EUROPEAN COMMISSION

Opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	05/10/2021
Notified Body number	0344
Internal CECP dossier #	2021-000207
Medical device type	The valve system consists of the following two components: 1) Percutaneous Pulmonary Valve (PPV) 2) Delivery System (DS), including Delivery Catheter System (DCS) and Compression Loading System (CLS) The PPV is a self-expanding heart valve designed to replace the native pulmonary heart valve without the need for open-heart surgery. The PPV is first crimped down by the CLS into the DCS and then moved through a femoral vein in the groin and into the right side of the heart where it is placed into position within the pulmonary valve.
Intended purpose	The intended purpose of the valve system is to replace the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach, to treat right ventricular outflow tract (RVOT) dysfunction and specifically for the dilated outflow tracts to restore pulmonary valve function.
Risk class / type	☒ class III implantable ☐ class IIb ARMP
Screening step: medical field / competence area	Circulatory system: cardiovascular / lymphatic system; Prosthetic heart valves and devices for heart valve repair

PART 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1 Decision of the screening experts

Table covers all three criteria, intended to support their consistent and conscientious application

Date of decision	22/10/2021
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information was found insufficient to reach a conclusion: summary of reasons (see MRD Annex IX Section 5.1 point c)	
BRIEF TEXT (indicatively max. 150 words)	
Summary as to why there is intention to provide an opinion	
The device analyzed here is a completely new market launch, it has no CE mark and only 2 limited studies are available in China and the EU, which reveal a clear risk potential. The technique and construction of this valve has never been used before in this position (pulmonary) or for this purpose. During follow up, severe health issues occurred as soon as in a 12 month follow up period – however the device is intended to be long-term-used in patients starting as young as 12 years.	
Summary as to why there is *no* intention to provide an opinion	
not applicable	
Any other comments	
not applicable	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Novelty of device and/or of related clinical procedure
☐ No novelty: Neither device nor clinical procedure is novel ☒ Novelty: **Device** is novel ☐ Novelty: **Procedure** is novel
Short description of the novelty, including main dimension(s) of novelty
The intended purpose of the device to replace the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach, to treat right ventricular outflow tract (RVOT) dysfunction and specifically for the dilated outflow tracts to restore pulmonary valve function. The device consists of a

Percutaneous Pulmonary Valve (PPV) which is for the first time mounted on a self expanding nitinol frame, a Delivery System (DS), including a Delivery Catheter System (DCS) and a Compression Loading System (CLS).

Thus, this device is a completely newly developed percutaneous pulmonary heart valve prosthesis.

Taken together, the system is due to its intracardiac implantation a RISK CLASS III medical product permanently implanted in children, adolescents and adults with permanent contact to the blood stream. It contains animal tissue.

The device consists of a self-expanding nitinol support frame with a tri-leaflet porcine pericardium tissue valve. Both technologies have not been used in the pulmonary artery /valve before. The device is made of a single layer of porcine pericardium built in a tri-leaflet configuration. These are attached to a scalloped skirt (which is also made of a single layer of porcine pericardium) on the inflow aspect of the valve using PTFE sutures (P-VALVE Valve sub assembly).

Novelty is not generated by the use of nitinol stents or porcine pericardium, as these have been used before in the aorta/aortic valve, but by its re-assembly and usage in the pulmonary artery /valve where it has never been used like this before. The delivery system is developed newly for this product together with a crimping tool that is newly developed.

Overall degree of novelty

Level of novelty:

☐ Low level *or*

☐ Medium level *or*

☒ High level

Uncertainties related to novelty

The device is the first generation of pulmonary heart valve product of the company. And the first self-expandable pulmonary valve prosthesis. No previous generation exists. The devices claimed to be similar in the CER are MelodyTM Transcatheter Pulmonary Valve from Medtronic and Sapien XTTM Transcatheter Heart Valve from Edwards.

Melody obtained the CE mark by Sep.2009 and it was approved by US FDA in Jan.2015(P140017); Sapien XT obtained the CE mark by May 2010 and it was approved by US FDA for pulmonic use in Feb.2016 (P130009S037).

However, this new device is a self-expanding interventional pulmonary heart valve. This technique has not previously been used in the pulmonary position. Balloon-expanding valves as mentioned in the CER that have been used to date are referred to as comparable products, but this product shows an uncertain long-term result in terms of stent integrity, long term valve embolisation, long-term vascular wall injury and the device safety of a self-expanding valve system in growing people with dilated pulmonary valves with severe regurgitation. In addition, the use of the pig pericardium is new in this position.

1.2 Possible negative clinical / health impact resulting from novelty

The new technology of the valve carries risks of stent integrity and stent fracture, valve migration and embolization as the patient grow, as well as a risk of infectious valve prosthesis inflammation (endocarditis) with high morbidity and mortality. These data originate from a limited number of publications so far. This is also favored by the previously unknown long-term integrity of the pig pericardium in this position. There is a risk of long-term pulmonary artery vessel injury from the spring forces of the valve stent used, resulting in

vascular ulcerations, dissections or transsections. Furthermore anatomical, often postoperative, irregular pulmonary artery courses, lengths, caliber and anastomoses can lead to malpositioning, vascular occlusion and paravalvular leakage with valve insufficiency, which appears to be particularly possible with insufficiently unfolded self-expanding valves in regular postoperative scar tissue, but is not reported so far in a well selected cohort of patients with pulmonary valve regurgitation. The access to the vascular system is venous. However, several bleeding complications are reported and might be related to the quite big-sized (22-24F) novel introducer in relation to small patients (weight ≥30 kg). Thus, gives evidence of a vascular complication rate associated to the newly developed delivery system.

Estimated severity of clinical and/or health impact

Severity of clinical/health impact:

☐ No clinical or health impact
☐ Minor clinical or health impact
☐ Moderate clinical or health impact
☒ Major clinical or health impact

Uncertainties related to clinical/health impact

The clinical trials report on a total number of 150 patients (15 / 80 / 55) treated with the device with a low number in each participating site and a limited number of patients with regard to individual age-levels. Besides excellent follow up and medical care in studies, a high number of complications that are maybe related to components, origin of materials were recorded in the Chinese trial and a smaller trial using the prior cohort for comparison. The European and worldwide study (VMT-001CE) bears some limitations as not the complete dataset of patients is reported / not all patients are followed to the endpoint. The small study of Ou-Yang et al. (2020) is limited due to a small case number, but reports on severe complications related to the valve. Midterm (12 month) device failure resulted in cardiac-death, in-hospital-treatment and re-operation and occurred mainly during long term follow up which is moreover crucial with regard to long therapy times in young patients.

Concerns about the components arise from the results data:

1 subject (1.9%) with valve displacement (Device China clinical trial)

1 subject (1.9%) with severe vascular complications (Device China clinical trial)

1 subject (1.9%) with embolism (Device China clinical trial)

Source of materials:

1 subject developed infective endocarditis after surgery (Device China clinical trial)

5 subjects (9.3%) developed infective endocarditis (Device China clinical trial)

Impact on health in case of device failure:

Within 12 months after surgery (CEC data), 2 subjects (3.6%) with arrhythmia, 1 subject (1.9%) with embolism, 1 subject (1.9%) with severe bleeding, 1 subject (1.9%) with valve displacement, and 1 subject (1.9%) with severe vascular complications (Device China clinical trial)

Ou-Yang et al. (2020) reported furthermore on infective endocarditis, cardiovascular death, pulmonary embolism, cardiac arrest, arrhythmia, deep vein thrombosis, pulmonary thrombosis

embolism/thromboembolism, severe bleeding, severe vascular complications, valve displacement/dislodgement, fever, femoral hematoma, chest pain, device migration/embolization, paravalvular leak, stent fracture, valvar thrombosis, valve infolding, valve regurgitation/paravalvular regurgitation and vascular perforation.

Due to the novel device specifications, it is possible that the complications and adverse events may be a result of the procedure, the new valve stent-platform or the porcine pericardium used.

However, the device produced a good primary success rate and, under study conditions, a low primary complication rate. In order to assess the applicability of such a new device, the long-term stable results are particularly important when used on children and adolescents. Although the primary treatment endpoints were successful, there was significant cardiac mortality and morbidity (endocarditis, device embolization, stent fractures) despite the very young target group.

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to **a) Component(s)** **b) Source material(s)** **c) Impact on health in case of failure of the device**	
2.1 Information received from Secretariat:	☐ Yes ☒ No
2.2 Other information available to experts:	☐ Yes ☒ No
2.3 Reference to peer-reviewed publications/information sources:	
ENTER REFERENCES HERE	
In case information was used from either the Secretariat or other sources	
2.4 Groups/categories of devices:	
BRIEF TEXT	
2.5 Relationship to component(s), source material(s) or health impact in case of device failure	
☐ Health concern(s) relates to **component(s)** ☐ Health concern(s) relates to **source material(s)** ☐ Health concern(s) relates to **impact on health in case of device failure**	
2.6 Description of health concern(s):	
BRIEF TEXT	
2.7 Reliability of information:	
BRIEF TEXT	
2.8 Relevance of information:	
BRIEF TEXT	

2.9 Summary:
BRIEF TEXT

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment ***(if information is available, it will always be provided by the expert panel secretariat)***	
3.1 Information received from secretariat?	☐ Yes ☒ No
In case information on incidents was received from the Secretariat	
3.2 How relevant is this information for the device under assessment?	
BRIEF TEXT	
3.3 Summary: BRIEF TEXT	

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☐	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☐ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☒	**Circulatory system**	☒ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☐ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
☐	**Neurology**	☐ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices
☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	07/12/2021
Expert panel name	Circulatory system
Sub-group of expert panel	Prosthetic heart valves and devices for heart valve repair

2.2 Summary of expert panel opinion

DEVICE DESCRIPTION: The device is designed to replace the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach. The device is used for the treatment of pulmonary regurgitation with or without stenosis in patients with native right ventricular outflow tracts, therefore, reducing pulmonary regurgitation. The device system is designed to treat right ventricular outflow tract (RVOT) dysfunction and specifically for the dilated outflow tracts to restore pulmonary valve function. The system is indicated for use in the following clinical conditions:

• Patients with significant pulmonary regurgitation (≥3+)

• With or without RVOT stenosis (mean Doppler gradient ≥35mmHg)

NOVELTY: The system is a RISK CLASS III medical product permanently implanted in children, adolescents, and adults with permanent contact to the bloodstream. It contains animal tissue. The device consists of a self-expanding nitinol support frame with a tri-leaflet porcine pericardium tissue valve and a porcine pericardium scalloped skirt on the inflow aspect of the frame. Both technologies have been used in the pulmonary artery/valve before. Nitinol stents, bovine and porcine pericardium have been used before in the aorta/aortic valve. Importantly, their usage in the pulmonary artery /valve has already been used in clinical settings and approved by the U.S. Food and Drug Association. Based on the literature review, the device presented for the review seems to be the third evolution of the Valve System, with the fourth device generation released for clinical use outside of Europe (data sourced from an Indian registry published in 2021). Description of device generations or the reasons for device upgrades are not provided by the manufacturer. In conclusion, neither the device nor the procedure is novel.

Adequacy of clinical evidence assessment by the notified body: The manufacturer provides preclinical evidence as well as clinical studies conducted by them. Relevant preclinical studies are related to biocompatibility. Data on the evidence for clinical safety and outcomes is accurate, yet the number of participants observed in the long-term follow up is small and selective, with no information on the reason of lost follow-up.

Sufficiency of clinical evidence: The clinical evidence is based on two single-arm prospective clinical trials sponsored by the manufacturer, with one performed in China on 55 patients and in Europe including 83 patients. Publications based on the results of these trials are not cohesive: the report on the European experience includes short term results on 15 out of 83 patients. Importantly, long-term data on clinical efficacy and device safety is missing.

Adequacy of benefit-risk determination:

Based on the lack of alternative treatments for the target population, high risk of surgery and good outcomes of the short-term observations in the provided publications benefit/risk ratio for the device was determined to be positive.

Post-market surveillance data or risk management documentation is scarce and should be developed by the manufacturer to provide systematic surveillance during the long-term patient follow-up.

Consistency of clinical evidence with purpose / medical indication(s): The Device System has clear clinical indications with information supported by IFU. Intended users requisites are also well established. Implantation of the device should be performed only by physicians, who have received and completed the device system training, and who are experienced in related heart valve disease treatment procedures

Procedural risks

Anatomical: Significant obstruction of the pulmonary artery branches is likely to require additional intervention, obstruction of the central veins preventing delivery of the valve system outflow tract and coronary artery relationship which may risk coronary artery compression.

Consistency of clinical evidence with purpose / medical indication(s): Clinical evidence related to the device in evaluation is mostly preclinical and robust regarding the product biocompatibility. There is no relevant clinical data, strong clinical data or expert recommendations regarding the device. No trials either ongoing or planned have been found related to the device. We conclude that the amount and quality of the clinical evidence supporting the device should be improved by the manufacturer.

Consistency of clinical evidence with PMCF plan: As mentioned before the manufacturer provides preclinical evidence that might be considered by this panel as relatively weak however there is no clinical evidence and a complete lack of PMCF information. They can conclude that the Post Medical Clinical Follow-up is compulsory.

Overall conclusions and recommendations on clinical evaluation: The device under evaluation is a RISK CLASS III medical product. Neither the device (including its design) nor the procedure is novel. The manufacturer supplies enough information about the device description, indications, intended users and preclinical studies, most of it according to biocompatibility. We consider there is a lack of strong clinical evidence related to the clinical used of the device, which may be attributed to infrequent treatment of patients with these indications. Importantly, PMCF plan is not thorough, and we recommend its strong development to the manufacturer.

2.3 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the notified body (CEAR)[1]
1. Overall opinion on the NB's assessment of the adequacy of the manufacturer's clinical evaluation report
The manufacturer provides a comprehensive Clinical Evaluation in accordance with the Medical Device Directive as well as with the MEDDEV Guidelines for evaluation of clinical data. The Clinical Evaluation

[1] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

provides data to support the intended use, clinical performance, safety and benefit, as well as to support the claims and intended use of the device system under evaluation. The manufacturer assessed Essential Requirements on safety, benefit/risk profile, performance and acceptability of side-effects, by considering the following: clinical evidence, preclinical data, Risk Management files and post-market information (although small) relevant to the device system under evaluation. The device under evaluation is a Valve System consisting of two components: 1. Percutaneous Pulmonary Valve, 2. Delivery System including Delivery Catheter System and Compression Loading System. Percutaneous Pulmonary Valve is a class III device; an implantable/long-term surgically invasive device to be used in direct contact with the heart containing animal tissue (porcine). Delivery System is a class III device, an invasive device for short-term use specifically to control, diagnose, monitor or correct a defect of the heart through direct contact. The Valve System is reported not to be commercialised in any country, yet according to current literature, it has undergone clinical studies and has been used on a compassionate basis in the United Kingdom, China and Taiwan. The Valve System is designed to replace the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach. The Valve System is used for the treatment of pulmonary regurgitation with or without stenosis in patients with native right ventricular outflow tracts, therefore, reducing pulmonary regurgitation. Therapeutic solutions were surgical until recently. These solutions have recently been replaced by percutaneous mechanical valves. They have limitations because for older patients they are potentially too small. The manufacturer offers a percutaneous mechanical valve for diameters between 28-36 mm.

The manufacturer offers a small record of clinical data, based on 5 publications and two unpublished studies. A Chinese prospective, single-arm, multicentre study and a European and worldwide study provide the largest evidence on 138 patients treated with the evaluated device system. Both studies are sponsored by the manufacturer. The follow-up 1-year clinical data is not complete for some patients.

Based on the above studies, the manufacturer provided small data confirming in selected patients who would likely have no alternative treatment options other than open heart surgery for valve replacement, the use of the Valve System has demonstrated:

- high procedural success rate, comparable to alternative therapies, no death or reoperation at 12 months (although the follow-up has been incomplete), good pulmonary valve competence, significant reduction in pulmonary regurgitation fraction, significant reduction in RVEDV index, significant improvement in NYHA class, lower pulmonary artery transvalvular pressure gradient, improved effort tolerance.

Complications and adverse events reported following implantation with the current version of the Valve System are also reported following the use of percutaneously implanted pulmonary valves. Importantly, the reports include various versions of the Valve System which were available prior to the design of the device under assessment. The manufacturer does not provide the reason for the evolution of generations of the devices, the identified need for their changes nor information on the latest generation device identified in the current literature published in 2021.

Based on the studies, the manufacturer provides sufficient data to assess the benefit to risk ratio. There is small, but positive information confirming the valve system safe and effective for the treatment of pulmonary regurgitation with or without stenosis in patients with native right ventricular outflow tracts, to replace the pulmonary heart valve and reduce pulmonary regurgitation, by replacing the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach.

The claim the device is unique in the system design based on the nitinol stent alloy and porcine leaflet tissue is unjustified, as a U.S. Food and Drug Association approved device alternative based on the similar design, function and indication is already available.

Although the manufacturer initiated a Post-Market Surveillance System in compliance with Quality Management Systems, which monitors safety data arising from the use of the device, the notified body received no data from the manufacturer regarding complaints or amount of units sold of the device system. The manufacturer claims PMCF data will be continuously assessed for the identification of any new risks once the device has been commercialized.

2. Opinion on the NB's assessment of the sufficiency of the clinical evidence provided by the manufacturer

The manufacturer provides detailed data on pre-clinical studies, clinical evidence and post-market surveillance and vigilance. The pre-clinical data provided are not associated with conflicting or equivocal results that impact the safety, the performance or the benefit of the Valve System in its IFU target treated population. Clinical evidence on device safety and performance is based on clinical data of 138 patients who received implantation of the Valve System. This included a Chinese multicentre non randomised study (n=55 patients, evidence level IIc) and a European and worldwide multicentre non randomised study (n=83 patients) (evidence level IIc) conducted by the manufacturer. In addition, a single case report is described on one patient. The number of patients included in the reports is limited. Studies comparing the percutaneous and surgical treatment of the target population are missing, including randomised clinical trials. Studies comparing the Device System and its percutaneous alternatives are missing too. Based on the presented clinical data, the Valve System appears to be as safe and effective as the currently available alternatives, taking into account limitations of the available clinical data. The main device benefit is a safe and effective percutaneous treatment of the pulmonary valve, including large RVOT anatomy.

As the manufacturer presents several generations of the device, it is not clearly specified which device generation has been used in clinical trials, as is the need for generation changes. Importantly, one scientific report presents the fourth generation of the device, which follows the device under review.

3. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

What is the panel's/sub-group's opinion on the NB's assessment of the manufacturer's benefit risk determination of the device under assessment? Do you agree with the conclusions of the NB? Please provide relevant observations in case you are of the opinion that the NB's assessment was not fully adequate or has overlooked inherent shortcomings in the manufacturer's benefit-risk determination.

The manufacturer provides an adequate assessment of benefit-risk determination.

The clinical benefit result mostly from symptom relief:

- Improvement in pulmonary regurgitation compared to pre-procedure as demonstrated by transthoracic echocardiography
- Significant improvement in New York Heart Association (NYHA) Functional Classification compared with pre-procedure.
- Improvement in right ventricular remodelling and right ventricular function 6 months after implantation.

The benefit has been evidenced in a Chinese multicentre nonrandomised study (n=55 patients) and a European and worldwide multicentre non randomised study (n=83 patients) conducted by the manufacturer. Clinical data collected from available clinical publications demonstrate short-term safety and clinical performance of the device when used to treat native dilated RVOT which have undergone the previous repair. Long-term hard point benefits are missing and should be collected by the manufacturer during an ongoing post-market registry and in future randomised controlled trials.

Complications reported by the manufacturer with the use of the Valve System are infective endocarditis, cardiovascular death, pulmonary embolism, cardiac arrest, arrhythmia, deep vein thrombosis, pulmonary thrombosis embolism/thromboembolism, severe bleeding, severe vascular complications, valve displacement/dislodgement, fever, femoral hematoma, chest pain, device migration/embolization, paravalvular leak, stent fracture, valvar thrombosis, valve infolding, valve regurgitation/paravalvular regurgitation and vascular perforation. Importantly, the risk of such events that have been reported in current studies seems low, with no device- or procedure-related deaths of re-interventions reported in 69 subjects who have completed the 12-month follow-up visits. Still, 1-year clinical performance data on the remaining 69 patients is missing and has not been reported.

The reported technical success of the device is comparable to outcomes of similar devices already approved in the U.S. (97%). The length and diameter of the valve are reported to significantly affect the stiffness of the loaded delivery system. This is relevant when faced with challenging anatomies such as stenosis, unusual angulation or pre-existing pulmonary artery stents. Difficulty in passing the delivery system into the pulmonary artery may be multifactorial, relating to the interaction between the anatomy and the relative stiffness of the delivery system after loading the valve, exaggerated by the presence of a stent in a branch pulmonary artery.

Valve migration and embolisation is a procedural concern, particularly in the absence of a previous conduit in the RVOT. The rate of valve embolisation is similar or smaller than reported for similar devices approved and used in the same indications. Fracture rates reported in the valve system are high, yet comparable to the systems currently approved and used for the same indications (20-30% on fluoroscopy). Stent fractures are reported in the region of the proximal flare. The fractures have not affected the function of the valve or frame integrity or stability. Repetitive muscular contraction of the RVOT may affect the proximal valve system flare resulting in stent fractures.

The reported annualised incidence of endocarditis appears low (<3%), with the anatomical substrate into which the valve is implanted being as important as the valve itself.

Some gaps have been identified between the clinical risks identified from the clinical evidence on the use of the Valve System and the current IFU. The clinical risks which are not listed in the IFU, are covered in the risk analysis. We advise that the risks be added to the IFU.

Based on this limited data, the benefit/risk ratio of the Valve System is proven to be acceptable when used to treat right ventricular outflow tract (RVOT) dysfunction and specifically for the dilated outflow tracts to restore pulmonary valve function in the patient population represented in the report.

In the context of non-surgical management, the unmet need is real when the diameter of RVOT is greater than 28mm. We are not there in the context of a novelty but rather in an addition to the range.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

The manufacturer provides a good presentation of the intended purpose and medical indications to the NB.

The Valve System is indicated for use in the following clinical conditions:

- 12 years old up to 70 years old
- Weight ≥ 30kg
- With evidence of moderate or severe (≥3+) pulmonary regurgitation by Transthoracic Echocardiography (TTE)
- With >30% pulmonary regurgitation fraction as defined by cardiac Magnetic Resonance Imaging (MRI)Subject is symptomatic from his/her pulmonary regurgitation or meets MRI criteria for intervention Right Ventricular Ejection Fraction (RVEF) < 45%, Pulmonary Regurgitant Fraction (PRRF) >30% and increased Right Ventricular End Diastolic Volume (RVEDV) Index (RVEDVI) >150ml/m²
- who are clinically indicated for surgical pulmonary valve replacement

The indications are included in the IFU.

Importantly, there is no data available on patients who are breastfeeding. The use in patients who are breastfeeding is not currently listed as a contraindication.

5. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

Although the manufacturer initiated a Post-Market Surveillance System in compliance with Quality Management Systems, which monitors safety data arising from the use of the device, the NB received no data from the manufacturer regarding complaints or number of units sold of the device system. The manufacturer claims PMCF data will be continuously assessed for the identification of any new risks once the device has been commercialized.

The planned PMCF aims to collect the following data:

- Confirm the long-term safety and performance of the device when used as mentioned in the IFU;
- Identify previously unknown side-effects and monitor the identified side-effects and contraindications;
- Identify the IE rates in longer-term follow-up, due to the potential for an increased IE rate reported in later studies compared to earlier studies
- Identify and analyze emergent risks on basis of factual evidence;
- Ensure the continued acceptability of the benefit/risk ratio, and identify possible systematic misuse or off-label use of the device, to ensure the intended purpose of the device is correct.

The PMCF is planned to extend the pre-market studies in China and Europe. There is no EU market study specified, with the focus planned on US IDE studies.

2.4 Overall conclusions and recommendations

Overall conclusions and recommendations on clinical evaluation

Recommendations:

The manufacturer should review the clinical and market availability of similar devices for the same indications as expressed in the Valve System IFU. Specifically, the expert panel identified one medical device

approved by the U.S. Food and Drug Administration for clinical use. The CER should discuss differences and similarities of the devices and include another device clinical evidence into the CER discussion. Misinformation on Valve System generations should be clarified, with specific indications on which generation types have been used in studies presented in CER, the reasons for generation improvements and the existence of the 4th device generation for clinical use in a clinical research study published in 2021.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.
The expert panel did not express divergent opinions.

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions
The expert panel unanimously approved the scientific opinion. Doubts on device generations and clinical availability of similar devices were discussed and expressed in the document.

Please indicate how many of the experts of the panel or sub-group had divergent views
None

[2] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.