EUROPEAN COMMISSION

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	21/04/2021
Medical device type	Ivory Dentin Graft™ is an implantable device in contact with bone which is mainly resorbed. Ivory Dentin Graft™ consists of porous granules of hydroxyapatite derived from porcine teeth.
Intended purpose	Ivory Dentin Graft™ is a medical device intended to be used as a bone graft material for the repair or augmentation of bone defects in dental procedures.
Risk class / type	☒ class III implantable ☐ class IIb ARMP
Screening step: medical field / competence area	Maxillofacial surgery & Dentistry (devices for dentistry/oral surgery, dental materials etc.) Maxillofacial surgery & Dentistry

PART 1 – DECISION OF SCREENING EXPERTS

1.1 Decision of the screening experts

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

Date of decision	11/05/2021
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
Summary of the reasons, in case the information is found insufficient to reach a conclusion (see MRD Annex IX Section 5.1 point c)	
Not applicable	
Summary of the reasons considered for decision to provide an opinion	

We realise that the interface for use of the device and the treatment of use described are not novel, and the device itself present a moderate degree of novelty. However, we find that there are some points concerning the device itself and its indications which are not clarified appropriately resulting in possible negative effects on human health after application that are need to be justified.

The main reasons of our decision to provide an opinion are the followings:

- Indication of use: The application of the product for lateral sinus floor augmentation lacks clinical evidence. In this case, about five to ten fold of volume is necessary compared to volume applied in the other indications. Therefore, the risk benefit profile cannot be determined. Especially, because adverse events in terms of adverse host reactions or inflammations of the medical device host region (=maxillary sinus) are accompanied by a higher impact on patients health, potentially calling for ENT or maxillofacial interventions to the maxillary sinus. Furthermore, with regard to the announced resorption rate (up to 7 years) it remains unclear if the amount/ volume of material applied in this surgical indication can be used as a vital implant site after 3-6 months as the formation of mature bone remains inconclusive.
- Device dysfunction or failure, in the indication of use mentioned above, will result in major problem for the patient. In the rest of the indications the failure of device will lead back to the initial clinical situation for the patient without additional problems.
- Short clinical evaluation: One major concern is that the clinical evaluation of the device is based only in 4-months data. Data presenting a good evaluation for a longer time are only based in the literature comparing the device with other similar but not equivalent devices.
  The PMCF Plan focuses on the evaluation of the same cases presented in the CER for the time period of 6-months up to 5 years. We believe that the thematic panel should evaluate the adequacy of the 4-months data. We consider that a successful clinical use longer than 4-months would be appropriate, as significant negative effects might arise in a later time point. This point affected our decision in a major dimension.
- Clinical data only for one indication: For the 6 indications for use no data are available indicating a high uncertainty related to the clinical impact in these cases, promoting our decision.
- Resorption time of 5-7 years: No evidence is given on this point.

Short summary, in case of *no* intention to provide an opinion
Not applicable
Any other comments
The application of the product solely for lateral sinus floor augmentation lacks clinical evidence. Since augmentations to the sinus floor in terms of external (=lateral) sinus floor evaluations are clinically, biologically as well as anatomically different to intrabony defects in the alveolar ridge. Strictly speaking, about five to ten fold of volume is necessary compared to volume applied in the other indications. Therefore, the risk benefit profile cannot be determined. Especially, because adverse events in terms of adverse host reactions or inflammations of the medical device host region (=maxillary sinus) are accompanied by a higher impact on patients health, potentially calling for ENT or maxillofacial interventions to the maxillary sinus. Furthermore, with regard to the announced resorption rate (up to 7 years) it remains unclear if the amount/ volume of material applied in this surgical indication can be used as a vital implant site after 3-6 months as the formation of mature bone remains inconclusive. Especially the resorption tendency of the hydroxyapatite (HA) is lacking a proof that it is comparable to established bone substitutes on HA basis for sinus augmentation. Even though it remains questionable if comparable to (chemically unprocessed) autologous dentin from extracted teeth. Both information would allow to convey the data to this indication. In consequence, it should also be stated (e.g. in the IFU) to which ratio the bone substitute should be mixed with autologous bone (i.e. the threshold of mg per cm^3 augmented volume) to obtain comparable results as presented in literature. Although the clinical use of the device is commented and discussed in CEAR, the possible transfer of cellular remnants from the porcine dentin to human should be taken in consideration in the stage of the toxicological evaluation, as no comments are made in CEAR and CER concerning this point. The sterilization of the product in not enough to avoid such transfer.

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 X Novelty: **Device** is novel ☐ Novelty: **Procedure** is novel
Short description of the novelty, including main dimension(s) of novelty
The device is a xenogeneic bone graft material. Although it is a new device, the level of novelty is not considered to be very high. The kind of the described device, the indications for use and the described treatment for application are not new. The only novelty seen in the present design is the origin of the hydroxyapatite. On this point is also the only innovation of the device. According to the "Procedure-related dimensions", the procedure of use of the evaluated device is not novel, as the treatment option; device-patient interface are the same with similar devices in the market. Concerning the device itself, the medical purpose, the design and the mechanism of action are not novel.
Overall degree of novelty
Level of novelty: ☐ Low level *or* ☒ Medium level *or*

☐ High level

Uncertainties related to novelty

Not applicable

1.2 Possible negative clinical / health impact resulting from novelty

Based on the data given by CEAR, the novelty of the device itself does not relate to major negative clinical effects. Data concerning the methodology are gained from the literature evaluating similar devices, preclinical investigation, short-term assessment from data from a clinical investigation and data from similar but not equivalent devices. Clinical studies given in CEAR evaluating the device in comparison to a similar device in the market, result in similar clinical findings.

However, all the information given in CEAR is based on the evaluation of the data gained after the clinical period of only 4 months. Evaluation periods of 6 months and more are presented as long term evaluation and are planned to be performed as PMCF. However, although 4 months might be enough to evaluate local reactions after the device use, this observation time is too short to evaluate a device failure. Therefore, although the clinical data given present for the evaluated device similar results to other devices existing in the market, this finding might be different after a longer clinical evaluation. Due to this, we cannot state for sure that the present device might not present health effects, and therefore we consider this point as a major uncertainty.

In addition to this, the slow resorption of the device is assumed to base on the fact that the origin of the hydroxyapatite is dentin porcine teeth instead of porcine bone. However only spare data are presented on this point as the clinical evaluation is only up to 4 months after the use of device. The progress of resorption cannot be fully justified.

No information is given concerning the existence of cells in the device coming from the animal origin. The existence of cellular remnants in the device might result in xenogenic immune responses in human. This point should be taken in consideration by the evaluation of the biocompatibility of the components of the medical device.

Estimated severity of clinical and/or health impact

Severity of clinical/health impact:

☐ 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

- One major concern is the short term clinical evaluation of the device and the uncertainty that comes out of it concerning its clinical impact. Therefore, although we have evaluated the severity of the present device based on the present data as “moderate”, we decided for an opinion of the thematic panel to evaluate the clinical performance focusing on the adequacy of the clinical data, based on this uncertainty.
- As highlighted above, the clinical/ health impact differs if the material is used in gross volume for external sinus floor evaluation.
- The clinical data given at CEAR apply only on one indication for use of the device. For the rest 6 indications no data are available indicating a high uncertainty related to the clinical impact in these cases. The PMCF plan does not include these indications either.

- Literature evidence show that xenogeneic bone materials for application in humans contained organic/cellular remnants which might be able to induce an immune response within the recipient. This point should be taken in consideration concerning the impact of the device on human health.

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 Information available to experts:	☒ Yes ☐ No

2.3 Reference to peer-reviewed publications/information sources:

- Damsaz M, Castagnoli CZ, Eshghpour M, Alamdari DH, Alamdari AH, Noujeim ZEF, Haidar ZS. Evidence-Based Clinical Efficacy of Leukocyte and Platelet-Rich Fibrin in Maxillary Sinus Floor Lift, Graft and Surgical Augmentation Procedures. Front Surg. 2020 Nov 24;7:537138. doi: 10.3389/fsurg.2020.537138. PMID: 33330603; PMCID: PMC7732646.
- Li J, Yang J, Zhong X, He F, Wu X, Shen G. Demineralized dentin matrix composite collagen material for bone tissue regeneration. J Biomater Sci Polym Ed. 2013;24(13):1519-28. doi: 10.1080/09205063.2013.777227. Epub 2013 Mar 13. PMID: 23848446.
- Khaled H, Atef M, Hakam M. Maxillary sinus floor elevation using hydroxyapatite nano particles vs tenting technique with simultaneous implant placement: A randomized clinical trial. Clin Implant Dent Relat Res. 2019 Dec;21(6):1241-1252. doi: 10.1111/cid.12859. Epub 2019 Nov 19. PMID: 31743571.
- Belouka SM, Strietzel FP. Sinus Floor Elevation and Augmentation Using Synthetic Nanocrystalline and Nanoporous Hydroxyapatite Bone Substitute Materials: Preliminary Histologic Results. Int J Oral Maxillofac Implants. 2016 Nov/Dec;31(6):1281-1291. doi: 10.11607/jomi.5237. PMID: 27861653.
- Ghanaati S, Barbeck M, Booms P, Lorenz J, Kirkpatrick CJ, Sader RA. Potential lack of "standardized" processing techniques for production of allogeneic and xenogeneic bone blocks for application in humans. Acta Biomater. 2014 Aug;10(8):3557-62. doi: 10.1016/j.actbio.2014.04.017. PMID: 24769111.
- Pohl V, Schuh C, Fischer MB, Haas R. A New Method Using Autogenous Impacted Third Molars for Sinus Augmentation to Enhance Implant Treatment: Case Series with Preliminary Results of an Open, Prospective Longitudinal Study. Int J Oral Maxillofac Implants. 2016 May-Jun;31(3):622-30. doi: 10.11607/jomi.4172. PMID: 27183071.

Additional information used besides the one received from either the Secretariat or coming from other sources

2.4 Groups/categories of devices:

Bone graft materials

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):

General health concerns: The short term evaluation is not adequate to certify the use of the device without problems, as a longer time period is necessary to state device failures etc. In addition, the missing clinical

evidence on the 6 indications for use causes major uncertainty. The PMCF plan does not include these indications either.

Health concern relates to component: As mentioned above, the preservation of organic/cellular remnants coming from the animal origin might be able to induce an immune response within the recipient.

Health concern relates to source material: Resorption behaviour and novel bone formation for application of higher volumes solely of the device, specifically in the maxillary sinus (no histological proof). Especially, inflammation / unknown host reaction during resorption or non-resorption with lack of vitality for osseointegration in this indication.

2.7 Reliability of information:

Best evidence available from literature.

2.8 Relevance of information:

General health concerns: The "time period" used for evaluation of such devices is very relevant to the device under assessment.

Health concern relates to component: The information has only indirect relevance as this point applies also to the devices applied in the market.

Health concern relates to source material: The proof of comparability to other materials is lacking for the device under evaluation regarding its physico-chemical structure. This implies an unknown behaviour of resorption in the indication "lateral sinus augmentation" with the application of gross volumes solely of the device.

2.9 Summary:

The information influenced our decision on two points:

- Adverse changes of the benefit-risk profile are assumed for the clinical application of the medical device in higher volumes, such as complete lateral sinus augmentation.
- The short term evaluation is considered as adequate to evaluate this device as in the literature longer time periods are examined.
- It remains unclear if the processed porcine dentine is comparable to autologous dentin commonly used in augmentation procedures.

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 Secretariat)*

3.1 Information received from secretariat?	☐ Yes ☒ No

In case information on incidents was received from the Secretariat

3.2 How relevant is this information for the device under assessment?

Not applicable

3.3 Summary:

Not applicable

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 BY THE THEMATIC EXPERT PANEL / SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	15/06/2021
Expert panel name	General & plastic surgery and dentistry
Sub-group of expert panel (where relevant)	Maxillofacial surgery & Dentistry

2.2 Summary of expert panel opinion

- **Device description**:
  The device is a xenogeneic bone graft material based on xenogeneic dentin derived particles. The device is intended to be used in the course of surgical procedures with the following claimed indications: (1) Augmentation or reconstructive treatment of alveolar ridge, (2) Filling of intrabony periodontal defects, (3) Filling of defects after root resection, apicoectomy and cystectomy, (4) Filling of extraction sockets to enhance preservation of the alveolar ridge, (5) Elevation of maxillary sinus floor, (6) Filling of periodontal defects in conjunction with products intended for GTR and GBR, and (7) Filling of peri-implant defects in conjunction with products intended for GBR.
- **Novelty:**
  Although it is a new device, the level of novelty is moderate. The kind of the described device, the indications for use and the described treatment for application are not new. Only the source of the device is new.
- **Adequacy of clinical evidence assessment by notified body:**
  Assessment of clinical evidence is based on (1) clinical data with the new device for one claimed indication and (2) a literature assessment of similar devices for the other claimed indications.
  The NB's assessment concerning the clinical study is challenged because of the **short period of the study (4 months)**. While for the clinical/morphological investigations of the inserted device a time period of 4 months seems adequate, there was no observation time to demonstrate functionality of newly formed tissue for implant placement. Instead torque resp. immediate implant stability (primary implant stability) was used as surrogate parameter which is not considered sufficient to demonstrate healing (secondary stability). PMCF included observation times 6 months, 10 months, 2.5 years and 5 years. However, at least **4** months for the implant being in situ are deemed necessary for the presented clinical study to control for successful implantation. The PMCF should be adjusted to 12 months, 2.5 years and 5 years.
  The NB's assessment of the other claimed indications is also challenged. The extrapolation of the data from the presented clinical study (indication #4) to other claimed indications is problematic because of different clinical circumstances/tissues, except for indication #3 and # 5.To compensate for the lack of clinical studies regarding the indications #1, 2, 6 and 7 CER contains an extensive literature evaluation. A main problem of this part of the assessment is that it is **based on the**

evaluation of similar, but not equivalent materials. PMCF plan does not include the mentioned indications and should be specified for each indication.

- **Sufficiency of clinical evidence:**
  Clinical evidence assessment is based on a presented clinical 4 month study and a literature survey. Possible risks and uncertainties are related to the lack of information on the functionality of the newly formed tissue with the risk of implant failure for indication #4. Clinical evidence for indication #4 is not considered sufficient. Possible risks and uncertainties for the other indications are related to the fact that the literature survey is based on similar but not on equivalent materials and the problem of unknown resorption behaviour of the new device. The risks involved are generally failure of the performed treatment. Possible risks due to the persistence of cellular components in the device are not discussed (see below). Clinical evidence for indications other than #3, 4, and 5 is not considered sufficient.
- **Adequacy of benefit-risk determination:**
  NB's assessment of benefit risk determination for indication #4 could be accepted after providing successful 4 months data after implant insertion. Extrapolation seems possible for indications #3 and #5 due to similarity of tissue environments. NB's assessment of benefit risk determination for other indications cannot be accepted due to lack of clinical data or equivalence of devices with those in the literature. Possible allergic reactions are covered by including a warning into the IFU. However, the potential effects of other than collagen proteins have not been adequately addressed nor are they mentioned in the IFU or in the PMCF.
- **Consistency of clinical evidence with purpose / medical indication(s):**
  Consistency of clinical evidence for indication #4 can be assumed after data for successful outcome after 4 months are provided. This can also be extrapolated for indications #3 and #5. Consistency of other indication cannot be seen due to lack of relevant information.
- **Consistency of clinical evidence with PMCF plan:**
  Consistency is given for indication #4, but should be modified regarding the time intervals (see above). Other claimed indications must be included into the PMCF plan.
- **Overall conclusions and recommendations on clinical evaluation:**
  The new device offers an interesting addition to the available portfolio of devices for the claimed indications. However, clinical data for one indication (#4) should be extended and the results can then also be used for a positive clinical assessment for indications #3 and #5. For the other indications clinical data and inclusion into the PMCF plan are deemed necessary. If relevant data are then available, the indications can be accordingly extended.

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

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

The device is a xenogeneic bone graft material based on xenogeneic dentin derived particles. The device is intended to be used in the course of surgical procedures with the following claimed indications: (1) Augmentation or reconstructive treatment of alveolar ridge, (2) Filling of intrabony periodontal defects, (3) Filling of defects after root resection, apicoectomy and cystectomy, (4) Filling of extraction sockets to enhance preservation of the alveolar ridge, (5) Elevation of maxillary sinus floor, (6) Filling of periodontal defects in conjunction with products intended for GTR and GBR, and (7) Filling of peri-implant defects in conjunction with products intended for GBR.

The NB's assessment concerning the Clinical study is challenged because of the short period of the study (4 months). While for the morphological investigations (histology of biopsies, bone radiodensity measurements, and alveolar ridge dimensions) a time period of 4 months seems adequate [1], there was no observation time to demonstrate functionality of newly formed tissue for implant placement, because the implants had been placed at the 4 month visit. Instead torque resp. immediate implant stability (i.e. primary stability) were used as surrogate parameters. This is not considered sufficient. A healing time of 120 days, which considers the initial stability gap in the first weeks after implant insertion, seems to fulfil optimal requirements for successful osseointegration of dental implants. While primary implant stability is an important factor for clinical success [2, 3, 4], it is not an unequivocal measure for successful implantation, because successful osseointegration is dependent on multiple factors and cannot be reduced to only one parameter [1, 5]. Therefore, clinical data for "secondary stability" i.e. clinical data after four months of implant healing, need to be provided within the presented clinical study.

The alternatively presented information from the literature in the CER is compromised by the fact that the device under investigation is similar but not equivalent to devices used so far (see here information from CEAR). The PMCF included observation times of 6 months, 10 months, 2.5 years and 5 years, which, however, should be adjusted according to the required extended period of the clinical study to 12 months, 2.5 years and 5 years. The PMCF then must be adjusted accordingly.

The NB's assessment of the other claimed indications is partially challenged. The extrapolation of the data from the presented clinical study (indication claim #4) – even if extended as required above – to other claimed indications is problematic because of different clinical circumstances/tissues. More information on resorption kinetics have been asked for by the NB (see CEAR, page 23) but only a mere statement has been provided in the revised CER that graft site remodelling is expected to continue over several years but with maintenance of graft site stability due to integration of graft particles with the bone. No data have been presented to support this statement.

In more detail, data from the (extended) clinical study could be extrapolated to indications #3 and #5, because surrounding tissues may regarded to be similar to the situation of the clinical study. However, an extrapolation for claim #1 (augmentation or reconstructive treatment of alveolar ridge), where comparatively larger amounts of material are needed than used in the presented clinical study, is not regarded to be possible. Implant placement in sites with xenogeneic bone augmentation have been shown to be associated with considerable clinical problems, including implant failures [6]. For the indications #2, #6 and #7 the special anatomical and microbial situation in periodontal/peri-implant pockets are not represented in the presented clinical study. To compensate for this lack, the CER regarding the indications # 1, 2, 6 and 7 contains an extensive literature evaluation. A main problem of this part of the assessment is that it is based on the evaluation of similar, but not equivalent materials. CEAR clearly states that the device under consideration is not equivalent to other market devices. Additionally, PMCF does not explicitly include the other indications, which is deemed necessary – besides providing appropriate data from clinical studies, as mentioned above.

References:

1. Vollmer A, Saravi B, Lang G, Adolphs N, Hazard D, Giers V, Stoll P. Factors Influencing Primary and Secondary Implant Stability—A Retrospective Cohort Study with 582 Implants in 272 Patients. Applied Sciences. 2020; 10(22):8084

2. Raghavendra, S.;Wood, M.C.; Taylor, T.D. Early wound healing around endosseous implants: A review of the literature. Int. J. Oral Maxillofac. Implants 2005, 20, 425–431

3. Huwiler, M.A.; Pjetursson, B.E.; Bosshardt, D.D.; Salvi, G.E.; Lang, N.P. Resonance frequency analysis in relation to jawbone characteristics and during early healing of implant installation. Clin. Oral Implants Res. 2007, 18, 275–280.

4. Monje, A.; Suarez, F.; Garaicoa, C.A.; Monje, F.; Galindo-Moreno, P.; García-Nogales, A.;Wang, H.-L. Effect of Location on Primary Stability and Healing of Dental Implants. Implant Dent. 2014, 23, 69–73

5. Takechi M, Ishioka Y, Ninomiya Y, Ono S, Tada M, Nakagawa T, Sasaki K, Murodumi H, Shigeishi H, Ohta K. Morphological Evaluation of Bone by CT to Determine Primary Stability—Clinical Study. Materials. 2020; 13(11):2605

6. Ortiz-Vigón A, Suarez I, Martínez-Villa S, Sanz-Martín I, Bollain J, Sanz M. Safety and performance of a novel collagenated xenogeneic bone block for lateral alveolar crest augmentation for staged implant placement. Clin Oral Implants Res. 2018 Jan;29(1):36-45

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

Clinical evidence is based on a presented clinical 4 month study and a literature survey. Possible risks and uncertainties are related to the lack of information on the functionality (secondary implant stability) of the newly formed tissue with the risk of implant failure for indication #4. Possible risks and uncertainties for the other indications are related to the fact that the literature survey is based on similar but not on equivalent materials and the problem of unknown resorption behaviour. The risks involved are generally failure of the performed treatment. Clinical evidence for indication #4 is not considered sufficient and an additional time period of 4 months required (see above). Amended clinical data can be extrapolated to support indications # 3 and #5.

Clinical evidence for all other indication is not considered sufficient and cannot be extrapolated from the presented (even when amended) clinical study. Therefore, for such indications appropriate clinical data are needed.

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

Device-patient interface is the same with similar devices in the market. Concerning the device itself, the medical purpose, the design and the mechanism of action are not novel. A possible negative clinical impact may derive from the special morphology and quantitative composition of the source of the dentin derived particles, e.g. influencing the resorption characteristics.

Also the source of the material is a point of concern (possible allergic reactions), which has been taken care of by including a general warning into the IFU. However, the material is made of native xenogeneic dentin that has mostly only been sterilized. It is clear that in addition to the proteins described and possible cell

remnants, a whole variety of non-collagenous proteins as well as non-human growth factors could be present (with batch-dependent levels) [7, 8]. The effect of these components is not known and especially the currently more frequently discussed alpha-gal syndrome cannot be excluded. Xenogeneic dental pulp and thus also dentin contains alpha-gal [9]. Allergic reactions caused by the use of e.g. porcine heart valves are described in the literature [8]. This must be stated clearly as a possible side effect, if the presence of such remnant cannot verifiable be excluded. In this context also reference to DIN EN ISO 22442 is missing. This must be addressed in the CER and evaluated in the CEAR.

Generally, the associated risk is generally regarded to be moderate. Further to this, for sinus lift elevation (indication #5) it should be realized that adverse host reactions or inflammations of the medical device in the host region (=maxillary sinus) may be accompanied by an impact, potentially calling for ENT or maxillofacial interventions to the maxillary sinus. Here, device dysfunction or failure will result in major problem for the patient.

NB's assessment of benefit risk determination for indication #4 could be accepted after providing 4 months data after implant insertion. NB's assessment of benefit risk determination for other indications (except indications #3 and #5) cannot be accepted due to lack of relevant information.

References

7. Widbiller M, Schweikl H, Bruckmann A, Rosendahl A, Hochmuth E, Lindner SR, Buchalla W, Galler KM. Shotgun Proteomics of Human Dentin with Different Prefractionation Methods. Sci Rep. 2019 Mar 14;9(1):4457

8. Kuravi KV, Sorrells LT, Nellis JR, Rahman F, Walters AH, Matheny RG, Choudhary SK, Ayares DL, Commins SP, Bianchi JR, Turek JW. Allergic response to medical products in patients with alpha-gal syndrome. J Thorac Cardiovasc Surg. 2021 Apr 9:S0022-5223(21)00586-9. doi: 10.1016/j.jtcvs.2021.03.100. Epub ahead of print. PMID: 33933257.

9. Matoug-Elwerfelli M, Nazzal H, Raif EM, Wilshaw SP, Esteves F, Duggal M. Ex-vivo recellularisation and stem cell differentiation of a decellularised rat dental pulp matrix. Sci Rep. 2020 Dec 9;10(1):21553.

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

Consistency of clinical evidence for indication #4 can be assumed after clinical data for 4 months after implant insertion are provided. Consistency of clinical evidence for indications #3 and #5 can be extrapolated from data for indication #4. Consistency of clinical evidence for other indication cannot be evaluated due to lack of data. Data from clinical tests demonstrating the suitability for the indications #1, 2, 6, 7 must be provided.

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

Consistency is given for indication #4 (and for indications #3 and #5), but should be modified regarding the time intervals: the 4 month time interval after implant insertion (i.e. 8 months in summary) should be part of the basic clinical study, the other time intervals should be adjusted to 12 months, 2.5 years and 5 years PMCF plan. All claimed indications must be included separately into the PMCF plan as follow-ups of the requested clinical studies. When relevant clinical data are generated, the indications can be extended according to the claimed indications. A general formulation such as post market

follow-up with doctors regarding clinical aspects by marketing and sales personnel, whether directly employed by the manufacturer or by distributors, following usage is not considered to be sufficient and should me more specific addressing all claimed indications. Possible Alpha-gal allergic responses of patients should be part of the PMCF protocol.

2.4 Overall conclusions and recommendations

The device is a xenogeneic bone graft material based on xenogeneic dentin derived particles. The device is intended to be used in the course of surgical procedures with the following claimed indications: (1) Augmentation or reconstructive treatment of alveolar ridge, (2) Filling of intrabony periodontal defects, (3) Filling of defects after root resection, apicoectomy and cystectomy, (4) Filling of extraction sockets to enhance preservation of the alveolar ridge, (5) Elevation of maxillary sinus floor, (6) Filling of periodontal defects in conjunction with products intended for GTR and GBR, and (7) Filling of peri-implant defects in conjunction with products intended for GBR. Although it is a new device, the level of novelty is moderate. The kind of the described device, the indications for use and the described treatment for application are not new. Only the origin of the device is new.

The new device offers an interesting addition to the available portfolio of devices for the claimed indications. However, presented clinical data for one indication (#4) are presently insufficient and should be extended to include at least the healing phase for the implant (additional 4 months) and the results can then also be used for a positive clinical assessment for indication #3 and #5. For the other indications data from clinical studies are missing and therefore the evidence for these indications in insufficient. Literature survey is flawed by the fact that the new device is similar but not equivalent to market products. The PMCF plan needs to be extended and specified e.g. to cover in detail the other claimed indications. If relevant data are available, the indications can be accordingly extended.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
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

[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.

2.6 Divergent positions in case no consensus was be reached

Summary of divergent positions
No divergent positions

Please indicate how many of the experts of the panel or sub-group had divergent views
none