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 decision

This decision reflects the views of independent experts (MDR Article 106) on the relevance to produce an opinion on the clinical evaluation assessment report (CEAR) of the notified body for this device. The expert decision 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).

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 start of procedure	13/11/2025
Notified Body number	NB 0344
Internal CECP dossier #	EMA/EX/0000309556
Medical device type	P0703
Intended purpose	The HighLife TSMVR system is intended for use in a single procedure to provide relief of severe and moderately severe mitral valve regurgitation. The procedure is conducted under anesthesia on a beating heart. Access for the loop placement and sub-annular delivery is through the femoral artery and access for the valve delivery is through the atrial septum via the patient's femoral vein. **Indications:** The HighLife TSMVR system is indicated for the treatment of moderate-to-severe or severe mitral valve regurgitation (MR) due to primary (i.e. degenerative) MR and/or due to secondary (i.e. functional) MR, in patients with left ventricular ejection fraction (LVEF) ≥ 30%, left ventricular end-diastolic dimension (LVEDD) ≤ 70 mm, who do not have severe mitral annular calcification and are deemed unsuitable for surgical repair/replacement and transcatheter edge-to-edge repair, as deemed by a multi-disciplinary heart team.
Risk class / type	Class III
Screening step: medical field / competence area	02 Circulatory system

2. DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

2.1. Decision of the screening experts

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

Date of decision	25/11/2025
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 MDR Annex IX Section 5.1 point c)	
N/A	
Summary as to why there is intention to provide an opinion	
Due to the completely new application system of the device under evaluation (DUE) and the procedurally complex components as the fixation ring, the screening experts consider that the criterion for novelty and related health impact is met. Furthermore, in the event of incorrect device positioning, surgical bailout might be required. Considering the high inter-individual variability of the subvalvular mitral apparatus, correct positioning of the ventricular components must be regarded as highly challenging. The health-associated risks are therefore to be considered very high. For these reasons, the screening experts consider that a scientific opinion from the thematic panel on this device is justifiable.	
Summary as to why there is *no* intention to provide an opinion	
N/A	
Any other comments	
N/A	

2.2. Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact

1.1 Overall degree of novelty

☐ No novelty: Neither device nor clinical procedure is novel
☐ Low level of novelty
☐ Medium level of novelty
☒ High level of novelty

Short description of the novelty, including main dimension(s) of novelty

The DUE, HighLife, is a Trans-Septal Mitral Valve Replacement System (TSMVR) that offers new possibilities to treat insufficient mitral valves using a novel technique.

HighLife TSMVR implantation uses transfemoral retrograde (transaortic path) approach for the subannular implant plus a transseptal approach for the valve implantation. Existing devices use a transapical or exclusively transseptal route. In addition, the anchoring technique is new, using a counter-ring that is introduced during the procedural intervention and assembled inside the patient.

1.2 Possible negative clinical / health impact resulting from novelty

Estimated* possible clinical and/or health impact related to the novel aspects of the device

* 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.

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

Possible major clinical or health impact related to the novel aspects of the device

The DUE aims to treat a population already well-identified with a need for new treatments. However, this approach is very novel and requires a specifical surgical training, what has an impact on overall safety and clinical performance of the device.

Furthermore, in the event of incorrect device positioning, surgical bailout might be required. Although the results of the clinical research carried out are favourable, the procedure is expected to be highly complex and unpredictable in its management at the level of the subvalvular apparatus for the anchoring system. Considering the high interindividual variability of the subvalvular mitral apparatus, correct positioning of the ventricular components must be regarded as highly challenging.

The health-associated risks are therefore to be considered high.

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 the secretariat:	☐ Yes ☒ No
2.2 Other information available to the 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 the secretariat?	☐ Yes ☒ No

2.3. 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 and dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry
☐	**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	20/12/2025
Expert panel name	02 Circulatory system
Sub-group of expert panel (where relevant)	Prosthetic heart valves

2.2. 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 manufacturer's clinical evaluation report
The expert panel acknowledges that the Notified Body (NB) performed a systematic and organized assessment of the manufacturer's clinical evaluation assessment report (CER). The clinical evaluation assessment report of the notified body (CEAR) reflects a correct understanding of the innovative nature of both the device's design and the implantation procedure. However, the panel considers that the CEAR would benefit from a more detailed and critical appraisal of certain methodological aspects of the clinical evidence. In particular, there is no discussion on the early discontinuation of the HL-2016-01 early feasibility study. Furthermore, while procedural unsuccessful implantations are reported, their implications for the overall robustness and reproducibility of the clinical results are not discussed in sufficient depth (the panel acknowledges that the NB provided further details on this analysis during the discussion meeting held for this procedure). The potential impact of surgeon's experience and the learning curve effects associated with the novel implantation technique could also have been addressed more explicitly (the NB also provided more details on this during the discussion meeting). Overall, while the CEAR provides a structured overview of the available clinical data, the panel is of the opinion that a more granular and critical analysis of the limitations of study HL-2018-01-TS could have been presented.

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

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

The clinical data presented for the assessment comes from HL-2018-01-TS, a manufacturer-sponsored single-arm clinical investigation of the use of the HighLife system in high-surgical-risk patients with moderate-to-severe or severe mitral regurgitation (MR).

This prospective, non-randomized trial uses endpoints defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria[2] and predefined the acceptance criteria benchmarked against state-of-the-art Transcatheter Mitral Valve Replacement (TMVR) procedures (e.g., [redacted].

The analysis cohort is composed of the first 80 patients with complete 1-year follow-up data from HL-2018-01-TS and all safety/performance endpoints were calculated using their parameters as baseline. The study will remain actively recruiting patients until it reaches 120 patients. The HL-2018-01-TS study will be continued to collect long-term safety and performance data as part of HighLife's post-market clinical follow-up program with a follow-up to 5 years.

The main results of this study are presented in tables 1 and 2.

Table 1: Clinical performance

Primary performance endpoint	**Timepoint**	**Acceptance criteria (vs. comparators like [redacted])**	**Observed results (n=80)**	**Criteria met?**
Mitral Regurgitation (MR) improvement (≤1+)	1 year	98–100%	100%	Yes
Secondary performance endpoints	**Timepoint**	**Acceptance criteria (vs. comparators like [redacted])**	**Observed results (n=80)**	**Criteria met?**
NYHA better than III/IV	1 year	72–87%	81.6%	Yes
Technical success (patient survival with successful device placement in intended location and acceptable function at procedure-room exit)	Procedure exit	82–95%	87.5%	Yes
6-Minute Walk Test (6MWT) improvement	1 year	≥40.1 m	+44 m	Yes
Kansas City Cardiomyopathy Questionnaire (KCCQ) improvement	1 year	Mean ~21.9 points	+17.7 points	Yes

[2] Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium, JACC, Vol 66, 3, 2015, Pages 308-321, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2015.05.049.

Table 2: Clinical safety

Primary safety endpoint	**Timepoint**	**Acceptance criteria (vs. comparators like [redacted])**	**Observed results (n=80)**	**Criteria met?**
All-cause mortality	1 year	24–38%	27.5%	Yes
Secondary safety endpoints (incidence event rate)	**Timepoint**	**Acceptance criteria (vs. comparators like [redacted])**	**Observed results (n=80)**	**Criteria met?**
Cardiovascular mortality	1 year	14–31%	22.5%	Yes
Intraprocedural mortality	Day 0	0%	0%	Yes
Heart failure hospitalisation	1 year	22–41%	26.3%	Yes
Left ventricular outflow tract obstruction (LVOTO)	1 year	0.01–2%	0%	Yes
Myocardial infarction (device/procedure-related)	1 year	1–10%	1.3%	Yes
Major Paravalvular Leak	1 year	0.01–3%	2.7%	Yes
Valve thrombosis	1 year	2–12%	0%	Yes
Device hemolysis	1 year	0.6–8%	0%	Yes
Endocarditis	1 year	0.02–7%	1.3%	Yes
Major/life-threatening bleeding (MVARC-2)	30 days	13–29%	12.5%	Yes
Disabling stroke	1 year	0.6–8%	3.8%	Yes

The study met the primary performance endpoint of mitral regurgitation (MR) grade reduction to none or trace/mild (≤1+) 1 year after the intervention, as all the 80 patients observed had a MR reduction to a grade ≤1+.

Technical success according to the MVARC criteria was 87.5%, with no intraprocedural deaths. The symptomatic status also improved substantially as 81.6% of patients were in a NYHA I–II class at 1 year, consistent with effective relief of heart failure symptoms.

The study also met the primary safety objectives, including a 30-day composite safety profile benchmarked against state-of-the-art TMVR devices (e.g., [redacted]).

Functional capacity showed a mean 6-minute walk test increase of +44 m at 1 year (from a ~270 m baseline), suggesting durable improvement in exercise tolerance. Health-related quality of life improved with a mean Kansas City Cardiomyopathy Questionnaire (KCCQ) increased 17.7 points at 1 year.

In the study, all predefined safety endpoints met their acceptance criteria: intraprocedural mortality was 0% (0/80) and 1-year all-cause and cardiovascular mortality were 27.5% and 22.5%, respectively, both within the expected ranges for this extreme-risk MR population. The hospitalisation for heart failure at 1 year was 26.3%, consistent with comparator ranges used for the acceptance criteria.

The study design is generally in agreement with recent European recommendations[3] suggesting the testing of high-risk medical devices against objective performance criteria as part of early clinical studies.

Left ventricular outflow tract obstruction rate was 0% at 1 year and valve thrombosis rate 0% at 1 year, both acceptable for this TMVR design. Major/fatal bleeding at 30 days was 12.5% and disabling stroke at 1 year was 3.8%, both within the predefined acceptable ranges and comparable to state-of-the-art TMVR interventions. Major paravalvular leak at 1 year was 2.7%, indicating good sealing and anchoring performance.

The panel recognises that the NB has considered the potential clinical benefits of the device in a patient population with limited therapeutic options and high unmet medical need. The CEAR reflects an understanding of the potential benefits of a transcatheter alternative for highly selected, inoperable or Transcatheter Edge-to-Edge Repair (TEER)-unsuitable MR patients and the evidence presented for the clinical assessment seems to point in that direction. However, it should remain within experienced centres and be accompanied by robust longitudinal follow-up and future confirmatory studies with comparative design[3].

Nevertheless, given the high degree of device and procedural novelty, the panel considers that the benefit–risk determination could be further substantiated. In particular, the consequences of procedural failure or device malposition, which may require surgical bailout, represent a clinically significant risk that warrants careful weighting in the benefit–risk analysis.

The reported rate of unsuccessful procedures in the clinical studies, while expected in early clinical experience, raises questions regarding the use of this device in the context of routine clinical

[3] Fraser AG, Buccheri S, Byrne RA et al. CORE–MD Consortium. Recommended methodologies for clinical investigations of high-risk medical devices-Conclusions from the European Union CORE-MD Project. Lancet Reg Health Eur. 2025 Sep 15;58:101460. doi: 10.1016/j.lanepe.2025.101460. PMID: 41262422; PMCID: PMC12624797.

application. The panel notes that these aspects are acknowledged but not fully explored in the CEAR's benefit–risk analysis.

In summary, while the NB's conclusions regarding a positive benefit–risk balance are supported in light of the target population, the panel considers that a more explicit discussion of clinical uncertainties would enhance the robustness of the benefit–risk determination, namely due to the limited sample size of the clinical investigation and its generalisability to routine clinical use.

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

The panel agrees that the clinical evidence generated by the manufacturer aligns with the intended purpose of treating severe mitral valve regurgitation in selected high-risk patients. The clinical investigation focuses on the target population described in the intended purpose, and the surgical procedural approach is consistent with the proposed indication.

However, the panel notes that the available clinical evidence is derived from a relatively limited and highly selected patient cohort treated in experienced centres. As such, the generalisability of the results to a broader clinical practice remains uncertain.

In addition, the anatomical variability of the subvalvular mitral apparatus represents a critical factor for procedural success. While this variability is acknowledged, the extent to which the existing clinical data sufficiently captures this heterogeneity is not fully demonstrated.

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

The manufacturer proposed specific activities for the PMCF-plan to address residual uncertainties associated with the device's clinical performance and safety. These are summarised in Table 3.

Table 3: Summary of the PMCF plan

Proposal	Description	Number of patients	Follow-up Duration
HL-2018-01-TS Pivotal Expanded Clinical Investigation	Continuation of the ongoing pivotal study after CE-mark to gather further data. First 80 patients provided primary evidence for CE-mark; expansion to support long-term monitoring.	Up to 120	Up to 5 years
Post-Market Registry Study	Initiation of a new registry post-CE-mark to gather real-world data.	Minimum 30 (contributes to a total of ≥150)	Up to 3 years

Given the high level of novelty and procedural complexity, the panel considers that the post-market clinical follow-up will be essential to further characterise long-term outcomes, durability, and the management of procedural failures. The alignment between the current level of clinical evidence and the objectives of the PMCF plan is generally appropriate.

However, the panel recommends that careful consideration should be given to ensure that the PMCF plan execution adequately captures clinically relevant information, including procedural success,

reinterventions, and outcomes related to device malposition or failure. The duration of follow-up and the inclusion of a sufficiently broad patient population is important to reduce remaining uncertainties.

2.3. Summary of expert panel opinion

The DUE is a novel transcatheter system intended for the treatment of severe mitral valve regurgitation in patients at high surgical risk. It employs an innovative implantation approach with a unique anchoring mechanism with an assembled counter-ring.

The expert panel considers that the NB has conducted a structured and generally appropriate assessment of the manufacturer's clinical evaluation. The CEAR acknowledges the innovative nature of the device and the unmet medical need of the target population.

However, the panel identified areas where the assessment could be strengthened, particularly regarding the limited size of the clinical dataset, the impact of procedural deviations, and the implications of the learning curve of the heart team for the maximisation of the safety and clinical performance of the device.

With respect to the benefit–risk determination, the panel recognises the potential clinical benefit for a selected high-risk population but notes that the risks associated with the procedural complexity and failure scenarios warrant careful consideration. The current benefit–risk ratio appears to be acceptable, but this is still uncertain due to limited clinical experience.

The panel considers that the available clinical evidence is broadly consistent with the intended purpose and clinical indication. Generalisability to a wider clinical practice remains to be demonstrated.

The proposed PMCF plan is appropriate in scope and will play a critical role in addressing remaining uncertainties related to long-term safety, performance, and durability.

2.4. Recommendations

The expert panel concludes that the NB's assessment of the clinical evaluation is broadly adequate but would benefit from a more detailed consideration of the limitations inherent to the available clinical evidence. In particular, the panel recommends:

- Further characterisation of procedural success and failure modes of the device
- Explicit consideration of the impact of the learning curve
- Continuous evaluation of the benefit–risk as additional clinical data becomes available
- Gathering comprehensive post-market clinical follow-up data to address residual uncertainties and long-term safety and performance of the device.

2.5. Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
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.
N/A

2.6. Divergent positions in case no consensus was reached

Number of experts of the panel/sub-group with divergent views
None
Summary of divergent positions
N/A

[4] 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.