P900009/S6

Exogen 2000® Summary of Safety and Effectiveness
Table of Contents

Exogen 2000® SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name:	Low-Intensity Pulsed Ultrasound Device for the Noninvasive Treatment of Nonunions
Device Trade Name:	Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®)
Applicant's Name and Address:	EXOGEN®, a Smith and Nephew Company 10 Constitution Avenue P. O. Box 6860 Piscataway, NJ 08855 (732) 981-0990
Date of Panel Recommendation:	None
Premarket Approval Application (PMA):	P900009
Supplement Number:	S006
Date of Notice of Approval to Applicant:	FEB 2 2 2000

II. Indications for Use

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 orthopedically managed by closed reduction and cast immobilization.

*A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

III. Contraindications

There are no known contraindications for the SAFHS® device.

IV. Warnings and Precautions

Warnings

- The safety and effectiveness of the use of this device has not been established in nonunions for the following:

  — nonunions of the vertebra and the skull.
  — individuals lacking skeletal maturity

Precautions

- The safety and effectiveness of the use of this device in pregnant/nursing women has not been established.

- Careful consideration of the use of this device must be decided on an individual basis in the presence of malaligned nonunion since the device will not correct or alter displacement, angulation or other malalignment.

- With active, implantable devices, such as cardiac pacemakers, operation may be adversely affected by close exposure to the SAFHS® device; therefore, evaluation during SAFHS® treatment by the attending cardiologist or physician is recommended.

- Patients in the clinical study were instructed to apply the device for one treatment period of twenty-minutes each day. The safety and effectiveness of the SAFHS® device when used for other than one daily twenty-minute treatment is unknown.

- The age range of the patients in this PMA nonunion study was 17- 86. The effect of SAFHS® therapy on patients outside this age range is unknown.

V. Device Description

The SAFHS® is a portable, battery powered, non-invasive ultrasonic bone growth stimulator. It incorporates the same technological features as the original SAFHS® device approved for treatment of fresh fractures (P900009, approved October 5, 1994).

The SAFHS® system provides a specifically-programmed low-level micromechanical force via ultrasonic acoustic pressure waves with an intensity of 30 milliwatts per square centimeter (mW/cm^2) [S.A.T.A. (Spatial Average-Temporal Average)]. The SAFHS® system low-intensity 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. Neither the physician nor the patient can select or change any of the low-intensity ultrasound signal specifications.

VI. Alternative Practices and Procedures

Alternative methods for treating nonunion are: 1) use of other approved bone growth stimulating devices; 2) surgical procedures which may involve internal fixation with a device and/or bone grafting; 3) procedures which may involve external fixation; or 4) conservative procedures.

VII. Marketing History

The SAFHS® device was initially approved for commercial marketing on October 5, 1994 with the indications of 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 orthopedically managed by closed reduction and cast immobilization. SAFHS® devices have been marketed for the approved indications in the United States (originally as Model 2A and since PMA Supplement Approval for Model 2000 in March of 1997 as either Model 2A or 2000) since October 17, 1994.The SAFHS® device has also been marketed in Germany, The Netherlands, France, Denmark, Sweden, Norway, Italy, United Kingdom, Israel, Spain, Belgium, Japan, Australia, Austria, Switzerland, Finland, and Luxembourg and has not been removed from the market in any of these countries.

VIII. Potential Adverse Effects of the Device on Health

No device-related adverse reactions or medical complications related to the use of this device were reported during the clinical studies. Two patients in a post-market registry reported mild skin irritation caused by skin sensitivity to the coupling gel. Both were resolved by a change of coupling medium to mineral oil or glycerine.

IX. Summary of Nonclinical Studies

Studies Previously Reported in PMA P900009[1]- Several studies were conducted for the initial fresh fracture PMA Application P900009 to assess the safety and effectiveness of the SAFHS® device. The i*n vitro* and *in vivo* animal studies showed no harmful thermal or genetic effects of low intensity pulsed ultrasound and suggested that the use of low intensity pulsed ultrasound would stimulate normal bone healing and other related biological responses.

Studies Reported in this PMA Supplement

Many fracture nonunions have metallic internal fixation devices present as the result of previous treatment. This PMA Supplement presents several reports of preclinical testing using internal-fixation animal models.

Two studies[2, 3] reported on ultrasound fracture treatment in a model of bilateral closed femoral shaft fractures made in skeletally male Long-Evans rats and stabilized by a 1.14 x 26 mm Kirschner wire, serving as an intramedullary rod. Fracture repair was evaluated on postoperative day 21, and treated fractures were shown to be significantly stronger and stiffer than the controls, showing that the stimulatory effect of ultrasound on fracture repair was not inhibited by the presence of a metallic internal fixation device.

In another case, the *in vivo* temperature changes in bone and surrounding soft tissues generated by pulse mode ultrasound beam were evaluated in the tibiae of the turkey and in the femora of the dog, with and without an intramedullary rod in place. The results indicate that ultrasound has a minimal influence of temperature, and that internal fixation devices do not affect the thermal field.

Several reference articles have focused on conventional therapeutic ultrasound's effect on surgical metallic implants. Lehman et al.[4] reported that, based on histological studies, ultrasound applied in the presence of metal implants did not produce any untoward effects. Gersten[5] reported that temperature rises in the region of maximal ultrasound field were smaller with metal than with bone at the same depth; the presence of metal was not a contraindication to the use of ultrasound. Lotsova[6] reported that investigations carried out with Kirschner needles used as fixation in ultrasound-treated patients did not affect migration of the pins or affect the structural integrity of the pins as determined by metallographic analysis. A canine study of the effect of ultrasound on internal fixation screws by Skoubo-Kristiansen and Sommer[7] concluded that no untoward effect of ultrasound was observed on the fixation screws and the torques used for loosening the screws could not be related to treatment with ultrasound.

The above studies on metal implants utilized ultrasound intensity levels ranging from 0.5 W/cm^2 to 2 W/cm^2 and no untoward effects were noted. These intensities are 16 to 60 times higher than the intensity used in the SAFHS® clinical and associated animal studies reported herein. Therefore, it is reasonable to conclude that metal implants such as plates, screws, and intramedullary (IM) rods present at or near a fracture would not affect the safety and effectiveness of SAFHS®.

This PMA Supplement reported on a study of whether SAFHS ultrasound at 3 times the intensity of the clinical signal for 30 hours would affect the composition of AISI 316-L stainless steel orthopedic fixation plates in a physiological medium. Metallographic analysis followed the routine procedures of electropolishing, chemical treatment, and optical microscope and photography with magnifications at 55, 110, 220 and 440X. No changes or effects were observed in the ultrasound-stimulated plate versus the non-stimulated plate.

Based on these references and this study, low-intensity ultrasound does not compromise the integrity of this commonly used orthopedic implant material even after 30 hours of continuous exposure.

X. Summary of Clinical Studies

A. Objectives

The objectives of the clinical studies were to assess the safety and effectiveness of SAFHS® in the treatment of nonunions.

Study Design

This PMA Supplement reports the retrospective analysis of a group of patients in Germany and Austria treated with SAFHS® for nonunions. 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.

The study includes nonunion cases treated with the SAFHS® device from the initial device introduction date. Each prescribing physician (investigator) provided initial fracture and nonunion 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.

B. Inclusion/Exclusion Criteria

For this PMA supplement, the primary criterion for the definition of nonunion cases was the minimum time from fracture of nine (9) months. Nonunion cases meeting the minimum 9 month criterion were then classified into two mutually exclusive categories descriptively characterized as "core group" and "non-core group". The core group category required nonunion cases to have established nonunions, to have completed treatment and to have no surgical intervention within the three months prior to SAFHS® treatment in addition to the 9 month minimum time from initial injury. The non-core group category included those completed cases that could not be validated as established nonunions by the PIs, those completed cases with surgical procedures within the three months prior to SAFHS® treatment, cases with incomplete data, and all incomplete cases (1 deceased, 2 non-compliant, and 2 withdrawals) in addition to the 9 month minimum time from initial injury. Exclusions for either group were pregnant females, nonunions of spine or skull, or tumor-related nonunions, and patients who could not comply with the required treatment regimen.

C. Criteria for Measuring Safety

The safety information provided in the approved PMA-P900009 for SAFHS® for the fresh fracture indication provided assurance that the pulsed, low-intensity ultrasound intensities transmitted to bone and surrounding tissue posed no observed or known risks. Additional preclinical studies reported in this PMA Supplement support this conclusion. Furthermore, adverse effects, complications, and complaints were monitored and no device related incidents were reported.

D. Criteria for Measuring Effectiveness

The clinical records and the radiographic series of all of the cases were reviewed by one or more of the PIs to insure adherence to the inclusion and exclusion criteria. The period between the initial injury and the time of the start of low-intensity ultrasound treatment was verified from the records. The radiographic series for each case was reviewed to determine that the healing process had stopped and that the nonunion line was visible in two views. The investigator provided the sponsor with the signed prescription form, demographic data, prior orthopedic and surgical history data, and orthopedic care data received by the patient prior to and at the time of the start of SAFHS® treatment. Investigators followed the standard orthopedic practice of taking anterior/posterior and lateral radiographs, with oblique views taken if the nonunion gap was more clearly seen on these views. Standard clinical examinations for pain upon gentle stress and upon weight bearing were performed at each follow-up visit to determine the extent of clinical healing. Investigators followed standard orthopedic management practice and scheduled 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.

Upon completion of SAFHS® therapy, the outcome of "healed" or "failed" was determined. Those cases with healed or failed outcome were designated as "completed cases" and cases that did not complete SAFHS® therapy were designated as "incomplete cases". A nonunion was determined as healed when it was both clinically healed [no pain upon gentle stress and weightbearing (for long bones only)] and radiographically healed [for long bones, at least three (3) of four (4) bridged cortices] and, for other bones, callus bridging the nonunion site. Failed outcome was defined as not meeting the criteria to be determined as healed, for cases with completed SAFHS® therapy. The three "incomplete cases" categories were deceased (died during the study), non-compliant (non-compliance with SAFHS® device use or prescribed treatment regimen), and withdrawal (withdrawal from the study prior to outcome determination, based on a decision by the investigator or the patient).

The primary efficacy parameter was outcome of "healed" due to SAFHS® treatment. The secondary efficacy parameter was heal time, defined as days from SAFHS® start to the healed outcome determination date. A descriptive parameter, reported for purposes of description or characterization and not for purposes of determining safety and effectiveness, was fracture age defined as days from initial injury to the start of SAFHS® therapy (Table 1 for completed cases). Table 2 provides an efficacy summary for a comparison of completed cases and its subsets of core and non-core groups and the intention-to-treat analysis. Table 3

presents the stratification analyses for categorical variables at the start of SAFHS® treatment with the percent healed compared for homogeneity across strata for the clinically relevant variables.

Statistical analyses were based on each specific nonunion case. All times to a specific response or event were calculated (number of days). 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. For comparisons between groups, the null hypothesis was that the distribution of the variable was the same (i.e., homogeneous) across the comparator groups. The alternative hypothesis was that the distribution of the variable was not the same across the comparator groups.

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%.

Comparability analyses were performed for 75 non-categorical and categorical variables.

E. Study Population

1. General - All cases with SAFHS® low-intensity ultrasound therapy started during the period of July, 1995 (the initial device introduction month) to April, 1997 were reviewed by the PIs to determine whether they met the study inclusion and exclusion criteria.

There was one patient in the study with more than one nonunion. To avoid the complications of patient and fracture number differences, each nonunion is considered a separate case. All comparability and effectiveness analyses refer to nonunion cases and not patients.

The study consisted of 79 patients with 80 nonunion cases from 54 investigators. Five cases were without a final healing status and were incomplete cases: 2 non-compliant, 2 withdrawn and 1 deceased.

Patient demographics for the eighty cases were summarized for age, sex, and weight. Females constituted 42% (33/79) and males were 58% (56/79) of the total number of patients. The average patient age was 46 years with a range of 17-86 years. The mean fracture age (days from initial injury to the start of SAFHS treatment) was 1136 days (3.1 years) with a range of 257 to 6011 days. The mean number of prior surgical procedures was 2.4. The mean number of days without surgery (days from last surgical procedure to SAFHS start) was 665 days (1.8 years).

2. Comparisons across investigators and comparability of groups - Comparisons were assessed for the non-categorical variables of patient age, weight (kg.), days without surgery, fracture age, total number of surgical procedures combining initial and all subsequent interventions and surgical and other procedures by type combining initial and all subsequent interventions. Comparisons were also assessed for the categorical variables of gender, age, weight, fracture age, total number of surgical procedures combining initial and all subsequent interventions, surgical and other procedures by type combining initial and all subsequent procedures, days without surgery, bone, long bones versus other bones, displaced at initial injury, long bone type, initial fracture type, fixation present at the start of and during SAFHS® treatment, medication, disease, concomitant clinical condition, smoking status, compliance with device use during SAFHS® treatment, and nonunion type.

a. **Justification for combining the data across investigators for all cases** - Since the data from many investigators were pooled for the effectiveness results, comparability across investigators was evaluated, in particular, for the categorical variable at the completion of SAFHS® treatment of both the outcome of healed or failed. A comparison across investigators was also performed for all categorical and non-categorical variables to assess the validity of combining the data from all investigators within each study, with a non-significant result for 95% (71/75) of the comparisons.

b. **Primary core group versus non-core group comparison** - As the primary comparison between groups, the core group was compared to the non-core group for the non-categorical variables and the categorical variables to assess for the potential introduction of bias by the classification of cases as core group or non-core group. For this study, 95% (71/75) of the total comparisons were non-significant.

3. Summary of Results of Comparability Analyses - The comparability across investigators showed that combining the data from all investigators for the evaluation of safety and efficacy was justified based on the results of the comparability analyses which did not identify systematic differences across investigators; it was also justified because of the common inclusion/exclusion criteria and evaluation definitions that were utilized across all investigators. Most importantly, the comparisons were non-significant for outcome of SAFHS® treatment across investigators.

There were no systematic clinically relevant differences for the primary comparability

analyses for the core group cases compared to the non-core group cases. This demonstrates that there was no introduction of bias by the classification of cases as core group and non-core group. The comparisons also established that there were similar characteristics in both groups.

F. Results

1. Safety - No device-related adverse reactions or medical complications related to the use of this device were reported during the clinical study.

2. Effectiveness - Outcome analyses were completed using the healed or failed outcome of the SAFHS® treated nonunion and the associated date as determined by the principal investigators. For the purposes of this summary, results are reported for completed cases, the core and non-core group subsets of completed cases, and for all cases in an intention-to-treat analysis. One case involving a failed cementless knee arthroplasty (tibial component) was included in the safety and intention-to-treat analyses but not the efficacy analysis.

a. Primary and secondary efficacy parameters, and descriptive parameter.

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 (Table 1.). The mean time to a healed fracture was 163 ± 9.4 days. The median heal time was 142 days with a range of 53 to 375 days. The mean fracture age for the healed cases in the core group was 934 ± 151.6 days or nearly 3 years and the median fracture age was 494 days with a range of 257-6011 days (Table 1).

In Table 2, a comparison summary provides the efficacy results for the core and non-core group subsets of completed cases. Of the 41 core group cases, 88% (36/41) healed and 12% (5/41) were failures of SAFHS® treatment. The healed rate for the non-core group was 85% (29/34). Both core and non-core group results were significant at p=0.00001 when compared to the paired control of prior failed treatment.

The intention-to-treat analysis evaluated 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.

b. Completed Cases Stratified by Variable (Table 3)

Healing rates were stratified by a number of variables, and were consistently similar across most variables including gender and age, . Statistically significant differences

in healing were seen in stratifications by bone, long bones versus other bones, and the fracture age stratum of over 5 years (≥1827 days). All three of these differences were attributable to the four scaphoid nonunion failures that were all more than 10 years in fracture age and, therefore, were very difficult and challenging cases.

3. Long-term Follow-up - A long-term follow-up was performed for all 80 cases by telephone to determine whether healed cases were still healed. This follow up documented 92% (60/65) as still healed with 8% (5/65) of cases that could not be located with an average long-term follow-up time of 407 ± 7.4 days and median time of 386 days with a range of 188-778 days.

4. Compliance with device usage - Patients were instructed to use their SAFHS® device at home for one continuous twenty-minute treatment per day until advised to stop treatment by their physician. The SAFHS® device recorded the actual usage time of the device. The patient compliance monitor (PCM) microprocessor storing the usage time was downloaded when the devices were returned to Exogen upon completion of treatment. For all 80 cases, twenty-two had missing PCM usage data either because the device was not returned or the battery powering the PCM circuit was discharged (low battery). The cases that had PCM data numbered 58 and an additional three cases without PCM data were termed "good" in compliance by the investigator's assessment. Of the 58 cases with PCM data, 43 used their devices over 2,000 minutes (100 days if used once a day), 12 used their devices for between 1000 and 2000 minutes, and 3 used their devices for less than 1000 minutes.

For the 47 healed cases with PCM data, the mean PCM device usage was 2661 ± 192.6 minutes with a median of 2254 minutes and a range of 490 to 6865 minutes.

5. Summary of Efficacy Results - The comparability of core and non-core group cases was established and the comparability across investigators did not identify any systematic differences that would preclude the combining or pooling of data from all investigators. Given the percent healed rate, number of cases (N) and alpha equal .05, the power of the analyses was at least 99.9%.

All healed analyses consistently demonstrated efficacy with the completed cases having a healed rate of 86% (64/74) while the core group subset of completed cases had a healed rate of 88% (36/41). The core group subset healed rate was similar to the completed cases non-core subset healed rate of 85% (28/33). The intention-to-treat analysis of all cases was 81% (65/80). The healed rate results were also consistently similar across stratification variables including gender and age; except for the decreased healing response rate for scaphoid nonunions which affected stratifications by bone, long bones versus other bones, and the fracture age stratum of over 5 years (≥1827 days). The scaphoid nonunion healed rate of 33% (2/6) was attributable to the four scaphoid nonunion failures that were all more than 10 years in fracture age and, therefore, were

very difficult and challenging cases. Cases with metal present during SAFHS® treatment such as those with ORIF and those cases with IM rods had a 88% (21/24) and 100% (16/16) healed rate, respectively. The results of this nonunion paired design clinical study established the safety and efficacy of the SAFHS® device in treating nonunions, including cases that had long fracture ages of up to 5 years but suggest that nonunions with fracture ages of over 5 years may have a decreased response to SAFHS® treatment.

*Table 1: Efficacy Results for SAFHS® Treated Completed Cases**

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

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)** Mean ± S.E.M.: 163 ± 9.4 Median: 142 days Range: 53 to 375 days Percentile Heal Time: 25% ≤ 104 days 50% ≤ 142 days 75% ≤ 211 days 90% ≤ 270 days	b. **Fracture Age (days)** Mean ± S.E.M.: 934 ± 151.6 Median: 494 days Range: 257 to 6011days Percentile Fracture Age: 25% ≤ 348 days 50% ≤ 494 days 75% ≤ 991 days 90% ≤ 1458 days
2. Failed Cases: N= 10	
a. **Fail Time (days)** Mean ± S.E.M.: 241 ± 42.7 Median: 218 days Range: 118 to 572 days Percentile Outcome Time: 25% ≤ 141 days 50% ≤ 218 days 75% ≤ 280 days 90% ≤ 453 days	b. **Fracture Age (days)** Mean ± S.E.M.: 2570 ± 674 Median: 2387 days Range: 272 to 5893 days Percentile Fracture Age: 25% ≤ 485 days 50% ≤ 2387 days 75% ≤ 4740 days 90% ≤ 5351 days

Table 2: Effectiveness Summary for Completed Cases and Its Subsets of Core and Non-core Groups and the Intention-to-Treat Analysis

	Total	Healed	Failed	% Healed	p-value*
Completed Cases:	**74**	**64**	**10**	**86%**	**0.00001**
Core Group:	*41*	*36*	*5*	*88%*	*0.00001*
Non-Core group:	*33*	*28*	*5*	*85%*	*0.00001*
Intention-to-Treat Analysis (all cases):	**80**	**65**	**15**	**81%**	**0.00001**

*p-value for comparison against prior orthopedic treatment results of 100% failed cases.

Table 3: Completed Cases - Stratification by Categorical Variables

*Two-sided exact p-value, Fisher's exact test, testing homogeneity of strata.

Row	Categorical Variable Prior to Start of SAFHS® Treatment		Completed Cases Fishers Exact Probability* Total	Healed	Failed	% Healed	p-value
1	**Gender:**	Female	30	28	2	93%	0.19
		Male	44	36	8	82%	
2	**Age:**	≤17	1	1	0	100%	
		18-29	12	9	3	75%	
		30-49	32	27	5	84%	0.52
		50-64	21	19	2	91%	
		≥65	8	8	0	100%	
3	**Weight (kg.):**	<65 kg.	12	11	1	92%	
		65-80 kg.	35	31	4	89%	0.65
		>80 kg.	27	22	5	81%	
4	**Fracture Age:**	256-365 days	20	19	1	95%	
		366-730 days	27	24	3	89%	0.001
		731-1826 days	17	16	1	94%	
		≥ 1827 days	10	5	5	50%	
5	**Total No. Surgical Procedures Combining Initial and All Subsequent Interventions:**						
		0	20	15	5	75%	
		1	15	12	3	80%	0.16
		2	24	23	1	96%	
		3 or more	15	14	1	93%	
6	**Prior Days Without Surgery (Days from Last Surgical Procedure to SAFHS® Start):**						
		≤ 82	9	9	0	100%	
		83-365	39	34	5	87%	0.03
		366-730	12	12	0	100%	
		≥ 731	14	9	5	64%	
7	**Bone:**						
	Tibia/Tibia-Fibula/Fibula		28	26	2	93%	
	Femur		13	12	1	92%	
	Radius/Radius-Ulna/Ulna		7	6	1	86%	
	Humerus		6	5	1	83%	
	Metatarsal		4	4	0	100%	0.03
	Other Foot Bones (calcaneus)		1	1	0	100%	
	Ankle*		2	1	1	50%	
	Scaphoid		6	2	4	33%	
	Other Hand Bones (metacarpal)		1	1	0	100%	
	Other (4-clavicle, 1-pelvis, 1-rib)		6	6	0	100%	
	*Tibio-talar arthrodesis						

Row	Categorical Variable Prior to Start of SAFHS® Treatment	Completed Cases Fishers Exact Probability*				
		Total	Healed	Failed	% Healed	p-value
8	**Long Bone vs. Other Bones:**					
	Long Bones	59	54	5	92%	
	- 28 tibia					
	- 13 femur					
	- 7 radius					
	- 6 humerus					0.02
	- 4 metatarsal					
	- 1 metacarpal					
	Other Bones	15	10	5	67%	
	- 1 calcaneus					
	- 4 clavicle					
	- 1 pelvis					
	- 1 rib					
	- 6 scaphoid					
	- 2 ankle					
9	**Displaced at the Start of SAFHS Therapy:**					
	Missing	(5)	(2)	(3)		
	No	56	50	6	89%	1.00
	Yes	13	12	1	92%	
10	**Long Bone Type: Only for Long Bone Cases:**					
	Missing	(5)	(3)	(2)		
	Metaphyseal	8	6	2	75%	0.05
	Diaphyseal	46	45	1	98%	
11	**Initial Fracture Type:**					
	Missing	(4)	(2)	(2)		
	Closed	40	34	6	85%	
	Open	22	21	1	95%	0.16
	Arthrodesis	2	1	1	50%	
	Osteotomy	6	6	0	100%	
12	**Fixation Present at Start of and During SAFHS® Treatment:**					
	IM Rod; Only for Long Bone Cases (N=59) No	43	38	5	88%	0.31
	Yes	16	16	0	100%	
	Open Reduction, Internal Fixation (ORIF) No	51	44	7	86%	1.00
	Yes	24	21	3	88%	
	External Fixation; Only for Long Bone Cases (N=59) No	50	46	4	92%	0.58
	Yes	9	8	1	89%	

Row	Categorical Variable Prior to Start of SAFHS® Treatment		Completed Cases Fishers Exact Probability* Total	Healed	Failed	% Healed	p-value
	Conservative	No	59	52	7	88%	0.44
	(Cast, Splint, Brace)	Yes	16	13	3	81%	
	IM Rod, or ORIF, or External	No	11	8	3	73%	0.16
	Fixation, or Conservative	Yes	64	57	7	89%	
13	**Prior Failed Lithotripsy Therapy:**						
		No	73	63	10	86%	1.00
		Yes	2	2	0	100%	
14	**Smoking Status:**						
		Missing	(2)	(2)	(0)		
	Never Smoked		34	31	3	91%	
	Stopped Smoking Prior to SAFHS® Start		10	8	2	80%	0.47
	Smoker at SAFHS® Start		28	23	5	82%	
15	**Nonunion Type:**						
		Missing	(22)	(17)	(5)		
	Atrophic		41	36	5	88%	0.57
	Hypertrophic		11	11	0	100%	

XI. Other Clinical Studies

There were two additional clinical studies reported on in this PMA as supportive data to the German study. These studies took place in the United States and in The Netherlands. In the United States, a registry of prescription use was maintained and data was reviewed for nonunion cases. In The Netherlands, a study identical to the German study was conducted.

The protocol details were similar for the inclusion/exclusion criteria, study design, and effectiveness measures in the United States study. Instead of independent evaluations by PIs, this study utilized the investigator determination of an established nonunion at the start of the study and a healed or failed outcome at the end of treatment. For the United States study, the completed cases group had an 82% (352/429) healed rate. When this healed rate is compared with the paired prior failed treatment control, the result is statistically significant at p=0.00001 in favor of the SAFHS® treated results. The core group healed rate of 80% (249/313) was similar to the non-core group healed rate of 88% (103/116). The intention-to-treat analysis resulted in a 64% (351/551) healed rate. The healed rate results were consistently similar across stratification variables including gender and age.

For the Netherlands study, the completed cases healed rate result was 90% (27/30). This healed rate when compared with the paired prior failed treatment was statistically significant at p=0.00001. The core group subset had a healed rate of 87.5% (21/24) which was similar to the non-core subset healed rate of 100% (6/6). The intention-to-treat analysis of all 33 cases was 82% (27/33). The healed rate results were consistently similar across stratification variables including gender and age.

The results of these two additional studies also support the safety and efficacy conclusion for the SAFHS® device in treating nonunions.

XII. Conclusions Drawn From the Studies

The information provided in the previous sections describing the nonclinical and clinical studies provides reasonable assurance of the safety and effectiveness of the Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) for the non-invasive treatment of established nonunions excluding skull and vertebra.

XIII. Panel Recommendation

This is a PMA supplement which did not require panel review

XIV. CDRH Decision

CDRH recommends approval for the Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) for the non-invasive treatment of established nonunions, excluding skull and vertebra.

XV. Approval Specifications

A Post-market Study will not be required for this device. No significant clinical issues of safety and effectiveness remain to be collected which would yield clinically significant information which would necessitate modifications to device indications, adverse events, contra-indications, precautions or warnings.

XVI. References

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