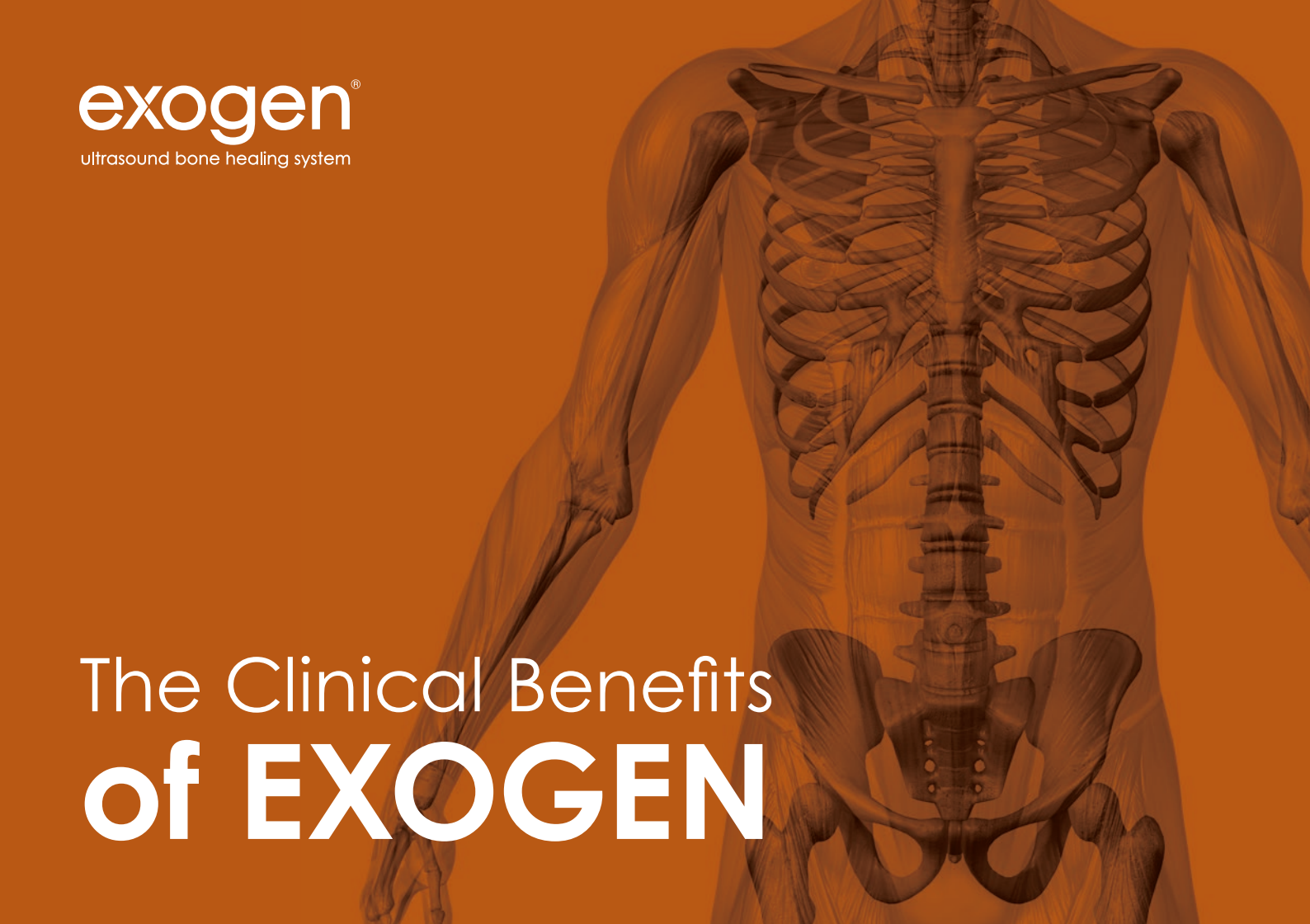
exogen®

ultrasound bone healing system



# The Clinical Benefits of EXOGEN

# **EXOGEN** Ultrasound Bone Healing System

EXOGEN is a unique, fracture-healing device that uses safe, effective, low-intensity pulsed ultrasound to help stimulate the body's natural healing process. Clinical studies show that EXOGEN heals fractures not healing on their own, and accelerates healing of indicated fresh fractures.[1,2,20]

EXOGEN is the only FDA-approved bone-healing device with:

- 20-minute, noninvasive, daily treatment that fits easily into patient's lifestyle
- 86% nonunion heal rate[1]
- Up to 58 days faster healing of fresh* tibial diaphysis fractures[2]
- 91% clinically proven compliance rate among patients[3]
- Exclusively recommended by The National Institute for Health and Care Excellence (NICE).[28]

The device's easy-to-use design, treatment tracking calendar, and short daily treatment time make EXOGEN an ideal option for patients and promotes treatment compliance.

*See Summary of Indications for Use.


exogen
ultrasound bone healing system
1-42
36 37 38 39 40 41 42
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91%
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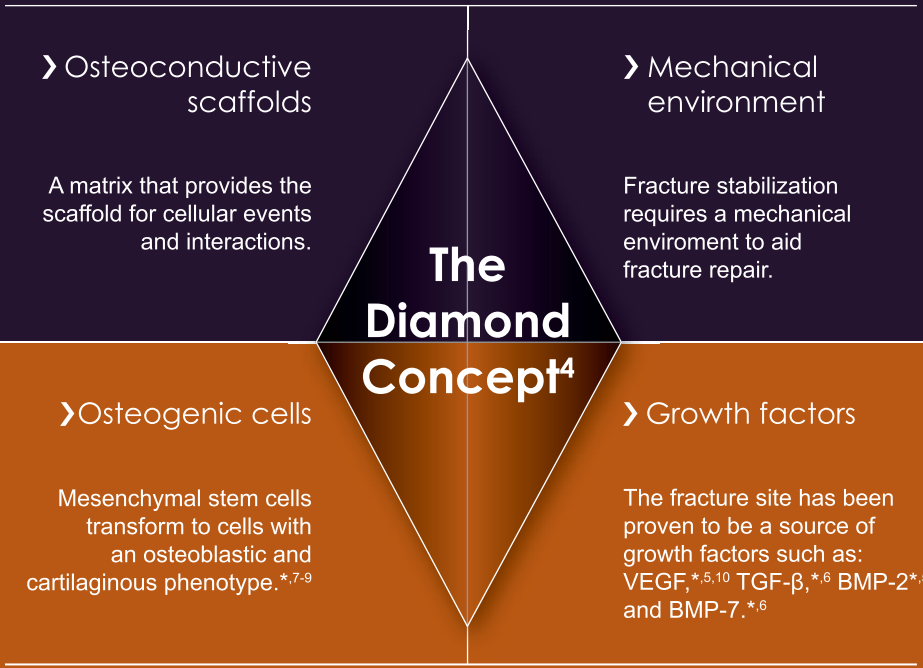
# **EXOGEN** complements your treatment

Four factors contribute to the process of bone restoration: osteoconductive scaffold, mechanical environment, osteogenic cells and growth factors. These form the diamond concept of bone healing.[4] Traditional fracture treatment can impact two of the four factors: osteoconductive scaffold and the mechanical environment. EXOGEN can complement treatment by stimulating the development of osteogenic cells and the expression of growth factors such as VEGF, BMP-2 and BMP-7.*[5,6]

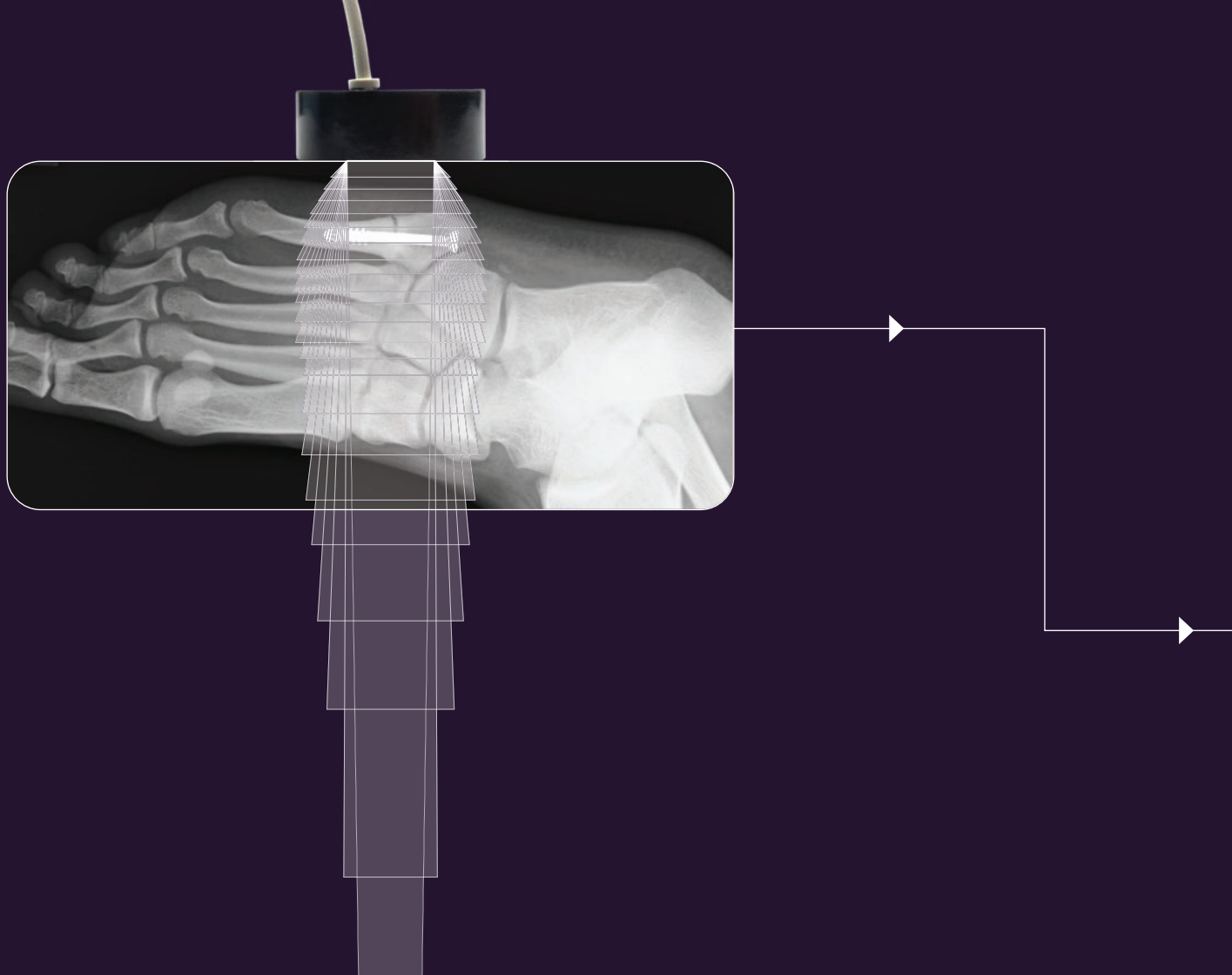
## You treat the injury. EXOGEN works on the biology.


*The clinical relevance of in vivo findings is unknown.

# Fracture healing managed through surgical intervention

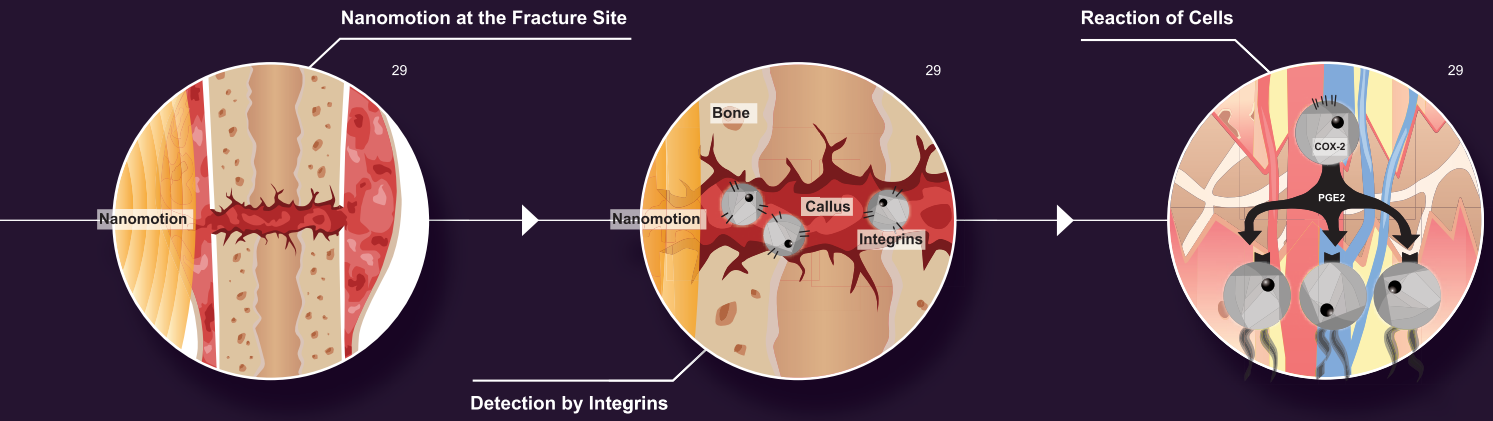



# Bone healing stimulated through EXOGEN's mechanism of action



# **EXOGEN** uses low-intensity pulsed ultrasound to stimulate a cascade of cellular reactions

EXOGEN uses an ultrasound mechanical pressure wave composed of 1,000 pulses per second to stimulate a response at the cellular level. The ultrasound wave has an intensity of 30 mW/cm$^2$, which is in the same range as fetal sonography.[11] The ultrasound wave penetrates up to 26 cm (10.5 inches) into the body, and is safe to use with metal fixation.[12,13] After contacting the bone, the mechanical pressure wave creates a nanomotion at the fracture site, producing a reaction at the cellular level.[11]



# **EXOGEN** jump starts bone healing by stimulating biological processes

When the ultrasound signal reaches the fracture site, it causes movement in the extracellular matrix, and is simultaneously detected by cells through mechanical surface receptors called integrins. When stimulated by a mechanical force such as the low-intensity pulsed ultrasound signal from EXOGEN, intracellular proteins such as paxillin and vinculin cause the integrins to cluster together, forming a complex known as a focal adhesion. There are many activities that are initiated by the formation of focal adhesions, such as cytoskeleton reorganization and intracellular signaling events. These activities create an intracellular cascade that ultimately enhances gene expression and protein production.[14-16]

## Mechanism of Action

### 1. Stimulation

EXOGEN sends ultrasound waves through the skin and soft tissue, creating nanomotion that stimulate cells at the fracture site.[11]

### 2. Activation

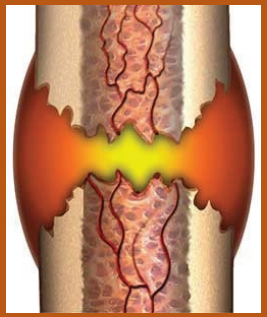
EXOGEN ultrasound activates cell surface mechanoreceptors called integrins, initiating an intracellular cascade that leads to gene upregulation.[14]

### 3. Upregulation

EXOGEN ultrasound increases upregulation of genes, and expression of proteins and growth factors critical to bone healing.[5]

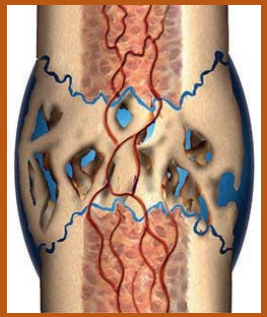

*The clinical relevance of in vivo findings is unknown.

# **EXOGEN** at every stage of the fracture healing process



**Inflammation**

**Soft Callus**



**Hard Callus**

**Bone Remodeling**

## Inflammation Stage

EXOGEN's ultrasound signal increases cell division among periosteal cells in culture and upregulates growth factors that trigger formation of new blood vessels.[10]

## Soft Callus Stage

The ultrasound treatment enhances the TGF-β-triggered differentiation of chondrocytes in culture and accelerates formation of the extracellular matrix.[9,17]

## Hard Callus Stage

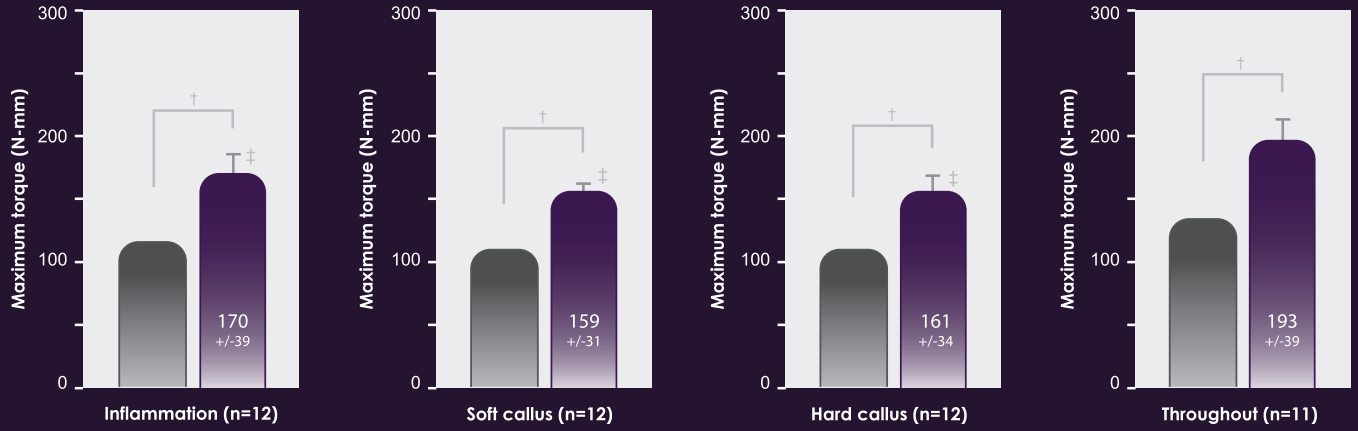
EXOGEN upregulates endochondral ossification and enhances osteoblast differentiation and mineralization.[8,14,18,19]

## Bone Remodeling Stage

Accelerating both the formation and resorption of bone, EXOGEN ultrasound treatment yields faster remodeling of the mineralized callus.[18]

# **EXOGEN** accelerates fracture healing at every stage

The fracture repair process is divided into four stages: inflammation, soft callus formation, hard callus formation, and remodeling. EXOGEN treatment has been shown to accelerate fracture healing at every stage, with maximum benefit achieved when applied throughout the entire healing process.*[19]

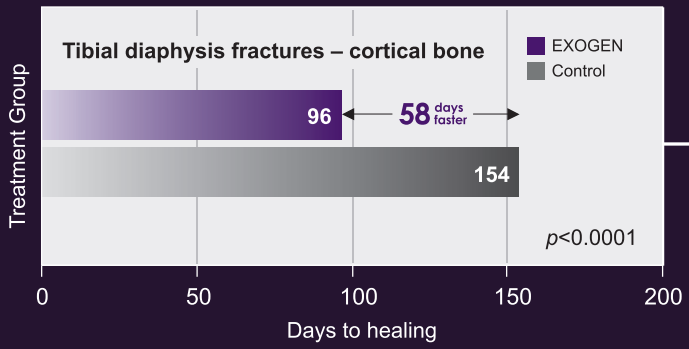



†$p$<0.01 treatment compared to contralateral control
‡$p$<0.05 treatment compared to treatment throughout

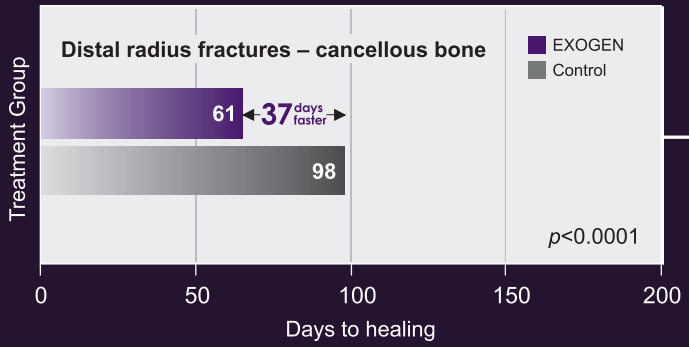
Error bars represent 1 standard deviation

*The clinical relevance of these findings is unknown.

# **EXOGEN** is the only FDA-approved bone healing device that delivers accelerated healing of indicated* fresh fractures




58 days faster with EXOGEN[2]

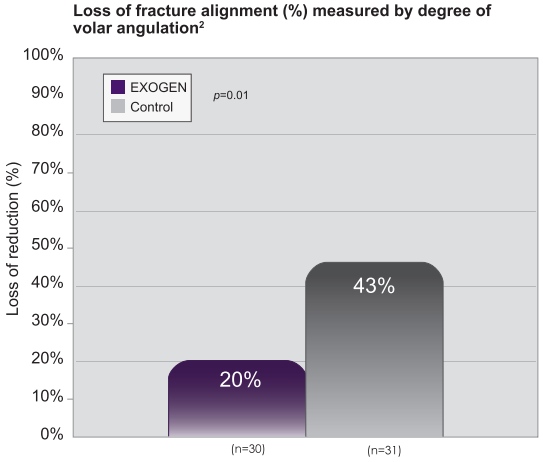



37 days faster with EXOGEN[20]

*See Summary of Indications for Use.

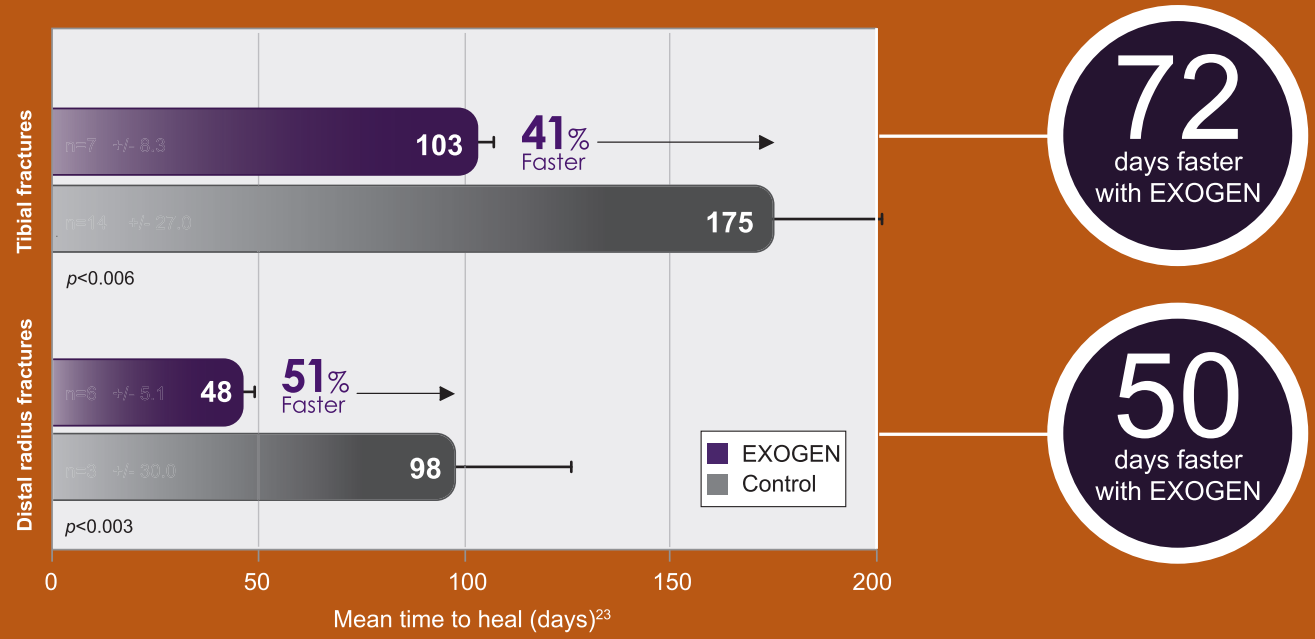
# **EXOGEN** is proven to heal nonunion fractures

For patients with nonunion fractures, a 20-minute daily treatment with EXOGEN is safe and effective. EXOGEN has a proven success rate of up to 86% when used to treat nonunion fractures.[1] EXOGEN's technology is successfully compatible with all types of conservative and surgical fracture management techniques, and has been shown to reduce loss of fracture alignment.[2,20,21]



# **EXOGEN** mitigates the negative impact of certain comorbidities on bone healing

Smoking and advanced age are just some of the risk factors known to impede fracture healing.[30,31]
One clinical study demonstrated that EXOGEN accelerated fracture healing by as much as 51% in patients who smoked.[23]



# **EXOGEN** is effective in healing challenging, established nonunions[1]

Numerus clinical studies with EXOGEN demonstrate high nonunion heal rates across various fracture types.

| Literature | Bone investigated | Fracture management | Patient numbers | Fracture heal rate |
|---|---|---|---|---|
| Romanò, et al.[24] | Tibia, humerus, fermur | Surgical | N=11 | **82%** |
| Nolte, et al.[1] | Scaphoid, malleolus, clavicle, humerus, femur, radius/ulna, tibia/fibula, metatarsal | Conservative, intramedullary nail, external fixation | N=29 | **86%** |
| Mayr, et al.[25] | Tibia/fibula, fermur, radius/ulna, humerus, clavicle, scaphoid, metatarsal | Conservative, intramedullary nail, external fixation | N=366 | **86%** |
| Lerner, et al.[26] | Femur, tibia, radius/ulna, humerus | External fixation, intramedullary nail | N=18 | **89%** |
| Gebauer, et al.[21] | Tibia/fibula, fermur, radius/ulna, humerus, metatarsal, scaphoid | Conservative, internal fixation, external fixation | N=67 | **85%** |
| Jingushi, et al.[27] | Femur, tibia, humerus, radius, ulna | Conservative, intramedullary nail, external fixation | N=72 | **75%** |

# **EXOGEN** Performance Program Guarantee

Designed to provide you added confidence that EXOGEN will help heal nonunion fractures.

The EXOGEN Performance Program guarantees that radiographic healing progression will be shown in nonunion fractures. If the requirements of the program are met and no healing progression is shown after 120 days, purchase cost of EXOGEN will be refunded to the buyer.*

## Adherence to prescribed treatment is essential

EXOGEN has been shown to be effective to treat nonunion when used daily for 20-minute treatments.[1,21]

Terms and Conditions*

To be eligible for the program, patients must treat their nonunion fracture with EXOGEN for 20 minutes a day, for a minimum of 120 days, with a minimum of 90% adherence to the treatment regimen.
The nonunion fracture must be stable, non-displaced, with a fracture gap of fewer than 10 millimetres.
Vertebra and skull fractures are excluded.

*See full terms and conditions on **EXOGEN.com**

**References: 1.** Nolte PA, van der Krans A, Patka P, Janssen IM, Ryaby JP, Albers GH. Low-intensity pulsed ultrasound in the treatment of nonunions. *J Trauma*. 2001;51(4):693-703. doi:10.1097/00005373-200110000-00012 **2.** Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am*. 1994;76(1):26-34. doi:10.2106/00004623-199401000-00004 **3.** Schofer MD, Block JE, Aigner J, Schmelz A. Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. *BMC Musculoskelet Disord*. 2010;11:229. doi:10.1186/1471-2474-11-229 **4.** Giannoudis PV, Einhorn TA, March D. Fracture healing: the diamond concept. *Injury*. 2007;38(suppl 4):S3-6. doi:10.1016/s0020-1383(08)70003-2 **5.** Naruse K, Sekiya H, Harada Y, et al. Prolonged endochondral bone healing in senescence is shortened by low-intensity pulsed ultrasound in a manner dependent on COX-2. *Ultrasound Med Biol*. 2010;36(7):1098-108. doi:10.1016/j.ultrasmedbio.2010.04.011 **6.** Sant'Anna EF, Leven RM, Virdi AS, Sumner DR. Effect of low intensity pulsed ultrasound and BMP-2 on rat bone marrow stromal cell gene expression. *J Orthop Res*. 2005;23(3):646-52. doi:10.1016/j.orthres.2004.09.007 **7.** Leung KS, Cheung WH, Zhang C, Lee KM, Lo HK. Low intensity pulsed ultrasound stimulates osteogenic activity of human periosteal cells. *Clin Orthop Relat Res*. 2004;(418):253-9. doi:10.1097/00003086-200401000-00044 **8.** Lai CH, Chen SC, Chiu LH, et al. Effects of low-intensity pulsed ultrasound, dexamethasone/TGF-ß1 and/or BMP-2 on the transcriptional expression of genes in human mesenchymal stem cells: chondrogenic vs. osteogenic differentiation. *Ultrasound Med Biol*. 2010;36(6):1022-33. doi:10.1016/j.ultrasmedbio.2010.03.014 **9.** Ebisawa K, Hata K, Okada K, et al. Ultrasound enhances transforming growth factor ß-mediated chondrocyte differentiation of human mesenchymal stem cells. *Tissue Eng*. 2004;10(5-6):921-9. doi:10.1089/1076327041348437 **10.** Coords M, Breitbart E, Paglia D, et al. The effects of low-intensity pulsed ultrasound upon diabetic fracture healing. *J Orthop Res*. 2011;29(2):181-8. doi:10.1002/jor.21223 **11.** EXOGEN Ultrasound Bone Healing System [package insert]. Durham, NC; Bioventus LLC; 2020. **12.** Bioventus LLC. EXOGEN ultrasound signal depth and penetration. Data on file, RPT-000368. **13.** Lehmann JF, Brunne GD, Martinis AJ, McMillan J. Ultrasonic effects as demonstrated in live pigs with surgical metallic implants. *Arch Phys Med Rehabil*. 1959;40:483-8. **14.** Tang CH, Yang RS, Huang TH, et al. Ultrasound stimulates cyclooxygenase-2 expression and increases bone formation through integrin, focal adhesion kinase, phosphatidylinositol 3-kinase, and Akt pathway in osteoblasts. *Mol Pharmacol*. 2006;69(6):2047-57. doi:10.1124/mol.105.022160 **15.** Mahoney CM, Morgan MR, Harrison A, Humphries MJ, Bass MD. Therapeutic ultrasound bypasses canonical syndecan-4 signaling to activate Rac1. *J Biol Chem*. 2009;284(13):8898-909. doi:10.1074/jbc.M804281200 **16.** Atherton P, Lausecker F, Harrison A, Ballestrem C. Low-intensity pulsed ultrasound promotes cell motility through vinculin-controlled Rac1 GTPase activity. *J Cell Sci*. 2017;130(14):2277-91. doi:10.1242/jcs.192781 **17.** Mukai S, Ito H, Nakagawa Y, Akiyama H, Miyamoto M, Nakamura T. Transforming growth factor-ß1 mediates the effects of low-intensity pulsed ultrasound in chondrocytes. *Ultrasound Med Biol*. 2005;31(12):1713-21. doi:10.1016/j.ultrasmedbio.2005.07.012 **18.** Freeman TA, Patel P, Parvizi J, Antoci V Jr, Shapiro IM. Micro-CT analysis with multiple thresholds allows detection of bone formation and resorption during ultrasound-treated fracture healing. *J Orthop Res*. 2009;27(5):673-9. doi:10.1002/jor.20771 **19.** Azuma Y, Ito M, Harada Y, Takagi H, Ohta T, Jingushi S. Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus. *J Bone Miner Res*. 2001;16(4) 671-80. doi:10.1359/jbmr.2001.16.4.671 **20.** Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. *J Bone Joint Surg Am*. 1997;79(7):961-73. doi:10.2106/00004623-199707000-00002 **21.** Gebauer D, Mayr E, Orthner E, Ryaby JP. Low-intensity pulsed ultrasound: effects on nonunions. *Ultrasound Med Biol*. 2005;31(10):1391-402. doi:10.1016/j.ultrasmedbio.2005.06.002 **22.** Heckman JD, Sarasohn-Kahn J. The economics of treating tibia fractures. The cost of delayed unions. *Bull Hosp Jt Dis*. 1997;56(1):63-72. **23.** Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fracture in patients who smoke. *Clin Orthop Relat Res*. 1997;(337):198-207. doi:10.1097/00003086-199704000-00022 **24.** Romanò CL, Messina JC, Meani E. Low-intensity, pulsed ultrasound for the treatment of septic pseudoarthrosis. *Quarderni di Infezione Osteoarticolari*. 1999;(suppl 561);83-93. **25.** Mayr E, Frankel V, Rüter A. Ultrasound--an alternative healing method for nonunions? *Arch Orthop Trauma Surg*. 2000;120(1-2):1-8. doi:10.1007/pl00021234 **26.** Lerner A, Stein H, Soudry M. Compound high-energy limb fractures with delayed union: our experience with adjuvant ultrasound stimulation (exogen). *Ultrasonics*. 2004;42(1-9):915-7. doi:10.1016/j.ultras.2003.11.014 **27.** Jingushi S, Mizuno K, Matsushita T, Itoman M. Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures. *J Orthop Sci*. 2007;12(1):35-41. doi:10.1007/s00776-006-1080-3 **28.** National Institute for Health and Care Excellence. EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. *Medical technologies guidance* [MTG 12]. Last updated 08 October 2019. www.nice.org.uk/guidance/mtg12/evidence **29.** Harrison A., Lin Sh., Pounder N., Mikuni-Takagaki Y. Mode and mechanism of low intensity pulsed ultrasound (LIPUS) in fracture repair. *Ultrasonics*. 2016;70:4552. doi:10.1016/j.ultras.2016.03.016 **30.** Bishop JA, Palanca AA, Bellino MJ, Lowenberg DW. Assessment of compromised fracture healing. *J Am Acad Orthop Surg*. 2012 May;20(5):273-82. **31.** Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J. Cigarette smoking increases complications[following fracture: a systematic review. *J Bone Joint Surg* [Am]. 2014 Apr 16;96(8):674-81. **32.** Hernandez RK, Do TP, Critchlow CW, Dent RE, Jick SS. Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database. *Acta Orthop*. 2012;83(6):653-60. doi:10.3109/17453674.2012.747054

**Summary of Indications for Use:** EXOGEN is indicated for the non-invasive treatment of osseous defects (excluding vertebra and skull) that includes the treatment of delayed unions, nonunions,* stress fractures and joint fusion. EXOGEN is also indicated for the acceleration of fresh fracture heal time, repair following osteotomy, repair in bone transport procedures and repair in distraction osteogenesis procedures.

There are no known contraindications for the EXOGEN device. Safety and effectiveness have not been established for individuals lacking skeletal maturity, pregnant or nursing women, patients with cardiac pacemakers, on fractures due to bone cancer, or on patients with poor blood circulation or clotting problems. Some patients may be sensitive to the ultrasound gel. Full prescribing information can be found in product labeling, at exogen.com, or by calling Bioventus Customer Care at 0800 05 16 384 (UK) / 1800 552 197 (IR).

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

Visit EXOGEN.com to learn more.



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