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	22/07/2022
Notified Body number	0344
Medical device type	The application concerns the [redacted] device, an iron alloy bioabsorbable stent.
Intended purpose	The [redacted] device is intended to improve the lumen diameter of the pulmonary blood vessels for the treatment of heart congenital diseases of pulmonary vessels in newborns and infants.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Circulatory system - Cardiovascular stents (metallic and bioresorbable) and vascular prostheses

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	10/08/2022
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 MDR Annex IX Section 5.1 point c)	
N/A	
Summary as to why there is intention to provide an opinion	
The device analysed here is a completely new market launch, that has never been marketed before in the EU. In relation to clinical performance, only 2 limited studies in human are available, which reveal a clear risk potential. During follow up, severe health issues occurred during the follow up period.	
Summary as to why there is *no* intention to provide an opinion	
N/A	
Any other comments	
No additional comments.	

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 DESCRIPTION: The device is an iron bioresorbable scaffold comprised of two main components, the 1) iron bioresorbable scaffold and the 2) balloon expandable delivery system. The claimed indication is to improve the lumen diameter of the pulmonary blood vessels of newborns and infants who require stent treatment, with reference vessel diameters of 2,25 to 4,25 mm and target segment length ≤ 35 mm. The pulmonary blood vessels include the right ventricular outflow tract, pulmonary trunk, branch pulmonary artery and ductus arteriosus. DEVICE NOVELTY: The [redacted] stent is the first iron bioresorbable scaffold specialized for improving the lumen diameter of the ductus arteriosus in clinic, so the device is not equivalent to any existing device. The device was developed based on IBS Sirolimus-eluting Iron Bioresorbable Coronary Scaffold System (IBS). PROCEDURE NOVELTY: For Persistent Ductus Arteriosus (PDA) treatment, the available treatment options are PDA stenting with permanent coronary stent, Blalok-Taussig shunt (B-T shunt) and medicine treatment (e.g. Alprostadil). So the procedure is not novel, as PDA stenting has been widely reported in the literature.
Overall degree of novelty
☐ Low level *or* ☐ Medium level *or* ☒ High level ☐ Not Applicable (neither the device nor the procedure is novel)
Uncertainties related to novelty
Uncertainties derive from: 1) Long term device durability in this setting is unknown. 2) The number of patients treated is very low (Chinese study, 45 patients with coronary artery disease treated with the device and the Malaysian study, 35 patients included, 32 of them treated with PDA stenting). The reported outcomes lack long follow up.
1.2 Possible negative clinical / health impact resulting from novelty
A pre-market **clinical study is being carried out in Malaysia.** This is a prospective, non-randomized clinical trial that evaluates the safety and efficacy of the device. The study has enrolled 35 patients, and

32 patients of them have received PDA stenting. 100% patients successfully implanted the [redacted] Scaffold. The procedural angiography images demonstrated that every patient had good stent flow immediately after stent implantation. During the limited available follow up, the reintervention rate was 12,5%, mainly due to restenosis. There were 3 patients who died during follow-up (mortality rate 9,38%), apparently not related to the device.

The **study carried out in China** was a prospective, non-randomized clinical trial to evaluate the feasibility, safety and effectiveness of IBS. A total of 45 subjects with primary, in situ, single coronary artery stenosis were included in the study. The immediate success rate was 100 % (45/45). There were no intra-procedure complications related to device. At 6-month follow-up, there was one serious adverse event related to the device (2,2%). At 2-year follow-up, there were three serious adverse events related to the device (6,7%).

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.

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

Uncertainties related to clinical/health impact

The claimed indication for the device is to improve the lumen diameter of the pulmonary blood vessels of newborns and infants who require stent treatment. The pulmonary blood vessels include not only ductus arteriosus, but also the right ventricular outflow tract, pulmonary trunk and branch pulmonary arteries. All the reported experience is focussed on PDA stenting. This means that the clinical impact of the claimed indication out of PDA stenting is uncertain.

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	23.09.2022
Expert panel name	Circulatory System
Sub-group of expert panel (where relevant)	Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses

2.2 Summary of expert panel opinion

- The device is a bioabsorbable stent system mounted on a balloon made of pure iron coated with pure zinc and polylactic acid. In the preclinical animal studies and in the clinical trial in Malaysia the intended purpose of the device is to improve the diameter of the persistent ductus arteriosus (PDA) in newborn and infants with a vessel diameter between 2,25 and 4,25 mm diameter and treatment length ≤35 mm. In the clinical trial 32 out of 35 patients were treated with PDA, and in 3 patients the device was implanted in other pulmonary vessels.
- The indication are cyanotic congenital heart diseases by a right to left shunt with palliative treatment to keep the ductus arteriosus patent. The procedure is an alternative to the open Blalock-Taussig shunt. This indication is believed to be a group of rare diseases and the global prevalence is about 67.000 cases per year.
- Up to date, there is no special designed stent on the market for this indication, the standard treatment is the Blalock-Taussig shunt, where a direct connection between the aorta (or subsequent branches) and the pulmonary circulatory is made. There are several reports, where coronary drug eluting stents were used for minimally invasive procedures with comparable results to the Blalock-Taussig shunt. The novelty of this device is that it is bioabsorbable. However, at the moment with the available data it is not clear how the exact absorption profile is and when the device is completely absorbed. In the Post-Market Clinical Follow-up (PMCF) plan, the manufacturer states that the device expires after one year and five months. If this should outline the complete absorption, it is not clear where the data comes from. The only available "long-term" data is an explantation 16 months after implantation. According to the manufacturer: *"the weight loss degradation was more than 60% and the scaffold degradation was obvious"*.
- The manufacturer presents preclinical and clinical data.

  In the preclinical animal testing 36 pigs were tested. The stent was implanted in the coronary arteries and not in the ductus arteriosus as intended for use. Nevertheless, there is no animal model specifically adequate for this condition and the intend of the experiments was the evaluation of the device in the sense of *in vivo* behaviour like endothelialisation, degradation, migration. So, the approach is acceptable. The degradation was absent until day 90 and partial at time point 180 days (the last examined time point). Endothelialisation was almost completed after 14 days, so faster as

the compared (a drug coated coronary stent). This was anticipated as the drug coating is used to slow down endothelialisation. Consistently the stenosis rate by neointimal hyperplasia was higher with the device under assessment than the comparative product (drug coated coronary stent). The effect of the restenosis rate remains unclear. No iron overload or other toxic side effects were seen.

- In the clinical trial in Malaysia 35 patients were enrolled: 32 who received ductus arteriosus stenting, 2 received right ventricular outflow stenting and 1 received pulmonary atresia stenting. The study started in 2018 with the maximum follow-up of 12 months. Not all patients had a complete follow up at the timepoint of the CER: 21 out of 32 cases completed a 1 year follow up. Mortality rate was 9,38%, which is similar to other reports and lower than with the Blalock-Taussig shunt. Unplanned reintervention rate was 12,5% what is also similar to other reports.
- Another clinical trial was conducted in China. Here 45 patients with coronary stenosis were treated with a device similar to the study device but coated with sirolimus. The purpose was to study the feasibility and safety of the scaffold. This trial is still running and the follow up time will be 5 years. This data is for the intended use of low interest because the implantation site is different as well as the age of the treated patients (adult population). The available follow up is no longer than in the trial in Malaysia. This study might be of interest as regards the absorption rate of the stent after completion of the follow up of 5 years.

  In all investigations the focus was on persistent ductus arteriosus stenting. Only 3 individuals received stenting other than the PDA in the clinical trial in Malaysia. The intended use was in all manufacturer's documents to improve the lumen diameter of the PDA in newborn and infants. A demonstration of equivalence was not done due to the fact, that the study device is unique.
- A major concern is the low number of treated patients in the clinical study and that the clinical data is based on results from only 32 patients. On the other hand, it must be stated, that the prevalence of the disease is also low. The published data about PDA stenting is spare. In the cited publications the multicentre workload was 20-45 patients over a period of 10 years, and in another publication 10 patients over 4 years. Therefore, the number of patients can be considered as representative of the difficulty to enrol a greater number of patients with this type of condition and the clinical data can be deemed as acceptable. In all such pathologies, a post market surveillance is important. The given Post Market Surveillance (PMS) plan is adequate, but with too short follow-up.
- The NB concludes that the benefit-risk profile of the device is acceptable due to the study results in Malaysia and the adequate risk management process. This must be criticised. In response to two questions from the NB the indication for RVOT and PA was deleted by the manufacturer as limited clinical data was available. Therefore, it is unclear why the intended purpose in the CEAR is still "pulmonary vessels". Also, in response to two questions from the NB (the NB states that the clinical benefits are not demonstrated and that the applicant has not defined the clinical benefit) the manufacturer states that the "*natural physiological changes of the ductus arteriosus is contractive. Therefore it is acceptable to have stent stenosis after palliative treatment.*" In the control group of the clinical trial in Malaysia there was no restenosis. The impact of stent restenosis remains unclear.
- Here is the major criticism the duration of the PMCF plan. There is no data about the absorption rate of the device, so it is not clear if 3 years of follow up is long enough.

Conclusion:

Several questions remain open. First the absorption rate, the late restenosis rate and the advantage of the device under evaluation. For those patients who don't need surgical correction it is unclear how long the PDA should be patent and when "self-occlusion" due to restenosis is necessary.

The inclusion criteria in the pre-clinical data and the clinical trials were different than in the intended purpose here in the CEAR.

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 CEAR reflects the assessment of the NB. The device is a class III (high risk) implantable device to be implanted in newborns and infants. The intended purpose is a rare disease, so the available clinical data is very limited. This requires in-depth analysis of the data. In several points the expert panel would suggest requesting additional data. A major unknown variable is the absorption rate of the device. There is not enough information about this topic neither from the pre-clinical data, nor from the clinical data. In the PMCF plan, the manufacturer states that the device expires after one year and five months. If this should outline the complete absorption, it is not clear where the data comes from. The only available "long-term" data is an explantation 16 months after implantation. The manufacturer states, "*The weight loss degradation was more than 60% and the scaffold degradation was obvious*". Until the submission of the dossier only 21 patients completed 1 year of follow up. However, as the clinical trial in Malaysia started in 2018, there might be longer-term data available in 2022. Maybe in the clinical trial in China that started in 2018 with a planned follow up of 5 years, although the implanted device was different (same scaffold but coated with sirolimus), there might be data of interest about the absorption rate. The evidence of the clinical benefit and the advantage over other devices is spare. There are several scenarios. First the patient is on palliative care and gets the device implanted, then the patient needs open surgery and the device is used for bridging. There is no available data on the advantage of a bioabsorbable device in this scenario and also not reasonable advantage over a non-bioabsorbable device for the surgeon or the patients. Next, the patient recovers and doesn't need open surgery. The manufacturer states that "*natural physiological changes of the ductus arteriosus is contractive. Therefore it is acceptable to have stent stenosis after palliative treatment*". So, the PDA will contract and occlude the vessel as intended. But there is no preclinical or clinical data about duration of resorption, or complete "disappearance". The impact of stent restenosis remains unclear. In response to a question from the NB (the NB states that the clinical benefits are not demonstrated and that the applicant has not defined the clinical benefit) the manufacturer states that the main advantage is that the stent is bioabsorbable. "*If the shunt flow does not impact the patient's physiological activity and surgical repair is not required, the ductus arteriosus will slowly contract and close automatically after the stent degradation without the need for removal.*" It is unclear how long it takes for complete absorption of the stent. The percentage of the patients where surgical repair

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

is not necessary is also not known/indicated and the timespan until the PDA should occlude is also not known or not indicated.

The next point, but of major concern, is the intended purpose. In all investigations the focus was on persistent ductus arteriosus stenting. Only 3 individuals received stenting other than PDA in the clinical trial in Malaysia. The intended use was in all manufacturer's documents to improve the lumen diameter of the PDA in newborns and infants. In the NB assessment the intended use is to improve the lumen diameter of pulmonary blood vessels. In response to two questions from the NB (where the NB stated that the clinical data was not sufficient for RVOT and PDA stenting), the manufacturer deleted the indication for RVOT and PA. So, it is unclear why the intended purpose in the CEAR is still "pulmonary vessels".

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

In the clinical trial in Malaysia 35 patients were included, and in 32 patients the device was implanted in the PDA. This number is very low. The indication are cyanotic congenital heart diseases by a right to left shunt with palliative treatment to keep the ductus arteriosus patent. The procedure is an alternative to the open Blalock-Taussig shunt. This indication is believed as rare disease and the global prevalence is about 67.000 cases per year. This reflects the difficulty in assessing the device. More evidence would be desirable, but obviously very difficult to collect.

The assessment of the clinical data is given in four questions from the NB to the manufacturer (the NB states in these questions that there is no clinical data about RVOT and PA stenting and also no demonstrated clinical benefit, so the manufacturer removed the indication for RVOT and PA stenting, and all questions of the NB were set as closed). The response to one question (the NB asked for the rational of using a bioabsorbable device) on the advantage of a bioabsorbable device over a standard device is inadequate. It is correct that if the patient doesn't need surgical correction and the PDA should occlude, but it remains unclear in which timeframe this occlusion should happen. The manufacturer states that the physiological changes are contractive, however the mechanism how the PDA occludes is unclear. If it is due to external compression or by "planned" restenosis (more restenosis compared with DES in the clinical trial in Malaysia) the advantage of a bioabsorbable device is not seen. The manufacturer states that "*the ductus arteriosus will slowly contract and close automatically after the stent degradation without the need for removal*". The time to complete degradation or degradation until instability of the device is unknown.

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

The NB concludes that the benefit-risk profile of the device is acceptable due to the study results in Malaysia and the adequate risk management process. This must be criticised. The indication for RVOT and PA was deleted in the manufacturer's documents, so it is unclear, why the intended purpose in the CEAR is still "pulmonary vessels". The manufacturer states that the "*natural physiological changes of the ductus arteriosus is contractive. Therefore it is acceptable to have stent stenosis after palliative treatment.*" In the control group of the clinical trial in Malaysia there was no restenosis. The impact of stent restenosis remains unclear. The manufacturer states that the main advantage is that the stent is bioabsorbable: "*If the shunt flow does not impact the patient's physiological activity and surgical repair is not required, the ductus arteriosus will slowly contract and close automatically after the stent degradation without the need for removal.*" It is unclear how long it does take until complete absorption of the stent. The percentage of patients where surgical repair is not necessary is also not known or not indicated and the timespan until the PDA should occlude is also not known or not indicated.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)
In all investigations the focus was on persistent ductus arteriosus (PDA) stenting. Only 3 individuals received stenting other than the PDA in the clinical trial in Malaysia. The intended use was in all manufacturer's documents to improve the lumen diameter of the PDA in newborn and infants. In the NB assessment the intended use is to improve the lumen diameter of pulmonary blood vessels although the manufacturer removed the extended intended purpose. It is unclear, why the intended purpose in the CEAR document is remains extended to "pulmonary vessels".
5. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan
The major criticism concerns the duration of the PMCF. There is no data about the absorption rate of the device, so it is not clear if 3 years of follow up is long enough to capture the risk and benefit related to the device. With the currently available data it is not clear how the exact absorption profile is and when the device is completely absorbed. In the PMCF plan the manufacturer states that the device expires after one year and five months. If this should outline the complete absorption, it is not clear where the data comes from. The only available "long-term" data is an explantation at 16 months after implantation. The weight loss degradation was more than 60% and the scaffold degradation was obvious according to the manufacturer's statement. Additional data would be needed to determine when the device is fully absorbed and when the integrity of the scaffold disappears.

2.4 Overall conclusions and recommendations

There are 2 major concerns

1. Indication: Considering the available clinical data, the intended purpose should be restricted to PDA stenting (in the same ways other indications, namely RVOT and PA stenting, were removed by the manufacturer after several questions of the NB).
2. Uncertainty about the clinical benefit: There is no data about the benefit compared over other therapeutic options, considering, that there is no dedicated device for this indication (PDA stenting). Advantage over other devices cannot be estimated neither from the available information nor from a rationale point of view with the background of unclear late restenosis rate. In particular, major uncertainty about the resorption rate of the device is considered a concern. The manufacturer highlights the advantage of the bioabsorption of the device but there is no available data about the absorption rate of the device. The bioabsorption rate should be investigated in a pre-clinical animal model with long term follow-up until complete absorption of the device. This data should be then verified in patients also with a long follow-up.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions
No divergent position.

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

[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.