

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

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

Contents

1	ADMINISTRATIVE INFORMATION
2	DECISION AND OPINION
	T 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE NTION TO PROVIDE AN OPINION
1.	
1.	2 ASSESSMENT OF THE THREE SCREENING CRITERIA
1.	3 INDICATION OF APPROPRIATE THEMATIC PANEL IN CASE OPINION IS REQUIRED
PAR	T 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP
2.	
2.	2 SUMMARY OF EXPERT PANEL OPINION
2.	3 DETAILED ASPECTS OF THE OPINION AS REQUIRED BY MDR ANNEX IX SECTION 5.1
2.	
2.	
2.	6 DIVERGENT POSITIONS IN CASE NO CONSENSUS WAS REACHED

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	28/04/2022
Notified Body number	0344
Internal CECP dossier # (e.g. 2021-000201)	2022-000216
Medical device type	The EVOQUE system is designed to replace the native tricuspid valve. This application concerns the Edwards EVOQUE Valve and the Edwards EVOQUE Tricuspid Delivery System. The EVOQUE valve consists of a trileaflet bovine pericardial tissue valve, self-expanding nitinol frame and intra-annular fabric skirt to be implanted in the native valve position.
Intended purpose	The EVOQUE tricuspid valve replacement system is intended for the reduction of tricuspid regurgitation (TR) for patients who remain symptomatic on medical therapy and in whom no other surgical or transcatheter treatment option exists per heart team decision.
Risk class / type	☑ class III implantable□ class IIb ARMP
Screening step: medical field / competence area	Circulatory system

2 DECISION AND OPINION

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	20/05/2022	

Screening panel decision		
Is there intention to provide a scientific opinion? Select <u>one</u> of the three answers	 ☑ 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)		
Not applicable		
Summary as to why there is intention to provide an opinion		
The device analysed here is a completely new market launch, it has no CE mark; only 3 limited studies on the compassionate use of tricuspid regurgitation are available, which reveal a clear risk potential. During follow-up, severe health issues occurred in a 12 month follow-up period.		
Summary as to why there is <u>no</u> 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

DEVICE: The EVOQUE tricuspid valve replacement system is a novel method for reducing and/or eliminating tricuspid regurgitation as currently there are no other valve replacement options for this intended purpose.

The device has no patient interface once implanted (i.e., there are no maintenance or adjustment procedures).

PROCEDURE: In general, the device is not novel in terms of transcatheter valve replacement but is novel for use in the tricuspid valve.

In terms of Procedure-related dimensions:

The design of the device leaflets that form the valve is leveraged from surgical and transcatheter aortic/mitral valve technologies (the native tricuspid leaflets (septal, anterior and posterior) is novel. The and capture of the free edge of the native tricuspid leaflets (septal, anterior and posterior) is novel. The EVOQUE valve does not grasp/facilitate coaptation of the native tricuspid leaflets like other tricuspid valve repair devices. The anchors capture the native leaflets and the native leaflets fully engage with the outer frame of the device.

One novel aspect of the delivery system is the ability of the device to steer in multiple planes as well as perform depth manoeuvres utilizing a single handle. This allows for intuitive positioning and use by the operator. Additionally, in order to accommodate controlled valve release, the delivery system provides a multistage valve expansion. This progressive expansion and release over the articulated bends of the system allows for controlled deployment of the device.

With respect to Device-related dimensions:

The device has a novel medical purpose (tricuspid valve replacement) vs. existing valve repair surgical options. The active part of the valve (leaflets) is leveraged from biologic surgical valves of Edwards, but the framework around the valve used for anchoring is novel, as is the deployment mechanism. Materials used are those in current designs of transcatheter heart valves. The manufacturing process for the EVOQUE valve and delivery accessories is new and specific to these devices with the exception of the bovine pericardial leaflets, which form the 'active functional' part of the valve. This structure is the same as that used on valves.

Overall degree of novelty

Level of novelty:

Low level or

☐ Medium level <u>or</u>

🛛 High level

Uncertainties related to novelty

Uncertainties derive from:

1) Long term valve durability in this setting is unknown.

2) The number of patients treated is quite low and the reported outcomes lack long follow-up.

1.2 Possible negative clinical / health impact resulting from novelty

In the TRISCEND Study, at the time of the **Exercise** data extract, 23 patients in the enrolled population experienced 31 MAEs, for a composite 30-day MAE rate of 18.5% (23/124). The majority of MAEs were

severe bleeding, which occurred in 17.7% (22/124) of patients in the TRISCEND study. In the TRISCEND Study, Kaplan-Meier estimates of MAE occurrence are 19.7% through 6 months and 21.7% through 1-year.

All-cause mortality was 0-3.0% through 30 days and 1.7-7.4% between 30-days and 1-year. Total mortality range was 4.5-7.4% through 1 year. In the TRISCEND Study, Kaplan-Meier estimates of survival occurrence are 96.0% through 6 months and 94.0% through 1 year.

Clinically significant PVL was detected in 2.5% (3/118) of patients at discharge. When assessed by echo core lab on a 5-grade scale, over 85% of patients had non/trace paravalvular leak (PVL), less than 15% had mild PVL, less than 3% had moderate PVL, and no patients had severe or greater PVL at all follow-up timepoints.

Of remark, postoperative pacemaker implantation is not uncommon. In total, 6.1-11% of patients required permanent pacemaker implants.

Device malpositioning (embolization, migrations, and misplacement) is a known potential complication of valve repair/replacement. In the TRISCEND Study, there were four instances (3.0%, 4/132) of device embolization/migration (2 valve embolizations and 2 valve migrations) and one instance (0.8%, 1/132) of valve misplacement (ectopic valve placement).

Estimated* severity of clinical and/or health impact

*) This can entail uncertainty. Not only known clinical / health impacts but also possible ones (conceivable uncertainties, hazards, risks) should be taken into account but need to be supported by a scientific, clinical or technical reasoning. Uncertainties need to be described.

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

Previously described

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefitrisk 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

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
--	------------

1.3 Indication of appropriate thematic panel in case opinion is required

India	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 	
Ø	Circulatory system	 I. 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	27/06/2022
Expert panel name	Circulatory System
Sub-group of expert panel (where relevant)	Prosthetic heart valves and devices for heart valve repair

2.2 Summary of expert panel opinion

• Device description:

The EVOQUE tricuspid valve replacement system is composed of the EVOQUE valve and its corresponding delivery system, the dilator kit, loading system, stabilizer, stabilizer base, and stabilizer plate. The EVOQUE valve is intended to replace the native tricuspid valve and prevent regurgitation from the right ventricle into the right atrium. The EVOQUE valve has a dual nitinol frame construction: an inner frame to house a tissue valve using bovine pericardial leaflets and a compliant outer frame with several axisymmetric anchors that engage with the native anatomy to enable anchoring and positioning. The prosthetic valve is delivered percutaneously via femoral vein access. The intended purpose within the current submission is the treatment of patients with severe tricuspid regurgitation who remain symptomatic on medical therapy and in whom no other surgical or transcatheter treatment option exists per heart team decision.

• Novelty:

All aspects of the EVOQUE tricuspid valve replacement system are novel with the exception of the inner tissue valve using bovine pericardial leaflets. In other words, the inner and outer nitinol frames, anchoring system, delivery system and loading system are all novel. It is also the first tricuspid replacement system to apply for the conformity assessment required for CE marking. Considering the design and procedure novelty, together with the limited clinical data available and the intended purpose of the device, a high level of uncertainty and high level of clinical risk has to be admitted.

Adequacy of clinical evidence assessment by notified body:

The NB adequately assessed and resumed the available evidence. The only aspect to point out is that the data provided is very limited (sample size, follow-up length, study design, etc).

• Sufficiency of clinical evidence:

The EVOQUE tricuspid valve replacement system includes a novel and high-risk biological valvular prosthesis intended to be implanted in severe and refractory patients with prohibited surgical risk and assumed not to be candidates to other percutaneous interventions. The procedure is also novel and to date there are no other tricuspid replacement device systems approved in Europe.

The clinical data comes from the TRISCEND study, a single-arm trial which enrolled 132 patients, of whom only 56 had their visit completed at 6-month follow-up. With regards to the safety outcomes, at 30 days, the rate of Major Adverse Events (MAEs) was 18.5%, including 17.7% of severe bleeding events. During the follow-up, there were 1.6% of non-elective reinterventions. Other performance and efficacy results from the study indicate a good rate of device and procedure success, and good results in terms of Tricuspid Regurgitation (TR) grade reduction and functional results, yet with the same limitation in terms of follow-up duration.

In summary, considering the uncertainty associated with the novelty of the device and the delivery system, the novelty of the procedure and the high-risk profile of the targeted population, it is critical to have access to more robust clinical data. A Randomized Controlled Trial (RCT) comparing percutaneous tricuspid valve replacement against Optimized Medical Therapy (OMT) is essential to understand if the rate of major adverse events associated with the EVOQUE system is balanced by a significant positive benefit. Such a trial design has been requested to support a Food and Drug Administration (FDA) Pre-Market Approval (PMA) request for this device in the United States.

• Adequacy of benefit-risk determination:

The benefit-risk ratio was assessed using only previously published data from cohorts of patients with TR treated with alternative therapies. The NB considered this indirect/historical analysis to be adequate/sufficient. As mentioned in the previous point, one should consider the uncertainty associated with the novelty of the EVOQUE device and delivery system, the novelty of the procedure, and the high-risk profile of the targeted population. Direct comparison in an RCT would be the appropriate study design to evaluate the benefit-risk of the proposed device.

• **Consistency of clinical evidence with purpose / medical indication(s):** The requested intended purpose is generally consistent with the provided clinical evidence. However, as previously pointed out, the study design of the submitted evidence is not optimal to mitigate the relevant uncertainties associated with the complexity and novelty of the device and the procedure.

• Consistency of clinical evidence with PMCF plan:

The NB considered the clinical evidence to support safety and performance claims. The NB also recognized the limitation of long-term follow-up and the inherent risk uncertainty acceptable given that the intended patient population has no other surgical treatment options. However, the NB did not consider the possibility that OMT could have a more favourable benefit-risk profile in this set of patients. The PMCF plan is based on the assumption that this intervention is superior to conservative treatment, which has not been demonstrated.

Overall conclusions and recommendations on clinical evaluation:

The device under assessment is a novel class III device for an also novel high-risk valvular replacement procedure intended to be used in patients with severe tricuspid regurgitation who are not candidates to alternative interventions (percutaneous or surgical). According to all the elements presented in the previous points, the panel's opinion is that a positive benefit-risk ratio for the intended purpose of the device is not sufficiently demonstrated. An RCT with a comparison to OMT alone would be relevant to adequately assess the clinical performance and safety of this novel technology.

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 NB adequately assessed and summarized the evidence provided by the manufacturer. However, there are many limitations in terms of quantity and quality of the data provided (sample size, follow-up duration,

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

study design, etc.). The EVOQUE tricuspid valve replacement system includes a novel and high-risk biological valvular prosthesis intended to be implanted in severe and refractory patients with prohibited surgical risk and assumed not to be candidates to other percutaneous interventions. The procedure is also novel and to date there is no other tricuspid replacement device systems approved in Europe. In the TRISCEND study, a single-arm study used as the main source of clinical evidence which enrolled 132 patients, there were 6 all-cause deaths and the rate of MAEs was 18.5% at 30 days. The rate of MAEs at 1-year follow-up was estimated to be 21.7% based on Kaplan Meier analyses but only 56 patients have completed their 6-month follow-up visits as of the questions the robustness of the estimates at 12 months. The benefit-risk ratio was only assessed considering previously published data from cohorts of patients with tricuspid regurgitation treated with alternative therapies. The NB did not consider relevant to suggest a randomized controlled trial (RCT) comparing percutaneous tricuspid valve replacement against optimized medical therapy, to better understand if the rate of major adverse events associated with the EVOQUE system is balanced by a significant positive benefit.

In summary, the uncertainties associated with the novelty of the device and delivery system, the novelty of the procedure and the high-risk profile of the targeted population are considerable. Based on this, the study design of the submitted evidence (a single-arm study with a small sample size and limited follow-up duration) is not ideal to mitigate the relevant uncertainties associated with the complexity and novelty of the device and the procedure.

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

In section H of the CEAR, the NB has considered that the clinical data presented by the manufacturer did provide sufficient clinical evidence to "demonstrate compliance with the relevant general safety and performance requirements, to support the intended purpose, the claims, and the information in the IFU and SSCP, as well as to indicate if unanswered questions regarding the device under evaluation were remaining".

Of the remaining unanswered questions regarding the device under evaluation, the NB has only indicated that the long-term follow-up was limited but did not describe how this limitation would be overcome with respect to the planed PMCF.

For the EVOQUE system, it is the panel's opinion that the assessment of the sufficiency of the clinical evidence provided by the manufacturer is not fully adequate. Indeed, neither the quantity nor the quality of the clinical evidence has been discussed.

In terms of quantity, the panel's opinion is that the clinical data available to support the benefit-risk ratio positivity of the EVOQUE Valve Replacement System in patients with severe TR is currently mostly based on a prospective single-arm, multicenter, study with incomplete follow-up and recruitment as of the United, of a total of 200 patients planned for enrolment, only 132 have been recruited among 14 sites in the United States (manufactor), date at which results were extracted), which questions the external validity of the findings beyond the current participating centers. Although the current follow-up of the enrolled patients (at 6 months) does cover the time needed to evaluate the primary endpoint (namely freedom from device or procedure-related adverse events at 30 days), the absence of follow-up beyond 6 months (total planned follow-up is 5 years) does not enable the evaluation of the procedure's benefit in the long-term. This is particularly evident for functional endpoints which can be subject to performance bias owing to the open-label nature of the trial. Of note, at 6-month timepoint, of the 94 patients out of 132 who were eligible for visit, only 56 had their visit completed (within or outside window). With regards

to safety outcomes, at 30 days the rate of MAEs was 18.5%, including 17.7% of severe bleeding events. During follow-up, there were 1.6% of non-elective reinterventions. The manufacturer did suggest that Annualized Heart Failure Hospitalizations were reduced 1 year prior and post, but the limited follow-up of patients, as previously emphasised, does limit the validity of these findings. Other main results from the study indicate a rate of 96.2% of device success, 97.5% of procedural success, 80.3% of clinical success, and good results in terms of TR grade reduction and functional results, yet with the same limitation in terms of follow-up duration.

In sum, the panel's opinion is that TRISCEND I is a feasibility study that needs further confirmation given the preliminary nature of results reported so far.

The sufficiency of the clinical evidence should also be assessed in terms of quality. In this regard, the demonstration of clinical benefit for the EVOQUE Tricuspid Valve Replacement System is questionable in the absence of a direct comparison against a group of medically treated patients. The manufacturer mentions in the CER the intention to conduct the TRISCEND II trial, an RCT comparing the safety and efficacy of the EVOQUE system with OMT to OMT alone in patients with severe TR. The study was agreed with the FDA as part of the PMA request for this device. Participating centers will be located in the United States and Germany. In the CEAR, the TRISCEND II trial was quoted as pivotal by the NB but not commented on.

Overall, the panel disagrees with the conclusions of the NB and considers that the clinical evidence provided by the manufacturer is not sufficient to ensure the demonstration of a positive benefit-risk ratio for the intended medical purpose of this device.

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

The NB has assessed the adequacy of the manufacturer's benefit-risk determination by reviewing the section of the CER relevant to "the conformity assessment with requirement on acceptable benefit-risk profile". In this section, the manufacturer has summarised its assessment on the benefits and the risks associated with the EVOQUE device. These were determined based on the preliminary findings from the TRISCEND study (n=132, follow-up of 6 months) together with the compassionate use experience consisting of two case-series (one of 25 patients with 30 days follow-up, and the other based on 27 patients [of whom 25 were included in the previous one] with one year follow-up).

In the CEAR, the NB has reported the main benefits highlighted by the manufacturer for the device but did not provide any critical view on the claimed benefits.

While it can be agreed that the procedure with the EVOQUE system resulted in a reduction of tricuspid regurgitation, the statement that the device "offers a safe treatment option for tricuspid regurgitation" could have been questioned. Indeed, the rate of MAEs at 30 days was 18.5%, including 17.7% of severe bleeding events, affecting nearly one patient out of five.

Similarly, the fact that the device "enables a less invasive tricuspid valve replacement procedure", as indicated by the manufacturer, does not seem to be relevant here since the intended purpose of the EVOQUE system addresses patients in whom no other surgical or transcatheter treatment option exists per heart team decision.

Last, the assertion on "clinical improvements in quality of life, functional status, and exercise capacity" resulting from the use of device should have been critiqued owing to a high risk of performance bias associated with these outcomes obtained from a single-arm open-label study.

While the panel agrees that the feasibility of the procedure has been shown in the TRISCEND study, as evidenced by high rates of technical success, device success, procedural success and clinical success, additional points from the CER may have been overlooked. For example, the statement that a reduction in Heart Failure Hospitalization (HFH) was observed with the EVOQUE system is confusing. Indeed, this effect was seen comparing the incidence of HFH one year prior and post procedure, but not against a control group who didn't undergo the procedure.

When considering alternative treatments in this population, the NB has emphasized the fact that "medical management with medication provides only temporary relief from some symptoms". Considering the population concerned by the intended purpose of the device, namely those patients in whom no other surgical or transcatheter treatment option exists per heart team decision, the panel agrees with the NB that the standard of care is represented by guideline-directed medical therapy (GDMT) which has only symptomatic effect. However, the NB has not discussed, in the benefit-risk determination section, the absence of comparison, whether direct or indirect, between the addition of Tricuspid Valve Replacement with the EVOQUE System to GDMT, versus GDMT alone. This limitation could have been highlighted considering the shortcomings of the presented clinical data (see section 2), and the fact that an RCT, which is currently ongoing to support future submission for FDA approval, would provide a considerably higher demonstration of clinical benefit, hence a higher level of evidence.

Overall, the panel's opinion is that the NB's assessment of the adequacy of the manufacturer's benefit-risk determination is not sufficiently thorough, and that there is not robust evidence yet to demonstrate that the benefits of using this device outweigh the risks.

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

As previously mentioned, the manufacturer requests an approval for an intended purpose generally consistent with the provided clinical evidence. However, as previously pointed out, the study design of the provided evidence it is not sufficient to mitigate the relevant uncertainties associated with the complexity and novelty of the device and procedure. In the panel's opinion, TRISCEND I is a feasibility study that needs further confirmation given the preliminary nature of results reported so far.

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

The PMCF plan was reviewed by the NB in section F of CEAR. Apart of a brief comment indicating that the PMCF plan was deemed appropriate by the NB, very few details were provided by the NB on the PMCF plan and the PMCF study planed was not mentioned, which is why the panel decided to report the main characteristics here. Briefly, the manufacturer has designed the EVOQUE PMCF Study consisting of a multicenter, single-arm, prospective study. Its objective is to collect data on the safety and effectiveness of the EVOQUE system in a post-market setting. A maximum of 500 patients with severe TR will be enrolled at up to 100 centers in Europe. The study has co-primary safety and performance endpoints together with a number of secondary and additional endpoints, with patients being followed-up to 5 years. The panel considers that the design of the EVOQUE PMCF study is appropriate. As part of the PMCF plan, this study will be complemented by the continued follow-up up to 5 years of patients enrolled in the TRISCEND study

and the results from a systematic literature review conducted consistent with the Literature Search and Review Protocol reported in the clinical evaluation report (CER).

Although the results from this RCT will be captured through the process of systematic literature review, the panel considers that the TRISCEND II RCT will represent a major source of additional evidence to support the benefit-risk ratio determination. As a result, the study may have been more highlighted as part of the PMCF plan. Second, it is unclear to the panel why the manufacturer has chosen to design the TRISCEND II as a premarket study only within the scope of future FDA approval in the United States, while it will solely represent a potential source of additional evidence of PMCF within the European market. The panel's opinion is that the results of the TRISCEND II RCT would be of great value to support a positive benefit-risk ratio.

Based on the limitations highlighted above, the panel's opinion is that the NB's assessment of the manufacturer's clinical evidence and its consistency with the PMCF plan is not fully adequate.

2.4 Overall conclusions and recommendations

The device under assessment is a novel class III device for a novel high risk valvular replacement procedure with the intended purpose to be used in patients with severe tricuspid regurgitation who are not candidates to alternative interventions (percutaneous or surgical). According to all of the exposed in the previous points, a positive benefit-risk ratio is not sufficiently demonstrated. A randomized controlled trial with comparison to optimized medical therapy alone would be relevant to properly assess the efficacy and safety of this novel technology.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable²

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.

Not applicable

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions

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.

No divergent positions.

Please indicate how many of the experts of the panel or sub-group had divergent views

No divergent positions.