INFUSE® Bone Graft

Oral Maxillofacial Bone Grafting Procedures

Dental Products Advisory Panel Committee

Ed Chin, DPh
Group Director, Regulatory Affairs

Medtronic Spinal and Biologics
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Additional Resources

- Leon Assael, DMD
- Philip Boyne, DMD, MS, DSc
- James T. Mellonig, DDS, MS
- Myron Nevins, DDS
- Daniel B. Spagnoli, DDS, MS, PhD
- R. Gilbert Triplett, DDS, PhD
- Pirkka Numnikoski, DDS
- Steve Cook, PhD
- Hal Mathews, MD
- Mildred Christian, PhD
- Scott Kern, MD
- Douglas Hawkins, PhD
- Barbara Boyan, PhD
- Jeffrey Toth, PhD
- Medtronic Staff
- Wyeth Staff
- Alquest Staff
BMP History

- 1965 Urist discovers demineralized bone induces new bone
- 1971 Urist coins the term BMP
- 1977 BMP extracted from bone is inductive
- 1988 First recombinant human BMP produced (Wozney)

“BMP is destined to bring osteogenesis under the control of surgeons…”
Urist MR, J NIH Res, 1997
Recombinant rhBMP-2 Manufacture

Cell Culture

Purification

Formulation
INFUSE® Bone Graft (rhBMP-2/ACS)

- recombinant human Bone Morphogenetic Protein–2 (rhBMP-2)
  - 4.2 or 12 mg vials
  - 1.5 mg/ml concentration

- Absorbable Collagen Sponge (ACS)
  - Carrier for rhBMP-2
  - Type I bovine collagen sponge
  - 1"x 2" or 3"x 4" size
  - Over 20 years of clinical use as Helistat®

- Same product used in OMF pivotal study
INFUSE® Bone Graft (rhBMP-2/ACS)

- Two PMAs proved safety and efficacy:
  - 2002: Single level spinal fusion procedures
  - 2004: Open tibia fractures
  - 437 patients received rhBMP-2/ACS in IDE clinical trials which supported these PMAs

- In addition, over 1,200 patients received INFUSE® Bone Graft or rhBMP-2 with other carriers in clinical studies
Overall Program Aim

INFUSE® Bone Graft

Bone Growth

Patient Therapeutic Benefit

Spine Fusion: 2002

Before

After

Acute Tibia Fracture: 2004

Before

After

Tooth Replacement

Before

After
Clinical Oral Indications

Models Examined

<table>
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<tr>
<th>SINUS AUGMENTATION IDE</th>
<th>EXTRACTION SOCKET IDE</th>
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<tbody>
<tr>
<td>INFUSE® Bone Graft</td>
<td>Dental Implants</td>
</tr>
<tr>
<td></td>
<td>Tooth Replacement</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SINUS AUGMENTATION IDE</th>
<th>EXTRACTION SOCKET IDE</th>
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</tr>
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</table>

\[3 \text{ Studies} \] \[2 \text{ Studies} \]
Oral Maxillofacial IDE Clinical and Pre-Clinical Evidence

Levels of Proof

- General Safety
- Lapine
- Feline
- Caprine
- Canine
- Non-human Primate
- Human Experience

- 32 Studies
- 1 Study
- 2 Studies
- 16 Studies
- 8 Studies
- 5 IDE Studies
"INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations and localized alveolar ridge augmentations for defects associated with extraction sockets."
INFUSE® Bone Graft Program Objectives

- Regenerates bone in these oral indications
- Supports dental implant placement
- Supports long term functional loading
De Novo Bone Induction by Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Maxillary Sinus Floor Augmentation

Philip J. Boyne, DMD, MS, DSc,* Leslie C. Lilly, BSN, RN,†
Robert E. Marx, DDS,‡ Peter K. Moy, DMD,§
Myron Nevins, DDS,|| Daniel B. Spagnoli, PhD, DDS,¶
and R. Gilbert Tripplett, DDS, PhD∥

Purpose: This phase II study was designed to evaluate 2 concentrations of recombinant human bone morphogenetic protein-2 (rhBMP-2) for safety and efficacy in inducing adequate bone for endosseous dental implant in patients requiring staged maxillary sinus floor augmentation.

The AAOMS Journal Editorial Board 2005
Daniel M. Laskin Award
Randomized Study Evaluating Recombinant Human Bone Morphogenetic Protein-2 for Extraction Socket Augmentation

Joseph P. Fiorellini,* T. Howard Howell,* David Cochran,† Jay Malmquist,‡ Leslie C. Lilly,§ Daniel Spagnoli,‖ Joseph Toljanic,¶ Archie Jones,* and Myron Nevins*‡

**Background:** Conventional dentoalveolar osseous reconstruction often involves the use of grafting materials with or without barrier membranes. The purpose of this study was to evaluate the efficacy of bone induction for the placement of dental implants by two concentrations of recombinant human bone morphogenetic protein-2 (rhBMP-2) delivered on a bioabsorbable collagen sponge.

The American Academy of Periodontology Foundation 2005 Tarrson Research Award in Oral Plastic Surgery

**Results:** Assessment of the alveolar bone indicated that patients treated with 1.50 mg/ml rhBMP-2/ACS had significantly greater bone augmentation compared to controls (P ≤0.05). The adequacy of bone for the placement of a dental implant was approximately...
Robert E. Marx, DDS

Professor of Surgery
Chief, Oral and Maxillofacial Surgery
University of Miami
Miller School of Medicine
Clinical Need for Maxillofacial Bone Grafting

- Regenerate bone lost due to disease, trauma or developmental defects:
  - Provide bone support to replace missing teeth
  - Restore structure and function
  - Improve patient’s appearance (esthetics and self image)
Current Standard - Autogenous Bone Graft

- **Advantages**
  - Patient’s own bone
  - Proven effectiveness

- **Disadvantages**
  - Donor site morbidity
  - Extended surgical and anesthesia time
  - Limited availability
Bone Graft Harvest Morbidity

- Hematoma
- Edema
- Erythema
- Exudate
- Infection
- Wound Dehiscence
- Blood loss
- Sensitive and painful scar
Oral Maxillofacial Human Clinical Trial Objectives

- Demonstrate that rhBMP-2/ACS
  - regenerates or grows normal physiologic bone
  - provides bone for dental restorations or placement of dental implants
  - produces stable bone under functional loading

- To demonstrate safety in oral maxillofacial indications
<table>
<thead>
<tr>
<th>Sinus Augmentation</th>
<th>Extraction Socket</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image of Sinus Augmentation" /></td>
<td><img src="image2.png" alt="Image of Extraction Socket" /></td>
</tr>
</tbody>
</table>
Sinus Augmentation Studies
Methods and Definition

- Prospective, multi-center (21), controlled human clinical trials with high level of evidence
  - Pilot: 0.43 mg/ml
  - Dosing (randomized): 0.75 and 1.50 mg/ml
  - Pivotal (randomized): 1.5 mg/ml

- Pooled Data - Dosing and Pivotal Studies (1.5 mg/ml)

- Efficacy Endpoint
  - Implant-borne restoration after 6 months of functional loading
  - Target Success Rate - Greater than 73%

- Safety Endpoints
Sinus Augmentation Studies
Primary Objectives

- **Effectiveness**
  - Induce bone to successfully support implant-borne restoration after 6 months of functional loading

- **Safety**
  - Evaluate the safety of rhBMP-2/ACS and autogenous bone graft in two-stage maxillary sinus floor augmentation procedures
Sinus Augmentation Studies
Secondary Objectives

- Evaluate new bone radiographically
- Evaluate histology of the new bone
- Functional loading: INFUSE® Bone Graft compared to autogenous bone graft
Sinus Augmentation Studies

Baseline

rhBMP-2/ACS Graft

Bone Formation

Dental Implant and Osseointegration

T=0 4-6 mos 6-12 mos 12-24 mos 24-36 mos

CT Scan

CT Scan

Biopsy

Periapical X-ray

CT Scan

Periapical X-ray

Safety Evaluation Throughout the Study
Study Design Schematic
Sinus Augmentation Dosing Study
N=48

Cohort 1 - 0.75 mg/mL

Acute Safety Established

Cohort 2 - 1.5 mg/mL

randomization

rhBMP-2/ACS (16 patients)

Bone Graft (8 patients)

randomization

rhBMP-2/ACS (16 patients)

Bone Graft (8 patients)
Study Design Schematic
Sinus Augmentation Pivotal Study
N=160

Randomization

Cohort - 1.5 mg/mL

RhBMP-2/ACS (80 patients)
Bone Graft (80 patients)
Prospective, Controlled Sinus Augmentation IDE Studies (N=220)

- Sinus Augmentation
  - Pivotal Study
    - rhBMP-2/ACS (1.5 mg/ml) 82
    - Bone Graft 78
  - Dosing Study
    - rhBMP-2/ACS (1.5 mg/ml) 17
    - Bone Graft 13
    - rhBMP-2/ACS (0.75 mg/ml) 18
  - Pilot Study
    - rhBMP-2/ACS (0.43 mg/ml) 12
CT Scan of *de novo* Bone Induced by rhBMP-2/ACS

Pre-op

16-weeks Post rhBMP-2/ACS Placement
CT Scan of *de novo* Bone

**Pre-Op**
*(3.9 mm Baseline)*

**6 months Post-Op**
*(16.0 mm)*
Sinus Augmentation Bone Growth
Treated with rhBMP-2/ACS 1.5mg/ml (N=98)

Bone Height Change by Subject

mean ± SD = 8.2 ± 3.8 mm
Primary Objective
INFUSE® Bone Graft
Functional Loading Success

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Sinus Augmentation Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental implants without augmentation</td>
<td>82.8% (82/99)</td>
</tr>
<tr>
<td>Received prosthesis (functionally loaded)</td>
<td>79.8% (79/99)</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td><em><em>79.6%</em> (78/98)</em>*</td>
</tr>
</tbody>
</table>

*Target Success Rate 73%
Secondary Objective
Functional Loading by Patient

Bone Graft
rhBMP-2/ ACS
(1.50 mg/ ml)

<table>
<thead>
<tr>
<th>DIP w/o add’tl augmentation</th>
<th>Received prosthesis</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Value</td>
<td>0.0683</td>
<td>0.1117</td>
<td>0.0667</td>
<td>0.0286</td>
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Secondary Objective
Functional Loading by Implant

<table>
<thead>
<tr>
<th></th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
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<tbody>
<tr>
<td>Received prosthesis</td>
<td></td>
<td></td>
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<td>6 months</td>
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<td>12 months</td>
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<td>18 months</td>
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<td>24 months</td>
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P Value

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<tr>
<th></th>
<th>0.8218</th>
<th>0.6645</th>
<th>0.4579</th>
<th>0.3643</th>
<th>0.2112</th>
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</thead>
<tbody>
<tr>
<td>Bone Graft</td>
<td>rhBMP-2/ ACS (1.50 mg/ ml)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Bone Density from CT Scan

Sinus Augmentation Dosing Study

Density at 4 months Post Grafting

Density at 6 months Post Prosthesis

Density (mg/cc)

Bone Graft 1.50 mg/ml rhBMP-2/ACS

Bone Graft 1.50 mg/ml rhBMP-2/ACS
Sinus Augmentation Histology Demonstrates Normal Physiologic Bone

- Longitudinal section core biopsy
- Samples taken at time of dental implant placement (6-12 months)
- Residual Bone Graft fragments were included in the quantitative histomorphometric measurements

rhBMP-2/ACS

10x Normal Trabecular Bone

Induced bone

Native Bone
Sinus Augmentation Studies
Bone Quality Supports Dental Implant

Bone Graft

- Similar Trabecular Volume and Thickness
- Both with 90-95% lamellar bone with small amounts of immature bone
- Residual lamellar bone fragments in Bone Graft group may have accounted for statistical differences
- Differences did not affect clinical outcomes
Sinus Augmentation De Novo Bone Formation

- **Labeling**
  - Yellow - 10 days post-op (tetracycline hydrochloride)
  - Orange - 3 months post-op (democlocycline)

- **rhBMP-2/ACS** demonstrated substantial, rapid *de novo* bone formation

- Bone Graft group demonstrated variable *de novo* bone formation
Histology Summary

“…autogenous bone and rhBMP-2/ACS grafted sites resulted in significant formation of new trabecular bone comparable in density and structure to the host site. The bone that formed was biologically and structurally normal…”

– Dr. Stephen Cook, Independent Histology Reviewer, Tulane University
Sinus Augmentation
Clinical Effectiveness Summary

INFUSE® Bone Graft:

- **Combined Study Result:** 79.6% Success Rate (exceeded target success rate)
- **Induced** *de novo* bone formation
- **Exceeded** primary outcome objective
- **Clinically effective for:**
  - Generating bone in the maxillary sinus allowing for
  - Dental restoration
David L. Cochran, DDS, PhD, MMSc

Chairman
Department of Periodontics
UT Health Sciences Center
at San Antonio
Extraction Socket Augmentation Clinical Need

Goal: Restore ridge width and preserve height to replace missing teeth
Extraction Socket Augmentation Methods and Definition

- Prospective, randomized, multi-center (8), double-blinded controlled 80-patient human clinical trial providing high level of evidence
- Buccal wall defect (~ 50% of the extraction socket depth)
- Effectiveness endpoint: adequate alveolar bone formation for implant placement
- Safety Endpoints
Extraction Socket Augmentation Studies

- Baseline
- rhBMP-2/ACS Graft
- Bone Formation
- Biopsy
- Dental Implant and Osseointegration
- Functional Loading

Timepoints:
- T=0
- 4 mos
- ~ 8 mos
- ~ 16 mos
- 18-36 mos

Evaluation:
- CT Scan
- Biopsy
- Periapical X-ray
- CT Scan

Safety Evaluation Throughout the Study
Study Design Schematic
Extraction Socket Study
N=80

Preceded by Pilot Study at 0.43 mg/ml

Acute Safety Established

Cohort 1 - 0.75 mg/mL
- rhBMP-2 (20)
- ACS Alone (10)
- Unfilled (10)

Cohort 2 - 1.5 mg/mL
- rhBMP-2 (20)
- ACS Alone (10)
- Unfilled (10)
Prospective, Controlled Extraction Socket IDE Studies

- Extraction Socket (N=92)
  - Dosing Study (80)
    - rhBMP-2/ACS (1.5 mg/ml) 21
    - Unfilled Control Treatment 20
    - ACS Alone (0.0 mg/ml) 17
    - rhBMP-2/ACS (0.75 mg/ml) 22
  - Pilot Study (12)
    - rhBMP-2/ACS (0.43 mg/ml) 12

rhBMP-2/ACS Effectiveness
N= 21
Extraction Socket Augmentation

Baseline

16-weeks Post rhBMP-2/ACS Placement (1.5 mg/ml)
INFUSE® Bone Graft Patient

Baseline

16-weeks Post rhBMP-2/ACS Placement (1.5 mg/ml)
Patient with **Unfilled Defect**

Baseline

16-weeks Post Extraction
Clinically Significant Results vs. Unfilled

Baseline

Unfilled Defect/Standard of Care

Unfilled defect at time of extraction

INFUSE® defect at time of placement

INFUSE® Bone Graft

16-weeks Post

Unfilled defect 16 weeks post extraction

INFUSE® defect 16 weeks post placement

De Novo Bone forms in INFUSE group
Patient Therapeutic Benefit

- Demonstrated

- Dental implant placed in *de novo* bone.
Extraction Socket Augmentation
CT Scan Measurement Methodology

Pre-op 16-week post rhBMP-2/ACS

Alveolar ridge height = D1 + D2
Width: perpendicular to line D2 at ¼, ½, and ¾
Height Change (Loss) at 4 months

- Unfilled: -1.17
- 0.00 mg/ml rhBMP-2/ACS: -1.00
- 1.5 mg/ml rhBMP-2/ACS: -0.02

Significance levels:
- Unfilled vs. 0.00 mg/ml rhBMP-2/ACS: p = 0.0070
- Unfilled vs. 1.5 mg/ml rhBMP-2/ACS: p = 0.0270
Width Change at $\frac{1}{4}$ at 4 Months

Mean Width Change at $\frac{1}{4}$

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean Width Change ± Standard Error (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfilled</td>
<td>0.57 ± 0.02</td>
</tr>
<tr>
<td>0.00 mg/ml rhBMP-2/ACS</td>
<td>0.82 ± 0.03</td>
</tr>
<tr>
<td>1.5 mg/ml rhBMP-2/ACS</td>
<td>3.27 ± 0.10</td>
</tr>
</tbody>
</table>

Significance levels:
- Unfilled vs. 0.00 mg/ml rhBMP-2/ACS: $p = 0.0002$
- Unfilled vs. 1.5 mg/ml rhBMP-2/ACS: $p = 0.0010$
Width Change at 1/2 at 4 Months

Mean Width Change at 1/2

- Unfilled
- 0.00 mg/ml rhBMP-2/ACS
- 1.5 mg/ml rhBMP-2/ACS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean Width Change ± Standard Error (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfilled</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>0.00 mg/ml rhBMP-2</td>
<td>1.62 ± 1.62</td>
</tr>
<tr>
<td>1.5 mg/ml rhBMP-2</td>
<td>3.97 ± 3.97</td>
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P-values:
- 0.0009
- 0.0026
Greater bone growth is associated with greater implant placement.
# Functional Loading Endpoint, By Patient

<table>
<thead>
<tr>
<th>Time Post Functional Loading</th>
<th>Unfilled</th>
<th>ACS Only (0.0 mg/ml)</th>
<th>INFUSE® Bone Graft</th>
<th>P Value Unfilled / ACS Only vs. INFUSE® Bone Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental Implant Placement</td>
<td>47% (9/19)</td>
<td>59% (10/17)</td>
<td>86% (18/21)</td>
<td>0.0171 / 0.0780</td>
</tr>
<tr>
<td>Received prosthesis</td>
<td>41% (7/17)</td>
<td>56% (9/16)</td>
<td>76% (16/21)</td>
<td>0.0458 / 0.2913</td>
</tr>
<tr>
<td>6 month</td>
<td>38% (6/16)</td>
<td>50% (7/14)</td>
<td>74% (14/19)</td>
<td>0.0442 / 0.2728</td>
</tr>
<tr>
<td>12 month</td>
<td>38% (6/16)</td>
<td>50% (7/14)</td>
<td>72% (13/18)</td>
<td>0.0824 / 0.2769</td>
</tr>
<tr>
<td>18 month</td>
<td>38% (6/16)</td>
<td>50% (7/14)</td>
<td>69% (11/16)</td>
<td>0.1556 / 0.4572</td>
</tr>
<tr>
<td>24 month</td>
<td>38% (6/16)</td>
<td>50% (7/14)</td>
<td>67% (10/15)</td>
<td>0.1556 / 0.4621</td>
</tr>
</tbody>
</table>

**INFUSE® Bone Graft is more successful.**
Dental Implant Placement w/o Augmentation: INFUSE® Bone Graft vs. ACS only vs. Unfilled by Patient
6 month Functional Loading: INFUSE® Bone Graft Compared with ACS only and Unfilled by Patient

Unfilled (N=19) | ACS Only (0.0 mg/ml) (N=17) | INFUSE® Bone Graft (N=21)
---|---|---
38% | 50% | 74%
Same Histology for Both Indications

Extraction Socket

• INFUSE® BONE GRAFT
• Samples taken approx. 7 months post-op
• Similar Qualitative Parameters including Trabecular Volume, Thickness, and Number

Sinus Augmentation
Extraction Socket Representative Histology

rhBMP-2/ACS induced bone

- Vascular marrow space
- Lamellar and immature bone
- Similar to the bone formed in the sinus studies

H & E stain, 10 X magnification
Summary of Clinical Effectiveness: Extraction Socket Augmentation

INFUSE® Bone Graft:

- Induced *de novo* bone formation
- Is clinically effective following tooth extraction for:
  - Preservation of the alveolar ridge and
  - Dental restoration
SAFETY OF INFUSE® Bone Graft
Safety Profile

- Two PMA approvals
  - More than 300,000 kits distributed worldwide
  - 437 patients received rhBMP-2/ACS in IDE clinical trials which supported two PMAs

- More Level I clinical evidence than any other bone grafting agent
  - 1,070 patients studied in FDA clinical trials
Prospective, Controlled IDE Studies (N=312)

Safety Data

- **Sinus Augmentation (N=220)**
  - rhBMP-2/ACS (1.5 mg/ml) 99
  - Bone Graft 91
  - rhBMP-2/ACS (0.43; 0.75 mg/ml) 30

- **Extraction Socket (N=92)**
  - rhBMP-2/ACS (1.5 mg/ml) 21
  - Unfilled Control Treatment 20
  - rhBMP-2/ACS (0.43; 0.75 mg/ml) 34
  - ACS Alone (0.0mg/ml) 17

Safety:
All rhBMP-2/ACS N= 184
1.5 mg/ml
rhBMP-2/ACS N=120
## Adverse Events > 10% Patients

<table>
<thead>
<tr>
<th>COSTART TERM</th>
<th>Bone Graft (n=91)</th>
<th>INFUSE® Bone Graft (n=120)</th>
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</thead>
<tbody>
<tr>
<td>EDEMA</td>
<td>37.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>FACE EDEMA</td>
<td>57.1%</td>
<td>67.5%</td>
</tr>
<tr>
<td>INFECTION</td>
<td>42.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>PAIN</td>
<td>50.5%</td>
<td>21.7%</td>
</tr>
<tr>
<td>ORAL EDEMA</td>
<td>64.8%</td>
<td>67.5%</td>
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<tr>
<td>ORAL ERYTHEMA</td>
<td>61.5%</td>
<td>47.5%</td>
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<tr>
<td>MOUTH PAIN</td>
<td>83.5%</td>
<td>85.0%</td>
</tr>
<tr>
<td>ECCHYMOsis</td>
<td>23.1%</td>
<td>15.8%</td>
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## Adverse Events > 10% Patients (cont.)

<table>
<thead>
<tr>
<th>COSTART TERM</th>
<th>Bone Graft (n=91)</th>
<th>INFUSE® Bone Graft (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERGLYCEMIA</td>
<td>16.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>ARTHRALGIA</td>
<td>26.4%</td>
<td>11.7%</td>
</tr>
<tr>
<td>BONE DISORDER</td>
<td>12.1%</td>
<td>11.7%</td>
</tr>
<tr>
<td>ABNORMAL GAIT</td>
<td>40.7%</td>
<td>0</td>
</tr>
<tr>
<td>HYPESTHESIA</td>
<td>16.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>SINUSITIS</td>
<td>16.5%</td>
<td>9.2%</td>
</tr>
<tr>
<td>ERYTHEMA</td>
<td>37.4%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
Adverse Events > 10% Patients (P<0.05)
### Adverse Event Summary

#### INFUSE® Bone Graft and Bone Graft

<table>
<thead>
<tr>
<th></th>
<th>Sinus Augmentation</th>
<th>Extraction Socket Augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone Graft N=91</td>
<td>rhBMP-2/ACS 1.5 mg/ml N=99</td>
</tr>
<tr>
<td>At Least One Event</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>rhBMP-2/ACS Procedure Related</td>
<td>Not Applicable</td>
<td>17%</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Grade 3 or 4 rhBMP-2/ACS Procedure Related</td>
<td>Not Applicable</td>
<td>0</td>
</tr>
</tbody>
</table>

One death unrelated to INFUSE® Bone Graft at 3 years post-implantation
rhBMP-2 and Collagen Antibodies

- Immune response evaluated in 184 rhBMP-2/ACS patients and 91 bone graft patients

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Bone Graft</th>
<th>rhBMP-2/ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-rhBMP-2</td>
<td>0.0%</td>
<td>2.2%*</td>
</tr>
<tr>
<td>Anti-bovine Type I collagen</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Anti-human Type I collagen</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Low titers, transient effect, clinically insignificant
# Bone Graft Patients: Harvest Site Pain and Morbidity

**N=91**

<table>
<thead>
<tr>
<th>Harvest Site</th>
<th>Conditions</th>
<th>2 days</th>
<th>10 days</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iliac Crest</strong></td>
<td>Pain</td>
<td>89.9%</td>
<td>44.4%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Sensory Loss</td>
<td>0%</td>
<td>0%</td>
<td>11.1%</td>
</tr>
<tr>
<td></td>
<td>Gait Disturbance</td>
<td>55.6%</td>
<td>44.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td><strong>Tibial Plateau</strong></td>
<td>Pain</td>
<td>66.7%</td>
<td>51.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>Sensory Loss</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Gait Disturbance</td>
<td>72.7%</td>
<td>45.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td><strong>Intra-Oral Bone</strong></td>
<td>Pain</td>
<td>58.6%</td>
<td>27.6%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Sensory Loss</td>
<td>27.6%</td>
<td>34.5%</td>
<td>17.2%</td>
</tr>
<tr>
<td></td>
<td>Gait Disturbance</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Timeline of Harvest Site Adverse Events

#### Bone Graft

No harvest site for INFUSE® Bone Graft patients!
Safety Summary

- Established safety profile
- Thoroughly evaluated in these RCT
- Significantly fewer adverse events than bone graft
- Eliminates bone harvesting morbidity
Conclusions

Ed Chin, DPh
Group Director, Regulatory Affairs
Medtronic Spinal and Biologics
"INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations and localized alveolar ridge augmentations for defects associated with extraction sockets."
Sinus Augmentation

Extraction Socket Augmentation

Implant and Tooth Restoration
Sinus Augmentation

Following INFUSE® Bone Graft, multiple implants, and prosthetic teeth replacement

Large bone loss on maxillary ridge
Extraction Socket Augmentation

Following INFUSE® Bone Graft, dental implants, and prosthetic teeth replacement

Non restorable teeth
SUMMARY

- INFUSE induced new bone allowing for dental restoration in 2 separate IDE evaluations
- INFUSE is Safe and Effective for
  - Sinus Augmentation and
  - Extraction Socket
- INFUSE eliminates the need to harvest autogenous bone graft in oral maxillofacial procedures
INFUSE® Bone Graft

SAFE and EFFECTIVE
Thank You