# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

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|---|---|
| Device Generic Name: | Noninvasive Bone Growth Stimulator |
| Device Trade Name: | AccelStim™ Bone Growth Stimulator |
| Device Product Code | LOF |
| Applicant's Name/Address: | Orthofix US LLC<br>3451 Plano Parkway<br>Lewisville, Texas 75056 |
| Date of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P210035 |
| Date of FDA Notice of Approval: | May 3, 2022 |

## II. INDICATIONS FOR USE

The AccelStim device is indicated for the noninvasive treatment of established non-unions excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature adult individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

## III. CONTRAINDICATIONS

There are no known contraindications.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the AccelStim™ Bone Growth Stimulator labeling.

## V. DEVICE DESCRIPTION

The AccelStim™ Bone Growth Stimulator (AccelStim) is an Ultrasound Bone Growth Stimulator. The device belongs to a general therapeutic group known as "LIPUS" (i.e., Low Intensity Pulsed Ultrasound System) (Griffin et al. 2014).

The AccelStim is intended to provide non-invasive therapy for healing non-unions (except skull and vertebra) and accelerating time to healing of fresh fractures (closed, posteriorly displaced distal radius fractures (Colles'), or closed or Grade I open tibial diaphysis fractures). The device, available by prescription, is intended to be used in a home use setting once daily for 20 minutes or as prescribed by a physician. Neither the physician nor the patient can select or change any of the low-intensity ultrasound signal specifications.

The AccelStim is a portable, handheld, battery powered, non-invasive bone growth stimulator that generates an ultrasound signal through a transducer. The device transmits a low intensity ultrasound signal to the fracture site through a coupling gel. The device can be used on fracture sizes that fall within the area covered by the ultrasound beam (i.e., average effective area 3.5 $cm^2$). LIPUS ultrasound level is comparable to diagnostic ultrasound intensity levels used in sonogram (fetal monitoring) procedures and is 1% to 5% of the intensities used for conventional therapeutic ultrasound.

The AccelStim is composed of the following parts (Figure 1):

1. Signal Generator
2. Transducer
3. External Power Supply/Cord
4. Transducer Holder with Elastic Strap
5. Ultrasound Gel

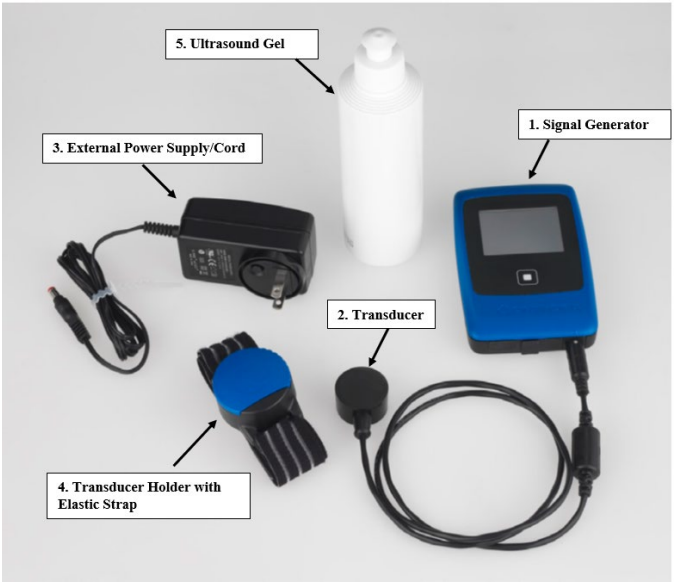


Figure 1: AccelStim Components

Each component is described in detail in the sections below. The AccelStim is used with an off-the-shelf, commercially available, ultrasound gel (K101952).

**Table 1: AccelStim Components**

| Component | Material |
|---|---|
| 1. Signal Generator | **Housing**: Acrylonitrile Butadiene Styrene (ABS) Terluran GP-35<br>**Buttons**: Thermoplastic Elastomers (TPE) Megol Adhesion Modified (AM) |
| 2. Transducer | **Housing**: Acetal Copolymer (Kocetal 700)<br>**Emitting Face**: Piezo-Ceramic Material |
| 3. External Power Supply | **Casing**: Black 94V-0 Polycarbonate |
| 4. Transducer holder with Elastic Strap | **Holder**: ABS Terluran GP-35<br>**Elastic Strap**: Polyester and Nylon Velcro |
| 5. Ultrasound Gel (K101952) | Deionized water, carbomer, triethanolamine, monopropylene glycol, 5-chloro-2-methy-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3 |

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives available for the treatment of established non-unions excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature adults when these fractures are orthopedically managed by closed reduction and cast immobilization.

- Nonoperative alternative treatments, which include, but are not limited to,
  - Casting and bracing
  - Other FDA approved Non-invasive Bone Growth Stimulators indicated for similar fracture types

- Surgical alternatives, which include, but are not limited to:
  - Bone graft/ bone graft substitutes (including vascularized fibula)
  - Internal fixation devices (e.g., plating systems, intramedullary (IM) rods)
  - External fixation devices

Each alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyles.

## VII. MARKETING HISTORY

A version of the Orthofix® AccelStim Bone Growth Stimulator (Model UBHS-02) is CE marked and has been marketed outside of the United States since 2014 in the United Kingdom, Germany, Canada, and Italy. The legal manufacturer in Europe is IGEA and the device is marketed under the tradename, FAST. As of July 2021, a total of 1,426 devices

have been sold in Europe. According to Orthofix®, the FAST device has not been withdrawn from any distribution/ marketing in any country for safety or effectiveness reasons. The AccelStim device will be marketed as Model 4300 in the United States.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse events (e.g., complications) associated with the use of the device:

- Pain
- Swelling
- Tenderness
- Skin Sensitivity
- Device Failure
- Inadequate bone healing

For the specific adverse events that occurred in the supporting clinical studies, please see Section X below. The German and the Netherlands Post-Market registries, along with the study by Kristiansen et al. 1997, reported no adverse events. The US Post-Market registry enrolled 551 subjects with non-unions, and the study by Heckman et al. 1994 included 67 fresh tibial fractures. The reported adverse events included 1 case of muscle cramping among patients receiving treatment from the EXOGEN device (Heckman et al. 1994) and twenty-two patient or physician "complaints" of pain (17), swelling (2), skin sensitivity (2), and pulsing sensation (1) (US Post-Market Registry).

## IX. SUMMARY OF NON-CLINICAL STUDIES

### A. Laboratory Studies

A summary of the laboratory testing conducted is presented in the following table (Table 2).

**Table 2: Summary of AccelStim Testing**

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Device Specific Verification and Validation** | Review of hardware requirements, product requirement specifications, and software requirements. | Verification testing demonstrates compliance with product requirements including display function, ultrasound generation, and user interface requirements. | Passed.<br><br>All features verified and validated led to the conclusion that the medical device satisfies the general description, intended use, and declared user's needs and intended uses. |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Electrical Safety Testing** | Testing was conducted in alignment with IEC 60601-1 and IEC 60601-1-11 to confirm device compliance with the general requirements for basic safety and essential performances. | Compliance with:<br>• IEC 60601-1 Ed. 3.0 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance<br>• IEC 60601-1-11:2010 Medical electrical equipment – Part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment. | Passed.<br><br>All requirements were met. |
| **Electromagnetic Compatibility (EMC) Testing** | Under the test conditions specified in sub-clause 8 of EN 60601-1-2:2015 the equipment or system shall be able to provide the basic safety and essential performance.<br><br>Essential performances are monitored in the following way:<br>• Watching at warning conditions provided by the medical device through visual (on display) and acoustic (buzzer) signals;<br>• Acoustic ultrasound output power is monitored using a second ultrasound transducer used as receiver and coupled with the ultrasound transducer of the EUT through ultrasound gel. | Compliance with:<br>• IEC 60601-1-2, Ed. 3.0 and 4.0 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests<br><br>Immunity test can be considered as "Pass" when:<br>• No warning conditions appear;<br>• The amplitude of the signal received by the second ultrasound transducer used as receiver remains within the allowed range declared on the | Passed.<br><br>The device met all requirements for EMC testing. |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| | The transducer used as receiver needs to be connected to a standard oscilloscope (in the case of the immunity radiation test, the oscilloscope needs to be placed outside the semi-anechoic chamber) and the amplitude of the signal received is monitored. A comparative test is performed between the normal condition and the condition when the disturbance is applied. | "Instructions for Use" manual. | |
| **Battery Safety and Functional Verification** | Requirements under IEC 62133 were reviewed for the rechargeable Li-ion cell battery to ensure the device was in compliance with the basic safety standards. | Lithium ion battery conforms to:<br>• IEC 62133 First edition<br>• UL Mark<br>United Nations (UN)/ Department of Transportation (DOT) 38.3, Edition 5, and Underwriters | Passed.<br><br>Test objects met all requirements. |
| **Other Electrical Testing** | Requirements under IEC 6061-2-5:2009 were reviewed for the UBHS-02 model (Orthofix® Model 4300) to ensure the device was in compliance with the basic safety and essential performance standards.<br><br>The ultrasound parameters were reviewed and characterized. | Compliance with:<br>• IEC 60601-1-6 Ed. 3.1 Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability<br>• IEC 60601-2-5:2009 Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment<br>• IEC 61689:2007 Ultrasonic physiotherapy equipment – Field | Passed.<br><br>Test objects met all requirements. |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| | | specifications and method of measurement in the frequency range 0,5 MHz to 5 MHz.<br>• IEC 60529 Ed. 2.2 b:2013 Degrees of Protection Electrical Enclosures Package | |
| **Software Verification & Validation** | A traceability matrix, hazard analysis, and software validation was performed. The software is considered low moderate of concern as it could not cause minor injury. | Compliance with:<br>• IEC 62304<br>• FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices | Passed.<br><br>All software validation/ verification requirements were met. |
| **Cybersecurity** | Information Security FMEA | Risk Analysis to identified and evaluate any vulnerabilities or potential threats. | Passed.<br><br>All risks were evaluated and appropriately mitigated. Additionally, a plan is in place to proactively monitor for new vulnerabilities. |
| **Packaging** | Verification and Validation were performed to ensure the packaging can adequately hold all components. | The packaging is able to hold all the components. Since the device is not intended to be used sterile there is no requirement to maintain a sterile barrier. | Passed.<br><br>All components fit within the packaging without issue. |
| **Shipping and Transportation** | Packaging configuration was tested according to the applicable requirements of International Safe Transit Association (ISTA) 3A:2008. | Device still within specification (81.2 mW - 150.8 mW output power) after testing. No damage to the packaging. | Passed.<br><br>The output after testing was within specifications. No visible damage was observed to the packaging. |
| **Shelf Life** | Accelerated aging of the system components was performed, followed by | Device must meet all specifications following aging. | Passed.<br><br>All devices met manufacturing output |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| | revalidation of device verification testing. | | specifications after aging. |
| **Biocompatibility** | Testing was performed according to ISO 10993-1 and the FDA guidance document, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The following testing was performed:<br>• Cytotoxicity<br>• Sensitization<br>• Irritation | Device components must past biocompatibility endpoints. | Passed.<br><br>All components were found acceptable for all endpoints. |
| **User Needs Validation Study** | Testing performed:<br>• IEC 60601-1-6<br>• IEC 62366<br><br>FDA Guidance: Applying Human Factors and Usability Engineering to Medical Devices – Guidance for Industry and Food and Drug Administration Staff | • Each task must be passed by 11 of 15 subjects on the first try.<br><br>• More than 70% of questionnaires report a compliance degree equal to or major of the fourth level for each statement. For each item evaluated using the user satisfaction rating scale in the questionnaires, any single item that receives a rank of 1 will be considered a validation failure.<br><br>• No problem, safety issues or dangerous errors reported. | Passed.<br><br>All 15 users were able to utilize the device and passed all the critical tasks. No user was observed failing any critical tasks. The satisfaction level was high with an overall satisfaction level of 86.7% (>4 score). Users also found the device easy to use (93.3% with a level >4). Furthermore, no problem or discomforts were noted. |

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| **Transducer Immobility Force Test** | Determine the force needed to maintain contact between transducer and skin to ensure treatments can be completed effectively. | Force required to maintain contact between transducer and skin should be significantly lower than the force that would be applied by a strap tightened per use instructions. | Passed.<br><br>The instructions describe tightening the strap to the point that it is snug but comfortable. The measured force was substantially lower than that of a snug but comfortably tightened strap. |

## B. Animal Studies

No animal studies were provided in this submission.

## C. Additional Studies

**Biocompatibility**

Biocompatibility of the patient contacting surfaces was evaluated according to International Organization for Standardization (ISO) 10993-1 and FDA Guidance Document "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process." All components of the AccelStim device are intended to have transitory contact. The biocompatibility tests conducted on the transducer, transducer holder, and wrist band included Cytotoxicity (ISO 10993-5), Irritation (ISO 10993-10), and Sensitization (ISO 10993-10). Results of testing, in combination with prior clearance of the supplied ultrasound gel and a biologic risk evaluation and labeling, demonstrated biocompatibility in line with the requirements of ISO 10993-1.

**Technological Comparison**

In lieu of providing a clinical dataset for AccelStim, the sponsor provided nonclinical studies comparing the AccelStim to a previously approved bone growth stimulator (BGS) (Table 3). The purpose of these nonclinical signal characterization tests was to establish sufficient similarity of the AccelStim and the EXOGEN type devices such that the FDA could apply Section 216 of the Food and Drug Modernization Act (FDAMA), i.e., the "six-year rule", to assess the safety and effectiveness profiles of the AccelStim.

**Table 3: Regulatory and Marketing History for Reference Device (EXOGEN)**

| Device Name | Sponsor or Manufacturer | PMA ID | Approval Date | Indication(s) |
|---|---|---|---|---|
| SAFHS® Model 2A* | EXOGEN™ Inc. | P900009 | 10/1994 | Accelerated healing fresh fractures tibia and distal radius |
| EXOGEN 2000® or SAFHS® | EXOGEN®, A Smith and Nephew Company | P900009/S006 | 02/2000 | Fracture non-union healing (excluding skull & vertebra) |
| EXOGEN® (Current Product) | Bioventus LLC | | | Both of the above |

*The Sonic Accelerated Fracture Healing System

According to FDA's "Guidance on Section 216 of the Food and Drug Modernization Act of 1997", available at https://www.fda.gov/media/71743/download, the FDA may choose to utilize the publicly available detailed SSED of a previously approved device to support approval of a PMA for a new device if the applicant provides "a detailed justification of how the information in the earlier SSED applies to the applicant's device" and if the applicant is able "to describe how the devices are similar enough to allow for the data from the earlier device to apply to the new device."

For the purpose of establishing sufficient similarity of AccelStim and EXOGEN, the applicant provided a comparison of Indications for Use (Table 4) and a comparison of key technological specifications (Table 5).

**Table 4: Indications for Use Comparison**

| AccelStim Device Subject | EXOGEN P900009/S006 | EXOGEN P900009 |
|---|---|---|
| The AccelStim™ is indicated for the noninvasive treatment of established nonunions excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature adults when these fractures are orthopedically managed by close reduction and cast immobilization. | The EXOGEN 2000 or Sonic Accelerated Fracture Healing System (SAFHS®) is indicated for the non-invasive treatment of established nonunions* excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are | Sonic Accelerated Fracture Healing System (SAFHS®) is indicated for the acceleration of the time to a healed fracture for fresh, closed, distal radius (Colles') fractures, and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization. |

| AccelStim Device Subject | EXOGEN P900009/S006 | EXOGEN P900009 |
|---|---|---|
| | orthopedically managed by closed reduction and cast immobilization.<br><br>*A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing. | |

**Table 5: Technological Comparison**

| Characteristic | AccelStim (Orthofix®) Subject | EXOGEN (Bioventus)* P900009/S006 |
|---|---|---|
| Ultrasound frequency | 1.5 ± 5% MHz | 1.5 ± 5% MHz |
| Modulating signal burst width | 200 ± 10% microseconds | 200 ± 10% microseconds |
| Repetition rate | 1.0 ± 10.0% KHz | 1.0 ± 10.0% KHz |
| Duty factor | 20% | 20% |
| Effective radiating area** | 3.5 ± 20% $cm^2$ | 3.88 ± 1% $cm^2$ |
| Temporal average power | 105 ± 20% $mW/cm^2$ | 117 ± 30% $mW/cm^2$ |
| Spatial average temporal average (SATA) | 30 ± 30% $mW/cm^2$ | 30 ± 30% $mW/cm^2$ |
| Beam non-uniformity ratio (BNR)*** | 3.8 ± 30% | 2.16 |
| Beam type | Collimated | Collimated |

*IFU Information

**The difference in effective radiating area is not expected to impact the safety or effectiveness of the AccelStim device compared to the EXOGEN device. The same ultrasound signal is emitted by both devices, but it is emitted over a smaller area of the AccelStim device. The difference is addressed in the labeling for the AccelStim device, where users are informed that the device should only be used to treat fractures that fall within the effective radiating area.

***While the AccelStim device emits a signal with a maximum BNR that is slightly greater than that of the EXOGEN device, it remains well below the maximum level of 8 recommended by IEC 60601-2-5.

**Note:** the effective radiating area percentiles reflect the standard uncertainty of measurement instrumentation, not standard deviation.

The AccelStim and the EXOGEN Indications for Use are equivalent differing only in the addition of the clarifying term “adult” to the AccelStim indication. This change limits AccelStim use to the subset of EXOGEN patients (adults) best characterized by the available clinical data.

The AccelStim, like the EXOGEN device, is intended to be used once daily for 20 minutes or as prescribed by a physician. Both devices contain an ultrasound transducer that is applied directly to the skin at the fracture site using coupling gel. Both devices are also held into place by a strap or placed within the cast. The AccelStim and the EXOGEN share the same frequency (1.5 MHz), single burst width (200 μsec),

repetition rate, and duty factor. Both the AccelStim and EXOGEN devices deliver the same type of ultrasound energy and for the same amount of time. The AccelStim has a slightly improved Beam Non-uniformity Ratio (BNR) compared to the EXOGEN device. The AccelStim BNR is within the parameters recommended by IEC 60601-1-5, and thus the signal remains within safe levels and provides a relatively even signal across the effective radiating area. The difference in BNR is not expected to impact the safety or effectiveness of the AccelStim device compared to the EXOGEN device.

Based on these comparisons, the AccelStim is sufficiently similar to the EXOGEN device, with no significant deviation in any area of characterization, such that the clinical dataset from the EXOGEN PMAs (P900009 and P900009/S006) can be leveraged to assess the safety and effectiveness profiles of the AccelStim.

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

The AccelStim has not been the subject of a published clinical study. Orthofix® is relying on using the "six-year rule" to leverage the clinical data supporting two previous PMA applications (P900009 – approved October 1994 and P900009, Supplement #6 (/S006) – approved February 2000) for the EXOGEN Bone Growth Stimulator (Table 6). P900009 (accelerated fresh fracture healing) was primarily supported by the two randomized, double-blinded, placebo-controlled multi-center trials performed by Heckman et al. 1994 (tibia diaphyseal indications) and by Kristiansen et al. 1997 (distal metaphyseal radius indications). P900009/S006 (non-union healing) was primarily supported by a German Post-Market Study with lesser contributions from similar registries / studies established in the United States and the Netherlands. A brief overview of the primary studies follows. Additional details regarding these studies can be found in their respective SSEDs.

**Table 6: Primary Clinical Studies Supporting P900009 (accelerated healing fresh fractures) and P900009/S006 (non-union healing)**

| # | Type | Reference | Anatomical Location | Enrolled # Patients / (# Fractures) | Lost to FU Or Excluded (active /control) | # Patients / # Fractures Included in Final Analysis |
|---|---|---|---|---|---|---|
| 1 | AH | Heckman et al. 1994* | Tibia | 96 / (97) | 13 / 17 | 66 / (67) |
| 2 | AH | Kristiansen et al. 1997* | Distal Radius | 83 / (85) | 3 / 21 | 60 / (61) |
| | | | | | | |
| 1 | NU | Germany Post-Market Study | Mixed (Excluding skull & vertebra) | 79 / (80) | 5 | 74 / (74) |

*FDA IDE Approved Study G850185 (tibia) / G870078 (radius); AH = accelerated healing fresh fracture; NU = fracture non-union healing, FU = Follow-up

The clinical studies leveraged to support the safety and effectiveness of the AccelStim device may not necessarily be applicable to patients of all races and ethnicities. Such demographic details were not provided in the referenced clinical studies.

**I. Accelerated Healing of Fresh Fractures - Diaphyseal tibia / Distal Radius (please refer to the P900009 SSED for further details).**

1. **Heckman et al. 1994 Acceleration of Tibial Fracture-Healing by Non-invasive Low-Intensity Pulsed Ultrasound.**

   A. **Study Design**

   Patients were treated between September 1986 and December 1990. The database for P900009 reflected data collected through a minimum of two years of follow-up and included 67 fractures in the statistical analysis. There were co-investigators from sixteen sites in various geographical areas of the United States and from one site in Israel.

   The study was a prospective, multicenter, randomized, placebo-controlled, double-blind clinical trial. Patients were randomized into groups of four at each study site to receive an active or a placebo-treatment device according to a pre-determined computer-generated code. The code was broken only after the radiographic reviews had been completed. Three statistical approaches are presented for all analyses. Analysis of variance was used to calculate the mean time and the standard error of the mean, in days, to the attainment of a healed fracture status for the active-treatment and placebo-treatment groups. Analysis of variance, Kruskal-Wallis analysis of variance by ranks, and log-rank life-table analysis was used to compare the mean times to healing for the two groups. In addition, Cox regression analysis was used to assess whether potential covariates, such as the sex and age of the patient, the days to the start of weight- bearing, and the grade, type, or location of the fracture, had an effect on the healing response in the active compared with the placebo treatment group.

   The control group used a placebo device that was identical in every way (same visual, tactile and auditory signals) except for the ultrasound signal emitted.

   1. Clinical Inclusion and Exclusion Criteria
      a. Study enrollment was limited to patients who met the following inclusion criteria:

         i. skeletally mature men and non-pregnant women;
         ii. at most seventy-five years old; and
         iii. who had a closed or grade-I open tibial diaphyseal fracture that was primarily transverse, short oblique, or short spiral and that could be treated effectively with closed reduction and immobilization in a cast.

b. Patients were not permitted to enroll in the Heckman et al. 1994 study if they met any of the following exclusion criteria:

i. if either the anteroposterior or the lateral radiographs showed that the length of the fracture line was more than twice the diameter of the diaphyseal shaft (a long spiral or long oblique fracture), the displacement was more than 50 per cent of the width of the shaft, or the fracture gap was more than 0.5 centimeter;
ii. open fractures, except grade I as defined by Gustilo and Anderson;
iii. fractures of the tibial metaphysis;
iv. fractures with persistent shortening of more than one centimeter after reduction; fractures that were not sufficiently stable (recurrent or persistent angulation of 10 degrees or more in any plane) for treatment with immobilization in an above-the-knee cast;
v. fractures with a large butterfly fragment (larger than two times the diameter of the tibial shaft); pathological fractures; and comminuted fractures (comminution with fragments of less than one centimeter in length was acceptable); or
vi. patients who stated that they could not comply with the protocol; were receiving steroids, anticoagulants, prescription non-steroidal anti-inflammatory medication, calcium-channel blockers, or diphosphonate therapy; had a history of thrombophlebitis or vascular insufficiency; or had a recent history of alcoholism or nutritional deficiency, or both.

2. Follow-up Schedule
   a. All patients were scheduled to return for follow-up examinations at four, six, eight, ten, twelve, fourteen, twenty, thirty-three, and fifty-two weeks after the fracture.

   b. Postoperatively, the objective parameters measured during the study included:

      i. Cortical Bridging - On each radiographic evaluation at each time-point, four cortices (two on the anteroposterior radiograph and two on the lateral radiograph) were evaluated for the amount of cortical bridging.
      ii. Endosteal Healing (gradual disappearance or obliteration of the fracture line and its replacement by a zone of increased density formed by endosteal callus).

3. Clinical Endpoints
   a. With regard to safety, adverse events were collected.

b. With regard to effectiveness, the endpoint of the study was a healed fracture, as judged both on clinical examination (the fracture was stable and was not painful to manual stress) and on radiographic examination (three of four cortices bridged).

c. With regard to study success/failure criteria:

i. time to clinical healing (active device versus placebo control);
ii. time to overall (clinical and radiographic) healing (active device versus placebo control).

## B. Accountability of PMA Cohort

Of 96 patients enrolled in this study, 66 patients (69%) were available for analysis at the completion of the study (Table 7).

**Table 7: PMA Cohort Accountability**

| Patients and / or (Fractures) | Active Device | Placebo Control | Total |
|---|---|---|---|
| Planned Enrollment (calculated) | 75 | 75 | 150 |
| Actual Enrollment | (48) | (49) | 96 (97) |
| Lost to Follow-up | 4 | 9 | 13 |
| Excluded (protocol deviations) | 11 | 6 | 17 |
| Included in Statistical Analysis | (33) | (34) | 66 (67) |

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are insufficiently known to determine whether they are typical for a clinical trial performed in the US. Only age (mean and standard deviation), and gender were provided (Table 8).

**Table 8: Demographic Comparison of Active Device and Placebo Control Patients**

| Study Parameter | Active Device | Placebo Control | P Value* |
|---|---|---|---|
| Age | 36 ± 2.3 years | 31 ± 1.8 years | 0.09 |
| Male / Female | 25 / 8 | 29 / 5 | 0.37 |

*performed with the Fischer exact test or chi-square test

## D. Safety and Effectiveness Results

1. Safety Results

There were two adverse reactions and one complication in the sixty-six patients in the core group. One patient (who had active treatment) reported muscle- cramping at one week. The cramping resolved without treatment by the second week. One patient (who had placebo treatment)

had swelling in the cast at the six- week follow-up visit. This problem had resolved by the next visit. No other adverse reactions were reported. One patient who used a placebo device had a pulmonary embolus at the four-week follow-up visit. The patient was managed successfully with anticoagulant therapy and remained in the study.

2. Effectiveness Results
   The analysis of effectiveness was based on the 67 evaluable fractures at the 52-week follow-up visit. At the end of the treatment, there was a statistically significant decrease in the time to clinical healing (86 ± 5.8 days in the active-treatment group compared with 114 ± 10.4 days in the control group) ($p = 0.01$) and also a significant decrease in the time to over-all (clinical and radiographic) healing (96 ± 4.9 days in the active-treatment group compared with 154 ± 13.7 days in the control group) ($p = 0.0001$).

3. Subgroup Analyses
   Effect of smoking. "Among the fractures in the remaining patients, who were ex-smokers or who were smoking during the treatment period, eleven that were treated with the active device healed in a mean of 115 ± 11.2 days, compared with a mean of 158 ± 28.6 days for thirteen fractures that were treated with the placebo device ($p = 0.09$)."

4. Pediatric Extrapolation
   In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

**E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. This pivotal clinical study included 5 authors of whom 1 was a full-time or part-time employee of the sponsor and one or more of the authors had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). Funds were received from the Sponsor in total or partial support of the clinical study.

**2. Kristiansen al. 1997 Accelerated Healing of Distal Radius Fractures with the Use of Specific, Low-Intensity Ultrasound.**

**A. Study Design**

Patients were treated between 1987 and 1990. The database for P900009 reflected data collected through a minimum of one year of follow-up and included 61 fractures in the statistical analysis. There were co-investigators from nine sites in various geographical areas of the United States and from one site in Israel.

The study was a prospective, multicenter, randomized, placebo-controlled, double-blind, FDA approved Investigational Device Exemption (IDE) clinical trial. Active and placebo devices were randomly assigned, in groups of four (two active and two placebo), to each investigational center, according to a computer-generated code developed by an independent statistical consultant. "The null hypothesis that the time to response for the active device was the same as or worse than that for the placebo device was tested against the one-sided alternative hypothesis that the time to response was superior for the active device, with superior defined as a shorter time to attain a specific healing response, such as a healed fracture. Therefore, p values were calculated in order to assess the superiority of treatment with the active device as compared with treatment with the placebo device. The per cent acceleration (also referred to as the per cent accelerated healing or decreased time to healing) for the two treatment groups was a descriptive statistic calculated as: ([mean for placebo device – mean for active device]/mean for placebo device) x 100. The Fisher exact test was used to compare categorical parameters (for example, the percentage of fractures that healed, according to follow-up week, and the percentage that lost no reduction) between the two treatment groups."

"The placebo device had a disconnected ultrasound transducer and emanated no ultrasound pressure wave; however, it was identical to the active unit with regard to all of its operations and its visual and audible characteristics."

1. Clinical Inclusion and Exclusion Criteria
    a. Study enrollment was limited to patients who met the following inclusion criteria:

        i. men and non-pregnant women;
        ii. at least twenty years old;
        iii. and who had a closed, dorsally angulated, metaphyseal fracture of the distal aspect of the radius within four centimeters of the tip of the radial styloid process; and
        iv. that was satisfactorily reduced after closed reduction and immobilization in a below the elbow cast. Satisfactory reduction was determined by the investigator on the basis of the radial height, radial angle, and volar angulation as seen on radiographs made after the reduction.

    b. Patients were not permitted to enroll if they met any of the following exclusion criteria:

        i. Fractures that necessitated additional reduction after the investigational treatment had begun;
        ii. if the fracture was another type of distal radius fracture such as a chauffeur, Barton, or Smith;

iii. if the distal radius fracture was associated with a fracture of the ulnar shaft;
iv. if the patient needed operative intervention;
v. if the patient was receiving steroids or anticoagulants;
vi. if the patient had a history of thrombophlebitis or vascular insufficiency involving the upper extremity; or
vii. if the patient had a nutritional deficiency or an alcohol dependency.

2. Follow-up Schedule
   a. All patients were scheduled to return for follow-up examinations at one, two, three, four, five, six, eight, ten, twelve, and sixteen weeks after the fracture.

   b. Postoperatively, the objective parameters measured during the study included:

      i. Cortical Bridging – On each radiographic evaluation at each time-point, four cortices (bridging of the dorsal, volar, radial, and ulnar cortices) were evaluated for the amount of cortical bridging.
      ii. Endosteal Healing (gradual disappearance or obliteration of the fracture line and its replacement by a zone of increased density formed by endosteal callus).

3. Clinical Endpoints
   a. With regard to safety, adverse events were collected.

   b. With regard to effectiveness, the endpoint of the study was a healed fracture, as judged both on clinical examination (palpation through the cast window or by manual application of stress after removal of the cast) and on radiographic examination (four of four cortices bridged).

   c. With regard to Study success/failure criteria:

      i. Time to clinical healing (active device versus placebo control);
      ii. Time to overall (clinical and radiographic) healing (active device versus placebo control).

## B. Accountability of PMA Cohort

Of the 83 patients enrolled in this study, 60 patients (72%) were available for analysis at the completion of the study (Table 9).

**Table 9: PMA Cohort Accountability**

| Patients and / or (Fractures) | Active Device | Placebo Control | Total |
|---|---|---|---|
| Planned Enrollment | | | 160 (max) |
| Actual Enrollment* | 40 (40) | 45 (45) | 83 (85) |
| Lost to Follow-up | 0 | 3 | 3 |
| Excluded (protocol deviations) | (10) | (11) | (21) |
| Included in Statistical Analysis | (30) | (31) | 60 (61) |

*Two patients had bilateral fractures; in both patients, one fracture was treated with the active device and the other, with the placebo device.

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are insufficiently known to determine whether they are typical for a clinical trial performed in the US. Only age (mean and standard deviation) and gender were published (Table 10).

**Table 10: Demographic Comparison of Active Device and Placebo Control Patients**

| Study Parameter | Active Device | Placebo Control | P Value |
|---|---|---|---|
| Mean Age ± SD | 54 ± 3 years | 58 ± 2 years | 0.41** |
| Male / Female | 6 / 24 | 4 / 27 | <0.03* |

*As determined with the Fisher exact test; **As determined with analysis of variance; SD = standard deviation.

## D. Safety and Effectiveness Results

1. Safety Results
   "There were no complications or adverse reactions attributable to any aspect of the treatment."

2. Effectiveness Results
   "The analysis of effectiveness was based on the 61 evaluable fractures at the 16 week follow-up visit. "The time to union was significantly shorter for the fractures that were treated with ultrasound than it was for those that were treated with the placebo (mean [and standard error], 61 ± 3 days compared with 98 ± 5 days; $p < 0.0001$)."

3. Subgroup Analyses
   a. Effect of smoking. "Use of the active ultrasound device significantly reduced the time to fracture-healing for the patients who had smoked during the study (mean, 48 ± 5 days for the patients managed with ultrasound and 98 ± 30 days for those managed

with the placebo; $p < 0.003$) and for those who had not smoked (mean, 66 ± 5 days for the patients managed with ultrasound and 100 ± 6 days for those managed with the placebo; $p < 0.0001$)."

b. Effect of age (for females). "The linear regression coefficient (slope) for the group treated with the placebo (a group essentially equivalent to a population that has normal healing) was 0.8, representing a significant ($p < 0.04$) increase in healing time of approximately 0.8 day for each additional year of age. In contrast, the linear regression coefficient for the group treated with ultrasound was 0.1, representing a slope that was essentially flat, with only a 0.1-day increase in healing time for each additional year of age; this value was not significantly different from zero ($p > 0.57$). Analysis of variance to test the hypothesis that the regression coefficient for the women managed with ultrasound was equal to that for the women managed with the placebo revealed that the regression coefficients were significantly different ($p < 0.03$).

4. Pediatric Extrapolation
In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

**E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. This pivotal clinical study included 5 authors of which 2 were a full-time or part-time employee of the sponsor (Bioventus) and one or more of the authors had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). Funds were received from the sponsor in total or partial support of the clinical study.

## II. Healing of Fracture Non-unions (please refer to the P900009/S006 SSED for further details)

### 1. German Study

**A. Study Design**

Patients were treated between July 1995 and April 1997. The database for P900009/S006 reflected data collected through a minimum of one year of follow-up.

The study was a retrospective, multicenter, non-randomized, non-blinded analysis of prospectively collected registry data. The study had a self-paired control design with each nonunion case serving as its own control, and with the

prior treatment result of failed orthopedic care as the control compared to ultrasound as the only new treatment.

Each of the 54 prescribing physicians (investigators) provided initial fracture and non-union data for their own cases, followed them, and provided clinical and radiographic assessment data, including any adverse reactions, complications, or complaints. Three principal investigators (PIs) determined whether cases met the study inclusion and exclusion criteria and determined radiographic outcome.

Statistics were presented relating to average or central tendency, e.g., mean or median, and percentage of cases and the numerator/denominator (in parenthesis) that were the basis for the percentage of cases. Standard error of the mean (S.E.M.) was the measure of variability presented. The Kruskal-Wallis test was utilized for each non-categorical variable and Fisher's exact test was utilized for each categorical variable. All hypothesis tests were performed with alpha equal 0.05; therefore, a p-value of less than or equal to 0.05 was the basis for declaring a result statistically significant.

1. Clinical Inclusion and Exclusion Criteria
   a. Study enrollment was limited to patients with non-united fractures who met the following inclusion criteria:

      i. minimum of 9 months (14-day window or 256 days) from the initial injury date to the start of SAFHS® treatment; and
      ii. minimum of at least 4 months without surgical intervention.

   b. Patients were not permitted to enroll in this study if they met any of the following exclusion criteria:

      i. pregnant females;
      ii. non-unions of spine or skull;
      iii. tumor-related non-unions; or
      iv. patients who could not comply with the required treatment regimen.

2. Follow-up Schedule
   a. All patients were scheduled to return for clinical and radiographic follow-ups at 1 to 2 month intervals. A long-term follow-up of the healed cases was conducted approximately one year after the patient was judged to be healed.

   b. Postoperatively, the objective parameters measured during the study included:
      i. Cortical Bridging - On each radiographic evaluation at each time-point, four cortices (two on the anteroposterior radiograph and two

on the lateral radiograph) were evaluated for the amount of cortical bridging.

3. Clinical Endpoints
   a. With regard to safety: "Safety was monitored by each investigator during regular follow-up visits for the assessment of adverse reactions, complications or complaints."

   b. With regard to effectiveness, the primary parameter was outcome to SAFHS® treatment.

      i. "Healed" which was determined by both (1) clinically healed as determined by each investigator when there was no pain upon gentle stress and weightbearing (for long bones only); and (2) radiographically healed. Following standard orthopedic practice, for long bones, a radiographically healed nonunion required at least three (3) of four (4) bridged cortices and for other bones, a healed nonunion was determined when callus bridged the nonunion site. Radiographic healed was determined by one or more of the 3 PIs.
      ii. "Failed"
      iii. "Incomplete" (Discontinued: Lost to Follow-up, Deceased etc.)

   c. The secondary effectiveness parameter was healing time, defined as days from SAFHS® start to the healed outcome determination date.

   d. With regard to Study success/failure criteria:

      i. "The outcome of SAFHS® treatment was the primary efficacy parameter for this paired design clinical investigation where each case served as its own control. Nonunion cases have essentially a zero probability of achieving a healed state without intervention; however, the sponsor conservatively assumed that the healed rate without SAFHS® therapy during the time period of this study would be 5% rather than 0%. Therefore, the null hypothesis was that the healed rate was less than or equal to 5%, and the alternative hypothesis was that the healed rate was greater than 5%."

## B. Accountability of PMA Cohort

Of 79 patients enrolled in this study, 74 patients (94%) were available for analysis at the completion of the study, the 1-year post-operative follow-up (Table 11).

**Table 11: PMA Accountability**

| Patients and / or (Fractures) | Total |
|---|---|
| Enrolled | 79 (80) |
| Lost to Follow-up / Excluded | 5 |
| Completed Cases* | 74 |

*The term "completed cases" designated cases with healed or failed outcome, and the term "incomplete cases" designated cases with incomplete outcome.

## C. Study Population Demographics and Baseline Parameters

The demographics of the German study population are insufficiently known to determine whether they are typical for a clinical trial performed in the US (data provided only on age, gender, and weight) (Table 12).

**Table 12: Demographic Comparison of Active Device and Placebo Control Patients**

| Study Parameter | |
|---|---|
| Age (Mean ± standard deviation) | 45 ± 2.3 years |
| Male / Female | 56 / 33 |
| Weight (Mean ± standard deviation) | 78 ± 1.5 kg |

## D. Safety and Effectiveness Results

1. Safety Results
   Adverse effects, complications, and complaints were monitored, and no device related incidents were reported.

2. Effectiveness Results
   Primary: Of the 74 completed cases, 86% (64/74) healed and 14% (10/74) were failures of SAFHS® treatment. When this healed rate was compared with the paired control of prior failed treatment, the result was significant at p=0.00001. The intention-to-treat analysis evaluated for all 80 cases and showed 81% (65/80) healed and 19% (15/80) as not healed (10 failed and 5 incomplete cases designated as not healed). A comparison with the paired control of prior failed treatment was significant at p=0.00001 (Table 13).

**Table 13: Germany Post-Market Registry: Effectiveness Results for EXOGEN-Treated Completed Cases.***

| **A. Primary Efficacy Parameter – Outcome, Number (and %) of Cases: N = 74** | | | |
|---|---|---|---|
| **Outcome** | **Prior Orthopedic Treatment Period** | **Ultrasound Treatment Period** | **Exact (one-sided) P-Value**** |
| Healed | 0 (0%) | 64 (86%) | 0.00001 |
| Failed | 74 (100%) | 10 (14%) | |
| Total | 74 (100%) | 74 (100%) | |
| **B. Secondary Efficacy Parameter-Heal Time and Descriptive Parameter of Fracture Age** | | | |
| **1. Healed Cases: N = 64** | | | |
| **a. Heal Time (days)** | | **b. Fracture Age (days)** | |
| Mean ± S.E.M | 163 ± 9.4 | Mean ± S.E.M | 934 ± 151.6 |
| Median | 142 days | Median | 494 days |
| Range | 53 to 375 days | Range | 257 to 6011 days |
| Percentile Heal Time | 25% ≤ 104 days<br>50% ≤ 142 days<br>75% ≤ 211 days<br>90% ≤ 270 days | Percentile Fracture Age | 25% ≤ 948 days<br>50% ≤ 494 days<br>75% ≤ 991days<br>90% ≤ 1458 days |
| **2. Failed Cases: N = 10** | | | |
| **a. Fail Time (days)** | | **b. Fracture Age (days)** | |
| Mean ± S.E.M | 241 ± 42.7 | Mean ± S.E.M | 2570 ± 674 |
| Median | 218 days | Median | 2387 days |
| Range | 118 to 572 days | Range | 272 to 5893 days |
| Percentile Outcome Time | 25% ≤ 141 days<br>50% ≤ 218 days<br>75% ≤ 280 days<br>90% ≤ 453 days | Percentile Fracture Age | 25% ≤ 485 days<br>50% ≤ 2387 days<br>75% ≤ 4740 days<br>90% ≤ 5351 days |

*Excludes five (5) cases with outcomes of non-compliant (2), withdrawal (2), and decreased (1).
** Binomial test of the null hypothesis that the ultrasound treatment period heal rate was less than or equal to 5%.

3. Subgroup Analyses

**Table 14: Subgroup Analysis of Effectiveness Results**

| **Categorical Variable Prior to Start of EXOGEN Treatment** | | **Completed Cases Fishers Exact Probability*** | | | | |
|---|---|---|---|---|---|---|
| | | **Total** | **Healed** | **Failed** | **% Healed** | **p-value** |
| Gender | Female | 30 | 28 | 2 | 93% | 0.19 |
| | Male | 44 | 36 | 8 | 82% | |
| Age | ≤ 17 | 1 | 1 | 0 | 100% | 0.52 |
| | 18 – 29 | 12 | 9 | 3 | 75% | |
| | 30 – 49 | 32 | 27 | 5 | 84% | |
| | 50 – 64 | 21 | 19 | 2 | 91% | |
| | ≥ 65 | 8 | 8 | 0 | 100% | |
| Weight (kg.) | < 65 kg. | 12 | 11 | 1 | 92% | 0.65 |
| | 65 – 80 kg. | 35 | 31 | 4 | 89% | |
| | > 80 kg. | 27 | 22 | 5 | 81% | |
| Fracture Age | 256 – 365 days | 20 | 19 | 1 | 95% | 0.001 |
| | 366 – 730 days | 27 | 24 | 3 | 89% | |
| | 731 – 1826 days | 17 | 16 | 1 | 94% | |
| | ≥ 1827 days | 10 | 5 | 5 | 50% | |

4. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

### E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The post-market German Registry was coordinated by an independent organization chosen and supported by the EXOGEN device manufacturer.

## XI. SUMMARY OF SUPPLEMETAL CLINICAL INFORMATION

Supplemental clinical information was derived from real world data, evidence, and expert opinion:

1. Systematic reviews and meta-analyses: (Rutten et al. 2016, Schandelmeier et al. 2017, Leighton et al. 2017, Puts et al. 2021 etc.)

2. Literature review of relevant clinical studies and registry data.

No published clinical studies are available for the AccelStim device. However, according to the sponsor, as of July 2021, a total of 1,426 devices have been sold OUS, with no safety issues or recalls.

## XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopaedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because there were insufficient unresolved issues regarding the Safety and Effectiveness of the Subject Device to justify an Advisory Panel Meeting. The primary issue raised by this PMA, is whether the subject device (AccelStim) was sufficiently similar to the reference device (EXOGEN) to permit approval based on EXOGEN-related clinical data.

## XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

In this PMA the sponsor provided adequate evidence of the sufficient similarity of the AccelStim device with regard to the delivered therapeutic signal power and waveform characteristics. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for the previously approved EXOGEN device (P900009 and P900009/S006) in support of the reasonable assurance of its effectiveness is directly applicable towards establishing reasonable assurance of the effectiveness of the AccelStim device. See also Table 15.

**Table 15: Effectiveness of EXOGEN Device for Accelerated Healing of Fresh Fractures (AH) or Healing of Non-unions (NU)**

| # | Type | Reference | Anatomical Location | # Patients / (# Fractures) | Effectiveness |
|---|---|---|---|---|---|
| 1 | AH | Heckman et al. 1994 | Diaphyseal Tibia | (67) | Reduction in Time to Healing: 38% (58 days) $p < 0.0001$ |
| 2 | AH | Kristiansen et al. 1997 | Distal Radius | 60 / (61) | Reduction in Time to Healing: 38% (37 days) $p < 0.0001$ |
| | | | | | |
| 1 | NU | Germany Post-Market Study (1995-1997) | Mixed (excluding skull & vertebra) | 84 / (85) | Non-union Healing Rate: 86% (64/74 completed cases) $p = 0.00001$ |

## B. Safety Conclusions

Based on the data provided in the primary clinical studies supporting PMAs 900009 and 900009/S006, there is reasonable assurance that the EXOGEN device is safe for the proposed indications when used as directed. A detailed review of the cumulative clinical data did not result in a new, unmitigated, or otherwise concerning safety signal. See also Table 16.

**Table 16: Safety of EXOGEN Device for Accelerated Healing of Fresh Fractures (AH) or Healing of Non-unions (NU)**

| # | Type | Reference | Anatomical Location | # Patients / (# Fractures) | Safety |
|---|---|---|---|---|---|
| 1 | AH | Heckman et al. 1994 | Diaphyseal Tibia | (67) | 1 Adverse Event in Treated Group : Muscle Cramping |
| 2 | AH | Kristiansen et al. 1997 | Distal Radius | 60 / (61) | None |
| | | | | | |
| 1 | NU | Germany Post-Market Study (1995-1997) | Mixed (excluding skull & vertebra) | 84 / (85) | None |

## C. Benefit-Risk Determination

Although there are limitations with regard to the identification, classification, and reporting of adverse events and complications related to use of the EXOGEN device, the consensus among FDA reviewers, industry, and study authors is that device safety is high with relatively low risks associated with treatment when used as directed for appropriate indications. The greatest risk is likely ineffectiveness which may necessitate additional operative intervention.

The probable benefits of the device are based on data collected in two multi-center clinical trials and a post-market study conducted to support PMA approval of the EXOGEN device (P900009 and P900009/S006, respectively). As described above, results of comparative non-clinical testing provided evidence of the sufficient similarity of the EXOGEN and AccelStim devices, such that FDA could then apply Section 216 of the FDAMA and cite evidence of clinical effectiveness presented in the SSED for the EXOGEN device in support of determination of reasonable assurance of the effectiveness of the AccelStim device.

As detailed in the SSED for the EXOGEN device approved in P900009, two randomized, double-blinded, placebo-controlled multi-center trials performed by Heckman et al. 1994 and by Kristiansen et al. 1997 successfully demonstrated a statistically significant decrease in the time to clinical healing for tibia diaphyseal and distal metaphyseal radius indications. As detailed in the SSED for the EXOGEN device approved in P900009/S006, a German post-market study with lesser contributions from similar registries/ studies established in the United States and the Netherlands successfully demonstrated healing of non-unions.

As detailed in the SSEDs for the EXOGEN device, there were no notable adverse events identified in the clinical trials or post-market study. The safety profile and probable risks of the AccelStim device were demonstrated to be similar to those of the EXOGEN device with a reasonable assurance through non-clinical testing.

Patient Perspectives

This submission did not include specific information on patient perspectives for the AccelStim device.

In conclusion, given the available information above and its applicability to the AccelStim device, the probable benefits of treatment with the AccelStim device outweigh the probable risks.

## D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the AccelStim device when used in accordance with the indications for use.

With regard to reasonable assurance of the safety and effectiveness of the AccelStim device, the sponsor provided adequate evidence of sufficient similarity of the AccelStim and EXOGEN devices. This similarity was established through non-clinical

characterization and testing of the AccelStim device compared to data published in the SSED for the EXOGEN device to demonstrate that a closely similar therapeutic ultrasound signal is generated and delivered to the subject. Additionally, safety was evaluated by demonstration that the AccelStim complies with appropriate safety standards including biocompatibility, ultrasound safety, electrical safety, and electromagnetic compatibility. Because of this, the FDA was able to apply Section 216 of the FDAMA and confirm that the clinical evidence for the EXOGEN device presented in the SSEDs for P900009 and P900009/S006 in support of the reasonable assurance of the safety and effectiveness of the EXOGEN device is directly applicable towards establishing a reasonable assurance of the safety and effectiveness of the AccelStim device.

## XIV. CDRH DECISION

CDRH issued an approval order on May 3, 2022.

The applicant's manufacturing facilities have been determined, through prior on-site inspection and (due to constraints posed by the COVID-19 pandemic) by a review of relevant manufacturing site documentation and compliance history, to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES


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