FDA Panel Meeting

Augment™ Bone Graft
BioMimetic Therapeutics Inc.
12 May 2011
Introduction and Product History

Russell P. Pagano, Ph.D.
Vice President
Clinical & Regulatory Affairs
BioMimetic Therapeutics, Inc.
## Overview of Augment™ Bone Graft presentation

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Presenter</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td><strong>Introduction and regulatory history</strong></td>
<td>Russell P. Pagano, PhD</td>
<td>BioMimetic Therapeutics, Inc.</td>
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<td></td>
<td>Christopher DiGiovanni, MD</td>
<td>Brown Medical School</td>
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<tr>
<td><strong>Biology of Augment™ Bone Graft and preclinical data</strong></td>
<td>Sheldon S. Lin, MD</td>
<td>University of Medicine and Dentistry at New Jersey</td>
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<td></td>
<td>Associate Professor of Orthopedic Surgery</td>
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<tr>
<td><strong>Preclinical safety data</strong></td>
<td>Barry S. Levine, DSc</td>
<td>Levine &amp; Associates LLC</td>
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<td></td>
<td>Diplomate, American Board of Toxicology</td>
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<tr>
<td><strong>Cancer incidence and evidence</strong></td>
<td>Mark Green, MD</td>
<td>Medical University of South Carolina</td>
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<td></td>
<td>Professor of Medicine, Hematology-Oncology, Emeritus</td>
<td></td>
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<tr>
<td><strong>Clinical summary</strong></td>
<td>Judith F. Baumhauer, MD, MPH</td>
<td>University of Rochester School of Medicine and Dentistry</td>
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<tr>
<td></td>
<td>Associate Chair of Academic Affairs, Professor of Orthopedic Surgery</td>
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<td><strong>Immunogenicity</strong></td>
<td>Leo B. Snel, PhD</td>
<td>BioMimetic Therapeutics, Inc.</td>
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<td></td>
<td>Sr. Vice President, Research and Development</td>
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<tr>
<td><strong>Statistical analyses</strong></td>
<td>Rafe M.J. Donahue, PhD</td>
<td>BioMimetic Therapeutics, Inc.</td>
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<tr>
<td></td>
<td>Director, Statistics</td>
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<td></td>
<td>Adjunct Associate Professor, Vanderbilt</td>
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<tr>
<td><strong>Conclusion and post-approval study</strong></td>
<td>Russell P. Pagano, PhD</td>
<td>BioMimetic Therapeutics, Inc.</td>
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<tr>
<td></td>
<td>Vice President, Regulatory and Clinical Affairs</td>
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## Other resources available to the Panel

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Gary Friedlaender, MD</td>
<td>Yale University School of Medicine</td>
</tr>
<tr>
<td>Wayne O. Southwick Professor and Chair Department of Orthopedic Surgery</td>
<td></td>
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<tr>
<td>Joseph M. Lane, MD</td>
<td>Weill Cornell Medical College Hospital for Special Surgery</td>
</tr>
<tr>
<td>Professor of Orthopaedic Surgery</td>
<td></td>
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<tr>
<td>Chief, Metabolic Bone Disease Service and Orthopaedic Surgeon</td>
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<tr>
<td>Peter T. Evangelista, MD</td>
<td>Brown Medical School</td>
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<tr>
<td>Assistant Professor of Diagnostic Imaging</td>
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<tr>
<td>Jeffrey O. Hollinger, PhD</td>
<td>Carnegie Mellon University</td>
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<tr>
<td>Professor of Biological Sciences &amp; Biomedical Engineering</td>
<td></td>
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<tr>
<td>Neil E. Green, MD</td>
<td>Vanderbilt Children’s Hospital BioMimetic Therapeutics, Inc</td>
</tr>
<tr>
<td>Professor of Pediatric Orthopedic Surgery Chief Medical Officer</td>
<td></td>
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<tr>
<td>Samuel E. Lynch, DMD, DMSc</td>
<td>BioMimetic Therapeutics, Inc.</td>
</tr>
<tr>
<td>Founder, President and CEO</td>
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<tr>
<td>BioMimetic Therapeutics, Inc.</td>
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</table>
Christopher DiGiovanni, MD
Chief of the Foot and Ankle Service
Professor of Orthopedic Surgery
Brown University

Letters of Support
- 37 PIs from Pivotal Trial
- Dr. David Thordarson, Editor -FAI
Disclosure Slide

• Investigator for Augment clinical trials
• Consultant to BioMimetic Therapeutics, Inc.
• Travel and time compensated for panel presentation
• Equity in BioMimetic Therapeutics, Inc.
37 Principal Investigators Across North America

- Christopher W. DiGiovanni, MD
- Sheldon Lin, MD
- Judith Baumhauer, MD
- Timothy R. Daniels, MD
- Nick Abidi, MD
- Jorge Acevedo, MD
- Robert Anderson, MD
- Gregory Berlet, MD
- Christopher Bibbo, DO
- Bradley Brainard, MD
- Keith Donatto, MD
- Mark Easley, MD
- Andrew Elliott, MD
- Wm Granberry, MD
- Justin Greisberg, MD
- Steve Haddad, MD
- Tony Hinz, MD
- Osarentin Idusuyi, MD
- Juha Jaakkola, MD
- Paul Juliano, MD
- Alastair S. Younger, MD
- Mark A. Glazebrook, MD
- John G. Anderson, MD
- Johnny T.C. Lau, MD
- David Katcherian, MD
- Karl-Andre LaLonde, MD
- Ian Le, MD
- Thomas Limbird, MD
- Richard Marks, MD
- Andrew Murphy, MD
- Steve Neufeld, MD
- Mickey Pinzur, MD
- Steve Raikin, MD
- Lew Schon, MD
- James Sferra, MD
- Naomi Shields, MD
- RJ Sullivan, MD
- Michael Swords, MD
- Brian Thomson, MD
- Troy Watson, MD
Augment™ Bone Graft

- Augment is a fully synthetic combination of β-TCP and rhPDGF-BB
- Indicated for foot and ankle fusions as an alternative to autograft
- Augment is approved in Canada for foot and ankle fusions (2009)
- rhPDGF-BB is well characterized
  - 20+ years of scientific discovery and 200+ publications
  - FDA-approved twice
- β-TCP
  - FDA-cleared bone void filler device
- β-TCP and rhPDGF-BB (GEM 21S®) approved for periodontal bone defects (2005)
Building upon 5 years of successful patient experience

GEM 21S®
(0.3 mg/mL rhPDGF-BB/β-TCP)

FDA-Approved (PMA) in 2005
Indicated for periodontal bone regeneration

~250,000 patients treated with GEM 21S®

Augment™ Bone Graft
(0.3 mg/mL rhPDGF-BB/β-TCP)
Indicated for bony fusions in foot and ankle
Augment™ Bone Graft

• Extensive safety testing with no concerns
• >600 patients in US, Canada and EU confirm safety
• No device-related SAE’s
• IDE- and ITA-approved by FDA and HC in 2007
• 414 patients treated in Pivotal RCT
• Largest RCT in foot and ankle
• PMA accepted for review by FDA in May 2010
Biology of Augment™ Bone Graft

Sheldon S. Lin, M.D.
Associate Professor of Orthopedic Surgery
University of Medicine & Dentistry of New Jersey
Disclosure

• Investigator for Augment clinical trials
• Consultant to BioMimetic Therapeutics, Inc.
• No equity in BioMimetic Therapeutics, Inc.
• Travel and time compensated for panel presentation
Augment™ Bone Graft

**Scaffold: β-TCP**
- Fills the bone defect
- Provides an osteoconductive matrix
- Prevents soft tissue prolapse
- Stabilizes the blood clot
- Delivers rhPDGF-BB
- Resorbs and replaced with bone

**Biologic: rhPDGF-BB**
- Triggers the wound healing / bone repair cascade:
  - Chemotactic (Fiedler et al., *J Cell Biochem* 2002)
  - Mitogenic (Wildemann et al., *J Orthop Sur Res* 2007)
  - Angiogenic (Bouletreau et al., *Plast Reconstr Surg* 2002)

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Augment based on the ‘triad’ of bone healing
PDGF triggers the bone healing cascade

activated platelets → FGF, PDGF, TGF → chemotaxis

progenitor cells → proliferation

angiogenesis → VEGF

blood vessels

injured bone

factors released from bone matrix → BMPs

osteoblasts → osteoclasts → remodeling → mature bone

PDGF is neither a differentiation nor a transformation factor
Turning PDGF into a therapeutic: rhPDGF-BB

- rhPDGF-BB produced using recombinant DNA technology
  - The human gene for PDGF-BB is inserted into yeast cells
    - *Saccharomyces cerevisiae*

- Recombinant human PDGF-BB:
  - Pure
  - Sterile
  - Synthetic protein
  - Consistent, predictable potency
    - 5000x whole blood
    - 1000x PRP
rhPDGF-BB in bone regeneration

Stages of bone regeneration:
- Hematoma: 1-3 days
- Inflammation: 1-7 days
- Granulation: 2-12 days
- Soft callus: 1-3 weeks
- Hard callus: 2-6 weeks
- Remodeling: 2-6 months

Time progression:
- Chemotaxis
- Mitogenesis
- Angiogenesis
- Remodeling

Primary influence of PDGF
Preclinical Orthopedic Studies

Efficacy
Recent preclinical studies – Efficacy

- Fracture healing of the tibia in geriatric-osteoporotic rats

- Fracture healing of the femur in a diabetic rat model

- Bone formation in a rat model of distraction osteogenesis

- Partial arthrodesis of the carpus in a canine model
  Manuscript in preparation
Fracture healing in geriatric-osteoporotic rats

This study was designed to evaluate:

• Enhancement of fracture repair by Augment in a model in which bone repair is impaired
• Dose-dependence of the rhPDGF-BB effect

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>No. Animals 3 weeks/5 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Untreated</td>
<td>10 / 10</td>
</tr>
<tr>
<td>2</td>
<td>Matrix + 20 mM sodium acetate</td>
<td>10 / 10</td>
</tr>
<tr>
<td>3</td>
<td>Matrix + 0.3 mg/mL rhPDGF-BB</td>
<td>10 / 10</td>
</tr>
<tr>
<td>4</td>
<td>Matrix + 1.0 mg/mL rhPDGF-BB</td>
<td>10 / 10</td>
</tr>
</tbody>
</table>

rhPDGF-BB in 20 mM sodium acetate, pH 6.0

Hollinger et al., J Orthop Res 2008
The mechanical strength of Augment-treated limbs is similar to contralateral normal limbs

Normalized mean torsional strength at 5 weeks (torque at failure)

* Significantly weaker than contralateral normal (p<0.05)
Augment accelerates fracture healing in geriatric-osteoporotic rats

Conclusions

• Matrix plus rhPDGF-BB accelerated fracture healing

• At 5 weeks, mechanical strength of Augment-treated tibias was not different from normal

• There were no adverse tissue responses
Fracture healing of the femur in a diabetic rat model

This study was designed to evaluate:

- Enhancement of fracture repair by rhPDGF-BB in an impaired healing model
- Dose-dependence of the rhPDGF-BB effect

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>No. Animals 4 days/6 weeks/8 weeks/ 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Untreated</td>
<td>6 / 8 / 10 / 5</td>
</tr>
<tr>
<td>2</td>
<td>Matrix + 20 mM sodium acetate</td>
<td>6 / 10 / 13 / 5</td>
</tr>
<tr>
<td>3</td>
<td>Matrix + 0.3 mg/mL rhPDGF-BB</td>
<td>7 / 7 / 10 / 4</td>
</tr>
<tr>
<td>4</td>
<td>Matrix + 1.0 mg/mL rhPDGF-BB</td>
<td>7 / 7 / 12 / 4</td>
</tr>
</tbody>
</table>

rhPDGF-BB in 20 mM sodium acetate, pH 6.0
rhPDGF-BB treatment enhances fracture healing in diabetic rats
The mechanical strength of Augment-treated limbs is similar to that of contralateral limbs.

![Bar chart showing normalized torque to failure and normalized torsional rigidity for different treatments.](image)

- Untreated
- Matrix
- Matrix + 0.3 mg/mL rhPDGF-BB
- Matrix + 1.0 mg/mL rhPDGF-BB

*: p < 0.02 versus matrix
Augment enhances fracture healing in diabetic rats

Conclusions

• Increased cellularity at 4 days
• Increased biomechanical strength as early as 6 weeks
• Increased bone content of the fracture callus at 12 weeks
• Neither abnormal nor ectopic bone formation
Bone formation in a rat model of distraction osteogenesis

This study was designed to evaluate:

- Enhancement of bone formation by rhPDGF-BB
- Dose-dependence of the rhPDGF-BB effect

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>No. Animals 5/6/7/8/9 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mM sodium acetate</td>
<td>3 / 3 / 3 / 3 / 4</td>
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<tr>
<td>2</td>
<td>Matrix + 20 mM sodium acetate</td>
<td>3 / 3 / 3 / 3 / 4</td>
</tr>
<tr>
<td>3</td>
<td>Matrix + 0.1 mg/mL rhPDGF-BB</td>
<td>3 / 3 / 3 / 3 / 4</td>
</tr>
<tr>
<td>4</td>
<td>Matrix + 0.3 mg/mL rhPDGF-BB</td>
<td>3 / 3 / 3 / 3 / 4</td>
</tr>
<tr>
<td>5</td>
<td>Matrix + 1.0 mg/mL rhPDGF-BB</td>
<td>3 / 3 / 3 / 3 / 4</td>
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</table>

rhPDGF-BB in 20 mM sodium acetate, pH 6.0

Moore et al., J Bone Joint Surg Am 2009
rhPDGF-BB accelerates the consolidation of the distraction callus

Distraction Callus at day 56
Conclusions

• rhPDGF-BB accelerated callus consolidation
• rhPDGF-BB decreased non-union rates
• No adverse events were noted
Partial arthrodesis of the carpus in dogs

The objective of this study was to determine bone fusion in a canine carpus fusion model

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>No. Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Autograft</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>β-TCP + buffer</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>β-TCP + rhPDGF-BB</td>
<td>10</td>
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</table>
rhPDGF-BB increases the number and extent of fused joints
rhPDGF-BB increases the number and extent of fused joints

![Bar chart showing the percentage of fused joints for different conditions: Autograft, β-TCP+ buffer, and β-TCP+ rhPDGF-BB.](image)

- Autograft: 70% of fused joints
- β-TCP+ buffer: 40% of fused joints
- β-TCP+ rhPDGF-BB: 60% of fused joints
Augment enhances joint fusion

Conclusions

• Augment increased number and extent of fused joints
• New bone formed was normal
• No evidence of ectopic bone formation
• No evidence of toxicity
Preclinical effectiveness established

• rhPDGF-BB/matrix combination outperformed the vehicle/matrix combination

• Established mechanism of action
  ❖ Chemotaxis
  ❖ Mitogenesis
  ❖ Angiogenesis

• Augment produced predictable biological outcomes:
  ❖ Accelerated bone formation
  ❖ Accelerated callus consolidation
  ❖ Promoted fracture healing
  ❖ Promoted joint fusion
Preclinical safety studies

Barry S. Levine, D.Sc.
Diplomate, American Board of Toxicology
Levine & Associates, LLC
Disclosure

• Consultant to BioMimetic Therapeutics, Inc.
• No equity in BioMimetic Therapeutics, Inc.
• Travel and time compensated for panel presentation
BMTI has conducted an extensive preclinical safety program in agreement with FDA

- rhPDGF-BB has an excellent safety profile:
  - Quickly released from implantation site
  - Rapid clearance from circulation
  - No adverse findings:
    - Single and repeat dose toxicity studies
    - Long term carcinogenicity and chronic toxicity study
    - Teratology study
  - No immunogenicity in treated animals
Preclinical studies

Pharmacokinetics
70% of the $^{125}\text{I}$-rhPDGF-BB is released from the implantation site in the first 60 minutes.

rhPDGF-BB released from implantation site within 7 days.
$^{125}$I-labeled rhPDGF-BB is rapidly cleared after IV injection in rats

Half-life ($T_{1/2}$) of rhPDGF-BB in circulation is 2.3 minutes
Preclinical studies

Safety
Comprehensive battery of safety studies completed

- **Carcinogenicity and chronic toxicity**
  - Evaluation of the chronic toxicity and carcinogenicity of rhPDGF-BB mixed with \( \beta \)-TCP (Augment™ Bone Graft) implanted in a rat model

- **Developmental toxicity**
  - rhPDGF-BB: an intravenous teratology study in the rat

- **Single-dose toxicity**
  - Acute toxicity of rhPDGF-BB following intravenous administration in rats

- **Repeat-dose toxicity**
  - Bone response to intramuscular injections of rhPDGF-BB

- **Genotoxicity**
  - Bacterial mutagenicity test - AMES assay

- **Safety study in baboons**
  - Evaluation of the safety of percutaneous injection of rhPDGF-BB combined with a collagen/\( \beta \)-TCP matrix into vertebral bodies of baboons

- **Biocompatibility studies (ISO 10993)**
- **Immunogenicity** (Antibody measurements in various studies)

No adverse finding in any study
Neither carcinogenicity nor chronic toxicity after implantation of Augment

- Study design approved by FDA
- No carcinogenicity
- No treatment-related mortality or effects on body weight, hematology, coagulation, clinical chemistry, or histopathology
- No differences in local tissue response among groups
- No anti-PDGF-BB antibodies in the Augment group

<table>
<thead>
<tr>
<th>Animals per sex</th>
<th>Article</th>
<th>Dose (µg/kg)</th>
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<tbody>
<tr>
<td>d 30</td>
<td>d 180</td>
<td>d 365</td>
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<tr>
<td>10</td>
<td>10</td>
<td>30</td>
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<td>10</td>
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<tr>
<td>10</td>
<td>10</td>
<td>30</td>
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</tbody>
</table>

rhPDGF-BB group contained 4 times the maximum clinical dose
No adverse findings in dams or fetuses after high dose administration of rhPDGF-BB

- Study design approved by FDA
- No maternal toxicity
- No adverse effects on embryo-fetal development
- Minor skeletal changes in high dose fetuses
  - Consistent with PDGF biology
  - Within normal historical range
- No ADA in dams or fetuses
- NOAEL for maternal toxicity: 400 µg/kg/day
- NOAEL for embryo/fetal development: 400 µg/kg/day

Cumulative high dose was 210 times maximum clinical dose
Favorable preclinical safety profile

• rhPDGF-BB is quickly released from implantation site
  ➢ 70% burst in 60 minutes
  ➢ 100% in 7 days
• Half-life in circulation is 2.3 minutes
• Studies demonstrate no adverse toxicity, carcinogenicity, or teratogenicity
• No antibodies detected in preclinical studies

No adverse findings in any preclinical safety studies
Augment Clinical Data

Russell P. Pagano, Ph.D.
Vice President
Clinical & Regulatory Affairs
BioMimetic Therapeutics, Inc.
PMA patient populations

Randomized Population (ITT)
- n = 434
- Augment (285) / Autograft (149)
  - Not defined in IDE

Treated Population (Safety)
- n = 414
- Augment (272) / Autograft (142)
  - Defined in IDE as ITT

Primary Analysis Population (mITT)
- n = 397
- Augment (260) / Autograft (137)
  - Defined in IDE as Per Protocol

Not treated
- n = 20
- Augment (13) / Autograft (7)

Major Protocol Violations
- n = 17
- Augment (12) / Autograft (5)

Prospectively determined by blinded review
## Subjects Excluded from Analysis

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Augment (12)</th>
<th>Autograft (5)</th>
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</thead>
<tbody>
<tr>
<td>Required plate for fixation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Required excluded procedures (midfoot, pantalar)</td>
<td>7</td>
<td>2</td>
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<tr>
<td>Required chronic steroids</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Subject weight-bearing at 2 weeks post-operatively</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Required more than 9 cc of graft</td>
<td>--</td>
<td>1</td>
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### 20 Subjects never treated

<table>
<thead>
<tr>
<th>Reason</th>
<th>Augment (13)</th>
<th>Autograft (7)</th>
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<tbody>
<tr>
<td>Subject withdrew consent</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Excluded based on requirement for exclusionary</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>hardware or surgical procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject not medically cleared for surgery</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Subject presented with infection at surgery</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Site closed prior to subject treatment</td>
<td>1</td>
<td>--</td>
</tr>
</tbody>
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**mITT is the most clinically relevant population**
Two pre-specified populations in the approved protocol

• IDE Intent-to-Treat = PMA Treated (n=414)
  ➢ All randomized subjects who receive treatment post-randomization
  ➢ Population prospectively specified in the IDE approved protocol

• IDE Per Protocol = PMA Modified Intent-to-Treat (n=397)
  ➢ Excludes 17 clinically important predefined protocol violations:
    ▪ Subsequent surgery, steroids, interfering medical conditions, and medications which impact healing or pain assessment.
  ➢ Population prospectively specified in the IDE approved protocol
  ➢ Most clinically relevant population for evaluation of safety and effectiveness of Augment compared to Autograft

Treated population and mITT are clinically relevant analyses
Definitions

- Any AE (clinical sign, symptom, or disease) temporally associated with the use of this study device, whether or not considered related to the study device.
- Adverse events coded to the most current version of the Medical Dictionary for Regulatory Affairs (MedDRA), using MedDRA Version 10.1 or higher at the time of the analysis.
- Complications associated with the surgical procedure may include pain, edema, nausea, vomiting, hypoaesthesia, skin and subcutaneous tissue ulcers, hardware irritation/complication, constipation, cast irritation, swelling, stiffness, warmth, pain and discomfort following surgery (typically worse with more severe pre-operative deformities), bruising, failure of fixation, infection, wound dehiscence, and pulmonary embolism. **These reported events were collected as AEs.**
- IDE Approved Protocol:

  “Due to the nature of the injury and subsequent surgical procedure involved in this study, certain adverse events may be considered normal sequellae [i.e., expected] associated with hindfoot and ankle fusions and will only be recorded if treatment is required or considered to be clinically significant.”
Adverse Events Reporting

- Adverse Events were collected consistently with the FDA and IRB approved study protocol
- Successful BIMO inspections completed 2009-2010 indicative of adequate adverse events reporting (no AE-related observations)
- In response to FDA questions regarding DMC that “FDA and the study’s DSMB have previously expressed concern that only certain events were being documented”

“There was not an underlying concern by DMC of under-reporting of adverse events or safety issues. Due to nature of arthritic conditions and invasive reconstructive surgery involved in study, certain events such as expected post-op swelling at surgical site not considered adverse events unless felt to be clinically significant by the surgeon, and or required treatment.”

Benedict F. DiGiovanni, MD
Chairperson of Independent Data Monitoring Committee
Summary of Physical Examination Data Collection

• Pain Assessments
  - Measurement: Pain was assessed by a visual analog scale (VAS). Please note that in addition to the study visits requiring the patient to complete a VAS assessment, all patients were to complete a VAS assessment post-operatively prior to discharge. Patients were asked to complete a VAS for the following parameters:
    • General foot/ankle pain,
    • Pain at fusion site with weight-bearing, and
    • Pain at autograft harvest site (autologous bone graft only).

• Motion at the Fusion Site
  - Measurement: Positive (+) or negative (-) for motion at the fusion site.

• Warmth at the Fusion Site
  - Measurement: None, mild, moderate, severe.

• Swelling
  - Measurement: None, mild, moderate, severe.

No difference observed between Augment and autograft
Summary of Physical Examination Data Collection

• Tenderness
  ➢ Measurement: Positive (+) or negative (-) for tenderness at the surgical site.

• Neurovascular Status
  ➢ Measurement: Intact or impaired.

• Infection
  ➢ Measurement: Positive (+) or negative (-) for infection at the surgical/fusion site.

• Weight-Bearing

• Clinical/Radiographic Assessment of Healing
  ➢ Measurement: Union, evidence of Progressive Healing (≤ 6 mo.), delayed union (12-36 weeks), non-union (at 36 weeks), uninterpretable at 24 and 36 weeks.

• Hardware Complications
  ➢ Assessment: None, fractured hardware, developing lucency surrounding screws.

No difference observed between Augment and autograft
Conclusion

• Adverse events were documented and reported consistently with the approved study protocol

• Physical examination observations, as collected, allow for more sensitive interpretation of data for expected outcomes that were not considered clinically relevant in the opinion of the investigator

• No significant difference in rates of post-surgical physical exam findings
Cancer Incidence and Evidence

Mark Green, MD

Professor of Medicine, Hematology-Oncology, Emeritus
Medical University of South Carolina

Chair, Data Safety Monitoring Board
NCI funded Cancer Cooperative Group [CALGB]

Clinical Associate, Hematology and Supportive Care
Branch (Former)
National Cancer Institute
Disclosure

• Consultant to BioMimetic Therapeutics, Inc.
• No equity in BioMimetic Therapeutics, Inc.
• Travel and time compensated for panel presentation
No trend of cancer incidence or deaths in the pivotal trial

- No trends noted in occurrence or recurrence of cancers
- Five cancer events – none in the Augment group at/near the site of Augment utilization

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of cancers</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augment Bone Graft (n=272)</td>
<td>3</td>
<td>1.1%</td>
</tr>
<tr>
<td>Autograft (n=142)</td>
<td>2</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

- Two non-malignant events (plantar fibroma and colon polyps with prior history) also coded as neoplasms

No cancer signal. No difference between Augment and autograft
No link between rhPDGF-BB and observed cancer events

<table>
<thead>
<tr>
<th>Subject ID No.</th>
<th>Age</th>
<th>Type/Location of Cancer</th>
<th>Clinical Outcome</th>
<th>Cancer History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augment Bone Graft</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64-01</td>
<td>65</td>
<td>Carcinoma/Prostate</td>
<td>Union</td>
<td>No known history</td>
</tr>
<tr>
<td>72-11</td>
<td>64</td>
<td>Carcinoma/Prostate</td>
<td>Union</td>
<td>Prostate cancer (1996)</td>
</tr>
<tr>
<td>69-04</td>
<td>58</td>
<td>Carcinoma/Infiltrating Lobular</td>
<td>Union</td>
<td>Basal Cell Carcinoma unspecified (2008)</td>
</tr>
<tr>
<td>Autograft</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42-07</td>
<td>76</td>
<td>Carcinoma/Renal</td>
<td>Union</td>
<td>Prostate cancer (2004); Basal Cell Carcinoma (2003)</td>
</tr>
<tr>
<td>69-06</td>
<td>60</td>
<td>Carcinoma/Endometrial</td>
<td>Evidence of Progressive Healing</td>
<td>No known history</td>
</tr>
</tbody>
</table>
No evidence of cancer promotion with rhPDGF-BB

- rhPDGF-BB-treated subjects: 
  \[ \frac{4}{605} = 0.7\% \]

- Control subjects: 
  \[ \frac{3}{227} = 1.3\% \]
Tumor promotion potential

• “There may be a risk for tumor promotion with use of the device”.¹

• This concern is based on epidemiologic findings regarding rhPDGF-BB used for the treatment of diabetic foot ulcers.²

• These findings and concerns for rhPDGF-BB led to an FDA public health advisory.”¹,³

• Prior to these findings, no clinical concerns about becaplermin and neoplasia had been reported or suggested. [“... combined results suggest that topical application of PDGF-BB is safe and well tolerated”]⁴

Initial abstract report leading to FDA Public Health Advisory

• Objective:
  - To determine incidence of cancer among becaplermin users relative to non-users

• Identified 2,102 eligible becaplermin initiators and 325,313 eligible non-initiators from a Health Insurance claim database
  - Developed a propensity matched cohort [1:2 ratio]
    ▪ Median follow up 20 months
  - Confirmed cancer cases 47 [initiators] and 86 [2x controls] respectively [RR = 1.2, 95% CI = 0.7–1.9 for all cancers]
    ▪ RR = 1.1, 95% CI = 0.4–2.8 for subjects with three or more becaplermin dispensings compared to those with none
    ▪ Separate mortality analysis in prolonged exposure cohort [≥ 3 becaplermin dispensings] vs. none → RR = 5.9, 95% CI = 1.7 – 20 (based on 4 vs. 0 cancer deaths)

• Conclusions:
  - “No relationship between becaplermin exposure and cancer incidence”
  - “Increased mortality in the highest exposure category .. may reflect chance or residual confounding in the mortality models”

A matched cohort study of the risk of cancer in users of becaplermin – final results

• Objective:
  
  “Further investigate any association between becaplermin use and the occurrence of cancer by following a large cohort of patients in a clinical practice setting”.
  
  - Additional follow up of original initiator and propensity matched pair analysis
  - Follow up 6 years for cancer incidence (up to 9 years for cancer mortality)

• Findings:
  
  “No increased risk of cancer with becaplermin (hazard ratio, 1.2; 95% CI, 0.7–1.9)”.
  
  “Additional follow-up through 2006 indicated no elevated cancer mortality risk overall (RR, 1.0; 95% CI, 0.5–2.3) and no statistically significant increase in the subgroup with more than 3 dispensings (RR, 2.4; 95% CI, 0.8–7.4)”.

• CONCLUSIONS:
  
  “Becaplermin does not appear to increase the risk of cancer or cancer mortality”.

rhPDGF-BB-containing products are safe

- No evidence of increased cancer risk with GEM 21S®
- No evidence of increased cancer risk with Regranex® (final analysis)

Augment

- No preclinical evidence of carcinogenicity
- No clinical evidence of increased cancer incidence
- Favorable safety properties:
  - Single administration
  - Short local residence time
  - Rapid systemic clearance
Augment Clinical Data

Judith F. Baumhauer, MD MPH
Professor and Associate Chair of Academic Affairs
Department of Orthopaedic Surgery
Foot and Ankle Division
University of Rochester School of Medicine and Dentistry
Disclosure Slide

• Investigator for Augment clinical trials
• Consultant to BioMimetic Therapeutics, Inc.
• Travel and time compensated for panel presentation
• No equity in BioMimetic Therapeutics, Inc.
Patient with ankle arthritis
Pre-operative
Ankle arthrodesis with Augment

Pre-Op
24 Weeks
52 Weeks
Clinical Relevance
Current state of foot and ankle fusion

- Arthrodesis (fusion) is a common procedure performed for end stage arthritis of the ankle, hindfoot and midfoot
- Multiple joints: talonavicular, calcaneocuboid, subtalar, triple or double, and ankle fusions
- Joints pooled:
  - Etiologies
  - Surgical approach
  - Fixation techniques
  - Healing rates
  - Vascularity
  - Post-Op therapy
The problem: nonunion

Emphasis has been **mechanical** stabilization.... **Biologic** intervention is needed to enhance fusion
Autograft

- Considered the “gold standard” for facilitating bony union
- Requires secondary surgical procedure – harvest bone from one site to use in another
- Large variation in quality and quantity of autologous graft

Summary: Information from 8 published studies (1086 patients)

- Donor Site Complications: 31%
- Major Acute Complications: 5%
- Severe Pain: 11%
- Chronic Pain: 27%

Typical Bone Grafting Sites:

- Hip
- Prox. tibia
- Heel
Risks of autograft

- Pelvic, tibial or calcaneal fracture
- Major hemorrhage
- Vascular injury
- Nerve injury
- Sacroiliac joint dislocation
- Peritoneal perforation
- Osteomyelitis
- Hematoma
- Nerve sensitivity/numbness
- Herniation at donor site

- Wound infection
- Wound dehiscence
- Unsightly scars
- Disabling pain
Augment™ Bone Graft (rhPDGF-BB/β-TCP)

- 3 mL rhPDGF-BB (0.3 mg/mL), mfg using recombinant DNA techniques
- 3 cc of beta tri-calcium phosphate (β-TCP), 1,000 – 2,000 μm
- rhPDGF-BB is a potent regenerative agent with an established clinical history (GEM 21S®, Regranex®)
- Fully synthetic replacement for the regenerative capacity of autograft

Augment is a completely synthetic alternative
Surgical procedure

- Standard anesthesia protocol (local or general)
- Perioperative antibiotics administered and recorded
- Entire joint exposed, denuded to subchondral bone
- Cortex is perforated to facilitate fusion
- Graft placement using standard grafting technique
- Hardware: 3.5 - 7.3mm screws, staples, pins only
Augment preparation and implantation

- Augment™ is packaged in a single use kit
- Hydrate β-TCP with rhPDGF-BB (1:1)
- Let sit for 10 minutes
- Up to 9 cc of graft implanted
- Care taken to minimize particle migration
Pilot Clinical Studies
Supportive Augment foot and ankle fusion trials

- Positive US Pilot Trial \( (n = 20) \)
- Positive Canadian Open Label Study \( (n = 60) \)
- Positive EU Open Label Safety Study \( (n = 108) \)

Orthopedic trials confirmatory of successful periodontal program
Conclusions from early Augment trials

- No device related serious adverse events
- No incidence of excess bone formation
- No concerning trends in adverse event data
- Effectiveness comparable to autograft

Proceed to randomized controlled pivotal trial (IDE)
Pivotal Trial Design
## Augment Pivotal clinical trial

### Design

<table>
<thead>
<tr>
<th>Enrollments</th>
<th>Prospective, randomized (2:1), controlled Augment : autograft</th>
</tr>
</thead>
</table>

### Enrollment

434 randomized, 37 centers in United States and Canada

### Indication

Hindfoot or ankle fusion requiring bone graft

### Study Hypothesis

Augment Bone Graft is non-inferior to autograft

### Primary Endpoint

Percent of patients fused at 6 months (≥ 50% osseous bridging via CT)

### Secondary Endpoints

Clinical, functional, radiologic, quality of life, and safety outcomes

### Regulatory Status

Protocol approved by FDA and Health Canada

---

Largest prospective randomized controlled IDE F/A trial
Radiographic endpoints: Independent masked radiologist

Independent radiologic assessment

- Independent radiologist: Dr. Peter Evangelista (RIH)
- Primary endpoint: fusion
  - CT Scan: % of Osseous Bridging (CT Scan);
    - ≥ 50% is required for fusion endpoint
- Plain films: ant., post., med., lat., (sup./inf.)
- Presence of abnormal / heterotopic bone formation
- Presence / resorption of β-TCP

High intra-rater reliability
Inclusion criteria

• IRB approved Informed Consent Form specific to this study prior to enrollment.
• Hindfoot or ankle requiring fusion with supplemental bone graft/substitute, requiring one of the following procedures:
  ➢ Ankle joint fusion
  ➢ Subtalar fusion
  ➢ Calcaneocuboid fusion
  ➢ Talonavicular fusion
  ➢ Triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints)
  ➢ Double fusions (talonavicular and calcaneocuboid joints)
• No more than 3 screws across fusion site. Supplemental pins may be used. Supplemental screws external to the fusion site(s) are also allowed. Plates excluded.
• The patient is independent, ambulatory, and can comply with all post-operative evaluations and visits.
• The patient is at least 18 years of age and considered to be skeletally mature.
Exclusion criteria

- The patient has undergone previous surgery of the proposed fusion site.
- The fusion site requires plate fixation, more than three (3) screws to achieve rigid fixation, or more than 3 kits, or 9 cc of graft material to completely fill the void in the fusion space.
- There is radiographic evidence of bone cysts around the fusion site that may negatively impact bony fusion.
- The patient currently has detectable untreated cancer (other than basal cell carcinoma) or is currently undergoing radio- or chemotherapy.
- The patient has a pre-existing sensory impairment (e.g. diabetics with baseline sensory impairment) which limits the ability to perform objective functional measurements and may place patients at risk for complications. For the purpose of this protocol, diabetics that are not sensitive to the 5.07 monofilament (Semmes-Weinstein) are to be excluded.
- The patient has a metabolic disorder known to adversely affect the skeleton, other than primary osteoporosis or diabetes (e.g., renal osteodystrophy).
- The patient uses chronic medications known to affect the skeleton (e.g. glucocorticoid usage > 10mg/day). Note: NSAIDs are allowable.
Exclusion criteria

- The patient has a pre-fracture neuromuscular or musculoskeletal deficiency which limits the ability to perform objective functional measurements.
- The patient is physically or mentally compromised (e.g., currently being treated for a psychiatric disorder, senile dementia, Alzheimer’s disease, etc.) to the extent that the Investigator judges the subject to be unable or unlikely to remain compliant.
- The patient has an allergy to yeast-derived products;
- The patient has received an investigational therapy or approved therapy for investigational use within 30 days of surgery or during the follow-up phase of this study;
- The patient is a prisoner, is known or suspected to be transient, or has a history of drug/alcohol abuse within the 12 months prior to screening for study entry.
- The patient is pregnant or a female intending to become pregnant during this study period. A urine pregnancy test will be administered within 21 days of the surgical visit to any female unless she is post-menopausal, has been sterilized, or is practicing a medically-accepted method of contraception;
- The patient is morbidly obese (BMI > 45 kg/m²)
Demographics
# Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 414)</th>
<th>Augment (n = 272)</th>
<th>Autograft (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>51% / 49%</td>
<td>47% / 53%</td>
<td>57% / 43%</td>
</tr>
<tr>
<td><strong>Age (Mean)</strong></td>
<td>57</td>
<td>56</td>
<td>58</td>
</tr>
<tr>
<td><strong>BMI (Mean)</strong></td>
<td>31</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic Arthritis</td>
<td>48%</td>
<td>49%</td>
<td>45%</td>
</tr>
<tr>
<td>Primary Arthritis</td>
<td>36%</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>Rheumatoid</td>
<td>7%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>49%</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>Smoking History</td>
<td>24%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Prior Surgery</td>
<td>23%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12%</td>
<td>11%</td>
<td>13%</td>
</tr>
</tbody>
</table>

No differences in treatment groups
## Procedure information

<table>
<thead>
<tr>
<th>Fusion Type</th>
<th>All Patients (n = 414)</th>
<th>Augment (n = 272)</th>
<th>Autograft (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle</td>
<td>38%</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>Subtalar</td>
<td>26%</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>Calcaneocuboid</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Talonavicular</td>
<td>6%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Double Fusion</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Triple Fusion</td>
<td>21%</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Total # of Joints</strong></td>
<td>(631)</td>
<td>(417)</td>
<td>(214)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Graft Volume</th>
<th>All Patients (n = 414)</th>
<th>Augment (n = 272)</th>
<th>Autograft (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 3 cc</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>4 – 6 cc</td>
<td>51%</td>
<td>52%</td>
<td>48%</td>
</tr>
<tr>
<td>7 – 9 cc</td>
<td>20%</td>
<td>19%</td>
<td>23%</td>
</tr>
</tbody>
</table>

No statistically significant differences
Product Safety
## Safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Augment (%)</td>
<td>Autograft (%)</td>
<td>Augment (%)</td>
<td>Autograft (%)</td>
</tr>
<tr>
<td>Tx Emergent Adverse Events (TEAE)</td>
<td>72</td>
<td>70</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>8</td>
<td>14</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Overall Complications</td>
<td>33</td>
<td>38</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>Surgically Related Complications</td>
<td>24</td>
<td>30</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Serious Complications</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Serious Surgical Complications</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Infections</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Fewer complications with Augment than autograft
Serious Treatment Emergent Adverse Events: Infections

• Serious Adverse Events
  ▶ 21 CFR 812.3(s)
  ▶ International Conference on Harmonisation (ICH)

• Serious Infection
  ▶ Any death.
  ▶ Any life-threatening event (i.e., an event that placed the patient, in the view of the investigator, at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form, might have caused death).
  ▶ Any event that required or prolonged in-patient hospitalization.
  ▶ Any event that resulted in persistent or significant disability/incapacity.
  ▶ Any congenital anomaly/birth defect diagnosed in a child of a patient who participated in this study following the study procedure.
  ▶ Other medically important events that in the opinion of the investigator may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed above.
  ▶ Any serious problem associated with the device that related to the rights, safety or welfare of study patients.
Treatment Emergent Adverse Events: Infections and Infestations

- Adverse Events: Infections and Infestations
  - All adverse events reported on Case Report Form
  - Categorized as “Infections and Infestations” as per MedDRA (10.1)
  - Includes all infection events regardless of etiology or causality

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>All Patients (N=414)</th>
<th>Augment (N=272)</th>
<th>Autograft (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Events</td>
<td>Subjects</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>317</td>
<td>76.6%</td>
<td>973</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>89</td>
<td>21.5%</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Infections

<table>
<thead>
<tr>
<th>Events Coded as Infections and Infestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
</tr>
<tr>
<td>Blastocystitis infection</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Candidiasis</td>
</tr>
<tr>
<td>Catheter related infection</td>
</tr>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>Clostridium difficile colitis</td>
</tr>
<tr>
<td>Conjunctivitis infective</td>
</tr>
<tr>
<td>Ear Infection</td>
</tr>
<tr>
<td>Cystitis</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Infections were further classified for clinical relevance into surgical complications.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=414)</th>
<th>Augment™ Bone Graft (N=272)</th>
<th>Autograft (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Events</td>
<td>Subjects</td>
</tr>
<tr>
<td>Any Infection</td>
<td>39 ( 9.4%)</td>
<td>46</td>
<td>23 ( 8.5%)</td>
</tr>
<tr>
<td>Systemic</td>
<td>2 ( 0.5%)</td>
<td>2</td>
<td>1 ( 0.4%)</td>
</tr>
<tr>
<td>Deep Wound</td>
<td>3 ( 0.7%)</td>
<td>5</td>
<td>2 ( 0.7%)</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>2 ( 0.5%)</td>
<td>2</td>
<td>2 ( 0.7%)</td>
</tr>
<tr>
<td>Superficial</td>
<td>6 ( 1.4%)</td>
<td>6</td>
<td>5 ( 1.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>29 ( 7.0%)</td>
<td>31</td>
<td>16 ( 5.9%)</td>
</tr>
</tbody>
</table>
Summary of serious adverse events

• No differences between study groups
• No SAEs related to the study device
• Pulmonary embolism death in Augment group
  ➢ Classified as “not related” to the study device
• No reported deaths due to existing cancers
rhPDGF-BB-containing products are safe

- No evidence of increased cancer risk with GEM 21S®
- No evidence of increased cancer risk with Regranex®
  (final analysis)

Augment

- No preclinical evidence of carcinogenicity
- No clinical evidence of increased cancer incidence
- Favorable safety properties:
  - Single administration
  - Short local residence time
  - Rapid systemic clearance
Anti-drug antibody results

• 14% of Augment subjects with antibody response
• 4% of autograft subjects with antibody response
• All subjects returned to baseline
• No subjects displayed neutralizing antibodies

Low, transient Ab response and no neutralizing Ab
Autograft patients experienced persistent pain

<table>
<thead>
<tr>
<th></th>
<th>24 Week</th>
<th>52 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone graft harvest site pain</td>
<td>55%</td>
<td>44%</td>
</tr>
<tr>
<td>Clinically significant (≥ 20mm) bone graft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>harvest site pain</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Chronic pain from bone graft surgical site
Autograft patients have increased risk

• Safety benefits trended in favor of the Augment™ group
  ➢ Serious treatment emergent adverse events
  ➢ Overall surgical and complication rates
• One patient required hospitalization due to graft harvest site infection
• Augment superior to autograft ($p < 0.001$) for graft harvest site pain

Superior safety profile for Augment
Safety conclusions

Augment patients experienced:

• No bone graft harvest site morbidity
• No serious device-related adverse events
• No exuberant bone growth
• No difference in cancer rates
• Fewer adverse events
• Fewer complications
• Fewer infections

Augment is safe for use in hindfoot and ankle fusion
Efficacy Results
Primary endpoint

- Fusion defined as ≥ 50% osseous bridging on CT scan
- Independent radiologist assessment at 24 weeks
- Full complement: success requires all treated joints assessed to be fused

“We believe the progress of the fusion cannot be determined accurately from standard radiographs. CT scanning appears to be significantly more reliable.”

Coughlin M, et al. Foot Ankle Int. 2006

50% osseous bridging is a rigorous endpoint
Augment U.S. Pivotal trial: Summary of mITT (397 patients / 597 joints)

Primary endpoint is measured at 24 weeks

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-inferiority established</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Weeks</td>
</tr>
<tr>
<td>CT Fusion (full complement)</td>
<td>Yes (p=0.038)</td>
</tr>
<tr>
<td>CT Fusion (all joints)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinical Healing (patient)</td>
<td>Yes (p=0.010)</td>
</tr>
<tr>
<td>Clinical Healing (all joints)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinical Success</td>
<td>No (p=0.071)</td>
</tr>
<tr>
<td>Non-Union/Therapeutic Failure</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Persistent Donor Site Pain</td>
<td>Yes (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Augment statistically significant in primary and key secondary endpoints
Augment U.S. Pivotal trial:
Summary of Treated (414 patients / 631 joints)

Primary endpoint is measured at 24 weeks

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-inferiority established</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Weeks</td>
</tr>
<tr>
<td>CT Fusion (full complement)</td>
<td>Yes (p=0.048)</td>
</tr>
<tr>
<td>CT Fusion (all joints)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinical Healing (patient)</td>
<td>Yes (p=0.006)</td>
</tr>
<tr>
<td>Clinical Healing (all joints)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinical Success</td>
<td>No (p=0.061)</td>
</tr>
<tr>
<td>Non-Union/Therapeutic Failure</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Persistent Donor Site Pain</td>
<td>Yes (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Augment statistically significant in primary and key secondary endpoints
Conventional radiographic results for mITT (397 patients / 597 joints)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-inferiority established</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Weeks</td>
</tr>
<tr>
<td>Radiographic Fusion 3 views (patient)</td>
<td>No (p=0.054)</td>
</tr>
<tr>
<td>Radiographic Fusion 3 views (all joints)</td>
<td>Yes (p=0.007)</td>
</tr>
<tr>
<td>Radiographic Fusion 2 views (patient)</td>
<td>No (p=0.194)</td>
</tr>
<tr>
<td>Radiographic Fusion 2 views (all joints)</td>
<td>Yes (p=0.049)</td>
</tr>
</tbody>
</table>
Conventional radiographic results for Treated (414 patients / 631 joints)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>24 Weeks</th>
<th>36 Weeks</th>
<th>52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic Fusion 3 views (patient)</td>
<td>No (p=0.054)</td>
<td>No (p=0.194)</td>
<td>Yes (p=0.021)</td>
</tr>
<tr>
<td>Radiographic Fusion 3 views (all joints)</td>
<td>No (p=0.091)</td>
<td>No (p=0.088)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Radiographic Fusion 2 views (patient)</td>
<td>No (p=0.223)</td>
<td>No (p=0.192)</td>
<td>No (p=0.109)</td>
</tr>
<tr>
<td>Radiographic Fusion 2 views (all joints)</td>
<td>No (p=0.072)</td>
<td>Yes (p=0.017)</td>
<td>Yes (p=0.011)</td>
</tr>
</tbody>
</table>
Functional, QOL and pain results for mITT (397 patients / 597 joints)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-inferiority established</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Weeks</td>
</tr>
<tr>
<td>Foot Function Index</td>
<td>Yes (p=0.012)</td>
</tr>
<tr>
<td>AOFAS Ankle-Hindfoot Score</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>SF-12 Mean PCS</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Fusion Site Pain</td>
<td>Yes (p=0.001)</td>
</tr>
<tr>
<td>Weight Bearing Pain</td>
<td>Yes (p=0.016)</td>
</tr>
<tr>
<td>Clinically Significant Graft Site Pain</td>
<td>Yes (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Statistically significant for non-inferiority
Exception: Superiority achieved for graft harvest site pain
Functional, QOL and pain results for Treated (414 patients / 631 joints)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>24 Weeks</th>
<th>36 Weeks</th>
<th>52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot Function Index</td>
<td>Yes (p=0.007)</td>
<td>Yes (p=0.002)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>AOFAS Ankle-Hindfoot Score</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>SF-12 Mean PCS</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p=0.018)</td>
<td>Yes (p=0.013)</td>
</tr>
<tr>
<td>Fusion Site Pain</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Weight Bearing Pain</td>
<td>Yes (p=0.011)</td>
<td>Yes (p=0.005)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinically Significant Graft Site Pain</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
<td>Yes (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Statistically significant for non-inferiority
Exception: Superiority achieved for graft harvest site pain
Primary endpoint: fusion success

- Percent of patients achieving $\geq 50\%$ osseous bridging at 24 wks
- Assessed by masked independent radiologist

Population: mITT (n=397)

- Augment rate (%), n=260
- Autograft rate (%), n=137

Rate difference (%)

Confidence limit

Augment is non-inferior to autograft for primary endpoint
Primary endpoint: fusion success

- Percent of patients achieving ≥ 50% osseous bridging at 24 wks
- Assessed by masked independent radiologist

Augment is non-inferior to autograft for primary endpoint
Primary endpoint: fusion success

- Percent of patients achieving ≥ 50% osseous bridging at 24 wks
- Assessed by masked independent radiologist

Population: Treated (n=414) Week: 24

- Augment rate (%), n=272
- Autograft rate (%), n=142

Rate difference (%)

Confidence limit

p = 0.048

Demonstrated statistical non-inferiority
CT fusion success for all joints

- Assessed for each individual joint (n=597)
- Percent of joints achieving ≥ 50% osseous bridging at 24 wks
- Assessed by masked independent radiologist

**Population: mITT**

- Augment rate (%), n=394
- Autograft rate (%), n=203

**Week: 24**

- Rate difference (%)
- Confidence limit

\[ p = 0.001 \]

Demonstrated statistical non-inferiority
CT fusion success for all joints

- Assessed for each individual joint (n=631)
- Percent of joints achieving ≥ 50% osseous bridging at 24 wks
- Assessed by masked independent radiologist

**Population: Treated**

- Augment rate (%), n=417
- Autograft rate (%), n=214

**Week: 24**

- Rate difference (%)
- Confidence limit

Demonstrated statistical non-inferiority
Clinical healing

- Investigator assessment of union
- Based on full complement of joints

Population: mITT (n=397)  Week: 24

Augment rate (%), n=260
Autograft rate (%), n=137

Rate difference (%)
Confidence limit

p = 0.011

Demonstrated statistical non-inferiority
Clinical healing

- Investigator assessment of union
- Based on full complement of joints

Population: Treated (n=414)  Week: 24

Augment rate (%), n=272

Autograft rate (%), n=142

Rate difference (%)  Confidence limit

p = 0.006

Demonstrated statistical non-inferiority
Clinical healing

- Investigator assessment of union
- Based on full complement of joints

Population: mITT (n=397)  Week: 52

Augment rate (%), n=260
Autograft rate (%), n=137

Rate difference (%)  Confidence limit

Demonstrated statistical non-inferiority
Clinical healing

- Investigator assessment of union
- Based on full complement of joints

Population: Treated (n=414)  Week: 52

Augment rate (%), n=272
Autograft rate (%), n=142

Rate difference (%)  Confidence limit

Demonstrated statistical non-inferiority
Clinical healing for all joints

- Investigator assessment of union
- Assessed for each individual joint (n=597)

Population: mITT

- Augment rate (%), n=394
- Autograft rate (%), n=203

Rate difference (%)

Confidence limit

Week: 24

p = 0.001

Demonstrated statistical non-inferiority
Clinical healing for all joints

- Investigator assessment of union
- Assessed for each individual joint (n=631)

Population: Treated

- Augment rate (%), n=417
- Autograft rate (%), n=214

Rate difference (%)

Confidence limit

Week: 24

p = 0.001

Demonstrated statistical non-inferiority
Clinical healing for all joints

- Investigator assessment of union
- Assessed for each individual joint (n=597)

Population: mITT

- Augment rate (%), n=394
- Autograft rate (%), n=203

Rate difference (%)

Confidence limit

Week: 52

p = 0.001

1.1

-3.6

Demonstrated statistical non-inferiority
Clinical healing for all joints

- Investigator assessment of union
- Assessed for each individual joint (n=631)

Population: Treated

Augment rate (%), n=417
Autograft rate (%), n=214

Rate difference (%)
Confidence limit

Week: 52

p = 0.001

Demonstrated statistical non-inferiority
Therapeutic failures

- Nonunion
- Delayed Union
- Secondary intervention for delayed union, including additional surgical procedures, therapeutic ultrasound, magnetic field, or electrical stimulation.

Population: mITT (n=397)  Week: 52

Augment rate (%), n=260  p = 0.001

Autograft rate (%), n=137

Rate difference (%)  Confidence limit

Demonstrated statistical non-inferiority
Therapeutic failures

- Nonunion
- Delayed Union
- Secondary intervention for delayed union, including additional surgical procedures, therapeutic ultrasound, magnetic field, or electrical stimulation.

Population: Treated (n=414)  Week: 52

p = 0.001

Augment rate (%), n=272
7

Autograft rate (%), n=142
8

Rate difference (%)  Confidence limit
-1.5  3.1

Demonstrated statistical non-inferiority
Clinical success

- Reduced weight bearing pain and absence of need for revision

**Population: mITT (n=397)**

- Augment rate (%), n=260
- Autograft rate (%), n=137

**Week: 24**

- Rate difference (%)
- Confidence limit

- p = 0.071
Clinical success

- Reduced weight bearing pain and absence of need for revision

Population: Treated (n=414)

Augment rate (%), n=272

Autograft rate (%), n=142

Rate difference (%)

Confidence limit

Week: 24

p = 0.061

74
77

-10.4 -3.2
Clinical success

- Reduced weight bearing pain and absence of need for revision

Population: mITT (n=397)  Week: 52

- Augment rate (%), n=260
- Autograft rate (%), n=137

Rate difference (%)  Confidence limit

p = 0.022

Demonstrated statistical non-inferiority
Clinical success

- Reduced weight bearing pain and absence of need for revision

Population: Treated (n=414)   Week: 52

Augment rate (%), n=272

Autograft rate (%), n=142

Rate difference (%)  Confidence limit

Demonstrated statistical non-inferiority
Significant graft harvest site pain

- Patient assessment on Visual Analog Scale (VAS)
- % of patients with clinically significant harvest site pain (≥ 20mm)

**Population: Treated (n=414)  Week: 24**

Augment rate (%), n=272

Autograft rate (%), n=142

Rate difference (%)

Confidence limit

Augment superior to autograft
Significant graft harvest site pain

- Patient assessment on Visual Analog Scale (VAS)
- % of patients with clinically significant harvest site pain (≥ 20mm)

**Population: Treated (n=414)  Week: 52**

\[ p = 0.001 \]

Augment rate (%), n=272

\[ 0 \]

Autograft rate (%), n=142

\[ 9 \]

Rate difference (%)

\[ -9.2 \]

Confidence limit

\[ -30 \] to \[ -5.2 \]

Augment superior to autograft
Cumulative distribution of graft harvest site pain for Treated population

One in ten patients have long-term significant pain

Source of autograft for VAS ≥ 20

<table>
<thead>
<tr>
<th>Source</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal tibia</td>
<td>23</td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>31</td>
</tr>
<tr>
<td>Calcaneus</td>
<td>31</td>
</tr>
<tr>
<td>Other – Tibial / Talar</td>
<td>8</td>
</tr>
<tr>
<td>Other - Talus</td>
<td>8</td>
</tr>
</tbody>
</table>

100
Pain while weight-bearing

- Patient assessment on Visual Analog Scale (VAS)

**Population: mITT (n=397)**

- Augment mean, n=246
- Autograft mean, n=132

**Week: 24**

- Mean difference: 4.3
- Confidence limit: 8.7
- Statistical significance: \( p = 0.016 \)

*Demonstrated statistical non-inferiority*
Pain while weight-bearing

- Patient assessment on Visual Analog Scale (VAS)

**Population: Treated (n=414)**

- Augment mean, n=257
- Autograft mean, n=137

**Week: 24**

- Mean difference: 4
- Confidence limit: 8.3
- p = 0.011

Demonstrated statistical non-inferiority
Pain while weight-bearing

- Patient assessment on Visual Analog Scale (VAS)

**Population: mITT (n=397)**

- Augment mean, n=240
- Autograft mean, n=132

**Week: 52**

\[ p = 0.001 \]

**Mean difference**

\[ -0.2 \]

**Confidence limit**

\[ 4.1 \]

**Demonstrated statistical non-inferiority**
Pain while weight-bearing

• Patient assessment on Visual Analog Scale (VAS)

Population: Treated (n=414)  Week: 52

Augment mean, n=251  p = 0.001
Autograft mean, n=137

Mean difference  0.3
Confidence limit  4.5

Demonstrated statistical non-inferiority
Foot Function Index*

- Patient assessment on Visual Analog Scale (VAS)
- Measures pain, disability, and activity restriction

Population: mITT (n=397)  Week: 24

Augment mean, n=249  Autograft mean, n=133

Mean difference  Confidence limit

\[ \text{Mean difference} = \frac{27 - 22}{27 + 22} \]

\[ \text{Confidence limit} = \pm 8.7 \]

*p = 0.012

*Demonstrated statistical non-inferiority

*Budiman-Mak et al, 1991
Foot Function Index*

- Patient assessment on Visual Analog Scale (VAS)
- Measures pain, disability, and activity restriction

Population: Treated (n=414)   Week: 24

Augment mean, n=260
Autograft mean, n=138

Mean difference
Confidence limit

\[ p = 0.007 \]

\[ \text{Mean difference} = 4.7, \text{Confidence limit} = 8.2 \]

*Demonstrated statistical non-inferiority

*Budiman-Mak et al, 1991
**Foot Function Index**

- Patient assessment on Visual Analog Scale (VAS)
- Measures pain, disability, and activity restriction

**Population: mITT (n=397)  Week: 52**

<table>
<thead>
<tr>
<th>Augment mean, n=241</th>
<th>Autograft mean, n=132</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

Mean difference

Confidence limit

\[ p = 0.001 \]

*Demonstrated statistical non-inferiority*

*Budiman-Mak et al, 1991*
Foot Function Index*

- Patient assessment on Visual Analog Scale (VAS)
- Measures pain, disability, and activity restriction

Population: Treated (n=414)  Week: 52

Augment mean, n=252
Autograft mean, n=137

Mean difference
Confidence limit

$\text{p} = 0.001$

20
17

2.9
6.3

*Budiman-Mak et al, 1991

Demonstrated statistical non-inferiority
Subject Performance Composite

- Composite Analysis requested by FDA
- Incorporates Clinical, Functional, and Safety Outcomes

Radiographic Primary Endpoint
Full complement CT ≥ 50% osseous bridging at 24 weeks

Clinical
≥ 20mm reduction in pain with weight-bearing and absence of secondary procedure

Functional
≥ 10 point Improvement in function via Foot Pain and Disability Index and < 20mm graft harvest site pain

Safety
Lack of Serious Adverse Event(s)

Subject Performance Composite

Radiographic + Subject Performance Composite
Subject Performance Composite

- Clinical, Functional, and Safety Outcomes

Population: mITT (n=397)

- Augment rate (%), n=260
- Autograft rate (%), n=137

Rate difference (%)
Confidence limit

Week: 24

p = 0.009

50
47
2.6
-6.1

Demonstrated statistical non-inferiority
Subject Performance Composite

• Clinical, Functional, and Safety Outcomes

Population: Treated (n=414)

Augment rate (%), n=272
Autograft rate (%), n=142

Rate difference (%)
Confidence limit

Week: 24

p = 0.007

Demonstrated statistical non-inferiority
Subject Performance Composite

• Clinical, Functional, and Safety Outcomes

Population: mITT (n=397)

- Augment rate (%), n=260
- Autograft rate (%), n=137

Rate difference (%)

Confidence limit

Week: 52

p = 0.047

48
50

-1.2
-9.9

Demonstrated statistical non-inferiority
Subject Performance Composite

• Clinical, Functional, and Safety Outcomes

Population: Treated (n=414)  

Augment rate (%), n=272

Autograft rate (%), n=142

Rate difference (%)  
Confidence limit

Week: 52

p = 0.037

49

-0.8

-9.3

Demonstrated statistical non-inferiority
Subject Performance Composite with CT

- Incorporates CT Scans, Clinical, Functional, and Safety Outcomes

Population: mITT (n=397)  Week: 24

Augment rate (%), n=260  p = 0.004

Autograft rate (%), n=137

Rate difference (%)  Confidence limit

31  35  0  25  50  75  100
-4.9  3.2

Demonstrated statistical non-inferiority
Subject Performance Composite with CT

- Incorporates CT Scans, Clinical, Functional, and Safety Outcomes

**Population: Treated (n=414)**

- Augment rate (%), n=272
- Autograft rate (%), n=142

**Week: 24**

- $p = 0.004$
- Rate difference (%)
  - Confidence limit: -5.1 to 2.9

Demonstrated statistical non-inferiority
Effectiveness summary

• Augment non-inferior to autograft:
  ➢ Primary endpoint
  ➢ Functional, clinical and radiographic endpoints
    ▪ Week 24 (15 of 17 endpoints statistically significant)
    ▪ Week 36 (11 of 17 endpoints statistically significant)
    ▪ Week 52 (15 of 16 endpoints statistically significant)
  ➢ FDA-requested composite endpoint

• Autograft has significant morbidity for graft harvest site pain

Augment is an effective alternative to Autograft for hindfoot and ankle fusion surgery
Overall summary

• >600 patients, 4 clinical trials including pivotal RCT
• Augment eliminates complications from autograft harvest
• Augment was statistically non-inferior to autograft for the primary endpoint
• Augment was statistically non-inferior to autograft in 16 of 17 endpoints at 52 weeks

Compared to autograft, Augment demonstrated equivalent effectiveness and superior safety
Special Topics

Russell P. Pagano, Ph.D.
Vice President
Clinical & Regulatory Affairs
BioMimetic Therapeutics, Inc.
Special Topics

- Immunogenicity - Dr. Leo Snel
- Statistical topics – Dr. Rafe M.J. Donahue
- Conclusions and Post-Approval plans
Immunogenicity

Leo B. Snel
Sr. Vice President
Research & Development
BioMimetic Therapeutics, Inc.
Determination of immunogenicity using a tiered approach according to FDA guidelines

Detection of all anti-rhPDGF-BB antibodies (ELISA)
- 14% Augment; 4% autograft
- Consistent results across clinical studies
- No issues raised by FDA

Detection of neutralizing antibodies (competitive ligand binding)
- No neutralizing antibodies (Nab) detected
- Assay prospectively agreed on by the FDA
- FDA-recognized alternative to cell-based assays

Neutralizing activity assessed by competitive binding to the PDGF β-receptor
Competitive ligand binding assays are a viable alternative to cell-based assays

“Our findings indicate that competitive ligand binding (CLB) assays are comparable to bioassays for the detection of NAbs, in some cases offering better detection sensitivity, lower variability, and less matrix interference.”

Finco et al., J Pharm Biomed Anal 2011
There were no ADA-positive neutralizing antibodies
Augment has low immunologic potential

- Single local administration of Augment
- Rapid release of rhPDGF-BB from β-TCP
- Local disappearance of more than 80% of the rhPDGF-BB within 24 hours
- Limited systemic exposure due to rapid clearance of rhPDGF-BB from circulation ($T_{1/2} = 2.3$ minutes)
- Human sequence, protein structure intact, no aggregates
- Preclinical studies showed no immunogenicity

No history of neutralizing anti-rhPDGF-BB antibodies from Augment, GEM 21S®, or Regranex®
Statistical Topics

Dr. Rafe M.J. Donahue
Director, Statistics
BioMimetic Therapeutics, Inc.
Statistical topics

- Poolability of patients (FDA Question 1b)
- Missing data, populations, and timepoints (FDA Questions 3d, 3b, 3c)
Primary endpoint shows poolability

- Breslow-Day tests on CT fusion at week 24 showed no significant departures from homogeneity of treatment response when examining:
  - Diagnosis ($p = 0.43$),
  - Joints to be fused ($p = 0.54$),
  - Number of screws used ($p = 0.56$),
  - Amount of graft material used ($p = 0.88$)

Effectiveness data support poolability
Primary endpoint showed non-inferiority treating missing CT scans as failures

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Success (n)</th>
<th>Failure (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augment</td>
<td>159</td>
<td>101</td>
<td>260</td>
</tr>
<tr>
<td>Autograft</td>
<td>85</td>
<td>52</td>
<td>137</td>
</tr>
<tr>
<td>Total</td>
<td>244</td>
<td>153</td>
<td>397</td>
</tr>
</tbody>
</table>

Non-inferiority $p$-value = 0.038

<table>
<thead>
<tr>
<th>Percent of subjects</th>
<th>Success (%)</th>
<th>Failure (%)</th>
<th>Total (%)</th>
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<tbody>
<tr>
<td>Augment</td>
<td>61</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td>Autograft</td>
<td>62</td>
<td>38</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
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<td>39</td>
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Primary endpoint showed non-inferiority treating missing CT scans as failures

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<tr>
<td>Augment</td>
<td>159</td>
<td>86</td>
<td>15</td>
<td>260</td>
</tr>
<tr>
<td>Autograft</td>
<td>85</td>
<td>42</td>
<td>10</td>
<td>137</td>
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<tr>
<td>Total</td>
<td>244</td>
<td>128</td>
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<table>
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<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Autograft</td>
<td>62</td>
<td>31</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
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Primary endpoint showed non-inferiority treating missing CT scans as failures

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</tr>
</thead>
<tbody>
<tr>
<td>Augment</td>
<td>61</td>
<td>33</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Autograft</td>
<td>62</td>
<td>31</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>32</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>
“Tipping-point” analysis

• Agency presents a “tipping-point” analysis of the primary endpoint on page 26 of its executive summary
• Yan, Lee, Li (2009) *J Biopharm Stat*
• Examine all possible imputations of the missing data as success or failure
• 176 unique assignments are possible
• Compute $p$-value at each one
“Tipping-point” analysis results

Tipping point graph (mITT analysis population)

- Blue dots are supportive of non-inferiority ($p < 0.05$)
- Red circles are not supportive of non-inferiority ($p \geq 0.05$).
- Green square = all failures (0.038)
- Purple star = LOCF (0.063)
- Green triangle = assume missing behave like treatment-group peers (0.058)

- Primary analysis $p$-value (0.038) near 0.05 implies that changing the data can easily push the $p$-value over the arbitrary 0.05 threshold.
Deeper “tipping-point” analysis results

• The inference statistic (p-value) is stable across sensible imputation strategies
• The 0.05 threshold decision criterion produces an artificial dichotomy

Tipping point analysis does not tell the whole story
Modeling the odds ratio allows more advanced investigations

- **Augment**: \( p(\text{fusion}) = 0.612 \)
  
  \[
  \text{Odds of fusion} = \frac{0.612}{1 - 0.612} = 1.577
  \]

- **Autograft**: \( p(\text{fusion}) = 0.620 \)
  
  \[
  \text{Odds of fusion} = \frac{0.620}{1 - 0.620} = 1.632
  \]

- **Odds ratio** = \( \frac{\text{Odds Augment}}{\text{Odds autograft}} = \frac{1.577}{1.632} = 0.966 \)
Modeling the odds ratio allows adjustments for imputations

- Odds ratio = 1: same odds
- Odds ratio > 1: numerator larger odds
- Odds ratio < 1: denominator larger odds
- Modeling allows
  - Adjustment for covariates
  - Implementation of a multiple imputations strategy
Odds ratios methodology can be used to evaluate non-inferiority

- Non-inferiority declaration can be made if odds on Augment relative to autograft exceeds 0.50 since
  \[
  \frac{0.75/(1−0.75)}{0.85/(1−0.85)} = 0.53 \approx 0.50
  \]

- Garrett (2003, Stat in Med), Wellek (2005, Biometrical J) both present 0.50 as threshold
- Tu (1998, J Biopharm Stat) uses 0.43
- Senn (2000, J Royal Stat Soc D) uses 0.55
Modeling CT fusion via logistic regression accounts for other sources of variation

• Impute missing data at week 24 several times using
  ✓ Treatment
  ✓ Investigative site
  ✓ Age (< 65 versus ≥ 65)
  ✓ Gender
  ✓ Risk factors
  ✓ Smoking
  ✓ Interactions between age, gender, risk factors, smoking, and treatment

• Examine odds of fusion via logistic regression

• Adjust LCL for variation due to imputation

• Compare LCL to threshold of 0.50
Multiple imputations analysis of primary endpoint shows non-inferiority

<table>
<thead>
<tr>
<th>Week</th>
<th>Population</th>
<th>n</th>
<th>Augment relative to autograft estimate</th>
<th>Lower confidence limit</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>mITT</td>
<td>397</td>
<td>0.65</td>
<td>1.07</td>
<td></td>
</tr>
</tbody>
</table>

Under a multiple imputations model, Augment demonstrates non-inferiority to autograft on the primary endpoint (mITT population, CT fusion, week 24).
Week 24 CT fusion also shows non-inferiority for Treated and ITT populations

<table>
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<td></td>
<td>Treated</td>
<td>414</td>
<td>0.64</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITT</td>
<td>434</td>
<td>0.65</td>
<td>1.08</td>
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</table>

At weeks 24, under a multiple imputations model, Augment demonstrates non-inferiority to autograft on CT fusion for the mITT, Treated, and ITT populations

Non-inferiority can be claimed for all populations
CT fusion at 36 weeks did not show non-inferiority treating missing CT scans as failures

<table>
<thead>
<tr>
<th>Number of subjects</th>
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<tbody>
<tr>
<td>Augment</td>
<td>165</td>
<td>95</td>
<td>260</td>
</tr>
<tr>
<td>Autograft</td>
<td>95</td>
<td>42</td>
<td>137</td>
</tr>
<tr>
<td>Total</td>
<td>260</td>
<td>137</td>
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Non-inferiority p-value = 0.202.

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<td>28</td>
<td>2</td>
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<td>Total</td>
<td>65</td>
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CT fusion at 36 weeks did not show non-inferiority treating missing CT scans as failures

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</table>
Week 36 CT fusion also shows non-inferiority for all populations

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At weeks 24 and 36, under a multiple imputations model, Augment demonstrates non-inferiority to autograft on CT fusion for the mITT, Treated, and ITT populations.
Statistical Conclusions

• Effectiveness data support poolability

• At weeks 24 and 36, under a multiple imputations model, Augment demonstrates non-inferiority to autograft on CT fusion for the mITT, Treated, and ITT populations
Conclusion and Post-Approval

Russell P. Pagano, Ph.D.
Vice President
Clinical & Regulatory Affairs
BioMimetic Therapeutics, Inc.
Augment has a favorable risk/benefit profile

• Augment Bone Graft has a superior safety profile to Autograft
  ➢ No bone graft harvest site complications
  ➢ Lower rate of serious adverse events
  ➢ No evidence of increased cancer risk

• Augment Bone Graft is non-inferior to autograft for:
  ➢ Primary endpoint
  ➢ 16 of 17 secondary endpoints at 52 weeks

Augment Bone Graft is safe and effective in hindfoot and ankle fusion as a bone graft substitute
Addressing FDAs questions to the Panel

• **Qu. 1a and b: Intended use appropriate? Poolability of populations?**
  - Study designed in conjunction with foot and ankle surgeons and FDA
  - Clinical and statistical support for poolability
  - Literature support

• **Qu. 2a: Composite endpoint appropriate?**
  - Additional Subject Performance endpoint based on FDA feedback
  - Subject performance statistically significant for non-inferiority

• **Qu. 2b: Validity of CT versus plain films?**
  - CT more predictive of clinical success than plain films
Addressing FDAs questions to the Panel

• Qu. 3a: Definition of populations?
  - PMA Modified Intent-to-Treat (n=397) = IDE Per Protocol
    - Excludes non-treated patients and major protocol violations
  - PMA Treated (n=414) = IDE Intent-to-Treat
    - Includes all treated patients
  - PMA ITT (n=434) = Not defined in IDE
    - Includes all randomized patients (20 not treated)
Addressing FDAs questions to the Panel

• **Qu. 3b, 3c and 3d: Statistical significance of primary endpoint?**
  - Multiple imputation model demonstrates significance for all populations
  - Multiple imputation model demonstrates significance at 24 and 36 weeks
  - Tipping point investigation is not as complete as the multiple imputation model
Addressing FDAs questions to the Panel

• Qu. 3e, 4a and 4b: Patient Accounting?
  - All adverse events captured and reported per protocol
  - Successful FDA clinical data audits of both BMTI and clinical sites
  - DMC had no AE reporting concern
  - Therapeutic failure is defined per protocol as documented non-union or secondary therapeutic intervention (e.g., bone stimulator).
Addressing FDAs questions to the Panel

• Qu.5: Tumor promotion study needed given existing data?
  - No evidence of carcinogenicity or tumor promotion in either preclinical, clinical and extensive commercial experience
  - Final analysis in Regranex® epidemiology study shows no increase in cancer mortality even with chronic use (FDA advisory was based on an interim analysis)
  - No biological rationale for carcinogenicity
    - Single administration
    - Short local residence time
    - Rapid systemic clearance
  - No additional testing is warranted
Addressing FDAs questions to the Panel

• **Qu. 6: Is there a need for additional repro-tox studies?**
  - Only finding in study was a minor increase in ossification rate
    - Parameters were within control ranges, and
    - No marked or persistent effect
  - Ongoing discussions with FDA on 2\textsuperscript{nd} repro-tox study
  - Consistent with literature, challenge is inability to induce neutralizing antibodies
  - No additional testing is warranted

• **Qu. 7: Immunological response to Augment?**
  - Neutralization tested via a scientifically valid and FDA-agreed upon method
  - Low, transient rate of antibody formation, with no NAb
Addressing FDAs questions to the Panel

• Qu. 8: Is a Post Approval Study necessary?
  - BMTI has agreed to 5-year follow up of pivotal trial patients
  - Prospectively collect and monitor:
    - Serious and device-related events
    - All cancers
    - Arthrodesis stability
Overall Conclusions

Augment™ Bone Graft

• Fully synthetic and safe product
• Eliminates complications from autograft harvest
• No adverse findings regarding immunogenicity or carcinogenicity
• Superior safety to autograft
• Equivalent effectiveness to autograft
• Exhibits a favorable risk to benefit ratio

Augment is a safe and effective alternative to autograft for foot and ankle fusion