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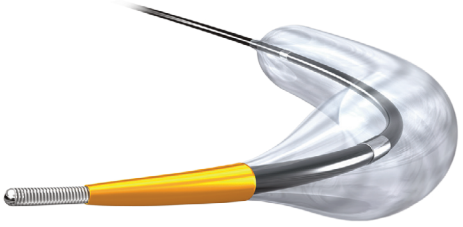
HEXACATH
PIONEER IN BIO ACTIVE COATING

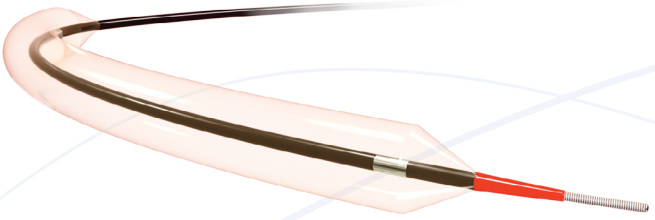
Summary of safety and clinical performance

Mistral Pro SC and Mistral Pro NC

Mistral Pro SC



Mistral Pro NC



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This Summary of Safety and Clinical Performance is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The Summary of Safety and Clinical Performance is not intended to replace the Instructions for use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name

The trade name are MISTRAL PRO SC (Semi-compliant) and MISTRAL PRO NC (Non-compliant).

Throughout the Summary of Safety and Clinical Performance, the mention "MISTRAL PRO" is used to refer to MISTRAL PRO SC and MISTRAL PRO NC.

1.2 Manufacturer's name and address

Name and address of the legal manufacturer are the following:

- Name: HEXACATH (Headquarters)
- Address: 4, passage Saint-Antoine, 92500 Rueil-Malmaison - FRANCE

1.3 Manufacturer's single registration number (SRN)

The EUDAMED single registration number of HEXACATH is FR-MF-000010342.

1.4 Basic UDI

Basic UDI-DI of MISTRAL PRO is: 37003857 MIS0001 BX

1.5 Medical device nomenclature description

- Global Medical Device Nomenclature (GMDN) Code

Code	Code description	Definition
47732	Coronary angioplasty balloon catheter, basic	*A flexible tube designed for percutaneous transluminal coronary angioplasty (PTCA) to dilate a stenotic coronary artery by controlled inflation of a distensible balloon(s) at its distal tip. It is typically available as: 1) an over-the-wire (OTW) type that has a double or triple-lumen, one for the guidewire and one or two for single- or double-balloon inflation; and 2) a rapid exchange (RX) type with a single-lumen. It is available in various sizes for the dilatation of small, narrowed, or obstructed coronary arteries or bypass grafts. It may also be intended for pre- or post-dilatation of a balloon-expandable stent (not included) in the coronary arteries. This is a single-use device.*

- « Classificazione Nazionale des Dispositivi medici » (CND) Code

Code	Category description	Code description
C010401020101	Cardiovascular devices	*"Angioplasty catheters, balloon dilatation, coronary"*

1.6 Class of the device

MISTRAL PRO catheters are class III medical devices according to rule 6 of the Annex VIII from the Regulation (EU) 2017/745 of the European Parliament and the Council. Indeed, MISTRAL PRO catheters are surgical invasive device, for temporary use, intended to correct a fault in the central circulatory system by direct contact.

1.7 Year when the first certificate (CE) was issued covering the device

MISTRAL PRO SC and NC are CE marked according to Regulation (EU) 2017/745 since August 2022 (certificate n° 39118 rev. 0).

1.8 Notified body's name and single identification number

The name and the single identification number of the notified body validating this Summary of Safety and Clinical Performance are the following:

- Name: GMED
- Single identification number: 0459

2 DEVICE DESCRIPTION

2.1 Description of the device

a) General description

The MISTRAL PRO SC and MISTRAL PRO NC catheters are Percutaneous Transluminal Coronary Angioplasty (PTCA) catheters with a rapid exchange design and a balloon at the tip.

The material used gives the balloon a controlled compliance allowing the diameter to be known in accordance with the inflation pressure (MISTRAL PRO SC: semi-compliant balloon, MISTRAL PRO NC: non-compliant balloon). Depending on its length, the balloon has one or two radiopaque markers for correct positioning under fluoroscopy.

The distal part of the catheter, coated with a hydrophilic coating, has a double coaxial lumen. The outer lumen is used to inflate the balloon and the inner lumen allows the introduction of a coronary guidewire to facilitate the catheter's progression towards the desired dilatation site.

The catheter is fitted with a tapered tip to facilitate its progress towards and through the stenosis.

The proximal part of the catheter consists of a stainless steel hypotube with a luer-lock connector at the tip for inflating and deflating the balloon.

Two markers located 90 cm (brachial/radial approach) and 100 cm (femoral approach) from the distal end of the catheter allow it to be positioned at the end of the guide catheter without the need for fluoroscopy.

A compliance card is supplied with the device to provide technical information to the user on the outside diameter of the expanded balloon as a function of the inflation pressure.
A protection tubing is placed over the balloon to maintain a low profile and a mandrel is inserted into the inner lumen to protect the integrity of the device.

The MISTRAL PRO catheters are provided sterile, sterilized with ethylene oxide. These products are for a single use only and packed in individual unit. The shelf life of the product is 3 years.

b) General description of the key functional elements

MISTRAL PRO catheters are composed of:
- An overmolded part with a hub, a strain relief, a hypotube;
- A middle tubing
- An inner tubing overlaid with 1 or 2 sleeve (depending of the product range);
- A balloon;
- A tip.

c) Materials or substances in contact with patient's tissues

The following materials are in contact with patient's tissues:
- Polycarbonate
- Stainless steel
- Polytetrafluoroethylene (PTFE)
- Polyamide
- Polyethylene

d) Principe of operation and mode of action

Percutaneous transluminal coronary angioplasty (PTCA) is a revascularization procedure used to increase the diameter of disease-related stenosed coronary arteries.

A sheath is introduced in the arm (or the groin) femoral or radial artery. Through this sheath a guiding catheter is advanced and the tip positioned into the opening of the coronary artery. The tip of the catheter is directed or controlled when the cardiologist gently advances and rotates the end of the catheter that sits outside the patient.

Once the catheter tip is seated within the opening of the coronary artery, x-ray movie pictures are recorded during the injection of contrast material.
After evaluating the x-ray movie pictures, the cardiologist estimates the size of the coronary artery and selects the type of balloon catheter and guide-wire that will be used during the case.

The guide wire is inserted through the catheter guide and into the coronary artery. The tip of the wire is then guided across the blockage and advanced beyond it. The cardiologist controls the movement and direction of the guide wire by gently manipulating the end that sits outside the patient. This wire now serves as a "guide" or rail over which the balloon catheter can be advanced up to the target lesion.

Then, the balloon is inflated by connecting it to an inflation device called "indeflator". A mixture of saline and contrast material is used to inflate the balloon. The balloon catheter also has radiopaque markers to be located. It enables the cardiologist to position the balloon at the stenosis. The balloon is kept inflated for a few seconds and then deflated.

The deflated balloon and guide-wire are withdrawn when the cardiologist is satisfied with the results. Final angiograms or movie x-ray pictures are taken upon completion of the case. The guiding catheter is then withdrawn.

2.2 Reference to previous generation and variants

a) Reference to previous generation

MISTRAL catheter is the first generation of percutaneous transluminal coronary (PTCA) balloon catheter system developed by HEXACATH.
The MISTRAL SC has been on the market since March 2012.
The MISTRAL NC has been on the market since September 2012.

MISTRAL 2 is an evolution of MISTRAL PTCA dilatation catheter, taking into account the gained market experience and customer's expectations on the first-generation product. MISTRAL 2 SC and NC models were CE marked in October 2016.

The main differences between MISTRAL and MISTRAL 2 are the following:

- Change of raw material for soft-tip, inner tubing and hub:
  - Use of hardest material for the catheter tip to improve lesion and stent crossability,
  - Use of softer material for the inner tubing to improve trackability of the distal part
- Change of the hub design:
  - The MISTRAL hub tends to catch on operating fields whereas the MISTRAL 2 hub design has a rounded shape to prevent this issue.

The MISTRAL 2 SC has been on the market since January 2017.
The MISTRAL 2 NC has been on the market since December 2017.

The MISTRAL PRO is an evolution of the device range MISTRAL 2 (presented as legacy device). The main differences between these devices are the following:

- Addition of a cavity angle clip to maintain the catheter inside the dispenser
- Change of hypotube. There will be no assembling of the hub, hypotube and strain relief using UV curing process as the component provided by the supplier will already be over moulded.
- Change on the strain relief from white PEBAX 5533 to blue PEBAX 6333 in order to reduce the number of components. The supplier is unchanged (CREGANNA).
- Addition of new sizes:

For MISTRAL PRO SC:

- New balloon diameters of 4.5 and 5.0 mm
- New balloon length of 40 mm.

For MISTRAL PRO NC:

- New balloon diameters of 4.5 and 5.0 mm
- New balloon length of 30 mm

b) <u>Various configuration and variants of MISTRAL PRO</u>

The MISTRAL PRO catheters contain two versions: the SC version is equipped with a semi-compliant balloon while the NC version is equipped with a non-compliant balloon. The SC version has a yellow distal tip whereas the NC version has a red distal tip.

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MISTRAL PRO SC: The catheter range starts from diameters (Ø) 1.25 to 5.0 with length from 10 mm to 40 mm.

Ø (mm)	Length (mm)				
	10	15	20	30	40
1.25	*	*			
1.5	*	*	*		
2.0	*	*	*	*	*
2.25	*	*	*	*	*
2.5	*	*	*	*	*
2.75	*	*	*	*	*
3.0	*	*	*	*	*
3.5	*	*	*	*	*
4.0	*	*	*	*	*
4.5	*	*			
5.0	*	*			

MISTRAL PRO NC: The catheter range starts from diameters (Ø) 2.0 to 5.0 with length from 8 mm to 30 mm.

Ø (mm)	Length (mm)				
	8	11	15	20	30
2.0	*	*	*	*	*
2.25	*	*	*	*	*
2.5	*	*	*	*	*
2.75	*	*	*	*	*
3.0	*	*	*	*	*
3.25	*	*	*	*	*
3.5	*	*	*	*	*
3.75	*	*	*	*	*
4.0	*	*	*	*	*
4.5	*	*	*	*	
5.0	*	*	*	*	

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2.3 Recommended equipment

- A puncture kit
- A guide catheter with a minimum diameter of 5F (0.058") and minimum of 6F (0.071") only for balloon with a diameter of 4.0 mm and a length of 40 mm and balloon diameters of 4.5 and 5.0 mm.
- A 0.014" coronary guidewire of appropriate length
- A suitable syringe
- An appropriately sized haemostasis valve
- A 3-way valve
- An inflation device (recommended with a pressure gauge)
- Contrast medium diluted with saline in a 1:1 ratio
- A flushing needle

3 INTENDED USE OF THE DEVICE

3.1 Intended purpose

MISTRAL PRO catheter is intended to be used in adult patients with clinical symptoms of myocardial ischemia related to the pathological condition of coronary arteries in order to re-open the artery to its native diameter at the level of a lesion, following angioplasty.

3.2 Indications and target population

a) Indications

MISTRAL PRO SC and MISTRAL PRO NC catheters should only be used by physicians trained in PTCA procedures. They are designed for use in adult patients with manifestations of myocardial ischemia related to coronary artery disease and who are candidates for myocardial revascularization.
MISTRAL PRO SC and MISTRAL PRO NC catheters are indicated for:

- Balloon dilatation of the stenotic portion of a coronary artery stenosis, for the purpose of improving myocardial perfusion
- Balloon dilatation of a stent after implantation.

The MISTRAL PRO NC catheter should preferably be used for expansion after stenting (post-dilatation), as well as for calcified and/or fibrous lesions.

b) Indented patient population

The MISTRAL PRO is intended to be used, in adult patients, with clinical symptoms of myocardial ischemia related to the pathological condition of one or more coronary arteries and who are regarded as being candidates for myocardial revascularization.

a) Intended user population

MISTRAL PRO catheters should be used only by physicians trained in PTCA procedures. They are characterized by their high competence in cardiology, in the management of stressful conditions related to the clinical act and their responsibility in the health of patients. They can be assisted by vascular surgeons, physicians, radiographer or nurses.
It is intended for use in the hospital/clinic environment (authorized for the practice of coronary angioplasty) and must meet specific hygiene requirements.

3.3 Contraindications

- Patients with chronic total occlusion of the target coronary artery
- Coronary artery spasm in the absence of a significant stenosis
- Severe stenosis of the unprotected left main coronary artery
- Allergy to contrast media

4 RISKS AND WARNINGS

4.1 Residual risks and undesirable effects

In the risk management process carried out by HEXACATH, all residual risks have been analyzed. The benefit / risk ratio of each individual risks is favorable to the benefit. In addition, all the risks in relation with the use of the MISTRAL PRO catheters have been reduced to an acceptable or tolerable level and the overall residual risk is low enough to put on the market the device with a favorable benefit/risk balance.

All residual risks are mentioned in the instruction for used of MISTRAL PRO in the section warnings and precautions.

The complaints reported on the legacy device MISTRAL 2 were only linked to a failure of the device without any clinical impact on the patient so, no adverse effect could be observed, nor quantified.

Observed adverse effects comes from a systematic review of the literature, and more specifically from clinical data on similar devices. As these devices are not implants (angioplasty catheters), only in-hospital outcomes have been taken into account, considering that long-term outcomes are related to the implant and not the effect of the dilatation balloon alone. They are summarized in the table below:

Adverse events	***Quantification (%) – [Occurrence/Total number of subjects involved in the study]***
Haemorrhage / haematoma	1,96%[1,2] - [1/51]
Unstable angina	1,7%[3] (non-compliant balloons) - [1/59] 3.3%[3] (compliant balloons) - [2/60]
Acute myocardial infarction	1,96%[1,2] - [1/51]
	6.7%[4,5] - [4/60]
Pseudoaneurysm	1,67%[4,5] - [1/60]

Other potential adverse effects associated with the angioplasty procedure, that are referenced in the instructions for use were not observed.

All adverse effect identified are considered in the risk analysis. There are the following:

- Infection
- Haemorrhage / haematoma
- Embolism
- Thrombosis
- Coronary spasms
- Coronary vessel injury (dissection, perforation, rupture)
- Arteriovenous fistula
- Restenosis of the dilated artery
- Total occlusion

[1] "Sprinter Legend Balloon Catheter - Study Results - ClinicalTrials.Gov", https://clinicaltrials.gov/ct2/show/results/NCT00961311.

[2] David E. Kandzari et al., « Clinical Outcomes Following Predilation with a Novel 1.25-Mm Diameter Angioplasty Catheter », *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions* 77, nº 4 (1 mars 2011): 510-14, https://doi.org/10.1002/ccd.22734

[3] Erdem Özel et al., « What Is Better for Predilatation in Bioresorbable Vascular Scaffold Implantation: A Non-Compliant or a Compliant Balloon? », *Anatolian Journal of Cardiology* 16, nº 4 (avril 2016): 244-49, https://doi.org/10.5152/AnatolJCardiol.2015.6184

[4] https://www.bostonscientific.com/content/dam/Manuals/us/current-rev-en/90990229-01A_Emerge_dfu_en-US_S.pdf

[5] "Evaluation of Coronary Luminal Diameter Enlargement With Emerge™ 1.20 mm PTCA Dilatation Catheter - Study Results - ClinicalTrials.Gov", https://clinicaltrials.gov/ct2/show/results/NCT01635881

- Low/high blood pressure
- Unstable angina
- Arrhythmias, including ventricular fibrillation
- Acute myocardial infarction
- Transient ischaemic attacks
- Death
- Need for immediate coronary bypass surgery
- Pseudoaneurysm

4.2 Warnings and precautions

a) Warnings

- These devices are sterilized with ethylene oxide and are intended for single use. Do not reuse, reprocess or resterilize. Reprocessing, resterilization and/or re-use of these devices may compromise their performance and integrity. Such actions may result in contamination of the device and/or cause patient infection or cross infection.

- MISTRAL PRO SC and MISTRAL PRO NC catheters should only be used in hospitals or clinics licensed to perform coronary angioplasty and in facilities that treat serious or life-threatening complications. Observe aseptic conditions during all phases of use.

- Inside the vascular system, the catheter must be observed under fluoroscopy throughout the procedure. The catheter should only be pushed or removed when the balloon is fully deflated. If any resistance is felt, the cause should be determined before proceeding. Moving the catheter in an attempt to overcome the resistance may result in vascular injury and damage to the catheter.

- Do not use or attempt to straighten a catheter, the body of which has been bent or twisted. This could cause the catheter body to rupture.

- The inflation pressure of the device must not exceed the balloon's rated burst pressure (RBP) shown on the compliance card. Excessive inflation pressure can cause the balloon to rupture.

- The diameter of the inflated balloon should not exceed the diameter of the vessel proximal and distal to the stenosis, to minimize the risk of vascular damage.

- Do not use air or gas to inflate the balloon.

- PTCA in patients who are not acceptable candidates for coronary artery bypass graft surgery requires careful consideration, including possible hemodynamic support during PTCA as treatment of this patient population carries special risk.

- Use extreme caution and careful judgment in patients for whom anticoagulation is not indicated and in patients with impaired renal function.

b) Precautions

- Use before the expiry date.
- Store above 0°C and below 40°C, away from light and moisture.
- Do not use if the packaging has been damaged or opened.
- Before performing the angioplasty, check that the device is working properly and that it is the right size and shape for the procedure. Do not use the device if there is any damage or if there is any doubt about its integrity.
- Before inserting the catheter, administer the appropriate dose of coronary anticoagulant and vasodilator.
- Check that the air venting in each system is complete and that there are no leaks in the various connections.
- Resistance may be experienced with a MISTRAL PRO catheter when inserting or removing it from the guiding catheter. In this case, choose a larger guiding catheter. For MISTRAL PRO with a diameter of 4.0 mm and a length of 40 mm and for MISTRAL PRO with a diameter of 4.5 and 5.0 mm, use a guiding catheter with a minimum diameter of 6F.

4.3 Other relevant aspect of safety

No filed safety corrective actions have been performed.

5 SUMMARY OF CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

5.1 Summary of clinical evaluation

The clinical evaluation of MISTRAL PRO is based on clinical data from the equivalent device MISTRAL 2 (legacy device).

a) Presentation of the equivalent device MISTRAL 2

MISTRAL 2 and MISTRAL PRO are Percutaneous Transluminal Coronary Angioplasty catheters with a rapid exchange design and a balloon at the tip. They are devices designed and manufactured by HEXACATH.

MISTRAL PRO is an evolution of the device range MISTRAL 2.
The main differences between the MISTRAL 2 and MISTRAL PRO are presented in section 2.2 “Reference to previous generation and variants”.

b) Equivalence between MISTRAL PRO and MISTRAL 2

An equivalence between MISTRAL PRO and MISTRAL 2 has been assessed in order to use the clinical data available on the MISTRAL 2 for the demonstration of clinical safety of the MISTRAL PRO.
A comparison of the clinical, technical and biological characteristics between the two devices has been performed and the equivalence has been established. Thus, the clinical data from the MISTRAL 2 is also applicable to the MISTRAL PRO.

c) Clinical evaluation

Based on clinical data of the equivalent device MISTRAL 2, the main outcomes of the present MISTRAL PRO catheter clinical evaluation are the following:

- In addition to post-market surveillance data on the equivalent device MISTRAL 2, allowable safety clinical data retrieved from clinical study and evaluation surveys on MISTRAL 2 are available. The safety risks in relation with the use of the MISTRAL 2 , and thus with the use of the MISTRAL PRO are however low and appropriately identified and addressed in the risk analysis and in the Instruction for use.

- All considered side effects are appropriately identified, relevant regarding the state of the art and considered as acceptable.

- The analyzed results retrieved from post market surveillance data and practitioner feedbacks of equivalent device MISTRAL 2 demonstrate the adequate performance achievement of the MISTRAL 2 and thus on the MISTRAL PRO catheters to their performance claims.

- Indications of MISTRAL PRO catheters are relevant regarding the state of art and the recent recommendations.

- Claimed clinical benefits for MISTRAL PRO catheters are relevant regarding the state of art.

- The risks associated with MISTRAL PRO, when used as intended, are acceptable when weighed against the benefits to the patients.

This clinical evaluation of MISTRAL PRO, based on the clinical data from MISTRAL 2 was assessed and endorsed by the notified body.

5.2 Summary of clinical data

Clinical data from MISTRAL 2

#1 Between January 2017 to March 2022, the MMISTRAL 2 SC was evaluated in 228 angioplasty procedures, by experienced physicians, in 3 centers and 2 European countries (France and Spain).

#2 Between August 2018 to March 2022, the MISTRAL 2 NC was evaluated in 25 angioplasty procedures, by experienced physicians, in 6 centers and 2 European country (France and Spain).

#3 Performance and safety evaluation of MISTRAL 2 SC/NC PTCA catheters (A clinical trial performed on large size MISTRAL 2 SC/NC device).
Initially, the range extension (large sizes) was planned for the MISTRAL 2 range (the most recent range at the time) and a clinical investigation was therefore set up to clinically validate these large sizes balloon. But, due to the regulatory context, this range extension was not CE marked.
Within the framework of the Regulation (EU) 2017/745, a new variant of MISTRAL 2 has been designed: MISTRAL PRO. It has been decided to maintain the MISTRAL 2 device as it is CE marked according to Directive 93/42 (as legacy device) and therefore to apply the range extension (large sizes) to the most recent version of the MISTRAL FAMILY range so that a complete range could be offered with the modifications applied to the MISTRAL PRO.

	#1 MISTRAL 2 SC	**#2 MISTRAL 2 NC**
Lesion characteristics	- 52,6% of nearly occluded or completely occluded lesions (n = 120 out of 228) - 64,0% of angular lesions above 45° (n =146 out of 228) - 3,9% of calcified and highly calcified lesions (n = 9 out of 228) - 27,2% of classification C lesions (n = 62 out of 228) - 62,7% of eccentric lesions (n = 143 out 228)	- 24,0% of nearly occluded or completely occluded lesions (n = 6 out of 25) - 56,0% of angular lesions above 45° (n = 14 out of 25) - 24,0% of calcified and highly calcified lesions (n = 6 out of 25) - 32,0% of classification C lesions (n = 8 out of 25) - 32,0% of eccentric lesions (n = 8 out of 25)
Performance assessment	- In 100% of cases, all performances (e.g., Pushability, Trackability, Flexibility, Crossability, Catheter guide compatibility, Guidewire compatibility, Marker bands radiopacity, Contrast injection) were rated excellent or good.	- In 100% of cases, Pushability performance was rated excellent. - For other performances, the rating of excellent/good is as following: 92% for Trackability (n = 23 out of 25); 80% for Guidewire compatibility, Marker bands radiopacity and Contrast injection (n= 20 out of 25); 76% for Catheter guide compatibility (n = 19 out of 25); 72% for Flexibility (n = 18 out of 25);

	#1 MISTRAL 2 SC	#2 MISTRAL 2 NC
	- In 100% of cases, the deflation time is lower than 10s i.e., lower to the claimed specification (< 20s). - In 25,9% of cases (n = 59 out of 228), the inflation pressure used was above the RBP (14bars). - In 100% of cases, The MISTRAL 2 SC overall performance was rate as excellent or good. - In 100% of cases, angioplasty procedure was considered successful with the MISTRAL 2 SC i.e., no crossing failure, no access failure (technical success).	60% for Crossability (n = 15 out of 25). - In 96% of cases (n= 24 out of 25), the deflation time is lower than 10s i.e., lower to the claimed specification (< 20s). - In 24,0% of cases (n = 6 out of 25), the inflation pressure used was above the RBP (20bars). - In 88% of cases (n = 22 out of 25) , The MISTRAL 2 NC overall performance was rate as excellent or good. - In 100% of cases, angioplasty procedure was considered successful with the MISTRAL 2 NC i.e., no crossing failure, no access failure (technical success).
Clinical outcome	- In 96,9% of cases, residual stenosis was ≤ 30%. - In 100% of cases, residual stenosis was ≤ 50%.	- In 96,0% of cases, residual stenosis was ≤ 30%. - In 100% of cases, residual stenosis was ≤ 50%.

	#5 Performance and safety evaluation of Extended Range
Study design	Prospective, monocentric, single arm data collection
Place of the study	Heart center of Satakunta central hospital, Pori – Finland
Identity of the device	Mistral 2 SC/NC Percutaneous Transluminal Coronary Angioplasty catheter line extension (non-CE marked Ø 4.5 & 5.00mm / L 30 & 40 mm))
Objectives of the study	Collecting clinical data on the line extension to support CE marking of balloon larger sizes Primary objective was to demonstrate that the larger balloon sizes (line extension) have an acceptable safety profile. Secondary objective was to demonstrate that the larger balloon sizes perform as expected in terms of lesion revascularization and procedural success.
Efficacy and safety endpoint(s)	**The primary efficacy endpoint** of this study was procedural success rate, defined as fulfilling all of the following objectives: (1) successful device delivery; (2) successful inflation and deflation of the balloon; (3) absence of perforation and flow-limiting dissection; (4) final achievement of TIMI 3 flow. **The primary safety endpoint** of this study was the in-hospital rate of major adverse cardiac events (MACE: composite of cardiac death, target vessel myocardial infarction [MI] and clinically driven target lesion revascularization [TLR]).
Number of patients	26
Study population	Mean age: 63.4 ± 12.8 years 19.2% were females 53.8% presented with acute coronary syndrome
Number of devices used	33 balloons 14 semi-compliant balloons (13 for pre-dilatation, and 1 for post-dilatation) 19 non-compliant balloons (6 for pre-dilatation, and 13 for post-dilatation)
Clinical outcome	Procedural success was achieved in all patients: - All balloons were successfully delivered, inflated, and deflated in all patients (lesions); - Final TIMI flow grade 3 was achieved in all cases; no perforation or flow-limiting dissection occurred. Lesion success was achieved with 29 (87.9%) balloons. - Acute lumen gain was adequate in the setting of pre-dilatation, as well as post-dilatation. - The cause of not achieving lesion success with 4 balloons was always residual stenosis ≥50% (50% in 2 and 60% in 2). No major adverse cardiac event occurred in any patient during hospital stay.

	#5 Performance and safety evaluation of Extended Range
	→ These results demonstrate favorable procedural safety and efficacy when using line extension. Taking these results into consideration, the risks associated with the line extension, when used as intended, are acceptable when weighed against the benefits to the patients.

5.3 Overall summary of the clinical performance and safety

a) Safety of the MISTRAL PRO

Claimed clinical safety of MISTRAL PRO is defined as a safe angioplasty procedure which is conditional upon no complications nor immediate cardiac events linked to the device.

Safety of MISTRAL PRO was assessed through risk analysis, as well as safety results retrieved from the study and evaluation surveys performed on equivalent device MISTRAL 2. None of the surveys mentioned any complications to perform the angioplasty nor any adverse effects linked to the device. Also, even if in several angioplasty procedures physicians did not respect the specifications for pressures to be used with the device, results showed that the devices remain safe to use. Indeed, a higher pressure than the RBP vas used. but without causing the balloon to burst.
The safety events and residual risks have been identified and taken into consideration in the risk analysis.
Finally, the safety information regarding adverse effect, precaution and warnings provided in the instruction for use are consistent with the safety information reported in the risk management report and congruent with the literature data.
Moreover, given the similarities between the MISTRAL PRO and similar devices on the market in terms of safety, as well as the long and extensive use of PTCA balloon catheter since more than thirty years as identified in the state of the art of the clinical evaluation report, allowed to stated that safety data are quantitatively and qualitatively sufficient to demonstrate the safety of MISTRAL PRO.

b) Performance of the MISTRAL PRO

Clinical performance claimed of MISTRAL PRO is ability to access the lesion, to open the stenotic artery or, for NC version only, to optimize stent deployment during "post-dilation".

Performances of MISTRAL PRO was assessed through performance data retrieved on the literature review of the state of art, and the performances of equivalent device. The performance surveys conducted in normal conditions of use highlighted satisfactory technical performances and a good customer acceptance supporting the conclusion that the devices fulfill user expectations.
Indeed, procedural success rate (defined as a residual stenosis less than or equating to 50%) equates to 100% for MISTRAL 2 SC and for MISTRAL 2 NC, meaning that in all cases, residual restenosis was ≤50%.
Angioplasty procedure was considered successful in 100% of cases i.e., no crossing failure, no access failure (technical success).
The results show that 100% of the time, all performances were rated excellent or good.
Moreover, regarding available data, performance criteria were assessed very positively for most or all performance criteria with an overall performance rated by practitioners as excellent or good for more than 94% for all devices (100% for MISTRAL 2 SC and 88% for MISTRAL 2 NC).

Finally, the information provided by the post market surveillance data of equivalent device MISTRAL 2 highlights that user complaints received since the devices were marketed do not raised any concern regarding device performances.

The analyzed results demonstrate the adequate performance achievement of MISTRAL PRO to their performance claims.

c) Benefit/risk profile of the MISTRAL PRO

The benefit/risk assessment of MISTRAL PRO is based on data from MISTRAL 2 and state of art:

- Regarding MISTRAL PRO indications

MISTRAL PRO PTCA catheters are designed for use in adult patients with manifestations of myocardial ischaemia related to coronary artery disease and who are candidates for myocardial revascularization.

MISTRAL PRO SC/NC catheters are indicated for:

- Balloon dilatation of the stenotic portion of a coronary artery stenosis, for the purpose of improving myocardial perfusion;
- Balloon dilatation of a stent after implantation.

The MISTRAL PRO NC should preferably be used for expansion after stenting (post-dilatation), as well as for calcified and/or fibrous lesions.

The different studies on Plain Old Balloon Angioplasty (POBA) related in the state of the art reported that:

- principal indications for POBA treatments are in-stent restenosis and de novo coronary lesions;
- the reported sizes of balloon used to treat coronary lesions or in-stent restenosis (ISR) ranges generally from 0.6 to 3.0 mm in diameter and 9.8 to 31.2 mm in length.

In conjunction with the state of the art and recommendation mentioned in the 2018 ESC/EACTS Guidelines, balloon angioplasty has become a useful adjunctive technique to coronary stenting to optimize stent deployment or to support complex PCI procedures such as bifurcations treatment. It is considered that balloon angioplasty is also a valuable tool when stenting is not indicated and when urgent flow restoration is required.

Guidelines also highlighted those final decisions regarding each individual patient must be made by the responsible health professional(s). In the case of myocardial ischemia, the choice of revascularization technique and associated devices (balloon angioplasty and/or stenting, SC and/or NC balloons) is made by cardiologists based on a risk-benefit assessment and according to each patient's characteristics.

Taken together with information mentioned in the instructions for use of the MISTRAL PRO, the identified indications are relevant regarding the state of art and the recent recommendations.

- Regarding MISTRAL PRO clinical benefit

The expected clinical benefit of the use of MISTRAL PRO is to help the restoration of arterial circulation permitting to prevent a heart attack (myocardial infarction) or to minimize the consequences of heart attack. As well, balloon angioplasty is a minimally invasive procedure which does not require general anesthesia and major surgery for the patient.

The device related mode of action, the procedure of use reported in the clinical data on the device and the description of PCI principle with POBA in the state of the art, all together allow to support the clinical benefit "minimally invasive procedure which does not require general anesthesia and major surgery".

According to the literature, the measurable outcome parameters used to evaluate the clinical benefit are:

- The measure of cardiac death rate after angioplasty (immediate or short-term results);
- The measure of nonfatal myocardial infarction (MI) rate (Immediate or short-term results).

The clinical benefit of MISTRAL PRO has been considered as reached as the cardiac death and non-fatal myocardial infarction rates after angioplasty (immediate or short-term results) obtained are non-inferior to similar device rates described in the literature. Indeed, in the clinical investigation, no in-hospital major adverse cardiac events occurred in patients. The rate of cardiac death and MI after angioplasty given is thus reported as 0% post-procedure during hospital stay.

- Regarding MISTRAL PRO benefit/risk ratio

The clinical benefit of the device is supported by allowable data from equivalent device that are evaluated, is considered as achieved.

The post-market and post-market clinical follow up data provide significant evidence that the residual risks associated with the use of an equivalent device; MISTRAL 2 are acceptable:

- The clinical results demonstrate an adequate safety profile in terms of procedural complications;

- The evaluation surveys highlighted a good practitioner acceptance and adequate peri-procedural safety results;
- The post market surveillance data sustained low user complaint rate and do not raise any safety concerned;
- All the residual risks are appropriately documented and are taken in consideration in the risk analysis.

In conclusion, it is considered that the risks associated with MISTRAL PRO, when used as intended, are acceptable when weighed against the benefits to the patients.

5.4 Post-market clinical follow-up

The method used to collect data in order to ensure a post market clinical follow up consists to carry out every year:

- Literature screening:

Any scientific publications, abstracts, articles relevant to similar or equivalent devices identified through research on dedicated database (such as PubMed, google scholar), subscription to online newsletter (PCRonline, interventional news, TCT magazine).

- Annual participation to international congress
- Review of vigilance databases for similar or equivalent devices such as MAUDE database, ANSM database.
- Collect and analyze complaints and vigilance data
- Clinical studies (if necessary)
- Evaluation performed by physicians

In addition, in order to confirm the compliance of the MISTRAL PRO with the requirements of the Regulation (EU) 2017/745 in terms of clinical performance, safety of use and benefit/risk ratio established in the device's clinical evaluation reports, HEXACATH has planned to collect clinical and angiographic data prospectively, in a real-life situation, in the context of the indications and on the population defined in the product instructions for use and to analyze them as part of its post-market clinical follow-up.

Primary objective chosen is the assessment of the clinical benefit and its quantification defined by the absence of cardiac events (MACE rate) during hospitalization.
Secondary objectives chosen are the assessment of the clinical performance and its quantification defined by a residual stenosis ≤50% and the observation of balloon-related adverse events.

To evaluate these criteria, a prospective, non-comparative study will be conducted in interventional cardiology departments with a high use of MISTRAL PRO dilatation catheters.

6 POSSIBLE THERAPEUTIC ALTERNATIVES

Treatments for coronary artery disease usually involves lifestyle changes and if necessary, drugs and certain medical procedures:

- Pharmacological treatment: it may include cholesterol-modifying medications, anti-thrombotic, anti-ischemic, and prophylactic or symptomatic lipid lowering drugs.

- Percutaneous Coronary Intervention (PCI): Mistral is a balloon angioplasty catheter. Usually, the PCI often combine balloon angioplasty and stent placement, a small wire mesh tube, more or less impregnated of antiproliferative drugs, that helps prop the artery open, decreasing its change of narrowing again. In this current context, advanced technologies applied to stent have been developed and includes in particular the titanium-nitride-oxide-coated bioactive stents.
  According to the 2018 ESC/EACTS Guidelines[6] the use of balloon angioplasty might be considered for the treatment of selected patients, for PCI of bifurcation lesions and for lesion preparation: Plain balloon angioplasty has been superseded in the treatment of de novo coronary lesions after demonstration of the superiority of stenting in terms of the requirement for repeat revascularization. Balloon angioplasty might be considered for the treatment of selected patients in whom implantation of stents is not technically feasible, or in a vessel that is considered to be too small to be stented. Balloon angioplasty is no longer preferred to stenting with DES for patients who require urgent non-cardiac surgery as short-duration DAPT may be reasonable with both strategies.

[6] Neumann et al., "2018 ESC/EACTS Guidelines on myocardial revascularization"

Stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch, is recommended for PCI of bifurcation lesions
Lesion preparation is critical for successful PCI. In addition to plain balloon angioplasty (with standard or non-compliant balloons), cutting or scoring balloon angioplasty or rotational atherectomy may be required in selected lesions—particularly those with heavy calcification in order to adequately dilate lesions prior to stent implantation. However, some studies investigating the systematic use of these adjunctive technologies, such as rotational atherectomy or pre-dilatation with balloon angioplasty, have failed to show clear clinical benefit."

This extensive review on percutaneous coronary interventions highlighted that, although balloon angioplasty alone is not recommended any more for the treatment of de novo coronary lesions, it has become a useful adjunctive technique to coronary stenting to optimize stent deployment or to support complex PCI procedures such as bifurcations treatment. Balloon angioplasty is also a valuable tool when stenting is not indicated and when urgent flow restoration is required.

- Coronary Artery Bypass Graft (CABG): CABG consists to use blood vessels from another part of the body and connects them to blood vessels above and below the narrowed artery, bypassing the narrowed or blocked coronary artery. One or more blood vessels may be used, depending on the severity and number of blockages. The blood vessels are usually arteries from the arm or chest, or veins from the legs.
  As the PCI often combine balloon angioplasty and in view of the explanation above, it is the PCI that could be compared to CABG: Indeed, as mentioned in the 2018 ESC/EACTS guidelines from expert consensus on myocardial revascularization, whether medical therapy, PCI, or CABG have to be preferred to treat CADs, should be depend on the risk–benefit ratios of these treatment strategies, weighting the risks of periprocedural death, myocardial infarction and stroke against improvements in health-related quality of life, as well as long-term freedom from death, myocardial infarction or repeat revascularization.

The decision of the appropriate treatment for patient depends therefore on the medical opinion of the physician.

7 REFRENCE TO HARMONIZED STANDARDS AND COMMON SPECIFICATIONS

HEXACATH applies the following harmonized standards and common specifications published in the Official Journal of the European Union, according to Decision (EU) 2021/1182 of 16 July 2021 and Decision (EU) 2022/6 of 4 January 2022:

- EN ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes

- EN 15223-1:2021 Medical Devices – Symbols to be used with medical devices labels, labeling and information to be supplied — Part 1: General requirements

- EN ISO 11135:2014 - Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices

- EN ISO 11737-1:2018 Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products

- EN ISO 11737-2 2020 Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

- EN ISO 14971:2019 Medical devices – Application of risk management to medical devices

Other standards applied by HEXACATH have not yet been harmonized with the Regulation (EU) 2017/745.