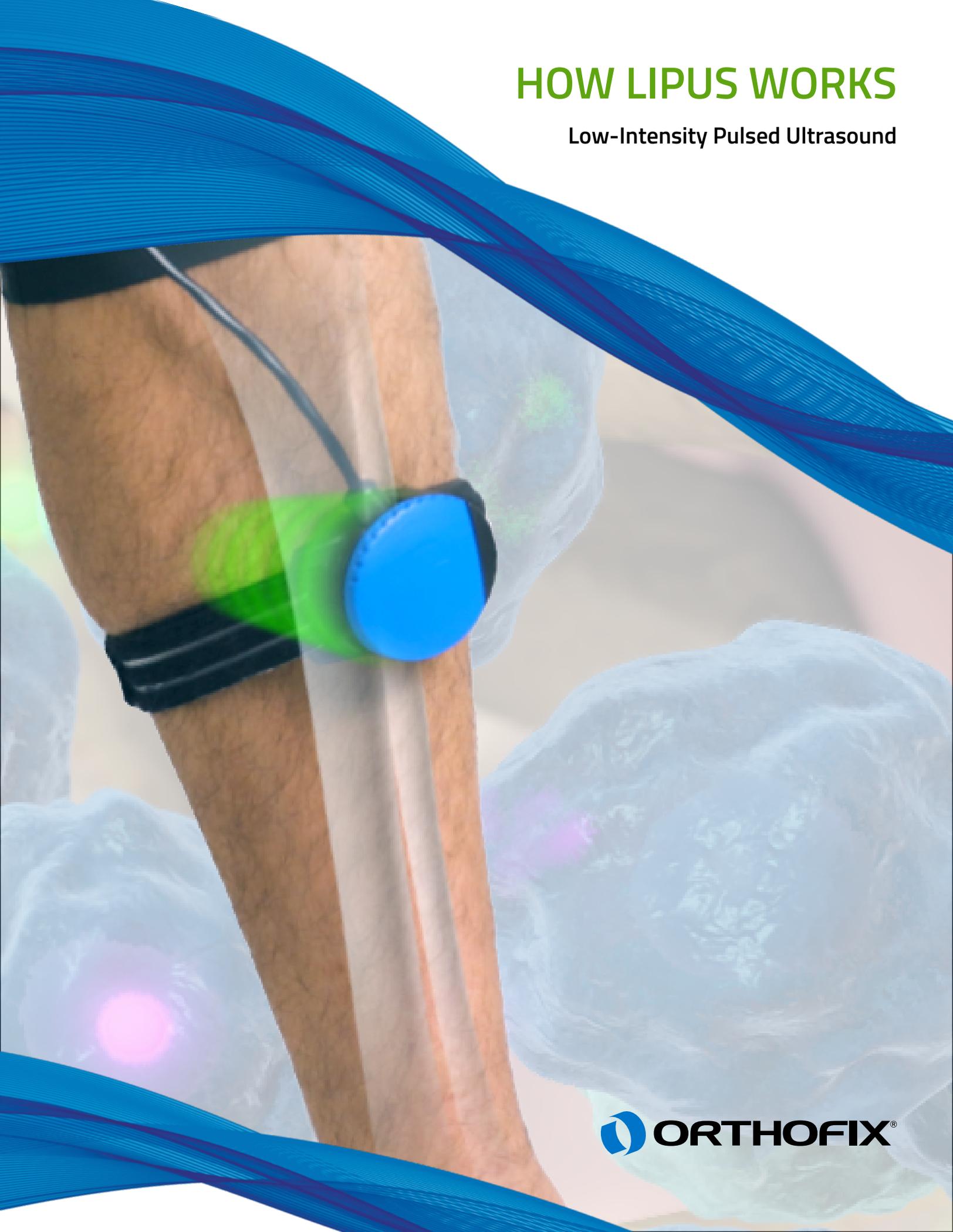


# HOW LIPUS WORKS

Low-Intensity Pulsed Ultrasound



# Table of Contents

<b>2</b>	<b>How LIPUS Affects Fracture Healing</b>
<b>3</b>	<b>LIPUS Amplifies Bone Healing</b>
<b>4</b>	<b>LIPUS at the Molecular Level</b>
<b>5</b>	<b>LIPUS at the Cellular Level</b>
<b>6</b>	<b>LIPUS at the Tissue Level</b>
<b>7</b>	<b>Four Phases of Bone Healing</b>
<b>9</b>	<b>Fracture Healing</b>
<b>10</b>	<b>References</b>

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Please visit [www.Orthofix.com/IFU](http://www.Orthofix.com/IFU) for full information on indications for use, contraindications, warnings, precautions, adverse reactions information, and sterilization.

# How LIPUS Affects Fracture Healing

The fracture repair process is divided into four stages: inflammation, soft callus formation, hard callus formation, and bone remodeling.<sup>1</sup> 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.<sup>1</sup>

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.<sup>2,3</sup> After contacting bone, the mechanical pressure wave creates nanomotion at the fracture site producing a reaction at the cellular level.<sup>2,3</sup>

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.<sup>4</sup>

The Orthofix AccelStim device uses a unique LIPUS signal to amplify your body's natural bone repair processes.<sup>4</sup>

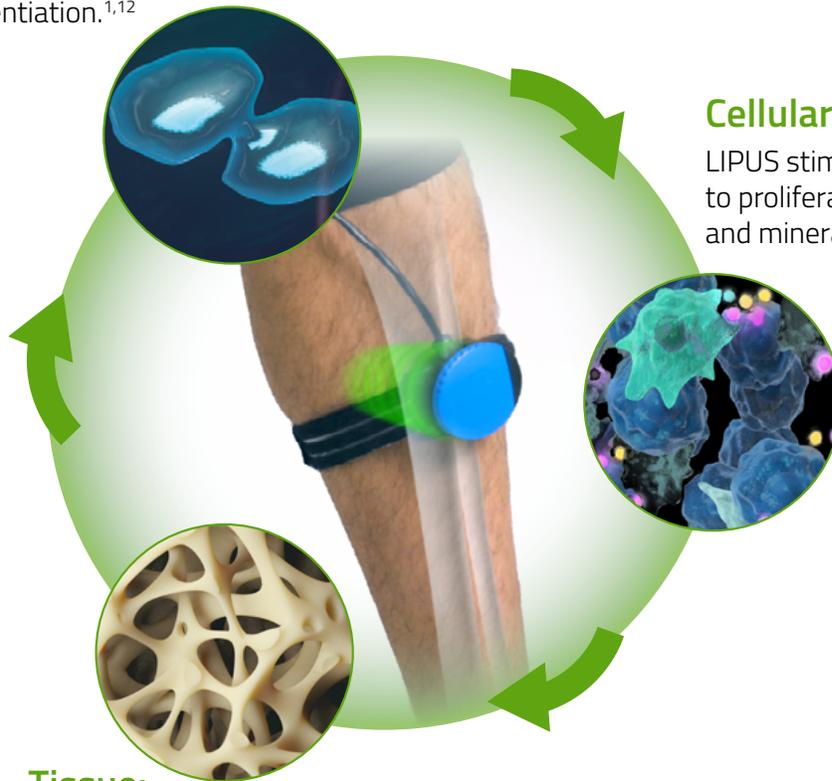


# LIPUS Amplifies Bone Healing

LIPUS works by sending ultrasound waves through the skin and surrounding soft tissue to reach the site of the bone fracture.<sup>5,6</sup> This stimulates signaling pathways,<sup>7</sup> which in turn promotes mesenchymal stem cells to migrate towards the site of the fracture.<sup>8</sup> The ultrasound waves activate certain cell receptors,<sup>9</sup> 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.<sup>8,10</sup> LIPUS increases upregulation of the processes critical to bone repair, thus increasing new bone formation.<sup>5,11</sup>

## Molecular:

LIPUS stimulates signaling pathways, leading to increased cell differentiation.<sup>1,12</sup>



## Cellular:

LIPUS stimulates bone cells to proliferate, differentiate, and mineralize.<sup>18</sup>

## Tissue:

LIPUS increases new bone formation.<sup>25</sup>

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.<sup>4</sup>

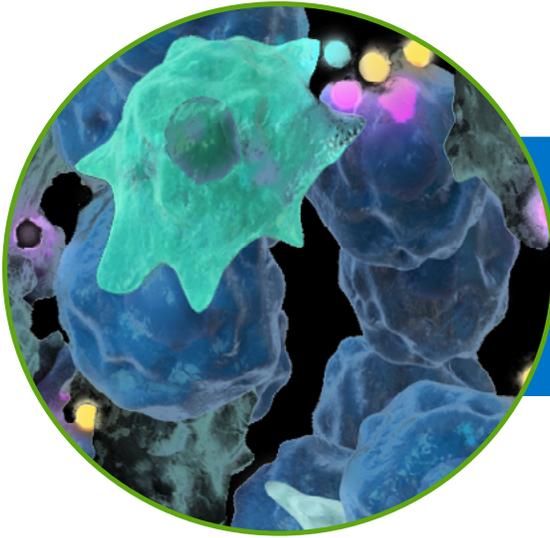
# LIPUS at the Molecular Level



LIPUS stimulates signaling pathways, leading to increased cell differentiation.

- LIPUS stimulates the expression of aggrecan in chondrocytes,<sup>12,13</sup> leading to accelerated cartilage formation, which is part of the initial phase of the fracture healing process.<sup>1</sup>
  - LIPUS increases aggrecan expression 10-20% as shown by immunohistochemical staining of chick embryos.<sup>13</sup>
- LIPUS stimulates integrin, a transmembrane cell receptor, leading to increased gene expression of osteogenic growth factors and markers of osteogenesis.<sup>7,14</sup> These include osteonectin, osteopontin, and insulin growth factor-1 (IGF-1).<sup>15</sup>
  - Staining by immunofluorescence showed a significant increase in integrin after 15 minutes of LIPUS exposure in rabbit synovial cells.<sup>7</sup>
- 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.<sup>16,17</sup>
  - LIPUS stimulates an anabolic response in osteocytes.<sup>17</sup>

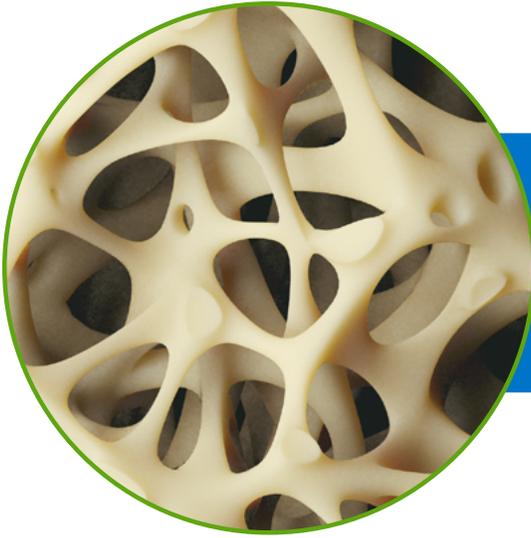
# LIPUS at the Cellular Level



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

- LIPUS stimulates undifferentiated mesenchymal stem cells to differentiate into osteoblasts.<sup>8,18</sup>
  - After 13 days of differentiation, mesenchymal stem cells treated with LIPUS were 10% more differentiated than the control group.<sup>19</sup>
- 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.<sup>20,21</sup>
  - Periosteal cell showed significantly more mineralization after four days of LIPUS treatment when compared to the control group.<sup>20</sup>
- Enhanced stimulation of osteogenic cells by LIPUS drive endochondral ossification.<sup>10,20</sup>
  - LIPUS treatment for 16 days accelerated endochondral ossification in mice, shown by histology.<sup>22</sup>

# LIPUS at the Tissue Level

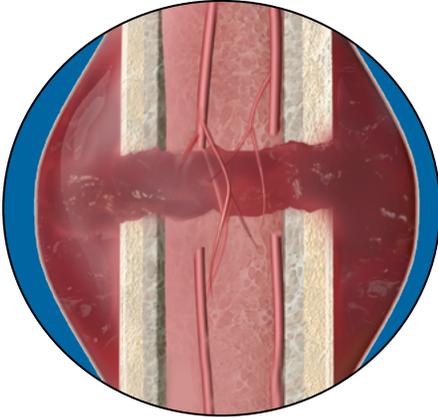


LIPUS increases new bone formation.

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

# Four Phases of Bone Healing

## Phase 1: Inflammation

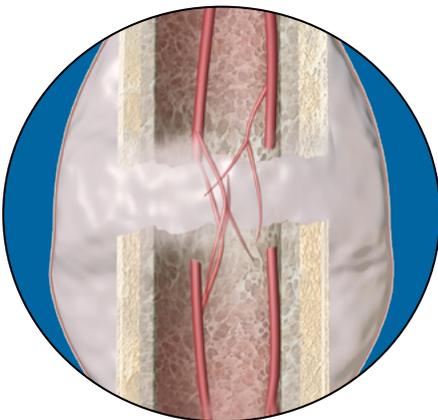


- When a bone breaks, blood vessels in the bone and periosteum are torn and hemorrhage, and a hematoma (blood clot) forms at the fracture site.
- Blood comes from blood vessels, marrow, and surrounding tissues, forming a hematoma that aids in cell recruitment to the fracture site.<sup>5</sup>

### LIPUS Benefit

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

## Phase 2: Formation of Soft Callus

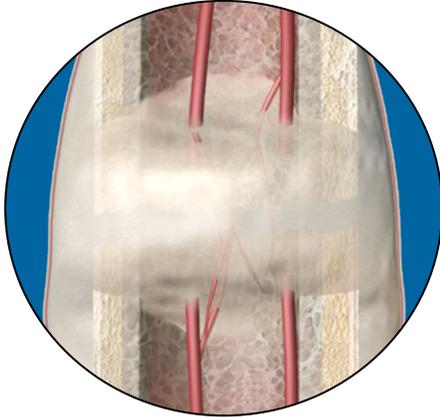


- New blood vessel formation occurs, which is called angiogenesis.<sup>5</sup>
- The major growth factor responsible for angiogenesis is VEGF. VEGF is produced by osteoblasts and periosteal cells.<sup>5</sup>
- Proliferation and osteoblastic differentiation of mesenchymal stem cells takes place to form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

### LIPUS Benefit

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

### Phase 3: Formation of Hard Callus

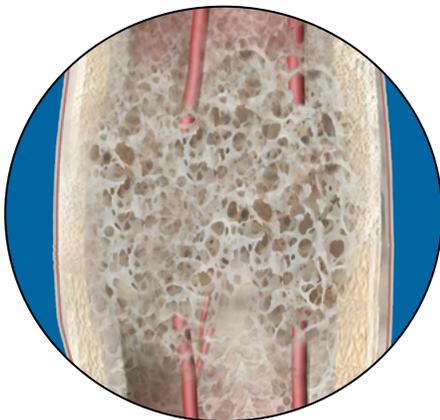


- Calcium is deposited in the new bone structure in a process called ossification. The hard callus continues to grow, bridging the gap in the broken bone until the two ends meet.<sup>31,32</sup>

#### LIPUS Benefit

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

### 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.<sup>33</sup>
- Eventually, the fracture callus is remodeled into a new shape which closely duplicates the bone's original shape and strength.<sup>33</sup>

#### LIPUS Benefit

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

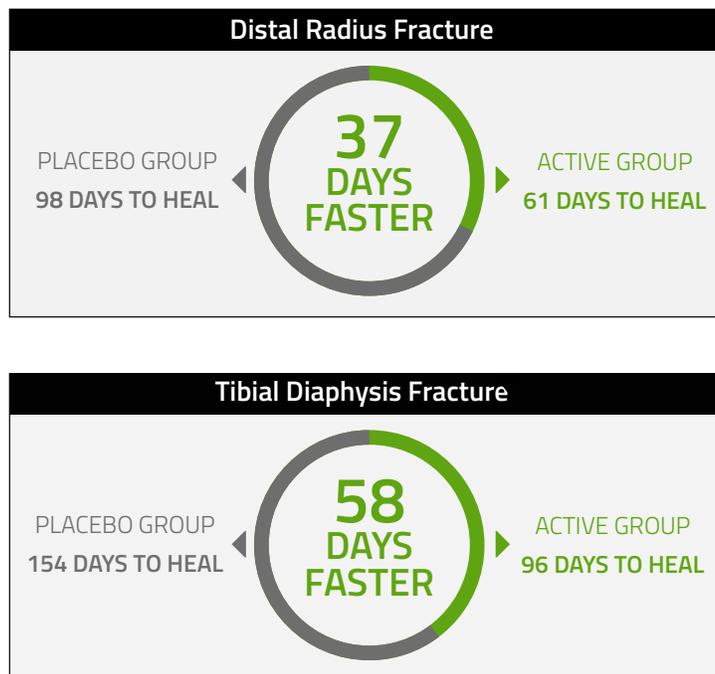
# Fracture Healing

## 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.<sup>9,34-37</sup>

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.<sup>34-38</sup> Treatment with LIPUS accelerated healing by 38% (96 days for LIPUS treated versus 154 days for control group).<sup>34</sup>

## 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.<sup>34-36</sup>

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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.

