DE NOVO CLASSIFICATION REQUEST FOR REMEOS™ SCREW LAG SOLID

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Absorbable metallic bone fixation fastener.** An absorbable metallic bone fixation device is an implant, such as a bone screw, pin, or Kirschner wire, composed of one or more absorbable metal or metal alloys and intended to provide rigid bone fixation suitable for osteosynthesis. The device is designed to fully absorb after osteosynthesis is achieved.

NEW REGULATION NUMBER: 21 CFR 888.3041

CLASSIFICATION: Class II

PRODUCT CODE: QJD

BACKGROUND

DEVICE NAME: RemeOs™ Screw LAG Solid

SUBMISSION NUMBER: DEN220030

DATE DE NOVO RECEIVED: May 4, 2022

SPONSOR INFORMATION:

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INDICATIONS FOR USE

RemeOs™ Screw LAG Solid is intended for the use in traumatic and orthopedic surgery for the fixation of bone fractures (osteosynthesis) and for the fixation after osteotomies, e.g., for the correction of deformities or malalignments. The absorbable implants serve as temporary fixation and stabilization by osteosynthesis of bone fractures and osteotomies until bony fusion has occurred.

The RemeOs™ Screw LAG Solid is intended to be used for skeletally mature adults.

The RemeOs™ Screw LAG Solid is indicated for the fixation of the medial malleolus.

LIMITATIONS

The sale, distribution, and use of the RemeOs™ Screw LAG Solid is restricted to prescription use in accordance with 21 CFR 801.109.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The RemeOs™ Screw LAG Solid is an absorbable metallic bone fixation fastener. The product is manufactured from an absorbable magnesium-based alloy containing magnesium, zinc (0.55% (w/w)) and calcium (0.45% (w/w)). The material corrodes under physiological conditions into magnesium, calcium and zinc oxides and hydroxides, while producing hydrogen gas as byproduct. The implant serves as temporary fixation and stabilization by osteosynthesis of bones and fragments until bony fusion has occurred.

The RemeOs™ Screw LAG Solid is provided in one design (Figure 1). The RemeOs™ Screw LAG Solid is a partially threaded solid headed screw with a diameter of 3.5 mm and is offered from lengths 24 to 40 mm in 2 mm increments.

Figure 1: RemeOs™ Screw LAG Solid

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The RemeOs™ Screw LAG Solid is manufactured from the following patient-contacting material:

Table 1: Manufactured Materials of Patient-Contacting Device Components

Description	Material	Direct Patient Contact	Contact Duration
Implant	Magnesium-alloy	Yes	Permanent (>30 days)

Biocompatibility evaluation has been completed according to 2020 FDA Guidance, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."

For this permanent implant, the following table shows the biocompatibility testing that was performed and the results, which were deemed acceptable for a permanent implant in contact with bone/tissue.

Table 2: Biocompatibility Testing Performed

Test Description	Result
Cytotoxicity (per ISO 10993-5 (Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity))	Non-cytotoxic
Sensitization (ISO 10993-10 (Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization))	Non-sensitizing
Irritation (per ISO 10993-10 (Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization)	Non-irritant
Implantation Effects (per ISO 10993-6 (Biological evaluation of medical devices — Part 6: Tests for local effects after implantation))	Null to minimal reactivity
Material Mediated Pyrogenicity (per ISO 10993-11 (Biological evaluation of medical devices — Part 11: Tests for systemic toxicity))	Non-pyrogenic
Acute/Subacute/Subchronic/Chronic Systemic Toxicity, (addressed through animal testing (Biological evaluation of medical devices —Part 11:Tests for systemic toxicity) and chemical characterization and toxicological risk assessment per ISO 10993-18 (Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process)/ISO 10993-17 (Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances))	Does not elicit systemic toxicity
Genotoxicity and Carcinogenicity (addressed through chemical characterization and toxicological risk assessment per ISO 10993-18 (Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process)/ISO 10993-17 (Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances)	Non-genotoxic/non-carcinogenic

PACKAGING, STERILIZATION, AND SHELF LIFE

Sterility

The RemeOs™ Screw LAG Solid is provided clean and sterile to the end-user.

Sterilization method (Dry Heat) of the device has been validated in accordance with ISO 20857, "Sterilization of health care products - Dry heat - Requirements for the development, validation and routine control of a sterilization process for medical devices" to ensure a minimum sterility assurance level (SAL) of 10^{-6}.

Packaging and Shelf-Life

The product packaging consists of an inner protective barrier made of silicone and outer sterile barrier system (SBS) made of nylon, which is placed into a protective cardboard box. Package performance and package integrity testing were performed in accordance with FDA recognized standard ISO 11607.

Accelerated and real time aging of the dry-heat sterilized device to support a 12-month shelf-life were performed in accordance with ASTM F1980, "Standard Guide for Accelerated Aging of Sterile Medical Device Packages" and supported a 12-month shelf-life. The expiration date of 12 months was verified by demonstrating package stability through visual inspection, seal width, dye penetration, and seal strength testing on the stored packaging.

Device packaging maintenance of sterility when subjected to the rigors of real-world shipping and handling was demonstrated by testing conducted in accordance with ASTM D4169, "Standard Practice for Performance Testing of Shipping Containers and Systems"

MAGNETIC RESONANCE (MR) COMPATIBILITY

To support MR conditional labeling for the RemeOs™ Screw LAG Solid implant, the following MR testing was conducted to evaluate device safety and compatibility:

- Magnetically Induced Displacement Force per ASTM F2052-15, "Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment";

- Magnetically Induced Torque per ASTM F2213-17, "Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment";

- Radiofrequency Induced Heating per ASTM F2182-19e, "Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging"; and

- Image Artifact as per ASTM F2119-07 (2013), "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants".

In magnetic field interaction tests, the RemeOs™ Screw LAG Solid implant showed a translational attraction of 1.53 Tesla, the spatial gradient magnetic field was 466 gauss/cm and no torque. In image artifact testing, the maximum image artifact was

measured for both spin echo and gradient echo pulse sequences in a 3.0 T MR scanner, and the maximum artifact size, on the gradient echo pulse sequence, extends a linear distance of 5 mm relative to the size and shape of the cannulated screw. In MRI-related heating testing, test results and in vivo modeling show that, the maximum temperature rise after 60 minutes continuous exposure is less than 6°C under the condition of the whole-body specific absorption rate (SAR) at 2 W/kg.

PERFORMANCE TESTING – BENCH

A summary of non-clinical mechanical performance evaluations is provided in **Table 3:**

Table 3: Summary of Non-clinical Mechanical Performance Evaluations

Test	Purpose	Method	Performance Criteria	Results
Torsional Testing	The aim of this test was to evaluate the maximum torsional strength of the RemeOs™ Screw LAG Solid prior to degradation when considering worst-case screw dimensions. Absorbable polymer bone screws were used as a comparator device.	Testing was conducted in accordance with ASTM F543-17 (Standard Specification and Test Methods for Metallic Medical Bone Screws).	The torsional yield strength should be statistically equivalent or greater to that of the comparator device.	All specimens exceeded the performance criteria.
Axial Pullout Testing	The objective of this test was to measure the axial tensile force required to fail or remove a bone screw from a defined material prior to implant degradation. Absorbable polymer bone screws were used as comparator devices.	Testing was conducted in accordance with ASTM F543-17 (Standard Specification and Test Methods for Metallic Medical Bone Screws).	The torsional yield strength should be statistically equivalent or greater to that of the comparator device.	All specimens exceeded the performance criteria.
Driving Torque Testing	The aim of this test was to measure the torque required to drive a bone screw into a standard	Testing was conducted in accordance with ASTM F543-17 (Standard Specification and Test	The maximum insertion torque in the driving torque test (ASTM F543-17 Annex 2) must	All specimens met the acceptance criteria.

Test	Purpose	Method	Performance Criteria	Results
	material prior to degradation.	Methods for Metallic Medical Bone Screws).	be statistically equal to or less than 80% of the minimum allowable yield torque of the corresponding screw type in the torsional strength test to allow for safe insertion.	
Mass Loss Testing	The aim of this test was to characterize the *in vitro* degradation profile of the RemeOs™ Screw LAG Solid by evaluating mass loss and dimensional measurements over time.	*In vitro* degradation testing was performed in accordance with ASTM F3268-18 (Standard Guide for *in vitro* Degradation Testing of Absorbable Metals). Test specimens (screws, rods, and discs) were tested in solution or mounted in artificial bone blocks.	The test specimens degrade in a controlled manner achieving steady or declining state (*in vitro* mass loss rate is steady or decreasing) by the end of the study (i.e., 26 weeks).	All specimens met the acceptance criteria. The results of this study were used to perform an *in vitro – in vivo* correlation analysis.
Longitudinal Flexural Static Testing	The objective was to study the *in vitro* static bending properties of the RemeOs™ Screw LAG Solid as the product is degraded *in vitro*. Absorbable polymer bone screws were used as comparator devices.	*In vitro* degradation was adapted from methods described in ASTM F3268-18 (Standard Guide for *in vitro* Degradation Testing of Absorbable Metals), ASTM F1635-16 (Standard Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants) and ASTM D790-17 (Standard Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials). The *in vitro* fatigue resistance to cyclic bending forces of the RemeOs™ Screw Lag Solid material must be at least statistically equivalent or better compared to that of the comparator device.	The *in vitro* flexural fatigue performance of the RemeOs™ Screw LAG Solid test specimens must be at least statistically equivalent or better compared to that of the comparator device after *in vitro* degradation.	All specimens exceeded the performance criteria.

Test	Purpose	Method	Performance Criteria	Results
		Cylindrical test rods were used as representative test specimens. Specimens were degraded *in vitro* in artificial bone blocks. Flexural testing was performed at 0, 4, and 8 weeks of *in vitro* degradation.		
Longitudinal Flexural Fatigue Testing	The aim of this study was to evaluate the fatigue performance of the RemeOs™ Screw LAG Solid as the product is degraded *in vitro*. Absorbable polymer bone screws were used as a comparator device.	*In vitro* degradation and flexural fatigue testing were adapted from methods described in ASTM F3268-18 (Standard Guide for *in vitro* Degradation Testing of Absorbable Metals), ASTM F1635-16 (Standard Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants) and ASTM F1264-16 (Standard Specification and Test Methods for Intramedullary Fixation Devices). Cylindrical test rods were used as representative test specimens. Specimens were degraded *in vitro* in artificial bone blocks. Fatigue performance was evaluated at 0, 4, and 8 weeks of *in vitro* degradation.	The *in vitro* fatigue resistance to cyclic bending forces of the RemeOs™ LAG Solid test specimen must be at least statistically equivalent or better compared to that of the comparator device after *in vitro* degradation.	All specimens exceeded the performance criteria.
Longitudinal Axial Pullout Strength	The aim of this study was to evaluate the axial pullout strength of the RemeOs™ Screw LAG Solid as the product is degraded *in vitro*. Absorbable polymer bone screws were used	*In vitro* degradation and axial pullout testing were adapted from methods described in ASTM F3268-18 (Standard Guide for *in vitro* Degradation Testing of Absorbable Metals), ASTM F1635-16 (Standard Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and	The axial pullout strength of the RemeOs™ test specimen must be statistically equivalent or greater to that of the comparator device after *in vitro* degradation.	All specimens exceeded the performance criteria.

Test	Purpose	Method	Performance Criteria	Results
	as comparator devices.	Fabricated Forms for Surgical Implants) and ASTM F543-17 (Standard Specification and Test Methods for Metallic Medical Bone Screws). Specimens were degraded *in vitro* in artificial bone blocks for up to 26 weeks.		

SUMMARY OF CLINICAL INFORMATION

The 'Clinical application of Magnesium (Mg)-based biodegradable material for fracture fixation in the adult skeleton - First in man study' (MGAS) enrolled otherwise healthy adults between 18 and 65 years of age presenting to a Level I outside the United States (OUS) trauma center with an unstable ankle injury that included a displaced medial malleolus fracture (displaced was defined as diastasis of the fracture in any direction of 2 mm or more).

All subjects underwent surgery during which the medial malleolus fracture was reduced and stabilized with either one (2 subjects) or two (18 subjects) ZX00 bioresorbable magnesium screws (3.5 x 40mm solid LAG; scientifically denoted as ZX00 and marketed as RemeOs™ Screw LAG Solid). Associated fractures, such as of the fibula, were treated with conventional titanium screws and plates. Outcomes were assessed by clinical (physical examination, talocrural motion, pain visual analogue scale (VAS), and American Orthopaedic Foot & Ankle Society (AOFAS) scores), laboratory (serum Mg^{2+}, Zn^{2+}, and Ca^{2+} concentrations, renal function) and radiographic evaluations performed at approximately 2, 6, 12, 24, 52, 104, and 130 weeks after surgery. All subjects were followed for close to 130 weeks (2.5 years) with the exception of one subject, who was healed at 12 weeks, but was subsequently lost to follow-up.

Clinical and radiographic healing of 90% of subjects (18 patients) occurred within 6 weeks with stable consolidation observed for the remaining 2 subjects at the 12 weeks follow-up appointment. Differences in the talocrural joint range of motion (dorsal flexion/plantar flexion) between the operated site and the contralateral non-operated side averaged 39° ± 12° after 2 weeks and declined to 2° ± 11° by 1 year. VAS scores averaged 1.6 ± 0.6 points after surgery, 1.3 ± 0.5 points after 2 weeks, and 1.0 (no medial malleolus pain) thereafter. At the 52-week follow-up examination, the AOFAS score was 90.8 ± 7.1 points and improved to 93.7 ± 5.2 by 130 weeks.

The MGAS investigators reported 12 mild to moderate non-serious adverse events (AEs) during an average subject follow-up of 2.5 years. These self-limited, likely non-device-related, AEs included mild post-operative discomfort (8 subjects), knee pain (1 subject), mild localized swelling (1 subject) and moderate self-limited pain of unknown origin (2 subjects). Two likely non-device-related serious adverse events were also reported. One subject experienced a pulmonary embolism, and a second subject underwent an additional surgery, an osteochondral

autograft transfer system (OATS) procedure 1 year post-injury to treat a persistent osteochondral defect of the medial talus ridge.

Although all fractures clinically and radiographically healed within 12 weeks of surgery, serial radiographs displayed radiolucent zones localized around the screws, attributed to absorption byproducts (i.e., hydrogen gas). In general, the radiolucencies increased up to post-operative week 6, remained constant until week 12, and then decreased. After 2.5 years (130 weeks average) bone loss was still visible on computed tomography (CT) scans; however, new bone formation was extensive. No refractures or new bone fractures were reported. Residual screw volume (y), as estimated from subject CT scans, linearly declined over time (x weeks) and approached 0 (full absorption) at 149 weeks ($y = -1.4664x + 218.02$ $R^2 = 0.976$). Serum concentrations of Mg^{2+} and Ca^{2+} and estimated renal function remained within normal physiological limits throughout the study.

Subject Demographics

A total of 20 patients were enrolled in the MGAS clinical study trial. Subjects' mean age and standard deviation was 40.1 ± 14.5 years. 11 subjects were male, and 9 subjects were female with an average Body Mass Index (BMI) of 26.25 ± 2.25 kg/m². Race and ethnicity data were not collected. Injury mechanisms and classification are provided in Table 4.

Table 4: Injury and Fracture Characteristics

Fracture Characterization	**Patient #**
Mechanism of Injury	
Walking	9
Fall	3
Sport Injury	4
Traffic Accident	4
Type of Ankle Fracture	
Isolated Fibular	7
Bimalleolar (total)	13
Bimalleolar with posterior (Trimalleolar)	10
Medial Malleolus Fracture Classification (Herscovici)	
A	1
B	6
C	13
Medial Malleolus Fracture Type	
Stable	0
Unstable	20

Tscherne Classification of soft-tissue injury	
Grade 0	20
Grade I	0
Grade II	0
Grade III	0

References:

Holweg P, Herber V, Ornig M, Hohenberger G, Donohue N, Puchwein P, Leithner A, Seibert F. A lean bioabsorbable magnesium-zinc-calcium alloy ZX00 used for operative treatment of medial malleolus fractures: early clinical results of a prospective non-randomized first in man study. Bone Joint Res. 2020 Aug 19;9(8):477-483. doi: 10.1302/2046-3758.98.BJR-2020-0017.R2. PMID: 32874554; PMCID: PMC7437522.

Herber V, Labmayr V, Sommer NG, Marek R, Wittig U, Leithner A, Seibert F, Holweg P. Can Hardware Removal be Avoided Using Bioresorbable Mg-Zn-Ca Screws After Medial Malleolar Fracture Fixation? Mid-Term Results of a First-In-Human Study. Injury. 2022 Mar;53(3):1283-1288. doi: 10.1016/j.injury.2021.10.025. Epub 2021 Oct 30. PMID: 34758916.

Note: As stated above, race and ethnicity data were not collected for this clinical dataset. For other patient demographics, such as gender and age, that were collected, the clinical dataset was insufficiently powered to evaluate the effect of these patient demographics on device performance.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The RemeOs™ Screw LAG Solid labeling includes the following: product description, indications for use, instructions for use, contraindications, warnings, precautions, shelf-life, material composition, absorption byproducts, time to complete absorption, summary of clinical data and surgical technique instructions. The labeling meets the requirements of 21 CFR 801.109. The labeling also includes additional information related to the time for complete product absorption and absorption byproducts.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of an absorbable metallic bone fixation fastener and the measures necessary to mitigate these risks.

Table 5: Identified Risks to Health and Associated Mitigation Measures

Risks to Health	Mitigation Measures
Loss of bone fixation resulting from: • Premature device absorption and formation of absorption byproducts • Device breakage • Galvanic corrosion • Device aging	Clinical data Non-clinical performance testing Shelf-life testing Labeling
Adverse tissue reaction resulting from: • Device material • Device absorption and absorption byproducts	Biocompatibility evaluation Labeling
Infection	Sterilization validation Shelf-life testing Pyrogenicity testing Labeling
Difficulties with revision surgery due to screw absorption	Clinical data Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the absorbable metallic bone fixation fastener is subject to the following special controls:

(1) Clinical data must demonstrate that the device performs as intended under the anticipated conditions of use. The absorption profile must be characterized to completion (e.g., full absorption). The difficulty of any revision surgeries must be documented.
(2) Non-clinical performance testing must demonstrate that the product performs as intended under anticipated conditions of use. Testing must:
    (i) Evaluate the complete degradation profile of the device;
    (ii) Evaluate the initial mechanical performance; and
    (iii) Evaluate the mechanical performance as the device degrades.
(3) The device must be demonstrated to be biocompatible.
(4) The device must be demonstrated to be non-pyrogenic.
(5) Performance data must demonstrate the sterility of the device.
(6) Performance data must support the labeled shelf-life of the device by demonstrating continued sterility, package integrity, and device functionality (i.e., degradation profile and mechanical performance) over the established shelf-life.
(7) Labeling must include:
    (i) Material composition;
    (ii) Absorption byproducts;
    (iii) A detailed summary of the product's technical parameters;
    (iv) An expiration date/shelf life;
    (v) Instructions for revision surgery;
    (vi) Time to complete absorption; and
    (vii) A summary of clinical data with the device.

BENEFIT-RISK DETERMINATION

The risks of the device are based on nonclinical laboratory as well as data collected in a clinical study described above.

BENEFITS:

1) Fracture fixation and osteosynthesis functionally equivalent to conventional (titanium or stainless steel) bone screws
2) Reduction in occurrence of long-term pain associated with permanently implanted hardware
3) Reduced second surgeries for screw removal and associated risks of additional surgical procedure
4) Avoidance of sensitivities to conventional metallic screws (i.e., nickel, titanium)
5) Improved clinical imaging (less metal artifact / no metal artifact post-absorption)
6) Reduced bone stress shielding

RISKS:

1) Absorption-related screw structural weakness
2) Absorption-related bone toxicity / device-related fractures
3) Systemic toxicity
4) Difficulties with revision surgeries (loss of screw head during absorption)
5) Reduced fluoroscopic and X-ray visibility
6) Galvanic corrosion if in contact with non-magnesium hardware

Based on the totality of the evidence, the RemeOs™ Screw LAG Solid demonstrated a reasonable assurance of safety and effectiveness for the device for its intended use/indications for use, and there is a low degree of uncertainty in this finding. In conclusion, the benefits of using the subject device for its intended use/indications for use outweigh the probable risks to health.

Patient Perspectives

Patient perspectives considered for the RemeOs™ Screw LAG Solid included Visual Analogue Scale (VAS) Pain Scale assessments as a secondary safety endpoint evaluated at 0, 2, 6, 12, 24, 52, 104, and 130 weeks. This patient reported outcome (PRO) assessment was used to demonstrate a clinically meaningful improvement in pain reduction.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> RemeOs™ Screw LAG Solid is intended for the use in 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 absorbable implants serve as temporary fixation and stabilization by osteosynthesis of bone fractures and osteotomies until bony fusion has occurred.

The RemeOs™ Screw LAG Solid is intended to be used for skeletally mature adults.

The RemeOs™ Screw LAG Solid is indicated for the fixation of the medial malleolus.

The probable benefits outweigh the probable risks for the RemeOs™ Screw LAG Solid. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the RemeOs™ Screw LAG Solid is granted, and the device is classified as follows:

Product Code: QJD
Device Type: Absorbable metallic bone fixation fastener
Regulation Number: 21 CFR 888.3041
Class: II