, longitudinal studies have shown that for every 1 cm in growth over 5 cm, the risk for rupture doubles (11). The arch and visceral segment are the most challenging portions of the aorta and are complicated by the presence of supra-aortic trunk, visceral, renal and intercostal branches. Currently, there are huge varieties of different aortic aneurysm treatments available but despite the numerous options there is no optimal solution.

2.1 Conventional surgical repair

In 1955, Etheredge *et al.* first described surgical repair of thoracoabdominal aneurysm, where aneurysms were approached via a left thoracoabdominal incision and included reconstruction of the visceral segment of the abdominal aorta. Prior to this, De Bakey and Cooley reported their experience with isolated thoracic aortic aneurysms. Over the next 10 years they amassed 42 patients who underwent repair utilizing Dacron interposition grafts (12). This conventional open TAAA repair became the mainstay of treatment for the following years (Figure 2) (13).

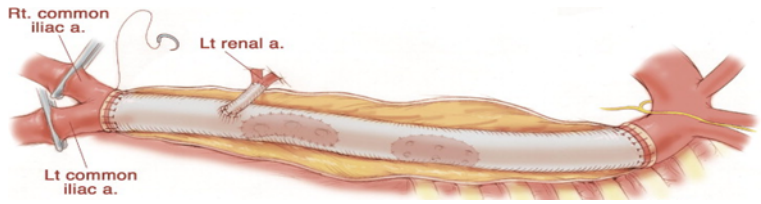


Figure 2: Thoracoabdominal aortic open surgery repair

The procedure has been improved by the use of techniques designed to limit visceral and lower extremity ischemia, by the minimization of the spinal cord ischemia risk and by the advances in critical care. However, the operation requires the surgeon replacing the aorta from above the aneurysm to a healthy distal aorta or iliac arteries, which necessitates the re-implantation of some or all of the visceral and intercostal arteries. Moreover patients selected to undergo such a repair are faced with a mortality risk ranging from 3% to 17% (5, 9). This rate continues to improve but still varies widely depending on patient presentation, extent of disease, comorbid factors and surgeon experience. Furthermore, the risk of spinal cord ischemia ranges from 4% to 11% (5, 10) the permanent renal failure from 17% to 25% (14) and respiratory failure from 4.4% to 33% (7, 9).

It should be noted that the results of these procedures are considered acceptable in the context of the untreated aneurysm rupture risk. In addition, the published results from high-volume centers may not be representative of the cardiovascular surgical community.

Thereby, several treatment alternatives using endovascular therapy alone or in combination with open surgery have been developed to repair these complex TAAAs. The general trend is toward a less invasive approach, improves patient outcomes, recovery time and quality of life. Despite major improvements in operative techniques and anesthesia, operative mortality after such an aneurysm open repair still ranges from 3% to 8% (15). Strategies aiming at aneurysm repair took a drastic turn after the first descriptions of an innovative technique for endovascular aneurysm repair by the team of Parodi *et al.*, 1991 using a transfemoral approach (16). This technology intends at reducing mortality and morbidity linked to open surgery. Continued effort since 1991 were made and led in 1994 to TAA repair by the team of Dake et al and resulting in successful exclusion of the aneurysm from the circulation (17). In 1999, the first EVAR (Endovascular Aneurysm Repair) was FDA approved for the treatment of AAA. The bifurcated stent AneurX AAAdvantage, from Medtronic, was made of Nitinol and Woven polyester and delivered in an integrated sheath (18). In 2005, the first thoracic endoprosthesis was FDA approved (19). The Gore TAG Thoracic Endoprosthesis Clinical trials aiming at demonstrating its efficacy and efficiency indicate that subjects receiving the graft are less likely to experience major adverse events, less intra-procedural blood loss, shorter intensive care unit and hospital stays, and reduced recovery times than surgical patients.

2.2 Hybrid procedure

Taking into account the limited role of total endovascular repair for TAAAs, the hybrid procedures have been introduced as a less invasive alternative to open conventional repair (Figure 3). The hybrid repair allows avoiding several shortcomings of open surgery: thoracotomy, single-lung ventilation, aortic cross-clamping and prolonged end-organ ischemia. Most centers with easy access to fenestrated and branched endografts have relegated hybrid procedures to high-risk patients who are neither candidate for total endovascular repair nor for open surgery. Its future applications may be for patients who fail total endovascular repair or in centers with no access or experience with fenestrated and branched endografts.

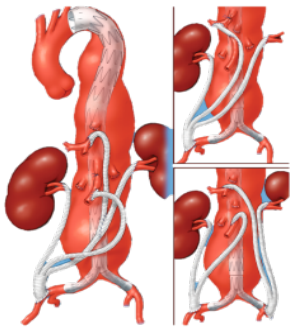


Figure 3: Hybrid procedure

The review of Moulakakis included 507 patients and 19 reports published since 1999. Aneurysm extent was classified as type I in 14%, type II in 27%, type III in 34%, type IV in 14% and type V in 11%. Thirty-day mortality was 13%, and the most common causes of death were multisystem organ failure, ischemic colitis, respiratory failure, and aneurysm

rupture prior to a second-stage procedure. Pooled rates of spinal cord injury were 7.5%, with irreversible paraplegia in 4.5% (20).

2.3 Endovascular repair

2.3.1 (b/f)-EVAR

Endovascular approaches to TAAAs have evolved during the past decade. The initial experiences with fenestrated and branched endografts have shown that total endovascular repair is effective and may reduce morbidity rates in patients with arch, thoracoabdominal and pararenal aneurysms (21, 22).

The Cleveland Clinic group has recently reported on their updated clinical experience with the first 633 patients treated by fenestrated and branched endografts. Operative mortality was 1.8% for pararenal, 5.2% for types I to III, and 2.3% for type IV TAAAs (21).
However, 30-40% of TAAA patients remain unsuitable for EVAR due to unfavorable proximal neck anatomy (20). There is also an increased incidence of type I proximal endoleak when established f-EVAR guidelines are disregarded, often leading to endovascular re-intervention or surgical conversion.

Currently, the use of the bifurcated stent-graft for the infrarenal aneurysm involving iliac arteries treatment has received wide distribution. The application of endovascular technology to treat infrarenal aneurysm is now commonplace because the implantation of an infrarenal endoprosthesis is a relatively simple procedure requiring adequately long proximal seal zone, diameter measurements and accurate longitudinal device placement. However, designing and implanting a device, which will accommodate the visceral branches, is more complex.

The infrarenal with unfavorable or insufficient proximal neck as well as juxtarenal aneurysms, which involve iliac arteries, could be treated by combination of the Fenestrated Stent Graft with the Bifurcated Stent Graft (Figure 4).

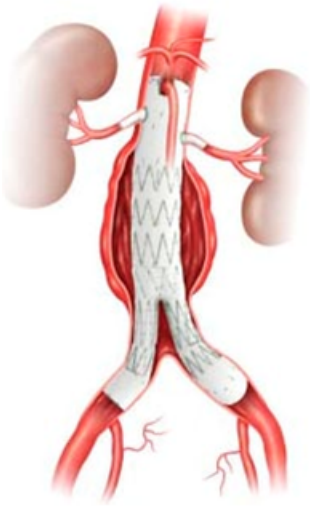


Figure 4: Combined stent Graft

The principal limitation of this technology is the customized nature of fenestrated stent-graft design. From planning to delivery, the process may take in excess of 6 weeks, which restricts the application of f-EVAR to stable elective patients. This procedure is complex, costly and the implantation time is quite long. It must be conducted in expert centers with sophisticated infrastructure (hybrid room). Preservation of visceral aortic branches requires precise graft construction and deployment.

There are reports in the literature of emergent f-EVAR, but the success of these procedures relies on on-site modification of commercially available endografts (23).

2.3.2 "Off label" devices or surgeon-modified devices

Until an "off-the-shelf'' device is designed to be compatible with the majority of patients, ''off-label'' surgeon-modified devices remain the only option in emergencies when open repair is prohibited. The "off-the-shelf" devices are likely to allow treatment of more than 60% to 80% of patients with complex aneurysms but these standardized designs have not yet been tested clinically in large number of patients with long follow-up (24).

In the absence of widely available endografts designs, a number of centers have reported creative techniques to incorporate the visceral arteries, such as "chimney" Figure 5, "sandwich" Figure 6, "octopus" Figure 7, "periscope" Figure 8 and physician-modified endografts.

However, these approaches are limited by off-label indications, lack of quality control, violation of basic engineering concepts and questionable durability (25).

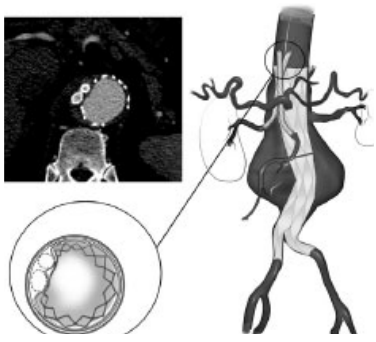


Figure 5: Chimney technique

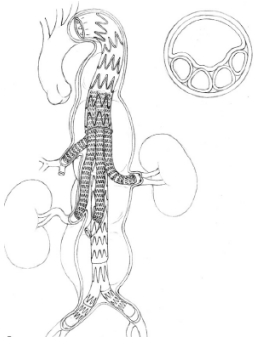
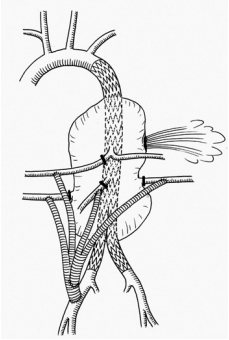


Figure 6: Sandwich technique



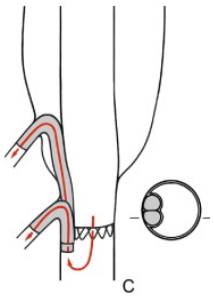


Figure 7: Octopus technique **Figure 8: Periscope technique**

One of the drawbacks linked to the use of parallel endografts (mainly for the "chimney technique") remains the imperfect seal inherent to this technique. This side by side configuration leads to gutter along the parallel endografts, which can result in type I endoleaks between the main body of the graft and branched grafts; "Gutter endoleaks" continuously pressurize the aneurysm (26, 27). The gutters between the main aortic graft, the chimney graft (GC), and the aortic wall should be as narrow as possible to avoid endoleaks, which can be harmful and –almost always- require re-intervention (27).

Gutters – and gutter endoleaks- could be eliminated by oversizing the aortic stent so that it wraps around the branch stent (6). In reality, though, endografts are simply not designed to deploy in such a manner. Further, the effect of post ballooning is to make the devices more round. In vitro studies have shown that 40% oversizing of the aortic stent can best minimize (but still does not eliminate) the gutters along a single parallel branch stent (28). However, this approach also led to significant infolding, leaving the authors to recommend 30% oversizing and accepting larger gutters (28).

Using this amount of oversizing without achieving the prime objective is just not a practical strategy, let alone a feasible one, in larger aortas with multiple parallel endografts (6). Alternatively, Lobato (78) has suggested overlap lengths of at least 5 cm to induce thrombosis of the gutters. However, persistent endoleaks with even 10 cm of overlap were observed (6). Further, longer overlap lengths may affect patency rates and sometimes necessitate sacrifice of additional lumbar or intercostal vessels. Orr et al (6) suggest that gutters can be eliminated by molding the parallel graft into an eye-shape so that the aortic graft can more easily conform to its exposed perimeter (6, 29).

2.3.3 The kissing Stent technique

As largely described in the literature, the treatment of bifurcation lesions is associated with high procedural complication and restenosis rates. Endovascular aorto-iliac kissing stent reconstruction in occlusive disease has been described as a solution in such cases (30-39) and has largely overcome the Kissing balloon angioplasty. The kissing stents technique, which involves simultaneous implantation of two stents at the aortic bifurcation, was presumed to overcome drawbacks linked to open surgery as well as those linked to the kissing balloon angioplasty (31-33). Today, with the refinements in stent technology, the kissing stents technique has largely replaced kissing balloon dilation for the treatment of aortoiliac occlusive disease. As described by Ylmaze et al in 2006 (39) on a series of 68 patients treated with the kissing stent technique, kissing stents implantation is a safe and effective alternative in the treatment of aortoiliac obstructions. The long-term patency is not significantly impaired in patients with distal runoff obstructions or in those with lesions up to 6 cm in length, as long as a favorable stent configuration is obtained. In patients >50 years and in those without iliac occlusions, the kissing stent technique should be preferred to surgery because the patency rates are comparable to surgery and the advantages of endovascular treatment are well known.

2.4 Branched endografts

2.4.1 Aortic aneurysm involving iliac arteries: anatomic suitability

Thoraco Abdominal Aneurysms involving iliac arteries remain a challenge for EVAR. Dilatation of the common iliac artery (CIA) often leaves no distal landing zone for commercially available stent grafts, which have a maximum diameter of 28 mm. Furthermore, aneurysms extended to the internal iliac artery (IIA) make endovascular repair even more difficult (40-42).

A common method allowing endovascular treatment of these aneurysms is occlusion of the IIA, thereby creating a distal landing zone in the external iliac artery (EIA). However, sacrificing the pelvic blood flow while occluding the internal iliac artery often results in buttock claudication and impotence, as well as other complications such as colonic infarction, gut or spinal cord ischemia. The frequency of these complications varies between 13% and 55% and they can impair quality of life substantially (40-42).

Successful treatment of aortoiliac aneurysms involves branch vessel preservation and long-term protection from rupture. While EVAR has totally eclipsed open surgery because of its lower mortality and morbidities, the durability of EVAR can be questioned because of the need for re-intervention and incidence of late aneurysm-related complications (43). Notably, long-term failure can arise because of the loss of proper seal at the proximal or distal landing zone of the stent-graft (type I endoleaks). Importantly, common iliac diameter can be considered as a predictor of late sac enlargement, as well as implantation outside Manufacturer's Instructions For Use (IFU) (44). Furthermore, Benharash *et al.* managed to demonstrate that iliac fixation is of high importance for the prevention of device migration, regardless of proximal attachment type (45).

Iliac artery involvement incidence in abdominal aortic aneurysms (AAAs) is estimated at 20 to 30 %. Hence, nearly a third of all patients presenting with AAAs for repair might not fit within the IFU for standard EVAR device based on iliac diameters (40-43). A common approach to ensure appropriate landing zone for iliac components of endografts involves extension into the external iliac artery, with or without concomitant hypogastric artery embolization and coverage (43). While unilateral coiling has been demonstrated to have relatively low rates of complication, occlusion of the hypogastric artery due to stent graft placement can lead to major complications, as mentioned above. Given the significant morbidity associated with these complications, industry has developed branch technology for hypogastric preservation.

These include surgical correction of the iliac bifurcation as well as surgeon-modified iliac stent graft components, aortouni-iliac endografting with contralateral external iliac to hypogastric artery stent graft, double barrel/snorkel/sandwich parallel endografts and trifurcated endografts. While innovative, these techniques are, by definition, outside the IFU for current endograft technology and the long-term implications of utilizing components in such a manner is not known. Furthermore, they require unique endovascular equipment and techniques that are not available to most practices (20, 23, 24, 43). Moreover, as only 18 – 24% of patients suffering from aorto-iliac aneurysm can be treated inside current devices IFUs, *the need for a more standardized and "off the shelf" device is obvious.*

2.4.2 Current spectrum of branched/fenestrated endografts

The need for fenestrations/branches in the design of aortic stent grafts, due to the presence of several major branches that cannot be occluded by the graft has made possible the apparition of several devices on the market. The preservation of blood flow to visceral branches as well as the hypogastric region is of high importance in order to prevent comorbidities such as visceral, spinal cord and pelvic ischemia, claudication and/or loss of sexual function. Until recently, it was not possible to wall off large portion of the aorta to treat aneurysms located close to the kidneys where multiple major arteries branch out. The Fenestrated endograft gets around this problem. For example, the **Zenith Fenestrated Aortic Endograft** was developed with two fenestrations for renal arteries and a scallop for the Superior Mesenteric Artery (SMA). Fenestrated Stent graft can be patient-customized by using Computed Tomography to map branches position. Fenestrations can then be created on the graft, which can correctly align with the anatomy of the patient (6, 43, 46).

Iliac involvement in abdominal aorta aneurysms have to be treated by branched stent-grafts. Those can extend to the iliac bifurcation by providing branched prostheses extending to the internal iliac or hypogastric arteries. However, exclusion of branches in the pelvic area due to the prostheses can still be of major concern (40-42). Branched stent grafts, such as the **Zenith T-Branch** EC marked in 2012 possess such geometry.

Sac sealing devices, such as the **Nellix sac-sealing endografts device** (46-47) were also developed in order to conform to the aortoiliac anatomy. Their polymer filled bags fill up the aneurysm, stabilize the lumen and prevents endoleaks. However, no branches can remain patent with such a system.

2.5 Multilayer Flow Modulator

The **Multilayer Flow Modulator** (MFM®) provides a less complex interventional approach for aortic aneurysm treatment. This device is an uncovered, self-expanding wire mesh with high radial force and flexibility. It is designed to modulate blood-flow dynamics by relieving local peak wall shear stress (PWSS), achieving stabilization of aneurysm-sac or false lumen pressure and preserving side-branch patency.

The clinical benefits of this technology have been assessed and shown in case reports and clinical studies of thoracoabdominal aneurysm, type B dissection, pararenal aortic aneurysm and peripheral artery aneurysm (celiac, hepatic, renal, iliac, subclavian) (48-79). Also the prospective multicenter registry of peripheral and visceral aneurysms (69) and the prospective multicenter STRATO Trial of TAAA (78), show good results at 12-month follow-up.

The MFM® eliminates flow vortex pressure and laminates the outside the device along the aneurysm wall in the same direction of the blood stream. Laminated flow possess unique and protective effects on endothelial cells as well as the ability to promote thrombus progressive formation within the aneurysmal sac. The MFM® addresses not only those issues in a very unique fashion, providing a uniform interface between the artery wall and the blood flow, but

its favorable compliance means the device will not be subjected to the same drag forces a conventional stent graft will undergo (74,64,65).

Laminating the blood flow within the aneurysm, promoting thrombus formation within the aneurysmal sac and re-establishing a favorable biochemical and biomechanical balance of endothelial homeostasis, the MFM® addresses aneurysm related issues and outcomes in a novel manner. With aneurysmal stabilization and thrombosis, the MFM® excludes the aneurysm from the circulation rather physically and physiologically than mechanically, as other conventional grafts do. Thanks to the intrinsic porosity of the device, branches are kept patent and well perfused, thus abolishing the risk for collaterals occlusion and consequent ischemia (48-79).

3 Description of the BMFM® kit

The studied device is the Bifurcated MFM® kit (BMFM® kit), it is a three parts modular system consisting of a Body (BMFM® Body) and two Leg Extensions (BMFM® Leg Extensions).

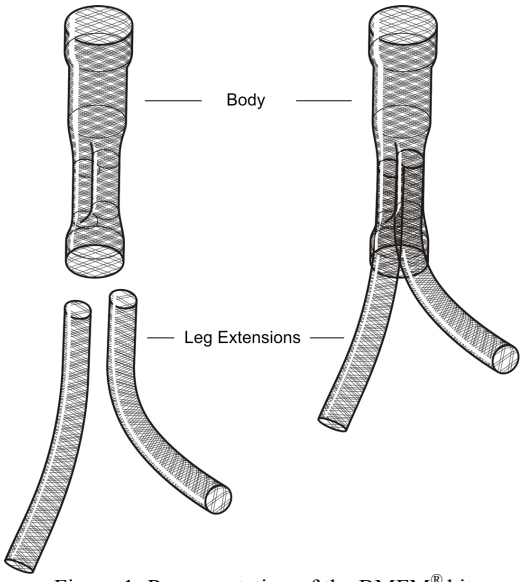


Figure 1: Representation of the BMFM® kit

The BMFM® Body is derived from the aortic MFM® (CTMS) that is CE marked and the Leg Extensions are equivalent to the peripheral MFM® (CPMS) that is also CE marked.
Finished products comprise the MFM® implant and its delivery system. The BMFM® Body and Leg Extension delivery systems are identical to respectively the aortic MFM® delivery system and the peripheral MFM® delivery system, both being currently CE marked.
The BMFM® kit with its delivery system is indicated in the endovascular treatment of the aortic aneurysms involving iliac arteries.

3.1 Properties of the BMFM® kit

Properties required of the flow modulator	Characteristics of the BMFM®kit
Material	Grade 2 Phynox is an alloy containing 42 % cobalt renowned for its biocompatibility and its high resistance to fatigue and corrosion. Compliant with ISO 5832-7 and ASTM F1058 standards.
Radio-opaciy	The density of 40Co-20Cr-16Fe-15Ni-7Mo (Phynox) is of approximately 8.30 g/cm³ (0.30 lb/in³) that is an intermediate radio-opacity. The wires used for this application have sufficient calibre to have a good clinical visibility during release and a good identification of the device. The 3D multilayer structure reinforces the absorption of X-rays as compared to a 2D structure, by amplifying radio-opacity.
MRI compatibility	Non-clinical trials have shown that the flow modulator made of Phynox is MRI conditional, as defined by the standard ASTM F2503. The patient can be safely scanned with MRI after the implantation of a flow modulator with a static magnetic field of 1.5 Tesla or 3.0 Tesla (maximum WB-SAR: 1W/kg for 15mn above the umbilicus and 2W/kg for 15mn above the umbilicus).
Radial Force	Oversizing of the flow modulator is recommended to ensure self-fixing of the BMFM® kit against the vascular wall. It is designed so as to resist the compressions exercised by the aorta while at the same time avoiding dilatation of the arterial wall. Study according to the recommendations of the standard ISO 25539-2,
Deployment	The delivery system is a pull-back type. The sheath liner is Teflon coated to help the flow modulator and guide wire sliding. It is also braided to resist the constrained flow modulator. It is designed to ensure safe and consistent access to the lesion, deployment of the BMFM® kit and withdrawal of the delivery system device.
Corrosion	According to ASTM F2129 standards, cyclic polarisation studies were carried out on the BMFM® kit and showed high corrosion resistance...
Fatigue durability and Erosion	The 3D multilayer structure is more resistant than a 2D structure.
Sterilisation	The flow modulator is sterilised with ethylene oxide. The sterilisation cycles for the flow modulator and the delivery system are validated and sub-contracted to Sterigenics (www.sterigenics.be/).

Permeability and Porosity of the flow modulator	The average rate of permeability for the MFM® is 95 % while its porosity is 65 %. The tests follow the recommendations of standard ISO 7189:1998. §8.2. The concept of the BMFM® kit is based on the following principles: • Reduction of the vortex velocity in saccular aneurysm up to 90%; ➢ Physiological thrombosis with a gradual reduction in the aneurysm • Reduction of the vortex velocity and flow lamination along the wall in fusiform aneurysms; ➢ Physiological wall thrombosis • Channelling flow to the branch in branching aneurysms, with wall shrinking (back to the normal wall); ➢ Retraction of the aneurismal sac and preservation of the branch • Flow lamination in the branches ensuring branch patency; ➢ Branch preservation • Shear stress flow acceleration (good shear range) in the parent vessel which induces endothelialization Preservation of intimal hyperplasia

3.2 Dimensional characteristic of the BMFM® kit and its delivery system

The BMFM® kits are available in the following length and diameter for clinical evaluation (see table below).

Table 1: References and dimensions

Commercial Reference	BMFM® body			Delivery system		
	Diameter (mm)	Length (mm)	Bifurcated length	Size (F)	Length (cm)	Guidewire (“)
Bifurcated MFM® body						
CAMS 30150/32	30	150	32	20	100	0,035
CAMS 30180/32	30	180	32	20	100	0,035
CAMS 30200/32	30	200	32	20	100	0,035
CAMS 30150/24	30	150	24	20	100	0,035
CAMS 30180/24	30	180	24	20	100	0,035
CAMS 30200/24	30	200	24	20	100	0,035
CAMS 35150/32	35	150	32	20	100	0,035
CAMS 35180/32	35	180	32	20	100	0,035
CAMS 35200/32	35	200	32	20	100	0,035

The BMFM® kit is a module consisting of three components, the Bifurcated MFM® body described above and two iliac leg extensions (cfr table below).

Table 2: References and dimensions

Commercial Reference	BMFM® leg extenstion		Delivery System		
	Diameter (mm)	Length (mm)	Diameter (Fr)	Usable Length (cm)	Guide (”)
BMFM® Leg extension					
CAMS16120	16	94	12	80	0,035
CAMS16150	16	116	12	80	0,035
CAMS16180	16	140	12	80	0,035
CAMS16200	16	157	12	80	0,035

4 Objective of the Study

To determine the safety and efficacy of the BMFM® kit in the use for the endovascular treatment of aortic aneurysms involving iliac arteries. The BMFM® kit is an adaptation of the aortic MFM® to the aortoiliac bifurcation morphology. It should be noted that the aortic MFM® has CE mark approval for the aortic aneurysm treatment.

5 Study Design

5.1 Overview of Study Design

STREAMLINER study is an international, multicentre, prospective, non-randomized study. It is designed to evaluate the safety and efficacy of BMFM® kit use. Approximately 40 patients, from up to 12 centres in Europe, Israel, Morocco, Bahrain and Turkey, will be enrolled and screened per the protocol-required inclusion, exclusion criteria, in order to obtain 30 completed patients. The results will be compared with published results for other treatment modalities in the literature. Patients will be included only after obtaining fully informed consent, after conducting all pre-operative examinations required, with respect for all inclusion and exclusion criteria. For early demonstration of efficacy and safety an interim analysis will be performed after the 10 first enrolled patients will complete their 6 months follow-up.

5.2 Enrollment and Study Duration

40 patients will be enrolled in this study with a view to determinate the safety and efficacy of the Bifurcated Multilayer Flow Modulator use in the endovascular treatment of aortic aneurysms involving iliac arteries.

Study initiation: Avril 2014
Enrollment period: 38 months
Duration of follow-up is 5 years

5.3 Clinical Sites / Investigators

Up to 12 centres in Europe, Israel, Morocco and Turkey will participate in this study.

5.4 Study Endpoint

5.4.1 Primary Endpoint

- Prevent aortic aneurysm rupture, in stabilizing it.
- Mortality 30 days, 6 months and 1 year aneurysm-related;

5.4.2 Secondary Endpoints

- Branch and collaterals permeability maintained;
- Mortality 30 days, 6 months and 1year not aneurysm-related;
- Major Adverse Events;
- Technical success (successful delivery and deployment of the BMFM® kit);
- Procedural/in-hospital evaluations (Anesthesia time; fluoroscopy time; contrast volume; estimated blood loss; procedure time; time to hospital discharge);

5.5 Study Population

The target population for this study is patients with aortic aneurysms involving iliac arteries and morphology suitable for endovascular procedure.

5.6 Patient eligibility

Subjects will be eligible to participate in the study if they fit all inclusion criteria and don't have any exclusion criteria mentioned below. All this patients for this study will be recruited from investigator clinical practices.
Eligibility for each patient enrolled will be documented appropriately in the medical records (source documents) and entered in the e-CRFs.

5.7 Inclusion Criteria

Patients must meet **ALL** of the following criteria:

- Age over 18
- Life expectancy > 12 months
- Aortic aneurysms involving iliac arteries
- Healthy proximal and distal landing zone
- Adequate arterial access
- Healthy branches and collaterals (no stenosis or previously treated by angioplasty)
- Informed consent understood, signed and patient agrees to all follow-up visits

5.8 Exclusion criteria

Patients will be excluded if **ANY** of the following conditions apply:

- Aneurysm rupture, impending or contained rupture
- Aortic dissection
- Aortic root aneurysm
- Pleural effusion
- Prior all surgical procedure within 30 days unless procedure is in preparation for device implantation or planned within 30 days post stent deployment
- Myocardial infarction or cerebral vascular accident within 6 weeks of treatment
- Presence/suspicion of connective tissue disorders, for example, Marfan or Ehlers-Danlos etc.
- Contraindications to the anticoagulant or/ and antiplatelet medications

- Allergic reaction to a contrast agent
- Patient with undergoing or planned chemotherapy
- History of bleeding disorder (coagulopathy) or thrombophilia
- Shaggy aorta
- Takayasu's arteritis
- Presence/suspicion of infection (for example: mycotic aorta)
- The use of the MFM® with stent-grafts or previously implanted stent-grafts
- Pregnant or breastfeeding woman
- Patients included in another clinical study

It should be noted that the contrast agent must be used with precautions when patient with renal insufficiency and/or creatinaemia > 200 micromol/l before injection of contrast agent.

5.9 Subject Assessments

The data will be recorded during the initial hospitalization phase and during the whole five years following the enrolment. Follow-up examinations will be required prior to hospital discharge, at 1, 6 months and 1, 2, 3, 4 and 5 years. The patients will be assessed according to the schedule of assessments given in table below.

Table 3: Schedule of Assessments.

Assessment	Baseline	Procedure	Discharge	1-Month (+/- 2 weeks)	6- Months (+/- 2 weeks)	12-Months (+/- 1 month)	24-Months (+/- 2 months)	36-Months (+/- 2 months)	48-Months (+/- 2 months)	60-Months (+/- 2 months)
Informed consent	**R**									
Allocation of patient number	**R**									
Medical History	**R**									
Clinical examination	**R**		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Imaging:										
Angiogram		**R**		**O**	**O**	**O**	**O**	**O**	**O**	**O**
CT-Scan with contrast	**R**		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Evaluation of the arterial lesion:										
Symptoms	**R**		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Evaluation of BMFM® kit permeability	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Evaluation of Branch patency	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Laboratory tests										
Full metabolic status	**R**		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
CRP	**R**		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
Coagulation test (PT, a PTT, TT, platelet count, fibrinogen, activated coagulation time)	**R**		**R**	**R**	**R**	**O**	**O**	**O**	**O**	**O**
Adverse events		**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**

R-Required, O-Optional, PT-prothrombin time, aPTT-activated partial thromboplastin time, TT-thrombin time.

5.10 Risk– Benefit Assessment

5.10.1 Benefits of BMFM® kit Placement

There are a number of benefits to having a BMFM® kit procedure. Some of these are listed below:

- The procedure is minimally invasive;
- The procedure can be performed under local anaesthesia;
- The patient may lose less blood during the procedure. This reduces the risk of blood transfusion;
- The patient may spend less time in the intensive care unit after the procedure, and have a short hospital stay;
- Stabilization and subsequent aortic aneurysm exclusion;
- Preservation of branches patency.

5.10.2 Risks of BMFM® kit Placement

The potential risks of using the system are not different from those likely to occur when using other available endovascular devices. Stenting in general may cause the following complications (list not exhaustive):

- Bleeding during or after the procedure;
- Problems with blood coagulation;
- Bruising or a blood clot including DVT;
- Haematoma;
- Development of a false aneurysm on or around the implantation or an artery, or new stenosis of an artery;
- Cardiac complications such as chest pain, irregular heartbeat, inadequate pumping by the heart muscle or heart attack;
- Pulmonary complications, such a pneumonia, pulmonary embolus, respiratory difficulties;
- Intestinal complications, such as paralysis, lack of bowel movements, reduced blood irrigation of the intestines;
- Complications caused by the wound, such as swelling of the leg or infection;
- Problems in gut, such as loss of blood supply which may be fatal;
- Complications to the arteries or veins with a small risk of amputation of the leg;
- Leakage of blood from an artery to a vein, or between the aorta and intestines;
- Obstruction of the blood flow into an artery or vein owing to a blood clot;
- Bleeding or a collection of blood from the artery used to implant the device;
- Complications affecting the nervous system, such as injury to a nerve;
- Stroke (either temporary or permanent);
- Lesion of certain spinal nerves or insufficient blood irrigation in the spine;
- Loss of ability to move and/or feel certain parts of the body (including paralysis of the legs);
- Impaired sexual function, either impotence or retrograde ejaculation for men;
- Infection;
- Fever;
- The need for an emergency operation;

- Death.

Other complications may arise, which were also observed in patients having received an implantation of this kind of device:

- Inability to implant the stent in the intended position, or incorrect placement;
- Rupture of part of the device being studied;
- Rupture of the catheter due to difficulty of passage;
- Movement of the device being studied within the aorta;
- Change in the shape or size of the arteries, which may affect the studied device.
- Medical and/or surgical intervention may be required to resolve the clinical complications associated with the implantation of the device.

5.11 Minimization of Anticipated Risks

All efforts will be made to minimize the aforementioned potential risks using the following approaches.

- Risks associated with the BMFM® kit placements are minimized by design;
- Selection of Investigators who are experienced and skilled in stenting and balloon angioplasty;
- Selection the centres with expertise in endovascular and surgical treatments;
- Clearly defined inclusion and exclusion criteria that ensure only appropriate patients are enrolled;
- Ensuring that treatment and follow-up of patients is consistent with current medical practice;
- To reduce the risk of thrombosis the aspirin administered concomitantly with clopidogrel for all patients at least 1 month after BMFM® kit implantation;
- Frequent monitoring visits to investigational sites.

5.12 Withdrawal

While study withdrawal is discouraged, patients may withdraw from the study at any time. The patient's withdrawal and the reason for the withdrawal (if any) should be documented in the patient's medical records. Withdrawn patients will not undergo any additional follow-up, nor will they be replaced. The justified sample size includes an estimated allowance for attrition.

Subjects may be terminated or withdrawn from the study for the following reasons:

- Subject death;
- Voluntary withdrawal: meaning that subject voluntarily chooses not to further participate in the study;
- *Loss to follow-up: meaning that the subject is more than one month late to a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up;
- *In the physician's opinion, it is not in the best interest of the patient to continue study participation.

**Where possible, patients will be followed for safety to study completion (1 year). Safety follow-up will include a review of adverse events (AEs). A safety follow-up assessment may be performed either via a phone contact or a physician visit.*

Site personnel to determine the reason for the missed appointment(s) should contact any study subject who does not attend a scheduled follow-up visit. The reason for the missed visit should be determined and documented in the patients study records. If the missed visit was due to an adverse event (AE), an AE electronic Case Report Form (e-CRF) must be completed and any reporting requirement met.
Per ISO 14155, all subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

6 Study Procedures

6.1 Written Informed Consent

Patients who meet the clinical eligibility criteria will be asked to sign the Independent Ethics Committee (IEC)-approved study Informed Consent Form (ICF) after being given time to review the ICF and have any questions answered and before any study-specific tests or procedures are performed.
All patients who meet the clinical and CT-scan eligibility criteria will be eligible for enrollment in the trial.

6.2 Day D-1 of the study (Baseline)

Prior to the procedure, the following assessments must be completed. The BMFM® kit electronic Case Report Form (e-CRF) identifies the specific data points to be collected.

- Confirmation of clinical eligibility criteria
- Demographics, including date of birth, gender
- Physical assessment
- Medical history (general medical, cardiac, neurologic, renal, aortic and peripheral history)
- Laboratory tests, same as in routine practice
    - Assessment of blood chemistries including renal function, liver function, and blood counts
    - Coagulation test
- Pregnancy test for women of child bearing potential with analysis per local practice (serum and/or urine) within 7 days prior to enrolment
- Current medications
- Examination of the arterial lesion

6.3 Required Concomitant Medications

Protocol-required concomitant medications must be reported in the e-CRF from the time of the pre-procedure visit through the 5 years follow-up. Information pertaining to the medication uses in particular the dual antiplatelet therapy, including dose changes, medication interruptions, and medication cessation, must be documented.

6.4 Day D0 of the study (procedure)

The BMFM® kit procedure will be performed according to the investigational Brochure.
Procedure-related information will be collected for all subjects undergoing the BMFM® kit placement procedure and recorded in the e-CRF.

6.4.1 Preparation of the patient

The pre-procedure treatments will be administered as usual in any interventional procedure.

6.4.2 Pre- and post-deployment imaging

It should be noted that the contrast agent must be used with precautions when patient with renal insufficiency and/or creatinaemia > 200 micromol/l before injection of contrast agent.

An angiographic assessment of the aortic aneurysm of incoming and outgoing flow shall be undertaken. The exact anatomical site of deployment shall be defined. The average arterial diameter and the length of the lesion shall be determined. The proximal (close to the heart) and distal (far from the heart) margins will be specified. Copies will be made of the angiogram film(s) before and after implantation of the BMFM® kit. A copy of each angiogram will be submitted to Cardiatis. The BMFM® kit size will be chosen with the help of the sizing table, available in the IFU.

6.4.3 Medication

Prescription of antithrombotic medications must be based on standard protocols like those used within routine clinical practices in hospital institutions. **The guidelines for antithrombotic medications come from Cardiatis and are given for information purposes and not with the aim to dictate the medical practice.**

Guidelines of the antithrombotic therapy in aneurysm repair by BMFM® kit:

During the procedure:

Standard intravenous bolus of 2500 U.I. Heparin (50 U.I./kg) (ACT must be greater than 200 seconds throughout the procedure)

After the procedure:

Dual antiplatelet therapy.

It is recommended that Clopidogrel 75 mg daily in addition to ASA 75-160mg daily be given for at least 1 months in all patients and that aspirin 75-160 mg daily be given indefinitely thereafter. Aspirin doses may be adjusted to the closest approximation based on local tablet formulation availability.

6.4.4 End of the procedure

The procedure is considered as over when the guiding sheath has been withdrawn. If a guiding sheath is subsequently reintroduced, this intervention will be considered as a new operation.

6.4.5 Disposal of the experimental design

Once the procedure is completed, the BMFM® kit release system shall be disposed of according to standard elimination procedures for biohazard waste. If the device is associated to an adverse event, a malfunction or a failure, it shall be returned to Cardiatis for evaluation. For the return of biohazard products, it is necessary to contact Cardiatis prior to the return of the product in order to receive manipulation instructions.

6.5 Day D1 of the study (Discharge)

6.5.1 Hospital stay

If there are no manifest complications, the patient may leave the hospital as per standard practices. If the patient's discharge is delayed, it is considered as an extension to hospitalisation and the "adverse effects" section of the case report form must be completed. However, if the policy of the hospital is to keep patients in for longer than two days for any reasons such as delay to get CT-scan, etc. This must be indicated on the Case Report Form; the "extension of hospitalisation" is then not considered as resulting from adverse effect, and the "adverse effects" section need not be completed.

6.5.2 Discharge from hospital

A CT-can will be performed prior to discharge and will be sent to the sponsor.

6.5.3 Follow-up assessments

Follow-up examinations will be required prior to hospital discharge and during the 5 years following the procedure (at 1, 6, 12, 24, 36, 48, 60 months), according to Table 3.
Patients requiring re-intervention should be treated according to the Investigator's discretion and standard of care.

6.5.4 Imagery Follow ups

Subjects will undergo a CT-scan with contrast at discharge, 1, 6 months and 1, 2, 3, 4, 5 years.
NOTE: CT-scan images should be submitted to the Sponsor as soon as performed.

7 DATA COLLECTION AND SUBMISSION

7.1 Source Documents and Electronic Case Report Forms (e-CRFs)

7.1.1 Source documentation may include any of the following:

1. Medical history/physical condition of the study subject before involvement in the study.
2. Dated and signed notes in the subject's medical record on the day of entry into the study that identify: the subject's date of entry into the study, the study Sponsor, the clinical site, the subject number assigned and a statement that informed consent was obtained.
3. Dated and signed notes from each study subject visit with reference to the e-CRFs for further information, if appropriate (for specific results of procedures and exams).
4. Description of device implantation procedure (material used, drugs administered during the procedure, date, time duration, echocardiographic and clinical findings, etc.).
5. Notations on abnormal lab results and their resolution.
6. Adverse event reporting and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).
7. Notes regarding concomitant medications taken during the study (including start and stop dates).
8. Study subject's condition upon completion of or withdrawal from the study.

7.1.2 Electronic Case Report Forms (e-CRFs)

Patient data will be collected in a secure electronic data capture (EDC) system via the Internet. The Principal Investigator or a Co-investigator must ensure the accuracy and completeness of the recorded data and provide his/her electronic signature on the appropriate (e-CRF).
The Investigator's electronic signature for specific e-CRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge and approve the changes.
Visual and/or computer data review will be performed to identify possible data discrepancies. Data cleaning will be performed on critical data used for analysis and results. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

To ensure proper tracking of e-CRFs obtained from the individual clinical sites, a master tracking system designed by Sponsor for e-CRFs will be utilized. Deficiencies identified by the master tracking system and any other specific clinical site needs will be communicated by e-mail, fax or teleconferences among the research coordinators and the Sponsor, as appropriate. Periodic teleconference calls between Sponsor and each clinical site may be performed to resolve any issues concerning the e-CRF and data collection methods. All responsibilities for completing e-CRF reported in Table 4.

Table 4: Responsibilities for completing e-CRF

Type of e-CRFs for all Groups	Expected
Baseline	Within 7 days of assessment
Procedure	Within 14 days of assessment
Discharge	Within 14 days of assessment
Within the 1-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 6-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 12-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 24-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 36-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 48-Months Follow-Up period post-treatment	Within 14 days of assessment
Within the 60-Months Follow-Up period post-treatment	Within 14 days of assessment

7.2 Quality Assurance & Access

The designated e-CRF Company will create and maintain the database per its internal procedures and policies and in accordance with applicable regulations on personal data protection. The company will also be responsible for verification and validation of the database (including applicable security methods). Data queries will be generated for entries that require additional clarification. Sites are responsible for resolving data queries within 14 days of receipt of the queries.

Data entered into the e-CRF database are the sole property of the Sponsor and the frequency for review and use of the data will be at its discretion. Only designated Sponsor personnel are authorized to access the database.

7.3 Data Protection and Retention

All subject data will be anonymized by the institution prior to review by the study monitor and submission of the data via internet-based e-CRFs. Sponsor will treat all data, in accordance with the European Directive 95/46/EC on the protection of personal data.
All study records and reports must remain on file for a minimum of two (2) years after the completion or termination of the investigation. Study records are to be discarded only upon notification by the Sponsor. The study physicians should contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be notified if the study physician plans to leave the institution.

7.4 Monitoring

Monitoring visits to clinical study sites will be made periodically during the study according the monitoring plan to ensure that all aspects of the current, approved protocol or protocol amendment are being followed. Original source documents will be reviewed for verification of 100% of data captured in the EDC system. For the STREAMLINER study, source documents include the ICF; patient medical records, including diagnostic imaging records; laboratory results; reports of SAEs. Data documented in the e-CRF relevant to device

malfunction(s); relationship of AE to study device(s), index procedure, and antiplatelet medication; and anticipated assessment of ADEs, may be considered source data for the study.
The Investigator and site guarantee direct access to original source documents by Cardiatis personnel and their designees. In the event that original medical records cannot be obtained for a patient who is seen by a non-study physician at a non-study institution, photocopies of original source documents must be made available for review.
It is important that the Investigator and relevant study personnel are available during monitoring visits and audits and that sufficient time is devoted to the process.

7.5 Study Closeout

7.5.1 Normal end

Upon completion of the study (when all subjects enrolled have been followed at 60 Months and the e-CRFs and queries have been completed), a closeout visit will be performed. All unused study materials and equipment will be collected and returned to the Sponsor or designee. The Monitor will ensure that the study physician's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved.

7.5.2 Early end

The study can be discontinued for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events;
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary;
- Insufficient recruitment of subjects;
- Unanticipated serious adverse device effect (USADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately);
- Persistent non-compliance with the protocol;
- Persistent non-compliance with Ethics Committee or regulatory requirements.

Per ISO 14155, if the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / investigational center(s) of the termination or suspension and the reason(s) for this. The Ethics Committee shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical investigator / investigation center(s). Regulatory authorities and the personal physician of the subjects may also need to be informed if deemed necessary.

7.6 Data reporting

For early demonstration of efficacy and safety an interim analysis will be performed after the 10 first enrolled patients will complete their 6 months follow-up, to issue an interim report.

The study report at 1 year will be issued as well, when all subjects enrolled have completed the follow-up (at one year) and queries have been completed. This report will include a descriptive analysis of outcome and the results will be compared with published results for other treatment modalities in the literature.

Study physicians may present or publish their site-specific data provided that the abstracts, manuscripts, etc. are submitted to the Sponsor for review and approval prior to submission for publication. The study physicians must also comply with applicable provisions governing the publication policy as outlined in the study Agreement.

8 STATISTICAL ANALYSIS PLAN

8.1 Introduction

The primary statistical analysis will be based on descriptive technics, with the aim of comparative analysis. The results will be compared to the results of published studies on similar patients having received existing endovascular treatment.

8.2 Statistical Analysis of the clinical data

All individual data will be recorded. Conformity with the protocol (e.g. inclusion/exclusion criteria, the times of taking measurements and the exhaustiveness and coherence of the data, etc.) will be verified upon analysis of the data recorded. Standard statistical parameters (number of values entered, mean, median, standard deviation, maximum and minimum) or tables of frequencies will be calculated in the required circumstances. Since the study does not fall within the context of a standard therapeutic approach, inferential statistical analysis is not required.
The primary and secondary endpoints will be analysed, included in a report, and presented comparatively. The incidence of symptoms will be presented according to their severity.
In addition to the descriptive technics, patients who have died or not attended monitoring visits will be the subjects of a notice in the report of the last monitoring, according to their clinical condition at this time. Each cause of the death will further be analysed. The cumulative probabilities of success will be estimated in accordance with the Kaplan-Meier method to take into account the stops due to the different numbers of monitoring visits of the patients. The standard errors in the Kaplan-Meier estimates will be calculated according to the Greenwood formula.

9 Device Accountability

The Investigator shall document in the procedure reports and e-CRFs the serial/lot number of the BMFM® kit as well as all additional devices used during procedures. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices. When the enrolment is complete, the investigator shall return to Cardiatis any unused devices and a copy of the completed device inventory.

10 Site Documentation

Each site will maintain a Regulatory Binder in which the following documents will be maintained:

1. Signed Investigator and Institutional Agreement
2. Signed protocol and Amendments including:
    a. Device Instructions For Use
    b. e-Case Report Forms

3. All Investigator and Co-Investigator CVs
4. If applicable for the participating site:
    a. EC documents, including member list and number
    b. EC approval letter and updates
5. Master copy of EC approved informed consent, advertising and recruitment materials
6. General Correspondence
7. Delegation of Responsibilities/Duties
8. Patient Enrolment Logs
9. Site Visit Log & Reports
10. Study communications including:
    a. Documentation of written and verbal communications with Sponsor
    b. Documentation of written and verbal communications with other Investigators

11 Study conduct, responsibilities & confidentiality

The study will be conducted in accordance with Good Clinical Practice (GCPs) and the Declaration of Helsinki and any additional provisions outlined in the Study Agreement.

The study physicians are responsible for obtaining the appropriate regulatory approvals (ethics committee and/or competent authority) prior to initiation of the study. The Investigator will provide current copies of the study protocol to all sub-Investigators or other staff responsible for study conducts.

11.1 Patient authorization

Patient authorization and written informed consent must be obtained prior to the patient's enrolment into the study and in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.
When the patient is unable to provide consent (e.g. minor, dementia i.e.), consent is provided by a legally acceptable representative (LAR).
If patient/LAR is unable to read – impartial witness is present during ICF process and also sign the ICF.

11.2 Patient Confidentiality

Patient confidentiality must be maintained in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

11.3 Physician Confidentiality

Study physicians will comply with the applicable provisions of the study Agreement with regard to non-disclosure and confidentiality.

11.4 Protocol Changes/Amendments

The study physician may not make protocol changes or amendments without prior written approval by the Sponsor.

12 ADVERSE EVENT REPORTING

12.1 Adverse events Definitions

The Adverse Events are defined as shown in table below.

Table 5: Adverse Event Definitions

Term	Definition [a]
Adverse Event (AE) Ref: ISO 14155	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) Ref: ISO 14155	Adverse event related to the use of an investigational medical device NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) Ref: ISO 14155	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in : 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) Ref: ISO 14155	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect (USADE) Ref: ISO 14155	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

a: Other definitions may apply per local reporting requirements.

12.1.1 Adverse Event Definitions and Classification Clarifications

An underlying disease should not be reported as an AE unless the severity or frequency of the underlying disease increases during the course of the trial.

Death should be recorded as an outcome of a specific AE. Death itself should not be recorded as an AE.

Device malfunctions and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate e-CRF. If an AE results from a device malfunction or other device issue, the AE should be reported on the appropriate e-CRF.

In-patient hospitalization is defined as the patient being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective / planned hospitalization(s) itself should not be reported as an SAE.

Clinical events to be considered and reported as SAEs include, but are not limited to, the following.

- Events that result in death
- Procedure-related vascular complication requiring surgical intervention or prolonged hospitalization

12.2 Recording of adverse event

An adverse event (AE) is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring in a subject that could be associated with the BMFM® kit or procedure.

Adverse event information will be collected throughout the observational study. AEs will be recorded per the study sites preferred method for data collection. Event, date of onset, severity, duration, and relationship to device or comparator treatment will be recorded. A list of potential AEs, which may result from the BMFM® kit or procedure, is included as part of the IFU.
The Sponsor or its designee will determine reportability of applicable adverse events according to its responsibilities for vigilance reporting.

12.3 Collection of information linked to medical events

The investigator will directly report all adverse events observed and all adverse events spontaneously notified by the patients. Furthermore, each patient will be questioned about any adverse effects on the day of leaving hospital at 1, 6 months and 1, 2, 3, 4, 5 years after implantation. Furthermore, any known adverse effect occurring outside of the period for reporting medical events but that the investigator considers as being linked to the device must be notified as adverse event.

13 Ethical Considerations

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP), and all country / state / local regulations, whichever provides greater protection to the patient.

13.2 Ethics Committee

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the EC for written approval. Cardiatis must receive a copy of the written EC approval of the protocol and ICF before recruitment of patients into the study. Cardiatis, the Investigator, or Site must submit and, where necessary, obtain EC approval for all protocol amendments and modifications to the ICF in accordance with local regulations.
Cardiatis, the Investigator, or Site must notify the EC; USADEs, SAEs.
Cardiatis, the Investigator, or Site is responsible for obtaining EC approval and renewal (periodically or per local regulations) throughout the duration of the study.

13.3 Informed Consent Form

Cardiatis will provide a sample ICF to the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population and administered according to national requirements.
The reviewing EC must first approve the ICF(s) before use at a site/centre. The ICF(s) must be in agreement with the current guidelines as outlined by the GCP guidelines, the Declaration of Helsinki, and the International Conference on Harmonization (ICH).
Before participating in the clinical trial, each patient must provide written informed consent after the context of the study has been fully explained to the patient in a language that the patient easily understands. The patient also must be given the opportunity to ask questions and have those questions answered to his/her satisfaction.
Written informed consent must be documented appropriately by means of the patient's dated signature, as well as the patient's legal representative's dated signature if required by local regulations. The informed consent process must be documented in the patient's medical chart.

13.4 Amending the Protocol

This protocol must be followed exactly, and can be substantively altered only by written amendments. Administrative changes that do not affect the patient benefit / risk ratio (e.g., editorial changes for clarity) may be made without any further approvals. Cardiatis, the Investigator, or Site must submit and, where necessary, obtain EC approval for all protocol amendments according to local regulations. Any change that would require alteration of the ICF must receive approval from all persons who approved the original protocol and from the EC prior to implementation.
According to individual country laws and regulations, the protocol amendment will not be implemented before the relevant regulatory authorities have approved it or the relevant

regulatory authorities have been notified. Following appropriate approval and/or notification, the revised protocol will be distributed to all protocol recipients.

13.5 Protocol Adherence

Prior to beginning the study, the Investigator must sign the Clinical Study Agreement and Investigator's Signature Page documenting his/her agreement to conduct the study in accordance with the protocol. The Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a patient in an emergency.

13.6 Protocol Deviations

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place. All the patients treated out of the protocol and Instruction For Use (IFU) indications are considered as deviating to protocol.

14 Study Administration

Cardiatis will make necessary efforts to ensure that this study is conducted in compliance with GCPs, ISO 14155, and all applicable regulatory requirements.

14.1 Pre-study Documentation Requirements

Prior to initiating a study site, the following documents must be on file at Cardiatis.

- Fully executed Clinical Study Agreement
- Signed Protocol Investigator Signature Page
- A copy (or original, if applicable) of the written EC approval of the protocol
- A copy (or original, if applicable) of the written EC approval of the ICF
- A current, signed, and dated copy of the Principal Investigator's and Co-investigator(s)'s (if applicable) curriculum vitae
- A list of Co-investigator(s) and study site personnel, as required by local regulations

14.2 Investigator Responsibilities

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the study protocol, ISO 14155, data protection regulations, the medical device laws, the Declaration of Helsinki and any other applicable Ethics Committee and regulatory requirements. In addition, each Investigator must sign the Investigational Plan Signature Page (provided as *Appendix II*) and Investigator Agreement (example provided as *Appendix III*) prior to patient enrolment.
The role of the investigator shall be responsible for the day-to-day conduct of the clinical investigation and to ensure the integrity of the data as well as protect the rights, safety and wellbeing of the subject's participation in the clinical investigation.
The investigator must:

- Have the resources to conduct the investigation properly;

- Ensure that conducting the investigation will not give rise to a conflict of interest;
- Obtain from the Sponsor the information which the Investigator(s) judges essential about the device and be familiar with this information;
- Be well acquainted with the IP before signing it;
- Support the monitor, auditor, if applicable, in their activities to verify compliance with the IP, to perform source data verification and to correct the e-CRF where inconsistencies or missing values are identified;
- Complete all e-CRFs in a timely manner;
- Discuss with the sponsor management any question of modification of the IP;
- Make sure that the IP is followed by all responsible for the conduct of the study at his / her institution. Any deviation shall be documented and reported to the study sponsor;
- Make the necessary arrangements to ensure the proper conduct and completion of the investigation;
- Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject;
- Ensure that appropriate EC approval is obtained prior to the start of the investigation;
- Provide the results from the EC to the study sponsor;
- Inform the EC about any serious adverse device effects;
- Inform Cardiatis about any adverse events and adverse device effects in a timely manner;
- Endeavour to ensure an adequate recruitment of subjects;
- Ensure that the subject has adequate information to give informed consent;
- Ensure that informed consent is obtained and documented;
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study;
- Provide subjects with will defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the IP shall not require the prior approval of the Sponsor or the EC. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to Cardiatis;
- Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to the Sponsor and, if pertinent to the safety or well-being of the subject, and the private clinician;
- Inform the subject and/or the subject's physician about any premature termination or suspension of the investigation with a rationale for study termination;
- Have primary responsibility for the accuracy, legibility and security of all investigation data, documents and patient records both during and after the investigation;
- Sign each subject's e-CRF;
- Be responsible for the supervision and assignment of duties at his / her clinical center;
- Ensure that all investigational devices are accounted for (number of devices used, discarded and returned to Cardiatis).

In order to ensure the correct execution of the study protocol, each investigator must appoint a study coordinator. Working in collaboration and under the supervision of the investigator, the study coordinator makes sure that all requirements of the study are fulfilled; he is also the on-site contact.

Per ISO 14155, the Investigator will allow auditing of their clinical investigation procedure(s).

14.3 Qualifications of the investigator

Sites will be selected based on Site Selection Form according to Cardiatis procedure. The investigator must be qualified through his education, training and experience for taking on the responsibility for the proper conduct of the clinical investigation pursuant to the standard ISO 14155.
The investigator must have experience in the field of application and trained in the use of the device under investigation. He must reveal any conflict of interest, particularly of a financial nature, which may interfere with the conduct of the clinical investigation or the interpretation of the results, and be informed of the method for obtaining informed consent.
The investigator must be a doctor specialized in interventional radiology, cardiology, thoracic and cardiovascular surgery or vascular surgery, pursuant to his experience and training, and familiar with the stenting technique.

14.4 Study Sites

A list of potential participating study centers is provided in the Annex I of the protocol.

14.5 Patient Reimbursement

There will be not reimbursement for travel and other expenses incurred by patients as a result of participation in the study.

15 Publication policy

A Publications Committee will be formed to review and publish the data from the clinical investigation. This committee will consist of investigators and representatives of Cardiatis. The Publications Committee will write/review all drafts of abstracts and full-length manuscripts, and will choose the appropriate journal (for manuscripts) or meeting (for abstracts) for submission.
The clinical investigation is a multi-center investigation, and an overall publication of results collected from all study sites is intended for initial publication. Each investigator will be free to publish his/her own results of the clinical investigation in accordance with the Investigator Agreement. In addition, individual Investigators will be free to publish multi-center clinical investigation results after: (a) the multicenter initial publication is published; (b) notification by Cardiatis that an initial publication is no longer planned; or (c) 12 months after termination of the clinical investigation at all sites; whichever shall occur first.

The Investigator will submit copies of proposed materials to Cardiatis prior to submission for publication or presentation. Cardiatis will have an appropriate period of time for review as specified in the Investigator's Agreement for each site.
Cardiatis reserves the right to delete any confidential information or other proprietary information from the proposed publication or presentation. In addition, Cardiatis may extend the review period for another 90 days to file patent applications or to take other steps to protect its intellectual property interests.
The Investigator will properly acknowledge Cardiatis in all publications or presentations resulting from the clinical investigation. Cardiatis will have the royalty-free right to reproduce, translate, and use publications and presentations for any and all purposes. Written permission must be obtained from the Investigator or Cardiatis to use the other's name in any form of publicity.

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