MicroPort CardioFlow

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Summary of Safety and Clinical Performance

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Summary of Safety and Clinical Performance （SSCP） for Healthcare Professionals

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1 Scope

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

The SSCP 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 healthcare professionals.

2 Device identification and general information

2.1 General information

Device trade name:	VitaFlow Liberty™ Transcatheter Aortic Valve System
Manufacturer's name:	Shanghai MicroPort CardioFlow Medtech Co., Ltd
Manufacturer's address:	1601 Zhangdong Road, Shanghai Free Trade Pilot Area,201203 Shanghai, China
Manufacturer's single registration name (SRN):	CN-MF-000002327
Basic UDI-DI:	697149353Z0213CEEU
EMDN code:	VitaFlow Liberty™ Aortic Valve P070301030101 STENTED BIOLOGICAL AORTIC VALVES FOR PERCUTANEOUS IMPLANT - VALVE TISSUE OF ANIMAL ORIGIN VitaFlow Liberty™ Delivery System P07038002 CARDIAC VALVE TRANSCATHETER IMPLANT ACCESSORIES
Class of device:	III

2.2 Authorized representative

EU representative:	MicroPort Medical B.V.
SRN:	NL-AR-000000166
Address:	Paasheuvelweg 25, 1105BP Amsterdam, The Netherlands
Contact person:	Ms. Chang
Contact information:	cs@microport-int.com +31205450100ext8

2.3 NB

Notified body:	DEKRA Certification B.V
Address:	Meander 1051, 6825 MJ Arnham, The Netherlands
Code:	0344

3 Intended use of the device

3.1 Intended purpose

VitaFlow Liberty™ Transcatheter Aortic Valve System is intended to be used by professional physicians to replace the native aortic valve of patients with severe symptomatic, calcific aortic stenosis. VitaFlow Liberty™ Aortic Valve is used in combination with VitaFlow Liberty™ Delivery System under the supervision of medical imaging equipment, and to be fixed at the aortic annulus to replace the degenerated valve and improve the function.

3.2 Indications and target populations

VitaFlow Liberty™ is indicated for transcatheter delivery in patients with severe, symptomatic, calcific aortic stenosis whoare considered at high risk for surgical aortic valve replacement (AVR) where high risk is defined as Society of Thoracic Surgeons operative risk score≥8% or documented heart team agreement of risk for AVR due to frailty or comorbidities.

3.3 Contraindications

VitaFlow Liberty™ is contraindicated for patients presenting with any of the following conditions:

1) A known hypersensitivity or contraindication to all anticoagulation/antiplatelet regimens (or inability to be anticoagulated for the index procedure), to nickel or titanium, to nitinol, to dairy products, to polyethylene terephthalate (PET) or contrast media;
2) Ongoing sepsis, including active endocarditis;
3) Pre-existing mechanical heart valve in aortic position.

4 Device description

4.1 Description of the device

4.1.1 VitaFlow Liberty™ Aortic Valve

VitaFlow Liberty™ Aortic Valve is a self-expandable bioprosthesis which is manufactured by suturing three bovine pericardial valve leaflets, inner and outer PET skirts, onto a self-expanding Nitinol frame. The frame consists of two parts: outflow and inflow. Refer to figures 1 for details. The bioprosthesis is available for a range of aortic annulus as shown in Table 1. The information on the materials which can be exposed to the patients are listed in Table 2.

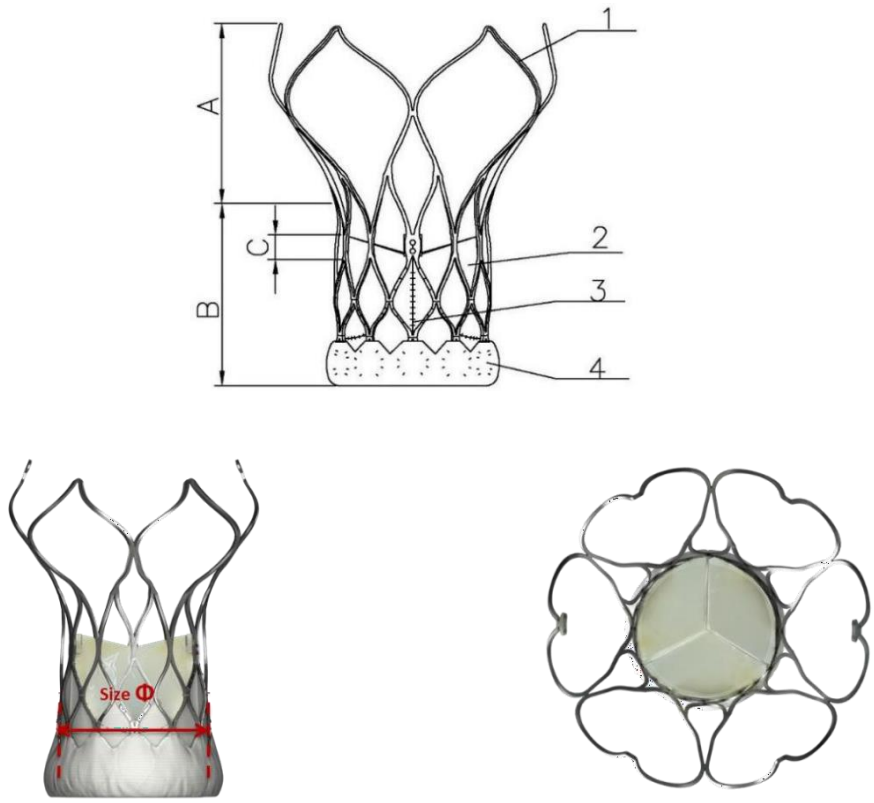


Figure 1- The structure diagram of the VitaFlow LibertyTM Aortic Valve
1 Frame, 2 Bovine Leaflets, 3 Suture, 4 Skirt,
A. Outflow, B. Inflow, C. Commissure

Table 1: VitaFlow Liberty™ Aortic Valve specification and aortic annulus compatibility

Model	Size (mm)	Available Aortic Annulus Diameter Range (mm)
TAV21	21	17-20
TAV24	24	20-23
TAV27	27	23-26
TAV30	30	26-29

Table 2: Material exposed to patients

Component	Material
Frame	Nitinol (NiTi)
Supporting Bar	
Leaflet	Bovine Pericardium
Suture	PTFE
Skirt	PET

Based on results of biocompatibility testing and clinical investigation, no substances causing sensitization or allergic reaction in patients or users are found.

4.1.2 VitaFlow Liberty™ Delivery System

VitaFlow Liberty™ Delivery System, shown as Figure 2 and 3, consists of catheters and one handle. The catheter portion includes inner shaft, outer shaft, stability shaft and integrated sheath. The inner shaft, outer shaft and stability shaft are connected with the handle. The inner shaft and stability shaft are fixed with the handle, the outer shaft can be moved forward and backward to load, deploy and recapture the bioprosthesis by clicking or pressing the button on the handle or rotating the manual knob. The motorized handle is on the proximal end of the catheter and a traditional manual knob at the near end of the handle is available as a backup. The distal end of the system features a capsule which houses the bioprothesis in a crimped condition and the bioprosthesis can be recaptured after partial deployment (up to 75% of maximal deployment). Four models are available. Refer to Table 3 for specification.

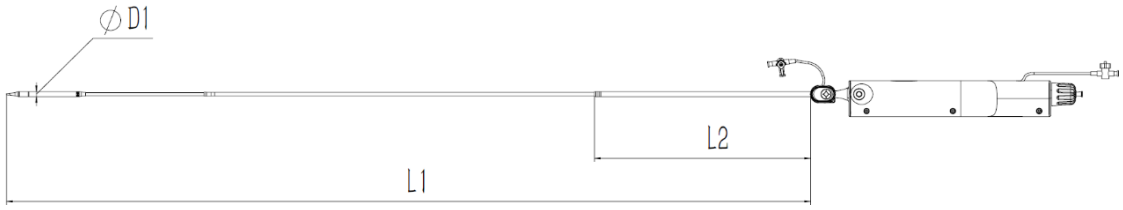


Figure 2 - The structure diagram of the VitaFlow Liberty™ Delivery System

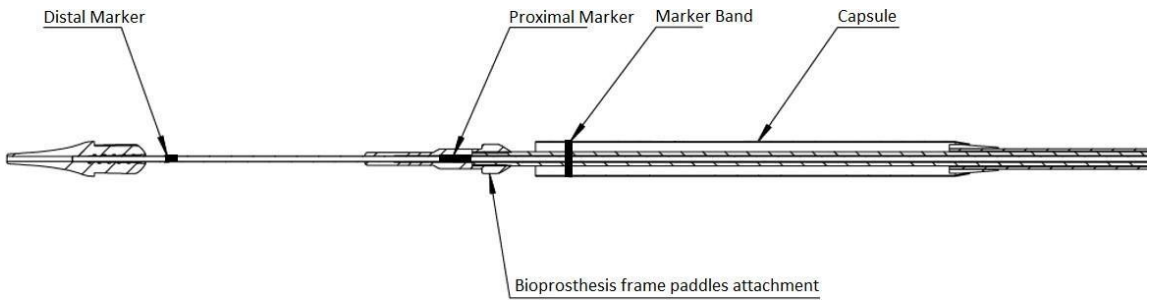


Figure 3 - The structure diagram of the capsule

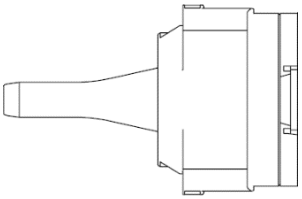
Table 3 - VitaFlow Liberty™ Delivery System specification

Model	Effective length L1 (cm)	Integrated sheath L2 (cm)	Capsule outer diameter D1(mm)
DSR21	112	30	6.8
DSR24			
DSR27			7.1
DSR30			

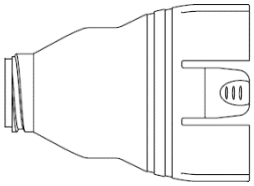
4.1.3 Loading Tool

Loading tool is an accessory of the VitaFlow Liberty™ Delivery System. It is designed to compress the bioprosthesis into the capsule of the VitaFlow Liberty™ Delivery System. Loading tool consist of inflow cone, outflow cone and capsule guide tube (Figure 4). Four models are available: LT-21,

LT-24, LT-27 and LT- 30.



Inflow cone



Outflow cone

Capsule guide tube

Forceps

Figure 4- The structure diagram of Loading Tool

4.2 Method of sterilization

VitaFlow Liberty™ Transcatheter Aortic Valve are delivered sterile, the components are for single use only, DO NOT re-sterilize or reuse.

- **VitaFlow Liberty™ Aortic Valve**

VitaFlow Liberty™ Aortic Valve is sterilized and stored in glutaraldehyde solution.

- **VitaFlow Liberty™ Delivery System**

VitaFlow Liberty™ Delivery System (including Loading Tool and Battery) are sterilized by ethylene oxide.

4.3 Previous generation or variants if such exist, and a description of the difference

Shanghai MicroPort CardioFlow Medtech Co., Ltd has developed two generation TAVI systems, the first generation system named as VitaFlow®Transcatheter Aortic Valve system (hereafter as "VitaFlow®"), it mainly consists of VitaFlow® Aortic Valve and VitaFlow® Delivery System.

VitaFlow Liberty™ Transcatheter Aortic Valve system also mainly contains a bioprosthetic valve and a delivery system. The bioprothetic valve is identical with the one in VitaFlow®, the delivery system has been upgraded into the VitaFlow Liberty™ Delivery System with retrieval function.

Comparing to the two generation, there is no difference between the designs of the bioprosthesis, the delivery system has been changed with additional new features as described

below:

The handle part underwent improvements for user-friendliness mainly in its appearance and touch feeling. Both the electrical use and the manual use features have been kept identical, the function for deployment and retrieval remained unchanged.

For the catheter part, to support the recapture function, the inner/outer shafts were reinforced by changing its materials.

VitaFlow Liberty™ Delivery System now has an integrated sheath allowing the catheter to be inserted percutaneously independent of the introducer sheath.

VitaFlow® has acquired the NMPA certificate and entered into China market in 2019. Besides, VitaFlow® obtained the registration certificate in Argentina and Thailand in 2020.

As for the long-term follow up of VitaFlow® pre-market clinical trial, the patients who enrolled will be annually followed up until 5 years post-procedure to monitor the long-term effectiveness and safety of VitaFlow®. Currently, 5 years follow-up of partial patients has been completed.

4.4 Devices required to work with VitaFlow Liberty™

NOTE: While extensive, this list is not meant to cover all possible scenarios.

- Anesthesia Machine
- Temporary pacing lead
- Temporary pacemaker
- Digital subtraction angiograph (DSA)
- Electrocardiographic Monitor
- Coagulation time tester
- Cardiac defibrillator
- Diasonograph (colour Doppler ultrasound)
- Conventional J-Type angiography guidewire 0.035’’x 1.5 m
- Super-smooth guidewire 0.032’’ x 1.5 m
- Straight-head super-smooth guidewire 0.032’’ x 2.6 m
- Puncture needle 18G
- Pigtail catheter 5F or 6F
- Lunderquist guidewire 0.032’’ x 2.6 m
- Kantley artery sheath 6F
- Guide sheath 14F
- Standard procedure supplies

5 Risks and warnings

5.1 Residual risks and undesirable effects

5.1.1 Description of residual risks and undesirable effects

Potential risks associated with the implantation of the VitaFlow Liberty™ Transcatheter Aortic Valve System (and Transcatheter aortic valve procedure) may include, but are not limited to, the following:

- Death(<14%);
- cardiac complications#(<2%);
  - cardiac arrest
  - heart failure
  - low cardiac output
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)*(<1%);
- emergent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant)*(<1%);
- myocardial ischemia/infarction(<4%);
- angina pectoris（<1%）;
- cardiogenic shock (<3%);
- conduction disturbances and arrhythmias(50-60%);
  - conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
  - cardiac arrhythmias
- vascular complications(<24%);
  - cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
  - ascending aorta trauma
  - vascular access related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome,arteriovenous fistula, stenosis)
- cardiac tamponade* (<1%);
- valve-related complications (<10%);
  - Bioprosthesis dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/misplacement; regurgitation; stenosis thrombosis/embolus (including valve thrombosis)
  - valve migration/valve embolization
  - ancillary device embolization
- mitral valve regurgitation or injury（<1%）;

- emergent balloon valvuloplasty（<1%）;
- emergent percutaneous coronary intervention (PCI)（<1%）;
- pericardial effusion（<1%）;
- major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding) （<47%）;
- anemia（<8%）;
- hemolysis（<1%）;
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia（<1%）;
- infection (including septicemia and endocarditis)（<1%）;
- inflammation（<1%）;
- fever（<1%）;
- multi-organ failure（<1%）;
- Stroke, transient ischemic attack (TIA), or other neurological deficits（<11%）;
- cerebral infarction-asymptomatic（<2%）;
- encephalopathy（<1%）;
- permanent disability（<1%）;
- renal insufficiency or renal failure (including acute kidney injury) （<32%）;
- tissue erosion（<1%）;
- pulmonary edema（<1%）;
- dyspnea（<1%）;
- pleural effusion（<2%）;
- respiratory insufficiency or respiratory failure（<1%）;
- peripheral ischemia（<1%）;
- bowel ischemia（<1%）;
- heart murmur（<1%）;
- non-emergent reoperation(<5%);
- hypotension or hypertension#（<1%）
- syncope（<1%）;
- abnormal lab values (including electrolyte imbalance)（<9%）;

*30-day events

5.1.2 Quantitative data

The residual risk and its quantification are derived from the CH3.2 Risk Management Report.

In the Risk Management Report, the quantification of the residual risks/side-effects are derived from the incidence of the corresponding adverse events at 1-year post-procedure (30-days or device-related events will be considered for specific events) obtained from SOTA and VitaFlow clinical investigations in a hierarchical order (table 4-5).

Among the pre-identified residual risks, there is a series of minor events that are also frequently observed in non-TAVI population and the event rates are not published by SOTA TAVR literature. Thus, the quantification will be derived from VitaFlow investigations using incidence of the device-related events.

Table 5-1Quantification of the residual risk and source of the data

SOTA	VitaFlow investigations
➢ Death ➢ Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) ➢ Myocardial infarction Emergent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant) ➢ Vascular complications ➢ Cardiac tamponade ➢ Stroke, transient ischemic attack (TIA), or other neurological deficits ➢ Conduction disturbances and arrhythmias ➢ Non-emergent reoperation ➢ Renal insufficiency or renal failure (including AKI); (5%) ➢	➢ cardiac complications; ➢ multi-organ failure; ➢ respiratory insufficiency or respiratory; ➢ valve-related complications; ➢ emergent balloon valvuloplasty; ➢ allergic reaction to antiplatelet agents, contrast medium, or anesthesia ➢ infection (including septicemia and endocarditis); ➢ permanent disability ➢ mitral valve regurgitation or injury; ➢ tissue erosion; ➢ encephalopathy; ➢ pulmonary edema; ➢ pericardial effusion; ➢ pleural effusion; ➢ peripheral ischemia; ➢ bowel ischemia; ➢ heart murmur; ➢ hemolysis ➢ cerebral infarction-asymptomatic; ➢ inflammation; ➢ fever; ➢ hypotension or hypertension; ➢ syncope; ➢ dyspnea; ➢ anemia; ➢ angina; ➢ abnormal lab values (including electrolyte imbalance);

5.2 Warnings and precautions

5.2.1 Warning

1) TAVI can only be permitted in hospitals where immediate aortic valve surgery is available in emergencies.

2) Choose the model of the bioprosthesis carefully, improper model might cause aortic annulus damage, valve shifting or fall off.

3) VitaFlow Liberty™ is designed for single patient use only. DO NOT reuse, reprocess, or re-sterilize this product. Reuse, reprocessing, or re-sterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
4) Before use, please check the package carefully. DO NOT use the product if the package has been damaged or opened.
5) DO NOT place the inner package of the products in the sterile area. The bioprosthesis and the glutaraldehyde storage solution are STERILE. The outside of the bioprosthesis container is NON-STERILE and must not be placed in the sterile area.
6) Before use, please inspect the color label of the 0℃ and 38℃ temperature indicators. DO NOT use the product if any temperature indicator has been activated.
7) DO NOT use an expired product. Before use, please check the expiration date.
8) VitaFlow Liberty™ Aortic Valve is to be used only in conjunction with the VitaFlow Liberty™ Delivery System.
9) Use of VitaFlow Liberty™ and implantation of VitaFlow Liberty™ Aortic Valve should be performed only by qualified physicians who have received the training on manipulation of the system and its valve implantation.
10) Prior to use, read the instructions carefully, with particular attention to various warnings and precautions in this section and in the step by step directions for use, otherwise may cause serious injury and death.
11) Current heart valve replacement guidelines recommended that: A bioproshtesis should be considered in patients>65 years of age for a prosthesis in the aortic position. Consider the applicable clinical guidelines for valve replacement when selecting the appropriate valve type for each patient.

5.2.2 Precautions

General

1) DO NOT expose VitaFlow Liberty™ Aortic Valve to organic solvents, such as alcohol.
2) DO NOT introduce air into the catheter.
3) DO NOT expose the bioprosthesis to solutions other than the storage and rinse solutions.
4) DO NOT add any other substances except heparin to either the storage or rinse solutions such as antibiotics.
5) DO NOT apply any other substances except heparin to the bioprosthesis.
6) DO NOT allow the bioprosthesis to be dry. Maintain the bioprosthesis with irrigation or immersion.
7) DO NOT attempt to use or repair a damaged bioprosthesis.
8) DO NOT handle or manipulate the bioprosthesis leaflet tissue with sharp or pointed objects or other forceps than the atraumatic forceps provided within the packaging.

9) DO NOT deform the bioprosthesis in excess of what is normal experience during crimping, loading and implantation of the bioprosthesis.
10) DO NOT use the VitaFlow Liberty™ Delivery System if it was dropped.
11) Keep the battery compartment of the delivery system dry.
12) This product is provided with the alarm prompt function of low-battery yellow indicator always on, which must be checked before opening the packaging and using, and the default value of low-power alarm is unique, which does not support adjustment. The alarm function is started when it is powered on.
13) Carefully check all the products for defects and DO NOT use any defective product

6 Summary of clinical evaluation and PMCF

6.1 Summary of clinical data related to equivalent device

No market approved equivalent device to be considered.

For the purpose of the clinical evaluation, an equivalence has been demonstrated between the VitaFlow™ TAV and VitaFlow™ Liberty as part of the justification for pooling the respective data of both devices.

6.2 Summary of clinical data from conducted investigations of the device before the CE- marking

A Pilot clinical investigation was conducted by Microport Cardioflow to demonstrate feasibility of the VitaFlow TAV system prior to starting the pivotal clinical investigations.

MicroPort CardioFlow initiated three pivotal clinical investigations:

- Prospective, clinical investigation data of VitaFlow® TAV System conducted in China(TAVI I)
- Prospective, clinical investigation data of VitaFlow Liberty™ TAV System conducted in China(TAVI II)
- Prospective, clinical investigation data of VitaFlow Liberty™ TAV System conducted in Europe (VITALE)

Among the above three data sets, the ***pivotal*** clinical evidence for the CE-mark is the combination of prospective, clinical investigation data for the VitaFlow Liberty™ TAV System(TAVI II) and VitaFlow® TAV System(TAVI I), with a comprehensive data set of 176 patients treated in total with 166 patients available for observation at 12 months and overall, more than 400 (482.83) patient years. The pooled data sets and their underlying study designs are aligned with the requirements outlined in ISO 5840-3 Cardiovascular implants — Cardiac valve prostheses —Part 3: Heart valve substitutes implanted by transcatheter techniques, supporting safety, clinical performance and effectiveness of the VitaFlow Liberty™ Transcatheter aortic valve replacement system.

In addition, since the the target patient population in the VITALE study is different from TAVI I

and TAVI II regarding the surgical risk (High surgical risk in TAVI I and TAVI II versus high risk and intermediate risk subjects in VITALE), the VTALE data are presented as a supplement to provide the implantability related information of VitaFlow Liberty™ TAV system in a Caucasian population.

6.2.1 Study overview（objective, study population, number of patients enrolled, summary of the study methods）

- **TAVI I (CIP-Valve-2014-04, Version 3, 15 April 2016)**

TAVI I, conducted in China, is a prospective, multi-centre, single-arm clinical investigation of the safety and effectiveness of the transcatheter aortic valve and delivery system (**VitaFlow™ Transcatheter Aortic Valve System**) in the treatment of severe aortic stenosis. Clinical follow-up data were collected at 30 days, 6 months, 12 months, 2-5 years annually post-procedure. Enrolment has been completed (A total of 11 sites in China enrolled 110 patients) and follow-up is ongoing. This study focuses on high surgical risk subjects only.

- **TAVI II (CIP-SUPERIOR-2017, Version 1.5, 20 February 2019)**

TAVI II is a prospective, multi-centre, single-arm, objective performance criteria-controlled clinical investigation of the safety and effectiveness of its transcatheter aortic valve and recapture delivery system (**VitaFlow Liberty™ Transcatheter Aortic Valve System**) in the treatment of severe aortic stenosis. Clinical follow-up data were collected at 30 days, 6 months, 12 months, 2-5 years annually post-procedure. Enrolment is ongoing (A total of 15 sites in China enrolled 66 patients by August 2019). This study focuses on high surgical risk subjects only.

- **VITALE (CIP-Valve-2018-01,Version 1.3.3, 28 October 2018)**

VITALE is a prospective, single-arm clinical investigation of the safety and effectiveness/performance of the MicroPort CardioFlow VitaFlow II – Transcatheter Aortic Valve System (**VitaFlow Liberty™ Transcatheter Aortic Valve System**) for the treatment of symptomatic severe aortic stenosis via transcatheter access in increased surgical risk patients. Clinical follow-up data were collected at 30 days, 6 months, 12 months, further follow up annually is foreseen up to 5 years post implantation. Enrolment started in December 2018 and was suspended due to COVID after 20 subject were enrolled of whom 8 were high surgical risk patients. This study aims to enrol both surgical high risk and intermediate risk subjects.

6.2.2 Study design

- **Sample size**

For all of the studies, the original sample size was calculated based on the non-Inferiority approach. Since each study had only one arm (no control), assumptions were based on literature to get a targeted value based on Objective Performance Criteria (OPC).

- **Primary Endpoint**

Consistent with other prospective, clinical investigations used to support CE Mark or FDA approval of the current state-of-the-art similar devices, all of the three studies use all-cause mortality at 12-month follow-up as the primary endpoint.

- **Secondary endpoints**

Consistent with other prospective, clinical investigations used to support CE Mark or FDA approval of the current state-of-the-art similar devices, secondary endpoints for the three studies were selected and defined per VARC-2 guideline. Secondary endpoints include post-procedure complication rates for assessing the safety, device success, procedure successfor assessing performance, and the bioprosthetic valve function, NYHA heart function, life quality for assessing effectiveness.

- **Inclusion/exclusion criteria for subject selection**

The key inclusion and exclusion criteria for the three studies are:

Inclusion criteria:

1) Severe symptomatic aortic stenosis
2) NYHA ≥Class II
3) Anatomically suitable for TAVI
4) Patients assessed and recorded as high/increased surgical risk for heart valve surgery
5) Patients, who can understand the clinical investigation purpose, voluntary agree and sign the informed consent form, and willing to comply with relevant trial assessments and clinical follow up

- **Exclusion criteria：**

1) Acute myocardial infarction (MI) occurred in the last 30 days before the treatment
2) Untreated clinically significant coronary artery disease requiring revascularization
3) Echocardiographic evidence of intracardiac mass, thrombus or neoplasm
4) A known sensitivity to, nitinol, dairy products, PET (Polyethylene Terephthalate) or contrast medium; inability to tolerate anticoagulation therapy)
5) Active and/or suspicion of endocarditis or ongoing sepsis
6) Severe aortic regurgitation (>3+),Severe mitral regurgitation (>3+)
7) Currently participating in another drug or device trial (excluding registries) for which the primary endpoint has not been assessed
8) Estimated life expectancy of less than 12 month

6.2.3 Summary of study results

The pooled results of TAVI I and TAVI II as well as the supplement analysis of VITALE are presented hereunder.

6.2.3.1 Patient baseline characteristics

A total of 176 patients were enrolled in the TAVI I and TAVI II. All of them were diagnosed as

severe, symptomatic AS at high surgical risk and multiple comorbidities. The mean age of the pooled study population was 77.61±4.66 years, with 42% of the female. They had low aortic valve area of 0.60±0.19cm^2, high transvalvular mean gradients of 61.21±20.18mmHg. The average STS of 8.4±4.6% and 81.2% of patients with NYHA Class III/IV. The overall bicuspid aorticvalve stenosis (BAV-AS) population was 38.6% and the tricuspid aortic valve population was 61.4%.

The average age for the patients enrolled in VITALE was 78.50±6.26 years of age with 45% of female population. The bicuspid aortic valve population was 10%.

6.2.3.2 Performance analysis

The performance of the evaluated devices was analysed based on the device success, the procedural success, and the recapture success.

The device success, which was defined as the successful access, delivery, deployment, implantation of the devices and the retrieval of the device delivery system, was achieved in 86.9% of all devices used in TAVI I and TAVI II at 30days. The procedural success, which was the successful implantation of the devices with absence of death, stroke, MI, renal failure or severe complications within 72 hours post procedure, was achieved at 80.5% for TAVI I and TAVI II.

In a total of 14 intra-procedure device failures required a TAV-in-TAV placement due to incorrect placement of the first valve. There was a clear improvement in the number of TAV in TAV placements when using the VitaFlow Liberty™ delivery system allowing recapturing of the valve for correction of position.

There were no difference in terms of device success (88.1% vs 92.3%, P=0.65) or procedure success (83.3% vs 73.3%, P=0.39) between TAVI II and VITALE. The recapture function of the VitaFlow Liberty delivery system was 100% when used for both studies.

6.2.3.3 Clinical benefits analysis

Overall effectiveness of the evaluated devices were measured in terms of the improvement of the valve function, heart function and life-quality at 12 months.

The main analysis of TAVI I and TAVI II(PP) effectiveness endpoint results reported an overall decrease in the pressure gradient - on the total of 158 subjects from both studies - from 61.21±20.18mmHg at pre-procedure to 9.52±4.94mmHg at 12 months. In terms of effective orifice area (EOA), the total 151 patients included in the PP analysis, demonstrated an increased orifice area from 0.60±0.19cm^2 at pre-procedure to 1.87±0.49 cm^2 at 12 months post-procedure, thus demonstrating an improvement in valve function. The overall paravalvular leak of the total 162 patients in the pooled PP analysis remained stable within 12-month post-procedure with 3.7% of moderate PVL at 12 months.

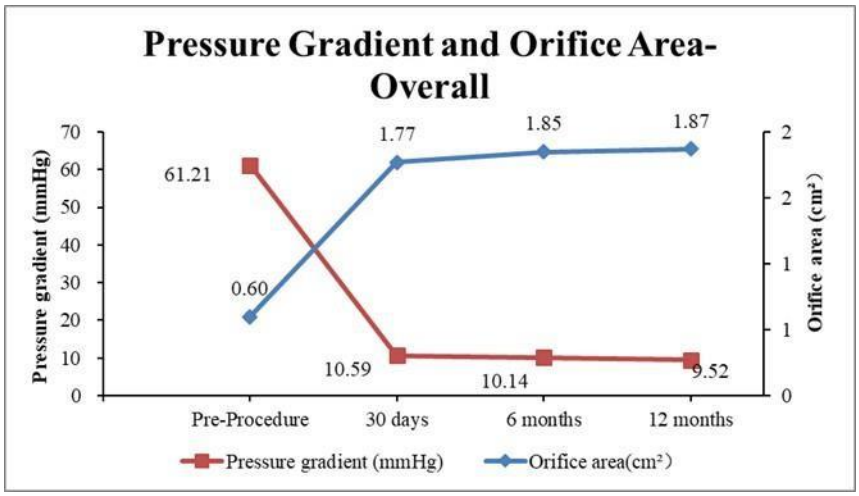


Figure 5 - Pressure Gradient and EOA for PP in Overall

It should be noted that similar improvement in the valve function could be observed in the supplement analysis of VITALE study.

In addition, there is an overall decrease in the percentage of patients with NYHA III/IV, from more than 80% at baseline to 3.6% at 12 months. Regarding the life-quality assessed by SF-12 physical and mental score, the patients had an improvement of 10.05±9.42 and 8.58±10.44 at12 months post-procedure compared to baseline respectively. This indicates the improvement on the heart function and life-quality receiving the implantation of the evaluated devices.

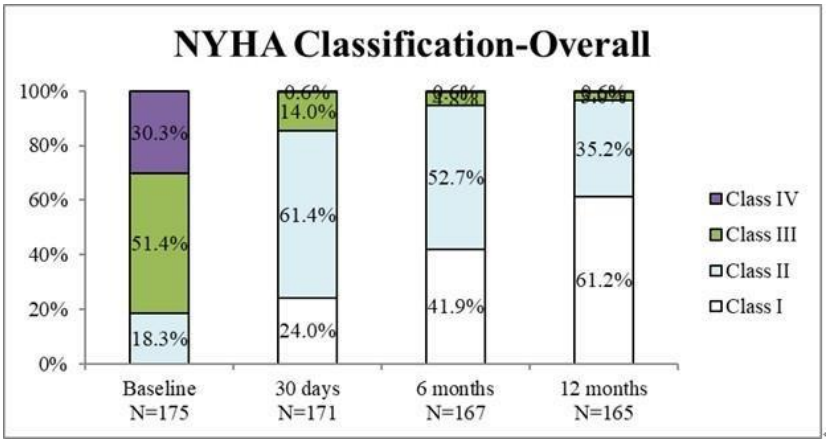


Figure 6 - NYHA Class for PP in Overall

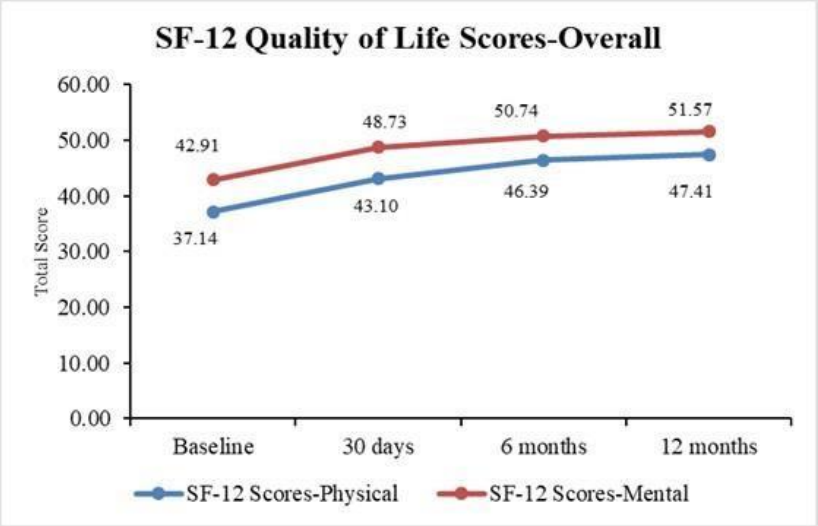


Figure 7 - Quality of Life Scores for PP in Overall

Overall, the findings demonstrate that the devices were able to meet their performance and effectiveness endpoints and that the implantation of the VitaFlow prosthesis relieved the valve stenosis and improved the hemodynamic function, heart function, and life-quality.

6.2.3.4 Safety analysis

The all-cause mortality at 12 months post- procedure was used as primary safety analysis to study the safety profile of the evaluated devices. Overall, the collective data of TAVI I and TAVI II demonstrated an all-cause mortality of 5.7%, with a 3.4% of cardiovascular death.

The secondary safety analysis includes VARC-2 defined safety event rate at 12 months : death 5.7%, disabling stroke 1.8%, myocardial infarction 7.4%, major vascular complications 1.7%, life threatening or disabling bleeding 4.6%, acute kidney injury 0.6%,new pacemaker implantation 20.2%.

In addition to 12 months result, the long-term follow-up of TAVI revealed a 2-year mortality of 7.4%, 3-year mortality of 13.6% and 4-year mortality of 15.4%.

These findings are comparable with the state-of-the-art similar devices with the same intended population, and also confirms the long-term acceptable safety profile of the bioprosthesis valve of the VitaFlow devices.

Overall, the safety data collected and subsequently evaluated by the independent clinical events committee as well as additional data analysed in the supplementary analysis show no un-anticipated events.

6.2.3.5 Any limitations of the study

TAVI I, TAVI II, and VITALE studies were non-randomized, single-arm study with the typical limitations associated with such a study design. The absence of a control group precludes the

direct comparison of the observed clinical outcomes in context of other commercially available TAVR devices. On the one hand, during the design of TAVI I and TAVI II study, there were no commercially available transcatheter aortic valve system available in China. On the other hand, the manufacturer performed a systemic literature search and a subsequent meta-analysis to pool the safety and performance/effectiveness outcomes from the state-of-the-art similar devices with the same intended population. The aggregated outcome from similar devices are considered as the acceptable criteria for the VitaFlow device.

6.2.3.6 Device deficiency

Overall there were 14 device deficiencies (DD) for TAVI I, 2 DD for TAVI II and 2 DD for VITALE study. For TAVI I, since the first generation VitaFlow delivery system does allow the valve repositioning, DDs were related to incorrect placement of the first valve (use error) leading to the second valve implantation or coronary obstruction. For TAVI II, DDs were related to challenging aortic root anatomy. For VITALE, one occurrence of difficulties in detaching the valvefrom the delivery catheter required minor manipulations but without any consequences and a successful valve placement, the other DD involved a problem with the electrical features for the retrieval of the delivery system after successful valve placement, requiring some minor manipulations without any consequence. A new recommendation were added in the Instructions For Use for guiding users on valve dis-detaching from delivery catheter.

Except for one DD in VITALE involving an electrical problem with the handle of the delivery system, none of the other DDs were caused by malfunctions of the devices and could be avoidedby adequately education to the operators. None of the device deficiencies were due to deficiencies in the labelling.

6.2.3.7 Conclusions

The TAVI I and TAVI II studies were conducted in a statistically sound manner and in line with the ISO 5840-3 standard on heart valve substitutes implanted by transcatheter techniques. The results of this pooled analysis including the supplementary analysis, demonstrate that the VitaFlow Liberty™ device met its primary and secondary objectives demonstrating successful treatment of aortic stenosis for the intended population. Overall, the device demonstrated a competent performance, effectiveness and safety profile when compared to well the published state of the art similar devices. No un-anticipated events occurred, nor does the overall event occurrence rate raise any concerns, thereby allowing the conclusion that the clinical benefits to the patients surpass the risks and demonstrating a positive benefit to risk ratio.

6.3 Summary of clinical data from other sources

6.3.1 Clinical data from scientific literature

Upon literature search, selection and appraisal, only one article reporting the clinical outcome of VitaFlow TAV system is retained. The reference is provided:

Zhou, D., et al., VitaFlow™ transcatheter valve system in the treatment of severe aortic stenosis: One-year results of a multicenter study. Catheter Cardiovasc Interv, 2020. 95(2): p. 332-338.

This article reports the 12 months safety and effectiveness of the pre-market, prospective, single-arm clinical investigation of VitaFlow TAV system (TAVI I study). Since the results of the TAVI I study were already pooled with those of TAVI II as the clinical evidence for the current clinical evaluation, we will not further analyze the corresponding content in this section.

In general, data from literature reveals the safety, performance and effectiveness of VitaFlow TAV system in the treatment of patients with severe aortic stenosis, including patients with bicuspid aortic valve.

6.4 An overall summary of the clinical performance and safety

MicroPort CardioFlow carries out the risk management activities for VitaFlow Liberty™ Transcatheter Aortic Valve System according to ISO 14971:2019. Both residual risk evaluation and overall risk evaluation were conducted. For each identified hazardous situation, corrective/preventive actions have been taken to reduce the risk as much as possible to the acceptance level while verifying that the risk control measures do not introduce new hazards or hazardous situations and do not affect the estimated risks for previously identified hazardous situations. And all of them were within acceptable range not outweighing the benefits to the patient. Residual risks are taken into account in the instructions for use of VitaFlow™ Liberty. These include warnings and precautions for valve and delivery system manipulation before and during implantation intended to prevent damage to the valve or delivery system and misuse that could lead to patient harm. Moreover, use of VitaFlow™ in patients with pre-existing conditions that would lead to unacceptable safety risk is contraindicated. Implantation of VitaFlow™ is restricted to qualified physicians who have received training on VitaFlow™ by MicroPort.

The safety and performance/effectiveness of the VitaFlow Liberty TAV has been established through extensive design verification and validation testing, including a detailed risk analysis process in compliance with ISO 14971:2019.

The pivotal clinical evidence for the CE-mark is the combination of prospective, clinical investigation data for the VitaFlow Liberty™ TAV System(TAVI II) and VitaFlow® TAV System(TAVI I), with a comprehensive data set of 176 patients treated in total with 166 patients available for observation at 12 months and overall more than 400 patient years. Clinical outcomes of TAVI I and TAVI II indicated that the VitaFlow Liberty has the acceptable safety profile comparable with the state-of-the-art similar TAVR devices for the same indications. As the non-absorbable implant, VitaFlow Liberty™ Aortic Valve is designed to have at least 5-year of lifetime.* The mid/long-term follow-up of TAVI I revealed a 12-months mortality of 5.7%, 2-year mortality of 7.4%, 3-year mortality of 13.6%, and 4-year mortality of 15.4%.

No un-anticipated events occurred, nor did the overall event occurrence rate raise any concerns. The VitaFlow Liberty does not present any new hazard as compared to what has been pre-identified in the risk management report. The performance and effectiveness analysis revealed VitaFlow Liberty is able to achieve its intended performance and clinical benefits.

Supplementary analysis compared the implantability outcomes of the VitaFlow Liberty TAV in Chinese (TAVI II) and European (VITALE). It can been seen that VitaFlow Liberty achieves the satisfying performance outcomes in both the Chinese and European population, including the

recapture function of the delivery system. No intra-procedure TAV in TAV placement for VITALE study, manifesting the clinical value of the recapture function of VitaFlow Liberty for allowing recapturing of the valve for correction of position.

Based on the pre-clinical data, published literature on similar devices, and clinical investigation outcome, it can be concluded that the VitaFlow Liberty is able to meet its performance claims of:

- Safe delivery and deployment of the TAV preloaded on the recapturable delivery and loading system via peripheral vascular access using the system's introducer sheath, into the aortic native valve position and subsequent retrieval of the delivery system through the introducer sheath.
- The Recapture Delivery System by its design allows ability to recapture the TAV (up to 75% of deployment) and reposition or retrieve it.

The clinical benefits of the VitaFlow Liberty are similar to those of state-of-the-art similar TAVR devices, including:

- Reduced risk for mortality
- Improvement in the aortic valve function(orifice area and pressure gradient) with acceptable /minimal paravalvular leak
- Improvement in the New York Heart Association functional class
- Improvement in the quality of life

It is concluded that TAVR using VitaFlow Liberty™ is a suitable alternative to SAVR in patients with severe, symptomatic, calcific aortic stenosis who are judged by a heart team, to be at high risk for open surgical therapy. VitaFlow Liberty™ meets its design and performance specifications in conformance with ISO 5840-3. When weighting the residual risks and uncertainties against the clinical benefits of the VitaFlow Liberty, clinical benefits to the patients surpass the risks thereby demonstrating a positive benefit to risk ratio. VitaFlow Liberty TAV system is considered State-of-the-Art and demonstrates conformity with the relevant EU-MDR GSPR1 and 8 relevant to clinical validation.

** based on the accelerated wear testing data on file at Shanghai MicroPort CardioFlow Medtech Co., Ltd.. The accelerated wear testing is performed to a minimum of 200 million cycles, conducted, with normotensive differential pressure conditions of 100mmHg across the closed valve being applied for 5% or more of a single cycle, at 37±2℃ and an appropriate test rate, in accordance with ISO 5840-1: 2021 and ISO 5840-3: 2021. For adults with normal heart rate of 70 cycles/min, 200 million cycles take more than 5 years in clinic. The lifetime may not be indicative of clinical performance due to individual difference in each patient.*

6.5 Ongoing or planned post-market clinical follow-up

Since longer-term safety and performance data are not yet available for VitaFlow Liberty™ Transcatheter Aortic Valve System, a post-market clinical follow up surveillance will be carried out to monitor the safety and performance of VitaFlow Liberty™ Transcatheter Aortic Valve

System, and contributing to life cycle management.

PMCF data is listed in table 11 with the information of activities descriptions, the timeline/frequency to update.

In addition, other activities such as literature research, market and industry dynamics will also be carried out to evaluate our device with the state of the art techniques.

Table 11 - PMCF plan

Description of activity	Timelines of the activity
Literature search for published data from patients exposed to VitaFlow Liberty™ TAV, VitaFlow® TAV, and similar devices, including the relevant EU and other national vigilance databases	Updated annually
Long-term follow-up of TAVI I/TAVI II/VITALE	annually report after the completion of the primary endpoint
PMCF study (Europe)	

If new or emerging risks, rare complications and unexpected device failures are detected, the information will be fed back into the risk management and clinical evaluation processes to confirm the benefit-risk ratio is still acceptable and to implement corrective actions when needed

7 Possible diagnostic or therapeutic alternatives

According to 2017 ESC/EACTS guidelines for the management of valvular heart disease, the treatment options of the severe, symptomatic aortic valve stenosis includes surgical aortic valve replacement (SAVR), balloon aortic valvuloplasty, medication, and transcatheter aortic valve implantation (TAVI).

It has been shown that treatment of aortic stenosis using medication or transcutaneous aortic balloon valvuloplasty suffer from limited efficacy. Although traditionally aortic stenosis was surgically treated, some patients are judged at high or excessive surgical risk. This particularly concerns the elderly population. TAVI, being minimally invasive, is an established treatment by various well-designed randomized trials and favoured by international guidelines for patients with severe aortic stenosis. It represents a solution for patients at high surgical risks and TAVI's safety profile is acceptable compared to the benefits it offers to these patients who have little alternatives.

8 Suggested profile and training for users

All the physicians who participate the VitaFlow Liberty™ TAVI program should have comprehensive knowledge of cardiac disease and cardiac intervention working experience.

Physicians should also be trained by CardioFlow's professional education team. The training curriculum includes VitaFlow Liberty™ product introduction, cardiac CT analysis, valve size selection strategy and valve implantation process etc.

In general, beginner physicians of VitaFlow Libety™ should be proctored by certified proctors.

Once some features of VitaFlow Liberty™ are changed or updated, physicians should be trained again accordingly by CardioFlow's professional education team.

9 Reference to any harmonized standard and CS applied

Standard Number	Standard Title	Version/ Year
EN ISO 13485	Medical devices — Quality management systems— Requirements for regulatory purposes	2016+AC:2018
EN ISO 14971	Medical devices — Application of risk management to medical devices	2019
EN ISO 14155	Clinical investigation of medical devices for human subjects — Good clinical practice	2020
MEDDEV 2.7.1	CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES	Rev. 4
EN ISO 5840-1	Cardiovascular implants — Cardiac valve prostheses Part1: General requirements	2015
EN ISO 5840-3	Cardiovascular implants — Cardiac valve prostheses Part 3: Heart valve substitutes implanted by transcatheter techniques	2013
ISO 20417	Medical devices — Information to be supplied by the manufacturer	2021
ISO 10555-1	Sterile, single-use intravascular catheters Part 1: General requirements	2013/AMD 1:2017
EN ISO 10993-1	Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process	2020
EN ISO 10993-3	Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	2014
EN ISO 10993-4	Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood	2017
EN ISO 10993-5	Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity	2009
EN ISO 10993-6	Biological evaluation of medical devices Part 6: Tests for local effects after implantation	2016

EN ISO 10993-7	Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals	2008 +AC:2009
EN ISO 10993-9	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products	2009
EN ISO 10993-10	Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization	2013
EN ISO 10993-11	Biological evaluation of medical devices Part 11: Tests for systemic toxicity	2018
EN ISO 10993-12	Biological evaluation of medical devices Part 12: Sample preparation and reference materials	2012
EN ISO 10993-17	Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances	2009
EN ISO 10993-18	Biological evaluation of medical devices - Part 18: Chemical characterization of materials	2020
ISO 10993-20	Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices	2006
IEC 60601-1	Medical electrical equipment Part 1: General requirements for basic safety and essential performance	2005 (Third Edition) + CORR. 1:2006 + CORR. 2:2007+ A1:2012
IEC 60601-1-2	Medical electrical equipment Part 1- 2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility	2014
IEC 60601-1-6	Medical electrical equipment Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	2013
IEC 62366-1	Medical devices — Application of Usability engineering to medical devices	2015
ISO 15223-1	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: Genera requirements	2021
EN ISO 11135	Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	2014+A1:2019
EN ISO 11138-1	Sterilization of health care products — Biological indicators	2017

	Part 1: General requirements	
EN ISO 11138-2	Sterilization of health care products — Biological indicators Part 2: Biological indicators for ethylene oxide sterilization processes	2017
EN ISO 11737-1	Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products	2018
EN ISO 11737-2	Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	2020
EN ISO 14937	Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	2009
ISO 14160	Sterilization of health care products -- Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives	2020
ISO 22442-1	Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management	2020
ISO 22442-2	Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling	2020
EN ISO 22442-3	Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents	2007
EN ISO 11607-1	Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems	2020
EN ISO 11607-2	Packaging for terminally sterilized medical devices –Part 2 : Validation requirements for forming, sealing and assembly processes	2020
EN 556-1	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices	2001+AC:2006
EN 556-2	Sterilization of medical devices - Requirements for medical devices to be designated ''STERILE'' - Part 2: Requirements for aseptically processed medical devices	2015
ISO 13408-1	Aseptic processing of health care products — Part 1: General requirements	2008
ISO 14644-1	Cleanrooms and associated controlled environments -- part 1: classification of air cleanliness	2015

ISO 14644-2	Cleanrooms and associated controlled environments — Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration	2015
ISO 14644-3	Cleanrooms and associated controlled environments — Part 3: Test methods	2019
ISO 14698-1	Cleanrooms and associated controlled environments -- Biocontamination control -- Part 1: General principles and methods	2003
ISO 14698-2	Cleanrooms and associated controlled environments -- Biocontamination control -- Part 2: Evaluation and interpretation of biocontamination data	2003
ISO TR 20416	Medical devices-Post-market surveillance for manufacturers	2020
IEC 62304	Medical device software — Software life cycle processes	2006
	MEDDEV 2.12.1 Rev 8 Guidelines on a medical devices vigilance system	
	MEDDEV 2.12.2 Rev 2 Post Market Clinical Follow-up	
ASTM F2052	Standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment	2015
ASTM F2503	Standard practice for marking medical devices and other items for safety in the magnetic resonance environment	2020
ASTM F2213	Standard test method for measurement of magnetically induced torque on medical devices in the magnetic resonance environment	2017
ASTM F2182	Standard test method for measurement of radio frequency induced heatingnear passive implants during magnetic resonance imaging	2019
ASTM F2119	Standard test method for evaluation of MR image artifacts from passive implants	2007
ASTM F 2063	Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants	2018
ASTM F2082 / F2082M	Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery	2016
ASTM F2004	Standard Test Method for Transformation Temperature ofNickel-Titanium Alloys by Thermal Analysis	2017
ASTM F2477	Standard Test Methods for in vitro Pulsatile Durability Testing of Vascular Stents	2013
ASTM F2338 - 09	Standard Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method	2020
ASTM D4169	Standard Practice for Performance Testing of Shipping Containers	2016

	and Systems	

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the NB
A	2021/12/27	New document	□Yes Validation language: ☑ No
B	2022/7/29	Updated Section(s) 4.1.1, 5 and 6	□Yes Validation language: ☑ No
C	2022/11/16	Update Section 3.2 Indications and target populations	□Yes Validation language: ☑ No
D	2023/01/05	1. Change Manufacturer's address in Section 2.1 2. Delete information of eIFU in Section 5.2.2	☑Yes Validation language: English □No