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)

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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	28/10/ 2024
Notified Body number	NB0123
Internal CECP dossier #	EMA/EX/0000235210
Medical device type	Q0299: Ophthalmic devices - other
Intended purpose	Continuous intravitreal delivery (refillable device) over time of a medicinal product
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Ophthalmology

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	02/12/24
Screening panel decision – Co-Rapporteur	
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	
N/A	
Summary as to why there is intention to provide an opinion	
This is a device for the passive diffusion of a medicine where a release control element is used. In the clinical development plan (CDP), the manufacturer claims this is an 'innovative device' (page 36). The notified body reviewer agrees that it is 'completely novel' (CEAR, page 10). Septum dislodgement events (CDP, page 37) required further evaluation with the notified body. This also resulted in a revised design, called the 'Post-septum improved commercial implant'. This includes design changes to reduce the 'septum dislodgement' risk. There was a voluntary / class II recall in the US due to this in 2022. No equivalent devices have been identified for the purpose of MDR equivalence (CDP, page 48). There are three other devices commercialised; however they deliver drugs for different diseases (poster segment uveitis and glaucoma). The degree of novelty in combination with a possibly high health impact for the patients justifies the application of criterion 1.	
Summary as to why there is *no* 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

This device is a novel, class III implantable device (refillable reservoir inserted into the eye through the pars plana). The implant provides a continuous release of ranibizumab by passive, concentration gradient-driven diffusion. The device is indicated for the treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to intravitreal vascular endothelial growth factor (VEGF) inhibitor medication.

This is a new implant for this disease. The product has been commercialised in the US but has no EU market history. As there are other refillable implants for the treatment of uveitis / glaucoma a 'medium' level of innovation might have also been considered.

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

This device would provide a new means of injectable therapy which would replace multiple individual injections. This could allow for reduced clinical visits and improved adherence to treatment guidelines.

The use of the Port Delivery System (PDS) introduces new risks. In particular, septum dislodgement has been identified and addressed with a new design to reduce this risk. There are a variety of other risks (clogging, implant dislocation, endopthalmitis etc.) that can occur.

The septum dislodgement was identified later in the development cycle for the device. This resulted in a voluntary recall in the US in 2022 and it resulted in a new design. The septum dislodgement reduces the ability to refill the implant, and it is not possible to ensure proper drug delivery when this happens.

This device has undergone extensive testing, and at the same time, a variety of design iterations have been undertaken to the PDS and Refill Needle (RFN) at a late stage of development.

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	12/01/2025
Expert panel name	Ophthalmology
Sub-group of expert panel (where relevant)	Devices for ophthalmology

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 notified body (NB) performed a detailed assessment of the manufacturer's clinical evaluation report (CER) and all the clinical evidence presented on the previous versions of the device. However, the clinical evaluation assessment report (CEAR) is not considered fully adequate, mainly due to assessment done of the serious adverse events (SAEs) associated with this novel device. As the post-septum-improved commercial implant is different from the previous pre-septum-improved commercial implant and from the versions used for the clinical trials, the panel considers that the clinical data presented in insufficient to appropriately assess this new device's safety and performance.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
During the phase III clinical program, events of septum dislodgement were observed following refill-exchange procedures. After additional testing conducted in the investigation of those events, Roche/Genentech initiated a voluntary recall of the Port Delivery System (PDS) Ocular Implant and Insertion Tool Assembly in October 2022[2] and paused all new implantations. As a consequence, changes were made to the implant and Refill Needle (RFN) and the impact of such changes on the device's performance was assessed by the manufacturer, concluding that the risks associated with those changes "have been assessed and mitigated to acceptable levels" and are not expected to affect the functionality and safety of the PDS. This new implant under evaluation (post-septum-improved commercial implant) is different from the pre-septum-improved commercial implant (and phase III and phase II implants) that was approved in

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

[2] https://www.gene.com/download/pdf/Susvimo_DHCP_Important_Prescribing_Information_2022-10-18.pdf

October 2021 by FDA in US as Susvimo (Genetch). This new device was first investigated in clinical trials in February 2024 and in July 2024, FDA approved its commercialization in the US.

Multiple serious adverse events have been described in the literature occurring after the use of the previous versions of device (pre-septum-improved implant, phase III and phase II implants). Results from the clinical trials (phase III ARCHWAY[3]; extended phase, 2-year ARCHWAY[4]; and interim results from ongoing PORTAL trial) show a 3-fold higher rate of SAEs – endophthalmitis (around 2% of patients receiving an implant experienced an episode of endophthalmitis). In the ARCHWAY trial (at week 40), comparing the device arm vs the intravitreal injections arm, the incidence of adverse events (AE) in general was 94.4% vs 35.5% and of SAE was 5.6% vs 1.2%. In the extension ARCHWAY trial (at week 96), device arm vs intravitreal injections arm, the incidence of AEs was 60.5% vs 49.1% and of SAEs was 8.9% vs 2.4%. Having in mind the seriousness of adverse events like endophthalmitis, rhegmatogenous retinal detachment, implant dislocation (device dislocation requires urgent surgical intervention), septum dislodgement, vitreous haemorrhage, conjunctival retraction, conjunctival erosion, and conjunctival bleb, this panel recommends that the incidence rate of each identified SAE is communicated to the users, either in the instructions for use or in the summary of safety and clinical performance. Patients should be instructed to report signs or symptoms that could be associated with these events without delay because additional surgical and/or medical management may be required.

Comparisons with similar drug-delivery systems on the market (none-refillable, with different mechanisms of action and different performance goals) are difficult due the fact that clinical trials are conducted under widely varying conditions. These differences can occur even within the same clinical trial. E.g., in the early stages of the LADDER phase II clinical trial[5], there was a high rate of vitreous haemorrhage after the implant was inserted (11/22 patients [50%]), which led to a temporary pause in patient enrolment. After the introduction of the new procedure, the incidence of any postoperative vitreous haemorrhage fell to less than 5% (7/157 patients).

This expert panel does not agree with the NB statement that "…the manufacturer adequately described the qualitative and quantitative aspects of clinical safety through evaluating. The on-average adverse events rates documented in the CER are higher compared to those reported for intravitreal injections but still in line with implants used in similar areas of the eye identified in the SOTA." It is our opinion that the safety of this new device cannot be fully assessed at present neither for the short nor for the long-term use, particularly considering that since July 31, 2024, only 13 patients were implanted with the post-septum improved implant.

The current number of patients reimplanted with this new device, as well as details on its safety and performance are currently unknown. Other clinical outcomes, such as reduction in number of clinical visits and patient compliance with this new device are also not known. The theoretical calculation of

[3] Holekamp NM, Campochiaro PA, Chang MA, et al. Archway Randomized Phase 3 Trial of the Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2022 Mar;129(3):295-307. doi: 10.1016/j.ophtha.2021.09.016. Epub 2021 Sep 29. PMID: 34597713.

[4] Regillo C, Berger B, Brooks L, et al. Archway Phase 3 Trial of the Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration 2-Year Results. Ophthalmology. 2023 Jul;130(7):735-747. doi: 10.1016/j.ophtha.2023.02.024. Epub 2023 Mar 2. PMID: 36870451.

[5] Campochiaro PA, Marcus DM, Awh CC, et al. The Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration: Results from the Randomized Phase 2 Ladder Clinical Trial. Ophthalmology. 2019 Aug;126(8):1141-1154. doi: 10.1016/j.ophtha.2019.03.036. Epub 2019 Apr 1. PMID: 30946888.

the treatment burden reduction was done only calculating the number of intravitreal injections and excluding the clinical visits due to possible complications.

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 clinical evaluation report (CER) and related documents used for the assessment of clinical evidence by the notified body provide sufficient data (except for SEAs) for the intended use. This medical device is indicated for treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to intravitreal vascular endothelial growth factor (VEGF) inhibitor medication.

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

Three PMCF studies are envisaged in the PMCF plan. The strategy foresees an extended duration of follow-up on the safety parameters of the device, including a follow-up study in a real-world setting, and will monitor the use of a siliconized version of the RFN and the post-septum-improved implant - a new implant configuration with improved septum retention.

This expert panel considers incorrect the proposed approach of combining all the safety data obtained from all the previous different versions of the device, like in the PORTAL trial, in which the majority of patients have received a pre-septum-improved implant. It is also not clear in that study how many patients will be followed up using this new device.

The panel also has reservations regarding the approach for the data acquisition in the proposed study "Assessment of Long-Term Safety and Performance of the Port Delivery System (PDS): Questionnaire-based User Survey" study that has a high risk of reporting bias. The panel would instead recommend the establishment of a product registry.

2.3 Summary of expert panel opinion

Device description and novelty

This device is a novel, class III implantable device (refillable reservoir inserted into the eye through the pars plana). The implant provides a continuous release of ranibizumab by passive, concentration gradient-driven diffusion. The release of ranibizumab into the vitreous decreases over time as the concentration in the implant decreases with a half-life of approximately 25 weeks. The ranibizumab serum concentrations with a 24-week treatment interval are maintained below the maximum and above the minimum concentrations experienced with monthly 0.5 mg intravitreal ranibizumab. This could reduce the number of clinical visits, the burden to the patients and their caregivers and enhance patient compliance. The device is indicated for the treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to intravitreal vascular endothelial growth factor (VEGF) inhibitor medication.

There is no other refillable ocular implant currently available on the EU market for this indication. In the US, the ranibizumab PDS received FDA approval in October 2021 as a surgically implanted, refillable device with a 24-week treatment interval that allows for the sustained release of ranibizumab into the vitreous cavity.

Overall opinion of the Notified Body's assessment

The panel disagrees from the notified body (NB)'s assessment that enough data was presented to fully assess the safety on the short or long-term safety of the device, mostly due to the SAEs associated with the device and the lack of evidence on the new post-septum improved device.

Adequacy of benefit-risk determination

The expert panel's view is that benefit-risk determination as assessed by the NB is not fully adequate having in mind insufficient evidence and follow-up of this new device, especially for safety. Some shortcomings of the submission should have been highlighted in the NB assessment. No formal critical evaluation of the results was presented, especially regarding the limited follow-up of patients and safety with this new device.

Consistency of clinical evidence with purpose / medical indication(s)

The clinical evaluation report (CER) and related documents used for the assessment of clinical evidence by the notified body provide sufficient data (except for the SEAs) for the intended use. The panel agrees with the NB that the clinical evidence submitted by the manufacturer supports the medical indications under assessment.

Consistency of clinical evidence with PMCF plan

The panel considers that the NB's agreement with the consistency of the manufacturer's clinical evidence with the PMCF plan can be followed, but some of the shortcomings of the PMCF plan have been underlined.

2.4 Recommendations

This expert panel considers that there is insufficient data on the safety and clinical performance of this new version of the device. To address this, the conduct of a study especially focusing on the safety and performance of this version of the device is recommended.

Having in mind the possibility of SAEs associated with this device, the panel recommends that the manufacturer lists the incidence rate of each of these SAE either in the instructions for use or the summary of safety and clinical performance.

It is also recommended the collection of specific data on patient's preferences, Quality of Life (QoL) and satisfaction of patients and ophthalmologists with the use of this device.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[6]
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

END OF TEMPLATE

[6] 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.