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 reception of the dossier	08/03/2024
Notified Body number	NB0344
Internal CECP dossier #	EMA/EX/0000171363
Medical device type	Bioabsorbable orthopaedic screws
Intended purpose	Traumatic and orthopaedic surgery for the fixation of bone fractures (osteosynthesis) and for the fixation after osteotomies e.g., for the correction of deformities or malalignments.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Orthopaedics

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	04/04/2024
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)	
Not applicable	
Summary as to why there is intention to provide an opinion	
Reabsorbable orthopaedics screws could result in a significant breakthrough in surgical fracture fixation and osteotomies, as there is no need for a second surgery to remove the implant (the implants are absorbed after the fracture site has been ossified). Amongst other benefits, the use of such devices may shorten the recovery time and potentially decrease adverse effects related to metal implants (e.g. pain due classical metal screws) contributing to better outcome for patients and lower healthcare costs if screws have to be removed. However, there are open issues regarding the safety and performance of this type of devices that need to be appraised systematically (see section on criterion 2).	
Summary as to why there is *no* intention to provide an opinion	
Not applicable	
Any other comments	
The device received Breakthrough Device Designation from the US Food and Drug Administration in 2021.	

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 group of devices was developed using a degradable metal alloy of magnesium (Mg), calcium (Ca), and zinc (Zn): BRI.MAG, Mg-0.5Ca-0.5Zn/ZX00 alloy. However, there are already on the European market other orthopedic fixation devices made of a Mg-alloy.
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
Beyond the easily recognizable advantages using reabsorbable metal orthopaedics screws in surgical fracture fixation and osteotomies, there are open issues regarding the safety and performance of this type of devices that need to be appraised systematically (see section on criterion 2).

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
2.3 Reference to peer-reviewed publications/information sources:	
[1] Ramos DM, Dhandapani R, Subramanian A, et al. Clinical complications of biodegradable screws for ligament injuries. Materials Science and Engineering: C. Volume 109, 2020, 110423, ISSN 0928-4931, https://doi.org/10.1016/j.msec.2019.110423. [2] Pisecky, L, Luger, M, Klasan A et al. Bioabsorbable implants in forefoot surgery: a review of materials, possibilities and disadvantages. EFORT Open Rev 2021;6:1132-1139. DOI: 10.1302/2058-5241.6.200157 [3] Antoniac I, Miculescu M, Mănescu Păltânea V, et al. Magnesium-Based Alloys Used in Orthopedic Surgery. Materials (Basel). 2022 Feb 2;15(3):1148. Doi: 10.3390/ma15031148. PMID: 35161092; PMCID: PMC8840615. [4] Söntgen S, Keilig L, Kabir K, et al. Mechanical and numerical investigations of biodegradable magnesium alloy screws for fracture treatment. J Biomed Mater Res. 2023; 111(1): 7-15. doi:10.1002/jbm.b.35127	

2.4 Groups/categories of devices:

Bioresorbable orthopaedic screws

2.5 Relationship to component(s), source material(s) or health impact in case of device failure

☒ Health concern(s) relates to **component(s)**
☐ Health concern(s) relates to **source material(s)**
☐ Health concern(s) relates to **impact on health in case of device failure**

2.6 Description of health concern(s):

Although bioresorbable orthopaedic Mg-alloy screws offer advantages like biodegradability and osteoconductive properties, managing their degradation behavior and associated risks (i.e. loss of biomechanical properties and local reaction due to degradation) is crucial for their safe and effective use in orthopedic applications.

2.7 Reliability of information:

There is a relevant amount of published evidence to support the conclusion that, although there are many potential advantages in the use of this type of implants, there are associated risks for which information is still not available, namely the correct composition of the alloy that provides the adequate balance between time for fracture healing and degradation of the implants.

2.8 Relevance of information:

The information is pertinent for bioabsorbable Mg-alloy orthopaedic screws.

2.9 Summary:

Bioresorbable Mg-alloy orthopedic screws offer several advantages over traditional metallic implants, but they also carry certain risks and potential complications. Being relatively new on the market, some of those risks or limitations that need to be carefully monitored:

1. Inflammatory reactions. These can lead to adverse effects like effusion and osteolysis around the implant site[1].
2. Lower load capacity compared to metallic implants. Bioresorbable screws generally have lower load-bearing capacity, which may limit their use in high-load applications[2].
3. Rapid degradation rate. Mg-alloys can degrade too quickly in the body, leading to premature loss of mechanical integrity before the bone is fully healed[4]. This rapid degradation can also lead to the formation of gas cavities around the implant site[3].
4. Hydrogen gas formation. During the degradation process, Mg-alloys release hydrogen gas, which can accumulate around the implant site and potentially delay healing or cause adverse effects[3,4].
5. Accumulation of degradation products. The buildup of magnesium salts and other degradation products around the implant site can potentially induce inflammatory responses or negatively impact new bone formation[3,4].
6. Premature loss of mechanical strength. The degradation process can cause a significant reduction in the mechanical properties of Mg-alloy implants before the bone has fully healed, increasing the risk of implant failure or fracture non-union[4].

7. Potential toxicity concerns. Although magnesium is generally considered to be biocompatible, some alloying elements, such as rare earth elements, may raise toxicity concerns[3]. 8. Difficulties in controlling the degradation rate. Achieving the optimal degradation rate for Mg-alloy implants (matching the bone healing process), remains a challenge and requires careful alloy design and surface modifications[3,4].

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	14/05/2024
Expert panel name	Orthopaedics, traumatology, rehabilitation, rheumatology
Sub-group of expert panel (where relevant)	Non-articulating devices, rehabilitation

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 NB´s CEAR provides a detailed assessment of the manufacturer´s clinical evaluation. However, in that review some important issues are not sufficiently addressed. Many of the studies referenced for the clinical evaluation include devices made also with a magnesium-alloy with zinc and calcium (ZX10, ZX20). Although these studies present comparable outcomes, the devices are not made exactly of the same alloy as the device under assessment. In other studies, the Mg-alloy used for the device has a very different composition, as is the case for MgYREZr, that includes rare earth elements. A major concern regarding this device (and similar) is the degradation of the magnesium alloy in contact with fluid (i.e. which starts at the insertion of the screw). Since most of these screws are cannulated, with a large surface exposure to fluids, this process will be accelerated. Although some of the small and large animal studies conducted seem to present positive results in regards of osteoinductive effects and bone healing, the confirmation in human patients is needed. Overall, this expert panel considers that there is not sufficient clinical data on this device to demonstrate the duration of the degradation process in humans and the stability of the implant over a certain period. The main source of information for the clinical data refers to an unpublished study presented as an internal report[2]. This is a prospective non-randomized feasibility study for the treatment of distal tibiofibular syndesmotic injuries (disruption of the distal tibiofibular joint) and dislocated fractures of the medial malleolus using this device. This study was conducted in a single center what increases the risk of bias.

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

[2] Bioretec Ltd., "243-02-CI-1 Clinical application of Mg-Based Biodegradable Material for Fracture Fixation in the Adult Skeleton

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

The benefit-risk determination was made using mainly non-clinical sources of information and a literature review that included many devices that are similar but not necessarily equivalent to the device under assessment. The clinical data was sourced from a single feasibility study.

Some of the conclusions presented, e.g., regarding the need for screw removal, the rate of bone in-growth, regeneration, and replacement of the implant with natural bone, and the bioactive and osteo-promotive properties, need to have further support from clinical evidence from a comparative well-designed prospective study. The information on the Mg-alloy screw degradation should be presented using adequate radiological images at fixed time intervals (e.g., 6- or 12-weeks radiographs and CT scan results after 1-year implantation).

In conclusion, it is this expert panel's opinion that additional clinical data is gathered for the benefit-risk determination to be dully assessed.

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 devices presented for assessment are intended for different indications (e.g. upper extremity: glenoid rim fractures, lateral/medial humeral condyle fractures, olecranon fractures, radial head fractures, distal radial fractures, hand fractures / lower extremity: ancle fractures, talar fractures, calcaneal fractures, fractures of the tarsal/metatarsal, fixation of metatarsal and phalangeal osteotomy (such as Akin, Scarf, Chevron, Weil) and subtalar/TMT1/IP Arthrodesis). However, the biomechanical aspects across these fractures and osteotomies are vary variable and thus need different fixation techniques and durability of fracture or osteotomy screw fixation (i.e. differences in biodegradability of the screws). The shear forces and stability needed in an olecranon fracture differs very much from a fixation of a small fragment of the glenoid rim.

This expert panel considers that a single feasibility study addressing only medial malleolar fractures as the basis to support all the indications mentioned above is insufficient and that each indication should be presented with a detailed description and the corresponding supporting data, including different types of fractures and osteotomies. If these Mg alloy screws are used in wrong indication (i.e. more forces at fracture or osteotomy site), this would interfere with both fracture healing and possible dislocation of fracture or osteotomy fragments, with subsequently worse outcome for patients, with more extensive new surgery.

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

The information provided on the PMCF-plan regarding the details of the clinical follow-up is very scarce. In particular, details are missing on how the clinical follow-up will be performed regarding bone healing, degradation of the implant, and gas formation over time. E.g., it is recommended to use imaging information (radiographs, CT scans) to get further insight of suspected osteolysis or other potential adverse events over time, but also the degree of degradation of the device. This needs to be further clarified and specified, including the timepoints at which the radiographs and the CT scans are to be performed and what are the respective measurements to consider.

No clinical evidence was provided to support that the initial stability across the fracture or the osteotomy lasts exactly 6 weeks. Furthermore, it is unknown if stress shielding is avoided and if the complete degradation process lasts 2-3 years. In fact, it is more likely that the degradation process starts at the moment the Mg-alloy screw is inserted, so that full mechanical strength is already changed early after insertion. Thus, an analysis of the degradation and relation to fracture or osteotomy stability in time should be evaluated.

It is also recommended to gather additional information on the different types of fractures for which the device can be used, including the more complex supination external rotation ankle fractures, and not only the fast-healing medial malleolar fractures.

Additionally, this expert panel recommends to the NB to request the manufacturer to conduct a clinical investigation as part of the PMCF-plan to address systematically some of the uncertainties still surrounding the safety and performance of this type of devices.

2.3 Summary of expert panel opinion

Introduction:

The device is a Mg-based biodegradable screw intended for traumatic and orthopaedic surgery for the fixation of bone fractures (osteosynthesis) and for the fixation after osteotomies e.g., for the correction of deformities or malalignments. The implants serve as temporary fixation and stabilization by osteosynthesis of bone fractures and osteotomies until bony fusion has occurred.

Overall opinion of the notified body's assessment:

Clinical data on Mg-alloy screw degradation should be presented (radiographs, CT scan) at fixed time intervals. There is literature that demonstrates a stable degradation process of ZX00 in vitro. The company concludes from these findings, that in an in-vivo situation the implant is fully resorbed after 2-3 year, without the support of clinical data.

This expert panel considers that additional clinical information is missing, recommending that such data can gathered from a well-designed clinical study, prospective in nature and comparing the Mg-alloy with conventional fixation systems considered standard in the different indication areas.

Adequacy of benefit-risk determination:

Some of the quoted literature references refer to devices composed of a Mg-alloy different from the one of the device under assessment. For this reason, the conclusions of those studies cannot be fully extrapolated to the safety and performance of the ZX00 Mg-alloy devices. The claim that there is "rapid bone in-growth, regeneration and replacement of the implant with natural bone", is not substantiated with clinical data.

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

Only clinical data on medial malleolar fractures (with no information on the type of malleolar fracture, e.g. simple or complex) treated with a biodegradable magnesium screw are presented, missing data for the other fracture and osteotomy types. Because different indications need different techniques and time periods needed for fixation and different biomechanical stresses across fractures will have an effect on fracture healing. For that matter, a minimum time needed to accommodate healing, e.g. the compression forces needed to have a stable fixation of the fragments in a proximal olecranon fracture

are much higher and completely different, than for example fixing a glenoid fracture with a slight dislocation. A detailed description of resorbable fixation devices should be presented for each group of indications (e.g. stress and share forces across the fracture or osteotomy, type of bone) with the corresponding clinical evidence.

Consistency of clinical evidence with PMCF plan:

The statement "clinical follow-up will be performed" in order "To follow the bone healing, degradation of the implant, and gas formation over time using X-ray imaging, and to get insight of suspected osteolysis or other potential adverse events over time on X-rays" should be clarified and specified (e.g, follow-up total duration, type and timepoints for radiological measurements – like radiographs and CT scans. The most important points to consider are stability of the device across the fracture or osteotomy in specific cases and rate of degradation of the device at certain timepoints.

2.4 Recommendations

The NB should ask the manufacturer to conduct the following studies:

1. Literature review on all Mg-alloy degradable screws, including adverse events and data on bone healing and time for degradation as well as methods used to measure it.
2. Pre-authorization clinical study on different groups of fracture or osteotomy indication, related shear / compression forces at that anatomical area. It should include a comparison with the gold standard of fixation.
3. Post-authorization clinical study on fracture healing in these different groups with post-operative radiographs at defined timepoints (6 weeks, 3 months and 1 year) and CT scans (6 months and 1 year) for evaluation of the biodegradation. If radiostereometric analysis (RSA) is used, the number of patients in each group can be limited due to high accuracy[3].

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.
Not applicable

[3] Bojan AJ, Jönsson A, Granhed H, Ekholm C, Kärrholm J. Trochanteric fracture-implant motion during healing - A radiostereometry analysis (RSA) study. Injury. 2018 Mar;49(3):673-679. doi: 10.1016/j.injury.2018.01.005. Epub 2018 Jan 12. PMID: 29397996.

[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.

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
Zero experts
Summary of divergent positions
Non applicable