



Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

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

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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	29/09/2025
Notified Body number	NB 0344
Internal CECF dossier #	EMA/EX/0000296384
Medical device type	Cardiac shunt device
Intended purpose	Intended to reduce elevated left atrial pressure (LAP) and preserve right heart function through transcatheter placement of a left atrium to coronary sinus shunt.
Risk class / type	Class III
Screening step: medical field / competence area	02 Circulatory system

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	07/10/2025
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 5.1point c)	
N/A	
Summary as to why there is intention to provide an opinion	
The device under evaluation possesses a high level of novelty and a high level of clinical impact.	
Summary as to why there is <u>no</u> intention to provide an opinion	
N/A	
Any other comments	
N/A	

1.2 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 device under evaluation is based on a new technology and is the first of its kind, with no equivalent or benchmark devices on the market. There is a high level of novelty in procedural details as well as device novelty.

Currently available devices on the market target the foramen ovale as the location to create an interatrial shunt in the mid-septum that results in shunting of blood flow from the left atrium (LA) to right atrium (RA). The device presented herein is differentiated from these devices as the shunt location preserves the natural flow path for blood entry into the RA by shunting via the coronary sinus (CS).

Shunting procedures which are performed now by intracardial septum-shunting are translocated to epicardial anatomical structures. Here, puncture related complications and bleedings into the pericardium may result that are highly uncommon in intracardial procedures. Moreover, management of these complications associated with bleedings from the coronary venous sinus to the pericardium is highly sophisticated and needs with respect to the magnitude of the shunt surgical intervention should be reviewed. Thus translocating the shunt-procedure to the epicardium means a high increase of the risk.

Traditional indications for shunting procedures are a) "infants with cyanotic heart disease" and b) "atrial septostomy in WHO Group 1 pulmonary hypertension patients". Here HFpEF and HFmrEF with an LVEF > 40% are addressed, which is a new cohort for this indication.

The device is the only LA to CS shunt and is novel in the way that its mechanism of action is to shunt blood from the higher-pressure LA to the CS and then to the lower pressure RA, the atrial septum is preserved as an access route for future interventions.

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

☒ High clinical or health impact

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

Anticipated adverse events within 1 year related to standard cardiac catheterization, the use of anaesthesia, and use of the APTURE transcatheter shunt system include but are not limited to:

cardiac arrest, cardiogenic shock, conduction system injury (defect) which may require replacement or implantation of a pacemaker (temporary or permanent), death, stroke or transient ischemic attack, valve damage including leaflet damage, chordal damage or rupture, pericardial bleeding, surgical intervention.

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 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 ☒ 3. Cardiac surgery ☐ 4. Structural interventions ☐ 5. Active implantable cardiac devices and electrophysiological 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	25/11/2025
Expert panel name	02 Circulatory system
Sub-group of expert panel (where relevant)	Cardiac surgery

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
<p>The panel concurs with the Notified Body's (NB) assessment that the clinical evidence provided by the manufacturer is adequate and sufficient to demonstrate the preliminary safety and clinical performance of the APTURE Transcatheter Shunt System, a very novel medical device. The CEAR provides sufficiently detailed information to support this conclusion.</p> <p>The main sources of clinical data include a First-In-Human study using compassionate-use cases (n=11) and the ALT-FLOW I study (NCT03523416 and NCT04000607). The ALT-FLOW I study was a prospective, multicentre, single-arm feasibility investigation evaluating the Edwards Atrial Flow Regulator (ALT-FLOW System) in patients with heart failure with preserved or mildly reduced ejection fraction (HFpEF/HFmrEF) who remained symptomatic despite optimal medical therapy. A total of 116 patients underwent successful percutaneous implantation and were followed for up to 24 months.</p>
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
<p>The panel agrees with the Notified Body's assessment of the manufacturer's benefit-risk determination for the device under evaluation (DUE), also taking into consideration the high degree of novelty of the device and the inherent uncertainties linked to its use.</p>

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

The ALT-FLOW I was the main source for the clinical data considered for this evaluation. This study recruited a total of 95 patients and had the following endpoints:

- **Primary safety endpoint:** composite of major adverse cardiac, cerebrovascular, and renal events (MACCRE), as well as any reintervention for study device-related complications occurring within 30 days post-implantation.
- **Clinical performance endpoints:**
 - **Device success:** Deployment of the device as intended and successful removal of the delivery system upon completion of the implant procedure.
 - **Procedural success:** Device success with confirmed shunt patency and hospital discharge without the need for any additional surgical or percutaneous intervention related to the study device, including interventions due to unacceptable Qp/Qs values.
 - **Clinical success:** Procedural success without MACCRE and without reintervention for study device-related adverse events within 30 days.

The endpoints of the ALT-FLOW study were appropriately designed to address the intended purpose of the device and to evaluate its clinical benefits, performance, and safety. These endpoints were defined and assessed using scientifically valid methodologies, as documented in the Clinical Evaluation Report (CER) and in the related publication².

In the ALT-FLOW I study, at 1-year follow-up, MACCRE or reintervention through 30 days occurred in 2.6% of the enrolled population. The device was successfully implanted in 90.5% of subjects, with 89.7% of device success, 88.8% of procedural success, and 87.9% of clinical success. At one year, the rate of cardiovascular mortality was low (2.6%), and heart failure-related hospitalizations occurred in 9.5% of patients².

Data from this single-arm experience demonstrated an acceptable safety profile and favourable clinical outcomes in implanted patients with LVEF >40%, including those with pre-existing pulmonary vascular disease (PVR ≥ 2 WU) or advanced heart failure. The device was associated with sustained reductions in pulmonary capillary wedge pressure (PCWP) and pulmonary capillary wedge load (PCWL) without adverse impact on the right heart function, together with clinically meaningful improvements in heart failure symptoms, exercise capacity, and quality of life throughout the reported follow-up period.

The panel also reviewed the data published regarding the 2-year follow-up of the ALT-FLOW I study³.

The primary hemodynamic signal was a substantial reduction in exercise PCWL, reflecting lower pulmonary capillary wedge pressure at a given workload and body weight. Mean PCWL fell from 131

² Urey MA, Hibbert B, Jorde U, et al. Left atrial to coronary sinus shunting for treatment of heart failure with mildly reduced or preserved ejection fraction: The ALT FLOW Early Feasibility Study 1-year results. *Eur J Heart Fail.* 2024 Apr;26(4):1065-1077. doi: 10.1002/ejhf.3241. Epub 2024 Apr 12. PMID: 38606485.

³ Fioretti F, Hibbert B, Eckman PM, Simard T, Labinaz M, Nazer B, Wiley M, Gupta B, Sauer AJ, Shah H, Sorajja P, Pineda AM, Missov E, Aldaia L, Koulogiannis K, Gray WA, Zahr F, Butler J. Left Atrial-to-Coronary Sinus Shunting in Heart Failure With Mildly Reduced or Preserved Ejection Fraction: The ALT-FLOW Trial (Early Feasibility Study) 2-Year Results. *JACC Heart Fail.* 2025 Jun;13(6):987-999. doi: 10.1016/j.jchf.2025.02.003. Epub 2025 Feb 11. PMID: 40019407.

± 74 mm Hg/W/kg at baseline to 76 ± 57 mm Hg/W/kg at 6 months ($P < 0.0001$), indicating meaningful unloading of the LA during exertion, which is central to HFpEF pathophysiology.

82.3% of evaluable patients (51/62) demonstrated an improvement in NYHA functional class, suggesting sustained symptomatic benefit. KCCQ scores improved by roughly one to one-and-a-half clinical categories: CSS $+25 \pm 20$, TSS $+26 \pm 23$, and OSS $+31 \pm 23$ points, all beyond the usual thresholds for a large, clinically important improvement.

These results seem to suggest that creating a LA-to-CS shunt with this device in HFpEF/HFmrEF patients is associated with durable hemodynamic and symptomatic benefit, without evident adverse remodelling of either ventricle.

Although the CS is smaller than the RA, it functions as a compliant conduit draining directly into the RA and central venous system rather than acting as a confined venous compartment. Consistent with this physiology, clinical data from ALT-FLOW I show effective left-atrial unloading without any increase in right-atrial pressure.

Theoretical concerns such as elevation of cardiac venous pressures, venous congestion, or impaired right-heart function are not supported by the available human data. Follow-up at 6, 12, and 24 months shows stable right-sided haemodynamics, no evidence of coronary venous hypertension, and no deterioration in RV structure or function despite sustained shunt patency. Concepts such as “natural flow patterns” into the RA remain mechanistic, yet the absence of adverse right-heart changes indicates that the drainage pathway does not create the anticipated hemodynamic burden.

Potential complications like coronary venous congestion or new or worsening heart failure are therefore included in the PMCF plan out of standard precaution for a heart-failure population, rather than based on any observed pathophysiological signal, as current evidence does not demonstrate these theoretical risks in clinical practice.

Based on the available clinical evidence, the use of the DUE in patients with symptomatic heart failure demonstrated an acceptable safety profile and resulted in reductions in PCWP, together with clinically meaningful improvements in heart failure symptoms and quality-of-life parameters.

The panel also notes that this is a nonrandomized, early-feasibility study, i.e., these data are hypothesis-generating rather than practice. However, the combination of durable patency, significant exercise hemodynamic improvement, and large, sustained gains in NYHA class and KCCQ is acknowledged.

The panel also highlights that ALT-FLOW II, a large, prospective, multicentre, randomized, sham-controlled, double-blinded clinical investigation (NCT05686317) is ongoing, and no preliminary data is available. Consequently, the current benefit-risk assessment is based primarily on early feasibility data and must be regarded as preliminary.

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 intended purpose of the device is to reduce elevated left atrial pressure (LAP) and preserve right heart function through transcatheter creation of a left atrium-to-coronary sinus (LA-CS) shunt in

patients with heart failure with preserved or mildly reduced left ventricular ejection fraction (LVEF > 40%) and elevated LAP who remain symptomatic despite guideline-directed medical therapy.

The ALT-FLOW I and II studies details (including the study design, methodology, patient population, results, and conclusions, are described in the Clinical Evaluation Report (CER). While the inclusion and exclusion criteria were broadly aligned with the intended purpose, it is noted that the ALT-FLOW I study also enrolled patients with reduced LVEF, although this group was not considered for the current intended purpose. Nevertheless, the overall study population and the outcomes reported are considered generally consistent with the claimed indications and intended purpose of the DUE as currently defined.

Accordingly, the panel concurs with the NB's assessment that the clinical data are consistent with the claimed intended purpose, acknowledging that the evidence available primarily supports the use of the device in patients with LVEF > 40%.

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

The panel agrees with the NB's assessment of the proposed Post-Market Clinical Follow-up (PMCF) strategy presented by the manufacturer. The plan includes gathering additional data from the ALT-FLOW I and from the ALT-FLOW II and APTURE PMS studies. All three will support the continued evaluation of the safety and performance of the DUE.

The ALT-FLOW II Study (NCT05686317⁴) is a prospective, multicentre, randomized, sham-controlled, double-blinded clinical investigation assessing the safety and performance of the device in patients with HFpEF/HFmrEF (LVEF > 40%) who remain symptomatic despite guideline-directed medical therapy. Published clinical data identified through systematic literature review will complement these studies to confirm the long-term safety and performance of the device, monitor known and emerging risks, and ensure the ongoing acceptability of the benefit-risk profile.

The manufacturer also plans a post-market study, the APTURE PMS, that will include approximately 150 patients treated with the DUE and with a minimum follow-up of two years to further substantiate the device's safety and performance during routine clinical use.

In addition, systematic literature reviews and vigilance data will be used to confirm the continued safety and performance of the device throughout its expected lifetime, to identify any previously unrecognized or emergent risks, and to ensure that the benefit-risk ratio remains acceptable.

The PMCF activities are therefore well aligned with the intended purpose of the device, the current level of clinical evidence, and the need for confirmatory data on long-term outcomes.

2.3 Summary of expert panel opinion

Introduction

⁴ <https://www.clinicaltrials.gov/study/NCT05686317#study-overview>

The APTURE Transcatheter Shunt System is a novel device designed to reduce elevated LAP and to preserve right-sided cardiac function by creating a controlled shunt between the left atrium and the coronary sinus (LA-CS) using a transcatheter approach. The device is intended for use in patients with heart failure with preserved or mildly reduced left-ventricular ejection fraction (HFpEF /HFmrEF; LVEF>40%) who remain symptomatic despite guideline-directed medical therapy (GDMT). The implantation procedure is performed percutaneously under imaging guidance and aims to decompress the left atrium, thereby lowering LAP, reducing pulmonary congestion, and improving exercise capacity and quality of life.

Overall opinion of the Notified Body's assessment

The panel agrees that the NB has conducted a thorough and methodologically sound assessment of the clinical evaluation. The NB's review appropriately reflects the quantity and quality of the available clinical data and provides a clear rationale supporting the preliminary demonstration of safety and performance of the APTURE system within its intended purpose. The CEAR offers sufficient detail to show that the clinical evidence has been critically appraised, that the endpoints used are relevant to the claimed indications, and that the remaining gaps have been identified and addressed through the manufacturer's PMCF strategy.

Adequacy of benefit-risk determination

The panel considers that the benefit-risk determination is adequate, also considering the degree of novelty of the device. The clinical endpoints used in the ALT-FLOW programme were appropriate to assess the intended therapeutic purpose and to evaluate both safety and clinical performance.

The results available from the ALT-FLOW I study demonstrate procedural feasibility, high implantation success, and a low incidence of MACCRE or reintervention at 30 days. Reported improvements in PCWP and patient-reported outcomes suggest a potential clinical benefit.

However, the panel notes that ALT-FLOW II clinical investigation is still ongoing and no results are available. Consequently, the current benefit-risk assessment is based primarily on early feasibility data and must be regarded as preliminary.

Consistency of clinical evidence with intended purpose and medical indication(s)

The clinical evidence presented is broadly consistent with the device's intended purpose and medical indications. The ALT-FLOW I feasibility study, together with compassionate-use data, supports use in patients with LVEF>40% who remain symptomatic despite GDMT. Although ALT-FLOW I also enrolled a small subset of patients with reduced LVEF, most data are relevant to the currently claimed indication. The observed reductions in LAP and improvement in functional parameters correspond to the proposed mechanism of action and intended clinical benefit. The panel concludes that the available data are consistent with the stated intended purpose, while acknowledging that confirmation in a larger controlled population is warranted.

Consistency of clinical evidence with PMCF plan

The manufacturer's PMCF plan is coherent with the existing clinical evidence and appropriately designed to address the residual uncertainties identified in the clinical evaluation. Evidence will

continue to be generated from ongoing studies to further evaluate the long-term safety and performance of the device. The manufacturer also plans a dedicated post-market study that will include approximately 150 patients treated with the device and with at least two years of follow-up.

In summary, the panel considers that the NB's assessment is methodologically appropriate and balanced. The current clinical data adequately support the preliminary demonstration of safety and performance of the DUE, while recognising that confirmation of sustained benefit and long-term safety will depend on the completion of ongoing studies.

2.4 Recommendations

N/A

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable⁵

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

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

None

Summary of divergent positions

N/A

⁵ 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.