EUROPEAN COMMISSION

Expert decision and 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	28/04/2022
Notified Body number	0344
Internal CECP dossier # (e.g. 2021-000201)	2022-000216
Medical device type	The [redacted] system is designed to replace the native tricuspid valve. [redacted] The [redacted] valve consists of a trileaflet bovine pericardial tissue valve [redacted] to be implanted in the native valve position.
Intended purpose	The [redacted] 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?	☒ **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 *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
DEVICE: The [redacted] 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 [redacted], but the method for deployment and capture of the free edge of the native tricuspid leaflets (septal, anterior and posterior) is novel. The [redacted] valve does not grasp/facilitate coaptation of the native tricuspid leaflets like other tricuspid valve repair devices. [redacted]

[redacted] This allows for intuitive positioning and use by the operator. [redacted]

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 [redacted]. Materials used are those in current designs of transcatheter heart valves. The manufacturing process for the [redacted] 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. [redacted]

Overall degree of novelty

Level of novelty:

☐ Low level *or*
☐ Medium level *or*
☒ 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 [redacted], at the time of the [redacted] The majority of MAEs were

[redacted] in the [redacted]. In the [redacted]
[redacted]

[redacted]

[redacted]

[redacted]

Device malpositioning (embolization, migrations, and misplacement) is a known potential complication of valve repair/replacement. [redacted]

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 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

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

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	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 [redacted] tricuspid valve replacement system is composed of the [redacted] valve and its corresponding [redacted] The [redacted] valve is intended to replace the native tricuspid valve and prevent regurgitation from the right ventricle into the right atrium. [redacted] 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 [redacted] tricuspid valve replacement system are novel with the exception of the [redacted] tissue valve using bovine pericardial leaflets. [redacted] 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 [redacted] 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 [redacted] study, [redacted]. With regards to the safety outcomes, at 30 days, [redacted]. During the follow-up, [redacted]. 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 [redacted] system is balanced by a significant positive benefit. [redacted]

- **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 [redacted] 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 [redacted] 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 [redacted] study, a single-arm study used as the main source of clinical evidence which [redacted], there were [redacted]. [redacted] which 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 [redacted] 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 [redacted] 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 [redacted] 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 June 2021. [redacted]), which questions the external validity of the findings beyond the current participating centers. [redacted] 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, [redacted] within or outside window). With regards

to safety outcomes, at [redacted]
During follow-up, [redacted]. [redacted]
[redacted] Other main results from the study indicate [redacted], 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 [redacted] 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 [redacted] Tricuspid Valve Replacement System is questionable in the absence of a direct comparison against a group of medically treated patients. [redacted]

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 [redacted] device. These were determined based on the preliminary findings from the [redacted] study ([redacted]) together with the compassionate use experience consisting of [redacted]

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 [redacted] 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, [redacted]

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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] System to GDMT, versus GDMT alone. This limitation could have been highlighted considering the shortcomings of the presented clinical data (see section 2)[redacted].

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, [redacted] 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 [redacted] PMCF Study consisting of a multicenter, single-arm, prospective study. Its objective is to collect data on the safety and effectiveness of the [redacted] 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 [redacted] 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 [redacted] 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).

[redacted]

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 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.
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.