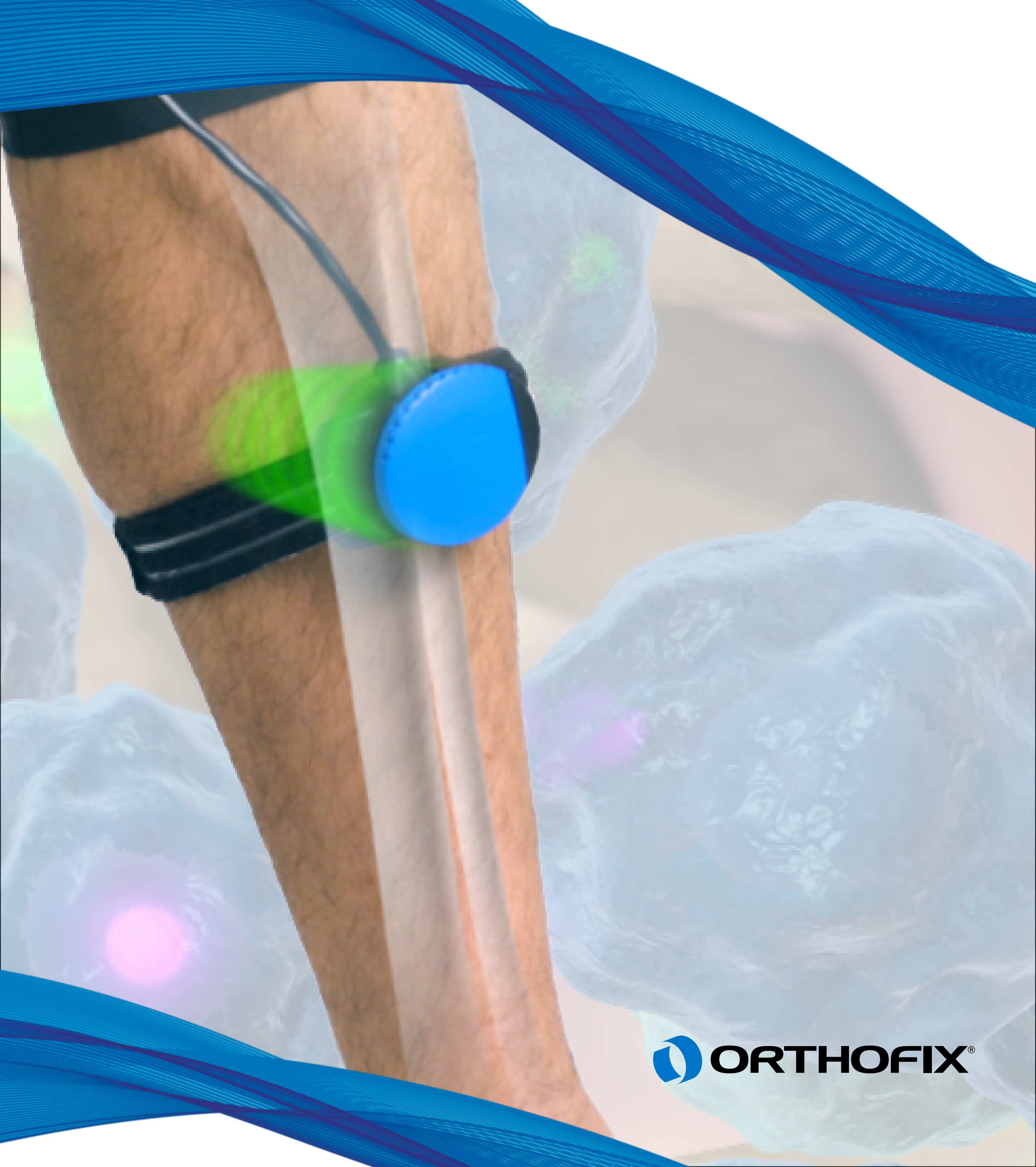
HOW LIPUS WORKS

Low-Intensity Pulsed Ultrasound



ORTHOFIX®

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How LIPUS Affects Fracture Healing

The fracture repair process is divided into four stages: inflammation, soft callus formation, hard callus formation, and bone remodeling.[1] Low-intensity pulsed ultrasound treatment (LIPUS) has been shown to accelerate fracture healing at every stage, with maximum benefit achieved when applied throughout the entire healing process.[1]

The Orthofix AccelStim™ device uses a low-intensity pulsed ultrasound mechanical pressure wave composed of 1000 pulses per second to stimulate a response at the cellular level.[2, 3] After contacting bone, the mechanical pressure wave creates nanomotion at the fracture site producing a reaction at the cellular level.[2, 3]

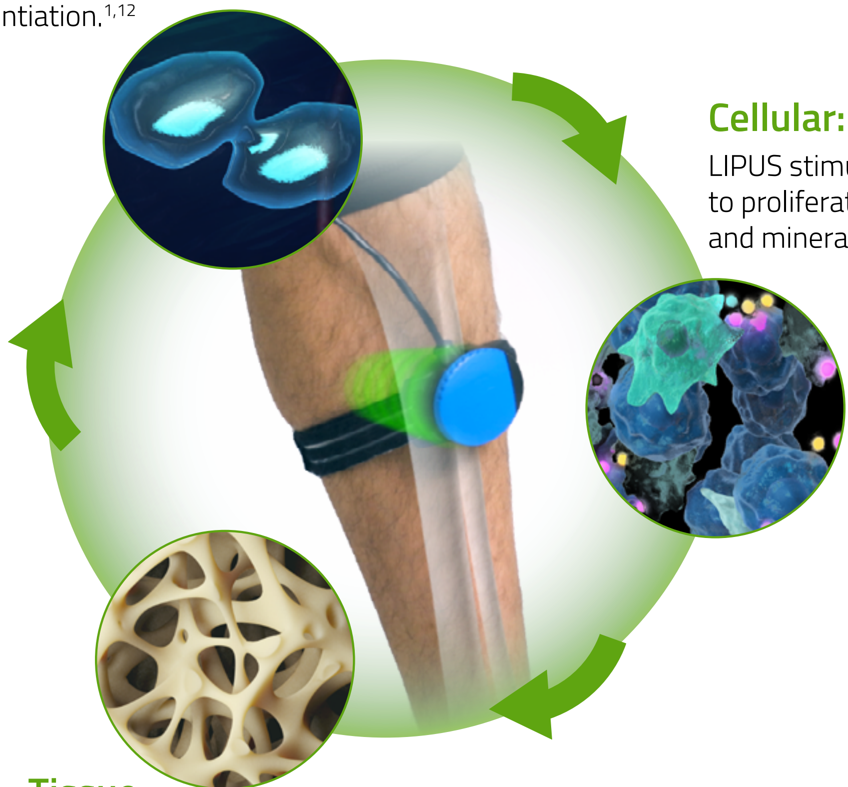
The Orthofix AccelStim device helps promote bone healing by providing non-invasive therapy for healing nonunion fractures and accelerating the time to healing of fresh fractures.[4]

The Orthofix AccelStim device uses a unique LIPUS signal to amplify your body's natural bone repair processes.[4]

LIPUS Amplifies Bone Healing

LIPUS works by sending ultrasound waves through the skin and surrounding soft tissue to reach the site of the bone fracture.[5, 6] This stimulates signaling pathways,[7] which in turn promotes mesenchymal stem cells to migrate towards the site of the fracture.[8] The ultrasound waves activate certain cell receptors,[9] setting off a series of reactions, referred to as a cascade.
One result of this event is that stem cells begin to proliferate, differentiate, and mineralize to form new bone.[8, 10] LIPUS increases upregulation of the processes critical to bone repair, thus increasing new bone formation.[5,11]

Molecular:
LIPUS stimulates signaling pathways, leading to increased cell differentiation.[1,12]

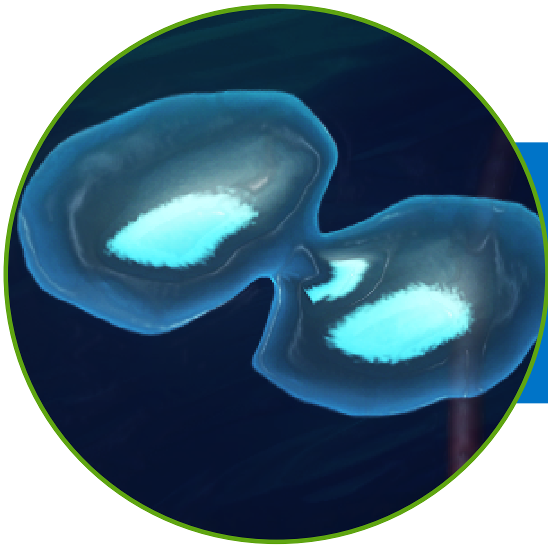


Cellular:
LIPUS stimulates bone cells to proliferate, differentiate, and mineralize.[18]

Tissue:
LIPUS increases new bone formation.[25]

The Orthofix AccelStim device helps promote bone healing by providing noninvasive LIPUS therapy for healing nonunions and accelerating time to healing of indicated fresh fractures.[4]

LIPUS at the Molecular Level



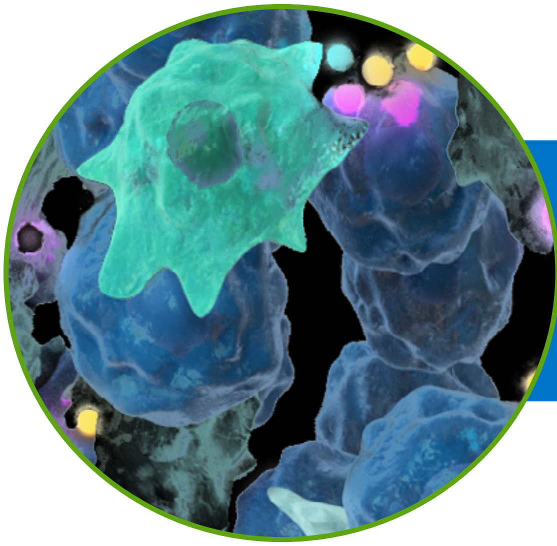
LIPUS stimulates signaling pathways, leading to increased cell differentiation.

- LIPUS stimulates the expression of aggrecan in chondrocytes,[12,13] leading to accelerated cartilage formation, which is part of the initial phase of the fracture healing process.[1]
    - LIPUS increases aggrecan expression 10-20% as shown by immunohistochemical staining of chick embryos.[13]

- LIPUS stimulates integrin, a transmembrane cell receptor, leading to increased gene expression of osteogenic growth factors and markers of osteogenesis.[7,14] These include osteonectin, osteopontin, and insulin growth factor-1 (IGF-1).[15]
    - Staining by immunofluorescence showed a significant increase in integrin after 15 minutes of LIPUS exposure in rabbit synovial cells.[7]

- LIPUS stimulation alters the gene expression profile in osteocytes thus modifying the function of osteogenic and inflammatory cells that are involved in the fracture healing process.[16,17]
    - LIPUS stimulates an anabolic response in osteocytes.[17]

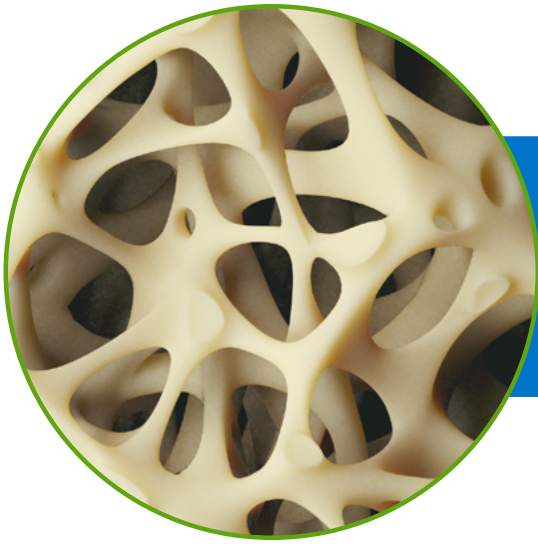
LIPUS at the Cellular Level



LIPUS stimulates bone cells to proliferate, differentiate, and mineralize.

- LIPUS stimulates undifferentiated mesenchymal stem cells to differentiate into osteoblasts.[8,18.]
  - After 13 days of differentiation, mesenchymal stem cells treated with LIPUS were 10% more differentiated than the control group.[19]
- In response to LIPUS, periosteal cells and osteoblastic cells increase expression of osteocalcin, alkaline phosphatase, and Vascular Endothelial Growth Factor (VEGF). These result in an increase in mineralization and enhanced angiogenesis.[20,21]
  - Periosteal cell showed significantly more mineralization after four days of LIPUS treatment when compared to the control group.[20]
- Enhanced stimulation of osteogenic cells by LIPUS drive endochondral ossification.[10,20]
  - LIPUS treatment for 16 days accelerated endochondral ossification in mice, shown by histology.[22]

LIPUS at the Tissue Level

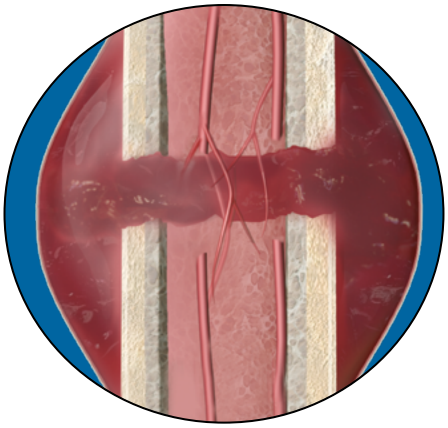


LIPUS increases new bone formation.

- LIPUS increases mineralization and calcium deposition.[23,24]
  - The volume and amount of new bone formation was greater in the LIPUS group than the control, shown by micro-CT.[24]
- LIPUS enhances bone formation.[25,26]
  - Bone formation in the LIPUS treated group started earlier and became more extensive than bone formation in the control group.[26]
- LIPUS improves osteogenic differentiation, mineralization, volume of newly formed bone, and osseointegration.[11,27]
  - The LIPUS treated group showed 86% spinal fusion in a rabbit model, compared to 14% in the control group.[27]
- LIPUS accelerates all stages of the fracture repair process (inflammation, bone formation, and bone remodeling), by increasing mineralization and reducing the inflammatory response.[1,22]
  - Early endochondral ossification in the LIPUS treated femur was greater than in the control, shown by histology and micro-CT, confirming a significant increase in newly formed bone.[1, 22]

Four Phases of Bone Healing

Phase 1: Inflammation

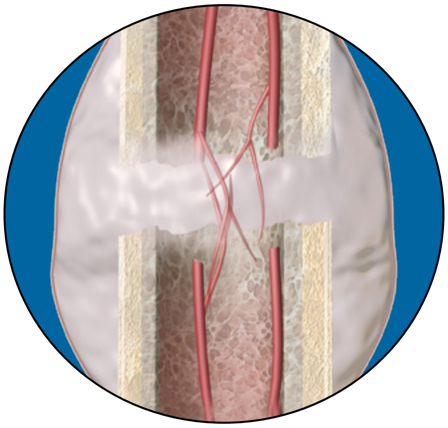


- When a bone breaks, blood vessels in the bone and periosteum are torn and hemorrhage, and a hematoma (blood clot) forms at the fracture site.
- Blood comes from blood vessels, marrow, and surrounding tissues, forming a hematoma that aids in cell recruitment to the fracture site.[5]

LIPUS Benefit

- LIPUS stimulates ultrasound waves through skin and surrounding soft tissue to reach the site of the bone fracture.[20,28]
- LIPUS activates anti-inflammatory response by upregulating the anti-inflammatory gene expression.[20,28]

Phase 2: Formation of Soft Callus

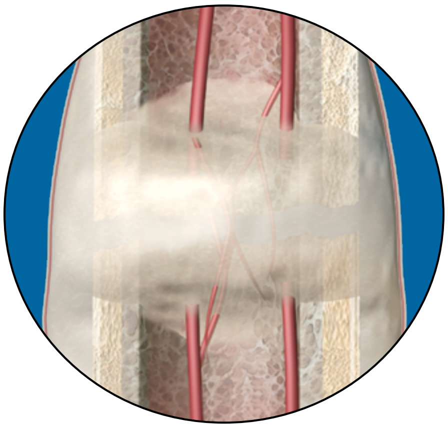


- New blood vessel formation occurs, which is called angiogenesis.[5]
- The major growth factor responsible for angiogenesis is VEGF. VEGF is produced by osteoblasts and periosteal cells.[5]
- Proliferation and osteoblastic differentiation of mesenchymal stem cells takes place to form the soft callus.[5]

LIPUS Benefit

- LIPUS helps to increase the formation of new blood vessels at the fracture site.[29]
- LIPUS treatment enhances the TGFB-triggered differentiation of chondrocytes in culture and accelerates the formation of extracellular matrix.[30]

Phase 3: Formation of Hard Callus

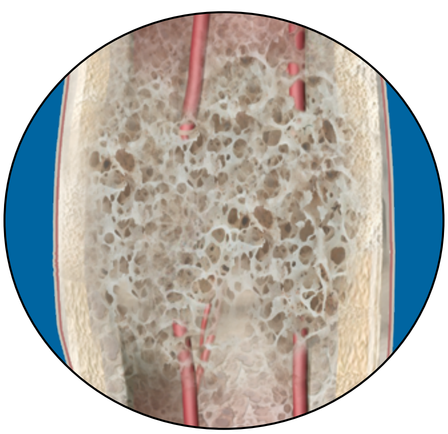


- Calcium is deposited in the new bone structure in a process called ossification. The hard callus continues to grow, bridging the gap in the broken bone until the two ends meet.[31,32]

LIPUS Benefit

- LIPUS treatment increases soft tissue mineralization to stabilize the fracture by adding a rigid structure and strength.[31,32]
- LIPUS activates anti-inflammatory response by upregulating the anti-inflammatory gene expression.[20,2.]

Phase 4: Bone Remodeling



- Mineralized callus is the outer layer of bone tissue that normally forms like scar tissue at the ends of a broken bone once it has healed.[33]
- Eventually, the fracture callus is remodeled into a new shape which closely duplicates the bone's original shape and strength.[33]

LIPUS Benefit

- LIPUS accelerates both the normal formation (remodeling) and recycling (resorption) of bone tissue, for a faster formation of the mineralized callus.[33]

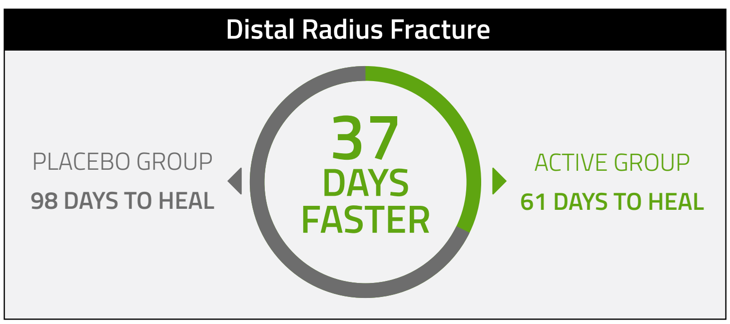
Fracture Healing

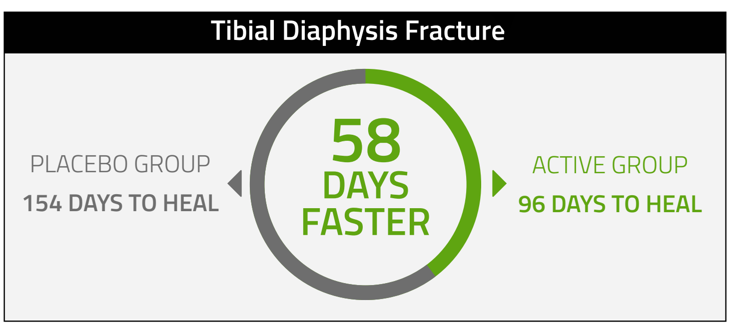
Clinical studies have validated the safety and effectiveness of LIPUS:

Clinical studies on LIPUS have successfully shown to resolve 86% of non-union fractures and this treatment induced a 38% acceleration in achieving clinical and radiographic healing.[9,34-37]

Studies show the safety and effectiveness of the LIPUS for non-invasive treatment of established nonunions, fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures.[34-38] Treatment with LIPUS accelerated healing by 38% (96 days for LIPUS treated versus 154 days for control group).[34]

Faster healing in both cortical and cancellous bone





LIPUS has been proven to be a safe and effective noninvasive treatment to improve overall nonunion fracture healing success rates and to accelerate the healing of indicated fresh fractures.[34-36]

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Brief Prescribing Information:
The AccelStim device 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 adult 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.

ORTHOFIX®