

**PMA-P100006**  
***Augment™ Bone Graft***  
**BioMimetic Therapeutics, Inc.**

**FDA Presenters:**

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# Overview

- ***Introduction***
- **Pre-clinical Testing**
- **IDE Clinical Study**
- **Statistical Analyses**
- **Post-Approval Study**
- **Panel Questions**
- **FDA Summation**

# Rationale for Presentation to the Panel

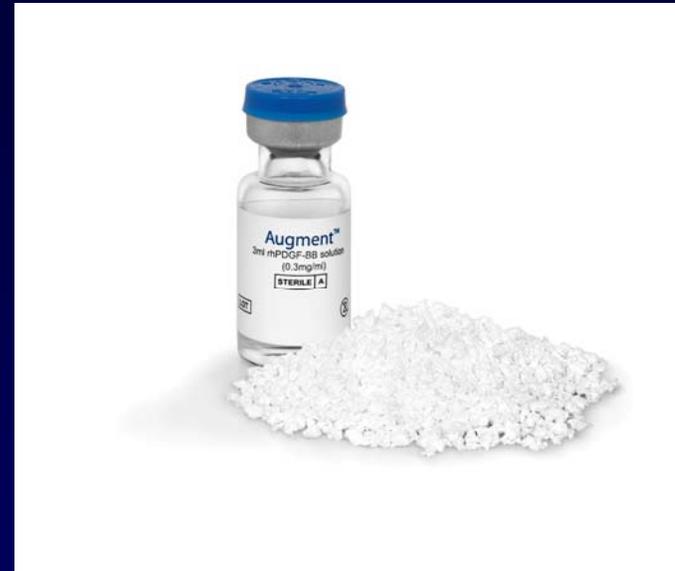
- **First rhPDGF-BB bone graft product for ankle fusion treatment of OA, RA and Post-traumatic injury**
- **Specific questions regarding possible carcinogenicity/tumor promotion, toxicity and immunologic concerns**

# Indications for Use

“as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions.”

# Product Description

- rhPDGF-BB
- $\beta$ -TCP
- Used in conjunction with Supplemental screws or pins



# Product Description

## rhPDGF-BB

- Role in chemo-attractant and mitogen for cells involved in wound healing
- Role in promotion of angiogenesis at the site of healing
- Supplied as 1.5 ml or 3ml vials of 0.3 mg/ml rhPDGF-BB of in 20mM USP sodium acetate buffer solution

## $\beta$ – Tricalcium Phosphate

- Osteoconductive scaffold material (1.5, 3, 6 and 9cc) (1000-2000 microns in diameter)
- rhPDGF-BB and  $\beta$  -TCP used in a 1 to 1 ratio

# Marketing History

- In the US, Augment studied in an IDE study, approved in Canada in 2009
- GEM 21S - rhPDGF-BB and  $\beta$ -TCP (approved PMA to treat periodontal defects)
- (Regranex) – rhPDGF-BB approved in a BLA for diabetic foot ulcers

# Pre-Clinical Testing

- **Biocompatibility**
  - Cytotoxicity
  - Sensitization
  - Genotoxicity
  - Implantation
  - Chronic toxicity
  - Carcinogenicity
  - Reproductive / Developmental

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# Pre-clinical Studies

Peter L. Hudson, Ph.D.

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Office of Device Evaluation

Center for Devices and Radiological  
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Food and Drug Administration



# Pre-clinical evaluations

- Product is intended as a permanent implant having contact with bone and tissue
- ISO 10993-1 recommends:
  - Cytotoxicity
  - Sensitization
  - Genotoxicity
  - Implantation
  - Chronic toxicity
  - Carcinogenicity

# **Pre-clinical Safety Evaluations Reproductive Toxicology/Teratology**

- **Permanent contact and/or potential effect on reproductive physiology – reproductive toxicology/teratology evaluations should be conducted**

# Pre-clinical Safety Evaluations Results

- Cytotoxicity
- Systemic toxicity
- Irritation
- Implantation
- Genotoxicity
- Sensitization

# **Pre-clinical Safety Evaluations**

## **Toxicity: I.M., I.V. and Implantation**

### **Assessment**

#### **Additional toxicity evaluations**

- **Bone responses to intramuscular injections of rhPDGF-BB for 2 and 8 weeks**
- **Evaluations of the acute toxicity of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) administered intravenously in a rat model**
- **Bone regeneration using the rat calvarial defect model (4 and 8 weeks)**

# Pre-clinical Safety Evaluations

## Toxicity: I.M., I.V. and Implantation

### Assessment

- **Bone responses to intramuscular injections of rhPDGF-BB for 2 and 8 weeks**
  - 10, 30 and 100  $\mu\text{g/mL}$  injected every other day for 2 weeks
  - Clinically relevant dose: 100  $\mu\text{g}$  translates to 160  $\mu\text{g/kg}$  or  $\sim 4$  times the maximum human dose (2700  $\mu\text{g}/79$  kg human or 39  $\mu\text{g/kg}$ )
  - Evaluations at 2 and 8 weeks

# Pre-clinical Safety Evaluations Toxicity: I.M., I.V. and Implantation Assessment

## Additional toxicity evaluations

- Bone responses to intramuscular injections of rhPDGF-BB for 2 and 8 weeks
- **Evaluations of the acute toxicity of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) administered intravenously in a rat model**
- **Bone regeneration using the rat calvarial defect model (4 and 8 weeks)**

# Animal Model Evaluations

## Proof-of-concept models

- Partial arthrodesis of the carpus in dogs
- Enhanced fracture healing in the geriatric-osteoporotic rat with rhPDGF-BB and  $\beta$ -TCP
- Enhanced fracture healing in a diabetic rat model with rhPDGF-BB treatment
- Periodontal regeneration with PDGF treated osteoconductive scaffolds



# Pre-clinical Evaluations

## Matrix/protein interactions

rhPDGF-BB released from  $\beta$ -TCP matrix

Time                      ELISA detected protein (% released)

10'	92-94
20'	101-103
30'	-----
40'	-----

# Pre-clinical Evaluations

## Matrix/protein Interactions

- Pharmacokinetics – radiolabeled rhPDGF-BB as implanted within a rat calvarial bone defect

<u>Time (hours)</u>	<u>Mean % rhPDGF-BB remaining</u>
0	100
1	39.3
24	18.3
48	13
72	11.3

# Adsorption, Distribution, Metabolism and Excretion (ADME)

- ADME evaluations
  - I.V. injection assessment with radio-labeled rhPDGF
  - Intramuscular implantation of radio-labeled rhPDGF combined with  $\beta$ -TCP
- While the evaluations provide information regarding the relative clearance rates of injected or implanted PDGF, they only approximate how the product will be implanted in ankle fusion procedures.

# **Pre-clinical Studies**

## **Carcinogenicity/Transformed Cell Promoter**

- **PDGF is a basic polypeptide growth factor that is understood to be a multi-functional molecule that regulates DNA synthesis and cell division and induces biological effects that are implicated in tissue repair, atherosclerosis, inflammatory responses, and neoplastic diseases.**
- **Due to its' cell-stimulative and differentiative properties, PDGF raises concern as a potential stimulant, or promoter of transformed cells.**

# **Pre-clinical studies**

## **Chronic toxicity/Carcinogenicity**

- **1 year rodent femur onlay animal model evaluation**
  - **Oppenheimer effect – rodents**
  - **Reasonable approximation to how the product is intended to be used**
  - **Not a true carcinogenicity evaluation**
  - **Used in evaluation of rhBMP-2 for the same concerns**

# **Rodent Femur Onlay Model**

## **Chronic toxicity/Carcinogenicity**

- **Study approximated standard carcinogenicity evaluations in terms of animal number and histopathologic assessments.**
- **There were 3 treatment groups: Control, test article and sham surgery. Each cohort contained 50 male and 50 female rodents.**
- **Assessments were done at 30, 180 and 365 days.**

# Rodent Femur Onlay Model Results

- Findings
  - On day 30 minimal foreign body granulomas were at the implant site within the skeletal muscle in a majority of animals across all treatment groups.
  - Minimal to mild granulation tissue was found in the control and test article implantation sites but not in the sham treatment implantation sites on days 30 and 180
  - There was 1 adenocarcinoma of the breast in a test article-treated animal at 180 days. No test article-related malignancies were determined throughout the study.

# **Additional Studies**

## **Transformed Cell Promotion**

- In review of other growth factors, concerns regarding the potential for the protein to promote transformed cells in the patient were raised. A series of *in vitro* *in vivo* experiments were identified for further investigation:
  - Cell proliferation studies – transformed cell lines
  - Receptor expression evaluation of the set of transformed cell lines
  - Implantation of responding cell lines into nude mice followed by stimulation with injected recombinantly-produced growth factors

# Chemical Induced Carcinogenesis Transformed Cell Promotion Assessment

- **Rat Liver Foci Bioassay**
  - Foci of altered hepatocytes (FAH) or preneoplastic lesions are formed due to chemical carcinogenesis
  - Does exposure to PDGF promote cellular transformation?
  - These studies are pending – you will be asked to discuss this evaluation and whether it should be provided as pre-market information.

27— PDGF/Regranex epidemiology evaluation



# Comparative Amounts of PDGF Regranex and Augment Bone Graft

Product	Typical, one time amount	Total potential maximum amount
Regranex	4.5-6.9 mg	98 mg
Augment Bone Graft	0.45-2.7 mg	2.7 mg

# Pre-clinical Studies

## Reproductive Toxicity/Teratology

- **Recombinant Human Platelet-derived Growth Factor-BB (rhPDGF-BB): An Intravenous Injection Teratology Study in the Rat**

# Pre-clinical Studies

## Reproductive Toxicity/Teratology

- **Results**
  - Reduction in incidence of fetuses/litters with complete ossification of the interparietal and hyoid bones as found in the 400  $\mu\text{g}/\text{kg}/\text{day}$  group.
  - Increase in the incidence of fetuses/litters with rudimentary 14th ribs was also observed for the 400  $\mu\text{g}/\text{kg}/\text{day}$  group.

# Pre-clinical Studies

## Reproductive Toxicity/Teratology

- **Immuno-knock-out experimental paradigm**
  - Patients exposed to rhPDGF-BB could form antibodies to the protein
  - The antibodies could cross the placental barrier in pregnant women
  - If the antibodies are of a neutralizing character, they could effectively knock out PDGF during embryogenesis
  - You will be asked whether you believe this information should be obtained as pre-market data.

**END**



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**AUGMENT™ Bone Graft**  
**BioMimetic, Inc.**

**FDA Presenter:**  
**Nona T. Colburn, M.D.**  
**Medical Officer**

# Study Purpose

- Evaluate safety and effectiveness of Augment Bone Graft
- Evaluate the ability to maintain successful ankle and hindfoot fusion in patients with bony defects
- Secondary assessments of clinical outcomes
- Demonstrate non-inferiority compared to control (autogenous bone graft)

# Study Design

- **Multi-center, prospective, randomized, concurrently controlled, partially blinded study**
- **435 randomized patients (2:1)**
- **38 clinical centers**
- **285 Augment rh-PDGF**
- **149 Controls**

# Evaluation Schedule

- **Preop (within 21 days of surgery),**
- **Postop at 7-21 days and at 6, 9, 12, 16, 24, 36, and 52 weeks**
- **Safety Dataset**
  - **Adverse events**
  - **Primary endpoint: graft harvest site pain scores**
  - **Secondary endpoints: operating room time and surgical wound infection rate**
- **Success determined at 6 months**
- **Effectiveness Dataset**
  - **Radiographic outcomes measures alone**
  - **Clinical outcomes measures were NOT considered as part of the product's primary effectiveness**

# Key Inclusion Criteria

- A bone defect in the hindfoot or ankle requiring open surgical fusion with supplemental bone graft/substitute of one of the following areas:
  - Ankle (tibiotalar joint)
  - Subtalar
  - Calcaneocuboid
  - Talonavicular
  - Triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints)
  - Double arthrodesis (talonavicular and calcaneocuboid joints)

Specific panel question regarding the heterogeneity of the intended patient population

# Key Inclusion Criteria

- **Fusion site rigidly stabilized with no more than 3 screws or pins across the site**
  - **Or more than 3 kits (9 cc) of graft material**
- **Supplemental pins and screws external to the fusion site used as needed**
- **Plate fixation was excluded**
- **No predefined measures of pain and function or baseline CT**

# Key Exclusion Criteria

- **Medications that interfere with fusion**
  - Steroids
  - NSAIDS during the first 6 weeks
- **Endocrine or metabolic disorder known to affect osteogenesis, but NOT**
  - Diabetes
    - Excluded only those not sensitive to the 5.07 Semmes-Weinstein monofilament (loss of protective sensation)
  - Primary osteoporosis
- **Presence of untreated malignancy at the surgical site or undergoing chemo or radiation therapy**
- **Autoimmune or autoinflammatory diseases NOT excluded**

# Patient Accounting

	Patient Accounting (ITT)			
	24 weeks		52 weeks	
	Augment	Control	Augment	Control
Number of Patients Enrolled	285	149	285	149
Theoretical Follow-up	243	133	243	133
Cumulative Deaths	0	0	0	0
Failures (Cumulative) <sup>1</sup>	0 (25)	0 (12)	0 (25)	0 (12)
Expected	243	133	243	133
Actual <sup>A</sup>	242	132	243	133
Percent Follow-up (%) <sup>A</sup>	100	99	100	100
Actual <sup>B</sup>	1	1	0	0
Percent Follow-up (%) <sup>B</sup>	0	1	0	0

# Patient Demographics

- **Subjects similar with respect to demographic variables except**
  - **Obesity: Greater in Controls (52% vs. 46%)**
  - **Gender: More females in Augment (52% vs. 43%)**
  - **Age of injury: Control group (315 weeks) higher than Augment (261 weeks)**
    - **Large number of missing injury ages**
  - **No pattern to support an effect of treatment differences by sensitivity analyses**

# Surgical Information

- Type of anesthesia, procedure time, and type of fusion used were similar between treatment and controls
- Areas of control bone graft harvest include
  - proximal tibia (50.4%)
  - distal tibia (16.1%)
  - calcaneus (13.9%)
  - iliac crest (11.7%)
  - “Other” (7.9%): fibula (5), medial malleolus (2), talus (2), and “local bone” (2)
  - 88.3% of the harvest sites associated with low or no pain
- Amount of graft material used similar between the two groups except in triple arthrodesis (> in controls)

# Safety

# Defining Adverse Events

- FDA requires that all adverse events, regardless of whether they are device (product)-related, procedure or operation-related or not, are reported as part of a composite endpoint to define device (product) safety
- “Any adverse event (clinical sign, symptom, or disease) temporally associated with the use of this investigational device, whether or not considered related to the investigational device, shall be documented in the adverse event (AE) CRF, except those events that are considered to be normal sequelae to the surgical procedure”.

# Not Reported As Adverse Events

- **Clinical indicators used to assess healing:**
  - **Abnormal swelling or warmth by palpation at the fusion site**
  - **Tenderness to palpation at the fusion site**
  - **Motion at the fusion site (i.e., no loss of reduction)**
  - **Pain with weight-bearing at the fusion site**
- **“Presence of any of the above underlying events are considered to be surgical complications and will not be documented as adverse events on the CRF”**
- **“As non-union is a known complication with any fusion procedure, it is expected that some patients will develop non-unions in this study, and these events will be reported as “therapeutic failures”, and not documented as adverse events**
- **Exclusion of such Pre-defined events as adverse interferes with the ability to understand a product’s safety profile and to determine product relatedness**

# Sponsor Defined Adverse Events

- Pre-treatment signs and symptoms
- “Treatment Emergent Adverse Events” (TEAEs) defined as AEs reported on or after the day of surgery
- “Complications” defined as complications associated with surgical procedures, a subset of the TEAEs
- “Serious Complications”
- Infections
- Related TEAEs
- Serious TEAEs

Specific panel question regarding the use of the sponsor defined methods of collecting and reporting adverse events

# Safety Evaluations

- Assessed as a separate subgroup analyses of all patients randomized and treated
- NOT part of the primary study endpoint for effectiveness
- Primary safety endpoint was graft harvest site pain scores in controls
- Secondary safety endpoints were operating room time and surgical wound infection rate
- Secondary surgeries (“Therapeutic Failures”)
- Antibody test results were NOT considered as part of the safety evaluation

# Summary of All Adverse Events

	Augment		Control	
	Patients (%)	Events	Patients (%)	Events
All TEAEs	212 (77.9)	657	105 (73.9)	316
Product Related AEs	1 (0.4)	1	0 (0.0)	0
Serious TEAEs	28 (10.0)	45	21 (14.8)	29
Product Related SAEs	0 (0.0)	0	0 (0.0)	0
Neoplasms/Cancer	5 (1.8)	5	2 (1.4)	2
Death	1 (0.4)	1	0 (0.0)	0
Infections by SOC	61 (22.4%)	86	28 (19.7%)	35

Note: Totals are for events to 52 weeks

# **Regranex (Becaplermin) and Cancer Association**

- **Same rh-PDGF molecule as Augment and implicated in an increase in mortality from pre-existing cancer**
- **Safety signal detected first in a post-market combined clinical trials study (Study PDGF-DBFT-0101)**
  - **Only 25% enrollment in this follow-up study**
  - **Relative Risk of developing a neoplasm was 2.7 (95% confidence interval of 0.6, 12.8)**
- **Phase 4 epidemiological study**
  - **1622 Regranex users 1998 to 2003**
  - **2809 “No Exposure” comparators matched by propensity scores algorithm**
  - **Average follow up approximately 20 months**
  - **NDI used to identify those who died by 12/31/2003**
  - **4 iterations of the original study, all reviewed by FDA**

# **Regranex (Becaplermin)**

## **Black Box Warning**

- **Reported mortality incidence from all cancers in patients who received 3 or more tubes**
  - 3.9 per 1000 person years with Regranex
  - 0.9 per 1000 person year with no exposure
- **5.2 adjusted rate ratio (confidence interval 1.6 to 17.6) for cancer mortality**
- **Early Communications and a Black Box warning issued in 2008**
- **Warning: Increase Rate of Mortality Secondary to Malignancy**
  - “An increase rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of Regranex gel in a postmarketing retrospective cohort study. Regranex gel should only be used when the benefits can be expected to outweigh the risks. Regranex gel should be used with caution in patients with known malignancy.”<sup>51</sup>

# **Regranex (Becaplermin) and Cancer Association**

- **Regranex cancer risk may actually be under-reported**
- **Problems interpreting exposure-safety response relationships with the original studies**
  - **Fewer number of patients treated with 3 or more tubes than single applications**
  - **Inconsistent changes in plasma levels**

# Neoplasms/Cancer Events

- 7 neoplasm events to date
  - 5 events/5 patients- Augment
  - 2 events/2 patients- Control
- All occurred within 9 months of treatment
- Outcomes
  - 4 considered as resolved or recovered
  - 3 outcomes are currently unknown (2 of the 3 in the Augment group)
  - 3/5 in the Augment group required chemotx or radiation
- Sponsor declares
  - No relatedness to the product
  - 2 as “benign” and not listed as a SAE
- No specific demographic relationship identified
  - Gender (3M/4F)
  - Age at surgery (42-75)

# Types of Neoplastic Events

## Augment N=5

- 2 prostate
- 1 breast
- 1 hyperplastic colon polyp
- 1 plantar fibroma

## Control N=2

- 1 renal cell
- 1 endometrial

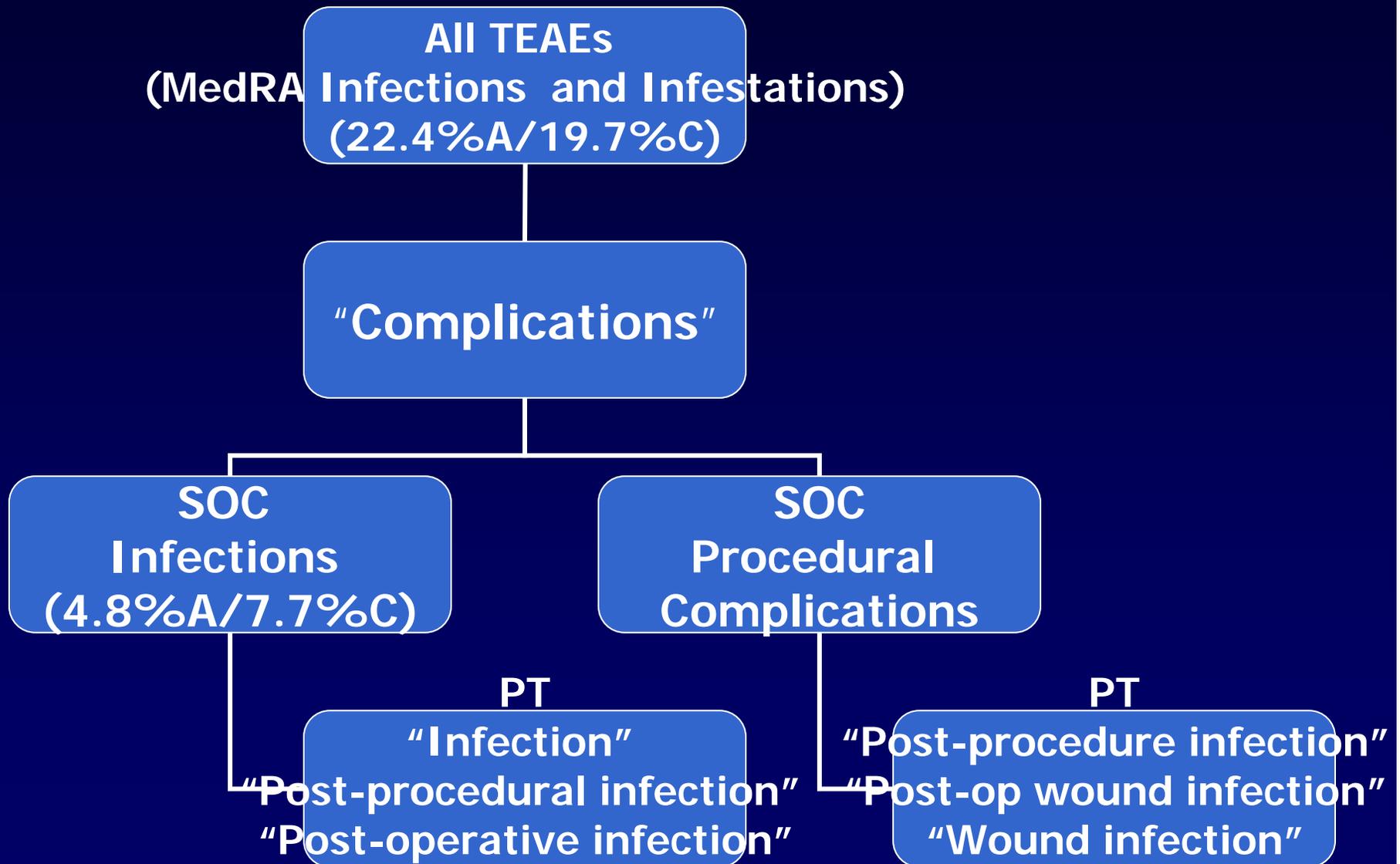
Specific panel question regarding the need for further pre-clinical or clinical assessment of the product's carcinogenic potential

# Deaths

Case ID	Treatment Group	Reported Term	Preferred Term	Investigator Causality	Event Outcome
GEM	Augment	PULMONARY EMBOLISM	Pulmonary Embolism	Not related	Death

- **52 week reporting time**
- **1 death in the investigational group**
- **None in the control group**
- **Patient died of a pulmonary embolism at 14 days post-op**
- **Assessed as “not related” to the study product**

# Infections



# Antibody Monitoring

## rh-PDGF (Anti-drug Antibody (ADA))

- Drawn at baseline, 7-21 days, weeks 6, 12, and 24
- ELISA method of analysis
- Reported in 414 patients
- Augment 13.1% (37/282)
  - 15 patients were high titer (1:400 or 1:800)
  - 12/37 (32.4%) ADA + at the 6 month time point
- Control 3.5% (5/141)
  - None with high titers

## Neutralizing Antibodies

- Assessed in all patients with + rh-PDGF antibodies
- None detected with RIA method of analysis
  - Deficient in the ability to directly interfere with drug activity in vivo
- FDA requested a bioassay but not provided to date
- True anti-drug neutralizing activity unknown

# Antibody Monitoring

## Augment

- 19 patients both ADA + and product failures
  - 42% with high titers
- Adverse Events with high titer ADA+
  - 2 Infections
  - 1 hardware complication
  - 5 not available

## Control

- 4 patients both ADA + and product failure
  - None with high titers

Specific panel question regarding the need for further pre-clinical or clinical assessment of the product's ability to elicit an immunological response

# Therapeutic Failures

- Defined as a secondary procedural intervention (bone stimulator or revision surgery) for
  - Non-union: Established at 36 weeks postop with no visibly progressive signs of healing for a minimum of 3 months (no change of fracture callus)
  - Delayed union: Established with insufficient healing between 24 and 36 weeks postop
- Standard criteria for secondary surgeries as “failures” not used

Specific panel question regarding the use of the sponsor defined “Therapeutic Failures” to define safety related to secondary surgical interventions

# Secondary Surgical Procedures

Procedure	# Patients (%) at 6 months	
	Augment	Control
<b>“Therapeutic Failures” total</b>	<b>24 (9.2%)</b>	<b>15 (10.9%)</b>
Removals (only for delayed or non-union)	3	1
Reoperations	2	2
Supplemental Fixations	0	0
Other interventions (hardware removal)	10	6

Specific panel question regarding other secondary surgeries as failures

# Safety Summary

- **Unconventional method of adverse events reporting**
  - FDA unable to interpret several major safety issues (surgical complications, infections)
  - FDA and DSMB independently raised related concerns at the IDE stage
- **Secondary surgeries considered as failures only as they relate to delayed or non-union**
  - FDA unable to interpret other secondary surgeries and potential product relatedness
- **Safety not considered in the success or failure of the product's primary effectiveness endpoint**

# Safety Summary

- **Antibody safety unknown**
  - Neutralizing antibody status not delineated
  - Long term effects in pregnancy and autoimmunity
- **Neoplastic safety unknown**
  - FDA Black Box warning for same molecule (rh-PDGF), different application (Regranex)
  - Supported by biological plausibility and observations of a clinical trial cohort
  - Dose-dependent effect not determined
- **Product complications unknown**
  - Certain procedural related events excluded from consideration
  - The death of the patient with a pulmonary embolus is likely a procedural related event

# Effectiveness

# Primary Study Endpoint

- **A single criterion for fusion Overall Success at 6 months defined as**
  - **CT evidence of > 50% osseous bridging**
  - **In a “full complement of joints”**
    - **a binary endpoint of “all treated joints”**
  - **Approved for analysis in an ITT population**
- **Success defined if the overall rate of success for Augment was non-inferior to the overall success rate for Controls**
- **Individual “failure” if the use of bone stimulators or revision surgery for non- or delayed union was required**

# **Primary Study Endpoint Inadequacy**

- **Used to indicate both radiographic and clinical success**
- **Did not consider product and/or surgical procedure associated adverse events**
- **Did not account for freedom from secondary surgeries other than those related to delayed or non-union**
- **Use of CT not validated in this patient population**
- **Data analyzed in a sponsor defined mITT “Effectiveness” population**

# Primary Endpoint: Fusion Status by CT at 6 Months

## Time Course of Fusion Status Success to 24 Weeks

	9 weeks		24 weeks		36 weeks	
	Augment	Cont	Augment	Cont	Augment	Cont
Fusion Success (%)	64/260 (24.6%)	51/137 (37.2%)	159/260 (61.2%)	85/137 (62.0%)	165/260 (63.5%)	95/137 (69.3%)
Non-inferiority p-value	0.70		0.04		0.20	

Specific panel question regarding the *a priori* primary endpoint which relates only to the radiographic success of fusion, and the use of CT for this assessment

# IDE Secondary Fusion Success by X-Ray

- Defined as 3 of 4 views (medial, lateral, anterior/superior, posterior/inferior) with osseous bridging and no visible joint space
- Classified as fused, not fused, or not evaluable
- Overall low fusion rates
- p-values not statistically non-inferior for Augment

Fusion Success Rate by Plain Radiographs			
	Augment	Control	p-value
3	mITT 30.8%	32.8%	0.054
	ITT 28.4%	31.5%	0.070
2	mITT 60.8%	66.4%	0.194
	ITT 57.9%	63.8%	0.200

# IDE Secondary “Composite Success”

- Treatment completed PP
- Osseous bridging of at least 25% by CT for full complement
  - Less stringent than 50%
- No product related SAEs
- VAS graft site control pain < 20 mm at week  $\geq$  6 wks
  - VAS for fusion site or weight bearing not considered
- No bone stimulator or revision surgery for non- or delayed union  $\leq$  24 weeks

	Augment Bone Graft (N=260)	Autologous Bone Graft (N=137)	Non-inferiority P-value
mITT Composite Success Achieved	174 (66.9%)	91 (66.4%)	0.02
ITT Composite Success Achieved	174 (61.1%)	92 (61.7%)	0.03

# IDE Secondary “Clinical Success”

- **Defined as the combination of :**
  - Improved pain with weightbearing compared to baseline as assessed by VAS
  - No revision surgery for non- or delayed union
- **No statistical non-inferiority for Augment at the primary endpoint with p-values unadjusted for multiplicity**
- **Success rates for control greater at most time periods**

<b>Clinical Success by Visit - mITT Population</b>			
	<b>Augment Bone Graft (N=260)</b>	<b>Autologous Bone Graft (N=137)</b>	<b>Non-inferiority p-value (unadjusted for multiplicity)</b>
<b>Week 6</b>	<b>55 (21.2%)</b>	<b>36 (26.3%)</b>	<b>0.141</b>
<b>Week 9</b>	<b>164 (63.1%)</b>	<b>89 (65.0%)</b>	<b>0.054</b>
<b>Week 12</b>	<b>181 (69.6%)</b>	<b>96 (70.1%)</b>	<b>0.024</b>
<b>Week 16</b>	<b>188 (72.3%)</b>	<b>105 (76.6%)</b>	<b>0.107</b>
<b>Week 24</b>	<b>194 (74.6%)</b>	<b>107 (78.1%)</b>	<b>0.071</b>

# Secondary QOL and Pain Endpoints

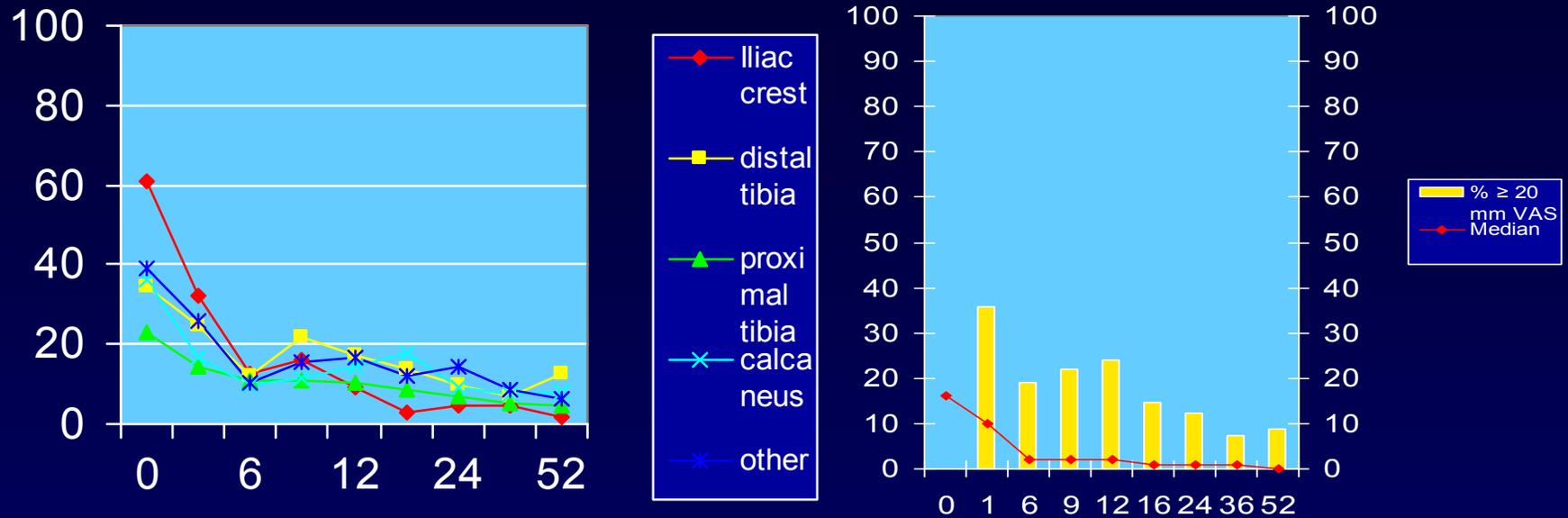
- **Quality-of-life questionnaires**
  - SF-12
  - FFI
  - AOFAS Ankle-Hindfoot
- **“Pain assessments” VAS scale for 3 components:**
  - Overall fusion site pain
  - Pain on weight-bearing
  - Pain at the graft harvest site (control group only).
- **QOL and Pain scores compared pre- to post-operatively without pre-defined enrollment criteria or declaration of clinically meaningful success**
- **Augment claims statistical non-inferiority in all of the above categories**

Specific panel question regarding the adequacy of secondary endpoints to determine primary clinical relevance

# Post-hoc “Subject Performance” Analysis

- FDA expressed concerns regarding the lack of clinical performance primary endpoints and safety concerns in an IDE supplement
- Sponsor withdrew this supplement and FDA requested a post-hoc analyses of a composite endpoint
- Sponsor provides a “Subject Performance” composite
  - VAS improvement of  $\geq 20$  mm with weight bearing
  - Absence of secondary procedures for delayed or non-union
  - Improvement of  $\geq 10$  on the FFI score
  - Absence of graft harvest site pain ( $< 20$  mm VAS)
  - Absence of SAEs
- Composite retains the same problems of clinical relevance as its individual endpoints
- Sponsor concludes that Augment remains “non-inferior” ( $p=0.004$ ) to control but at a much lower rate of fusion (34.6%A/31.4%C)
  - Addition of SF-12 or AOFAS would further decrease fusion rates <sup>71</sup>

# Product Benefit: Graft Site Pain



- ICBG only 11.7% of all site materials used
- Highest mean VAS < 40mm for other sites at time of surgery
- > 60% had overall VAS pain < 20 mm
- Highest median overall VAS was 16 at time of surgery

# Effectiveness Summary

- **Reliance on a single radiographic measure of effectiveness to determine the overall relative clinical benefit and to estimate the absolute risk**
- **Differential secondary clinical success depending on the sub-population used for analyses**
  - **Questionable clinical significance of composite endpoints**
  - **Problems with increased variance**
- **Quality of Life and pain assessment measures based on pre to post-op differences without pre-defined determinants of success lack the ability to determine a clinically meaningful effectiveness of treatment**
- **Low overall success rates in a population that historically consist of varying success rates based on anatomical area (ankle versus hindfoot)**

# Clinical Summary

- **Heterogeneous intended patient population**
  - **Confounds success/failure as it relates to adverse events and secondary surgeries**
  - **Ankle fusions are technically more demanding than hindfoot fusions**
  - **Impacts poolability of the subject populations**
- **Any potential benefits are of a limited time course (6 months)**
  - **Ankle fusions can require 1 year or more for clinical success**
  - **Long term consequence of cancer promotion and immune modulation unknown**
- **Effectiveness based on a Primary radiographic evaluation is not clinically relevant**
  - **CT assessment of fusion has not been externally validated**

# Clinical Summary

- **Early withdrawals, protocol violations, and other types of secondary surgeries should be analyzed as failures in the ITT data set and sensitivity analyses provided**
- **All 3 data sets (ITT, mITT, and PP) should be consistent and robust**
- **Study not designed and executed in a manner that allows interpretation of major safety issues**
  - **Product related adverse events**
  - **Secondary surgeries**
  - **Cancer**
  - **Antibody mediated adverse events**

# Clinical Issues for Discussion

- **Who is the treatment intended for? (Diverse heterogenous patient population of historically varying success rates analyzed together for success determination)**
- **What does it do? (Achieves primary radiographic Fusion Success by CT without considering clinical outcomes)**
- **How durable is the treatment? (Fusion success without delayed or non-union is declared at 6 months at a marginal p-value)**
- **Is it better than what is used now or the same?**
- **Is it worth the risk? (Based on avoiding low morbidity graft site pain as the major benefit and a potential cancer association and immunological consequences as the major risk with no clear understanding of the safety and effectiveness profile as the study is designed)**

# Overview

- Introduction
- Non-clinical Testing
- IDE Clinical Study
- ***Statistical Analyses***
- Post-Approval Study
- Panel Questions
- FDA Summation

# Statistical Considerations

**Scott W. Miller, PhD**  
**Mathematical Statistician**  
**DBS, OSB, CDRH, FDA**



# Overview

- **Synopsis of pivotal trial**
  - Design
  - Conduct
- **Selected effectiveness analyses**
- **FDA's statistical concerns**
  - Analysis population
  - Missing data / tipping point analysis
  - Sample size mis-estimation

# Synopsis of pivotal trial: Design

- Multi-center, randomized (2:1), active-control, partial-single blind, non-inferiority trial ( $\delta=10\%$ )
  - IDE G050118
- Augment bone graft vs. Autologous bone graft
- Treating ankle or hindfoot fractures
- 1<sup>o</sup> effectiveness endpoint:  $\geq 50\%$  fusion by 24 week CT
  - Blinded assessment of fusion

# Synopsis of pivotal trial: Conduct

- 456 subjects enrolled between April 2007 to July 2009
- 38 clinical centers in US and Canada
- 435 subjects randomized
- 2 mis-randomizations
  - 1 subject randomized to Augment received Autograft
  - 1 subject randomized to Autograft received Augment

# Analysis populations

- **Modified Intent to Treat (mITT):** All randomized subjects who were eligible, properly randomized, and received treatment according to the protocol. Excludes intra-operative screen failures. Subjects are analyzed according to treatment received.
- **Intent to Treat (ITT):** All randomized subjects, including intra-operative screen failures and patients randomized but never treated. Subjects analyzed according to treatment randomized.
- **Safety:** Subset of ITT dataset with all patients treated with either Augment or autologous bone graft. Subjects analyzed according to treatment received.

# Analysis populations (per PMA)

Analysis population	Total	Augment	Autograft
<b>ITT</b>	434	285	149
- not treated	20	13	7
<b>Safety</b>	414	272	142
- excluded from mITT analysis	17	12	5
<b>mITT</b>	397	260	137

# Table of non-treatment or exclusion

Reason for patient exclusion		Augment	Autograft
Intra-operative and immediate post-surgical failure	Too much or prohibited hardware	9	5
	Midfoot procedure	3	2
	Hindfoot + ankle fusion	2	1
	Too much graft material used	0	1
	Use of allograft	1	0
	Infection at fusion site	1	0
	Second procedure required	1	0
	Early immobilization	1	0
<b>Total</b>		<b>18</b>	<b>9</b>

# Table of non-treatment or exclusion (2)

Reason for patient exclusion		Augment	Autograft
Excluded prior to treatment	Patient withdrew consent	4	1
	Not medically cleared	1	2
	Investigative site closure	1	0
	Use of a prohibited medication	1	0
Total		7	3
Reason for patient exclusion		Augment	Autograft
Intra-operative and immediate post-surgical failure		18	9
Excluded prior to treatment		7	3
Total		25	12



# Early discontinuations

Discontinuation category	N	Augment	Autograft
Subject or investigator request	8	5	3
Inability to return for follow-up	1	0	1
Non-compliance to protocol	2	2	0
Loss-to-follow-up	5	5	0
Death	1	1	0
Revision surgery required	7	6	1
<b>Total</b>	<b>24</b>	<b>19</b>	<b>5</b>

# Primary effectiveness endpoint

Analysis population	Augment	Autograft	Difference (Augment-Autograft)	1-sided 95% lower bound*	Non-inferiority <i>p</i> -value
<b>mITT</b> (N=397)	61.2% (159/260)	62.0% (85/137)	-0.8%	-9.3%	0.038
<b>ITT</b> (N=434)	57.9% (165/285)	60.4% (90/149)	-2.5%	-10.7%	0.065

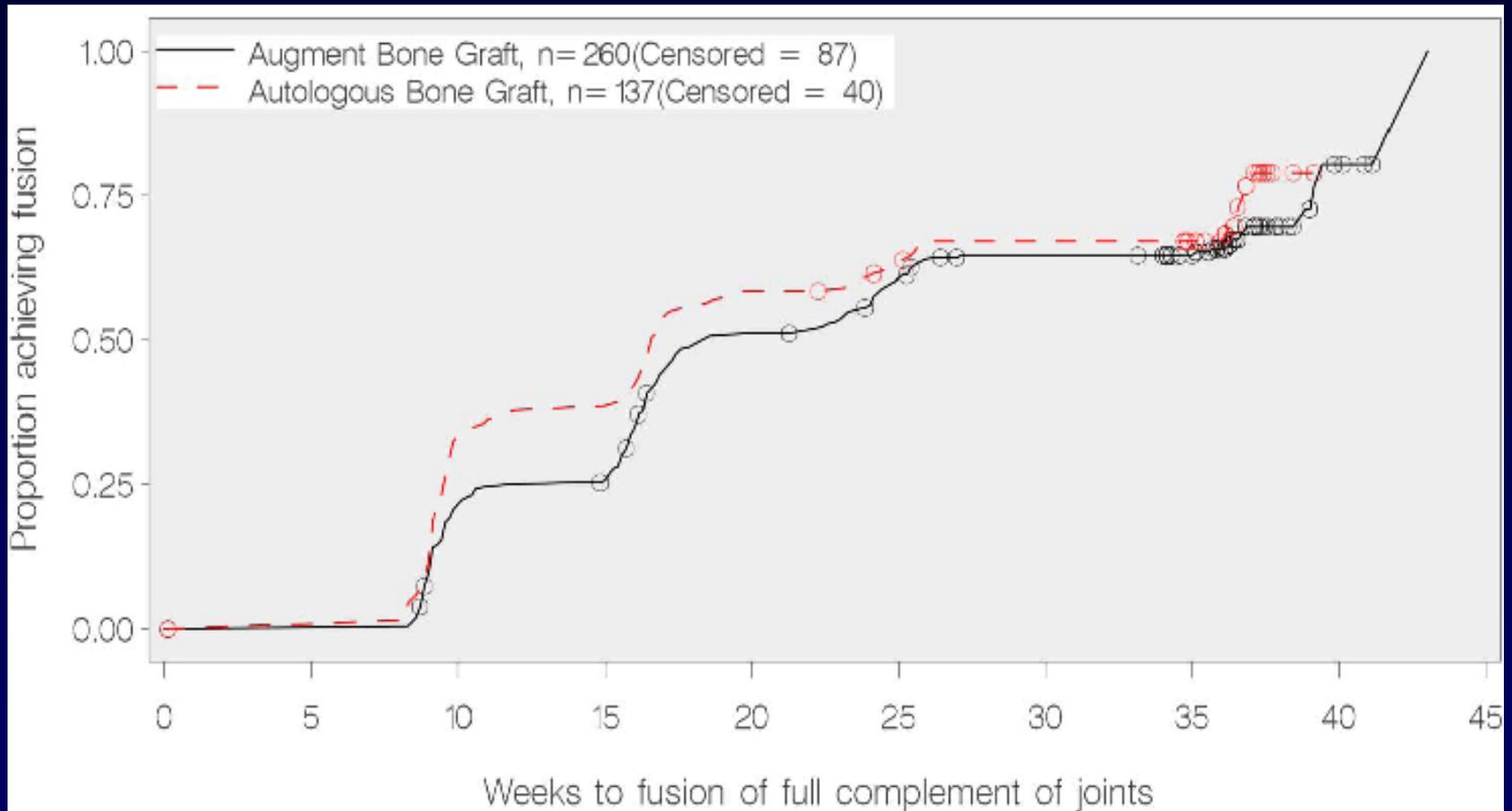
•The non-inferiority margin was 10%; thus, to be statistically non-inferior, the 1-sided 95% lower bound on the difference between Augment and Autograft must be greater than -10%.



# Protocol violations

- **1,457 violations for 456 enrolled subjects**
- **Majority (69%):**
  - Missed study visit (39%)
  - Out of window study visit (30%)
- **Per Guidance:**
  - Reflect in the patient accounting table
  - Include and exclude out of window visits as a sensitivity analysis

# CT fusion rates over time (mITT)



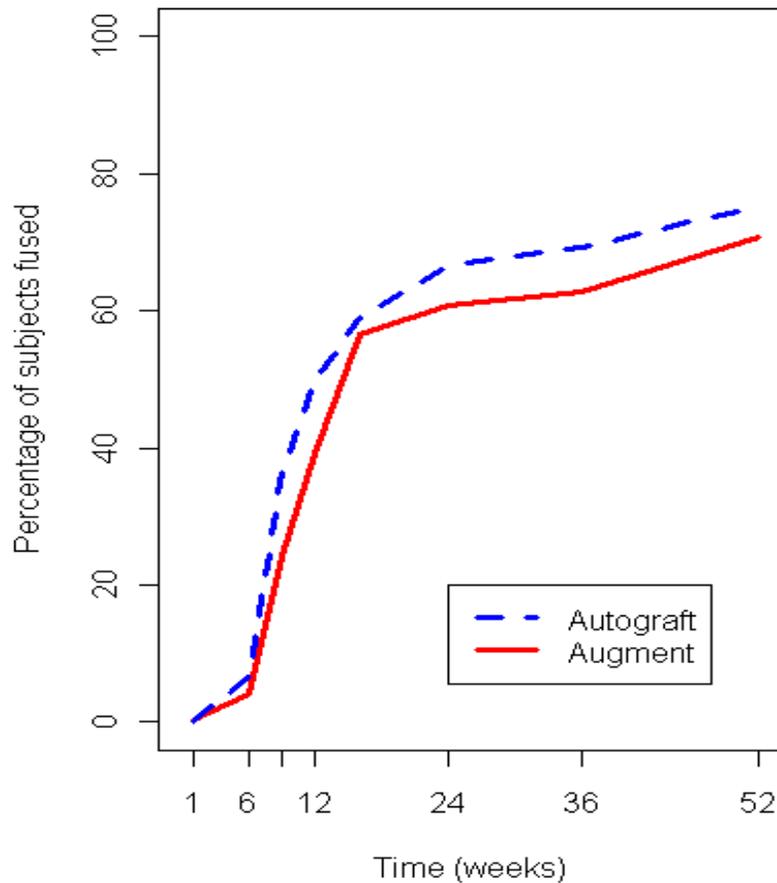
ooo = Censored patients.

Fusion is defined as at least 50% osseous bridging of the joint(s).

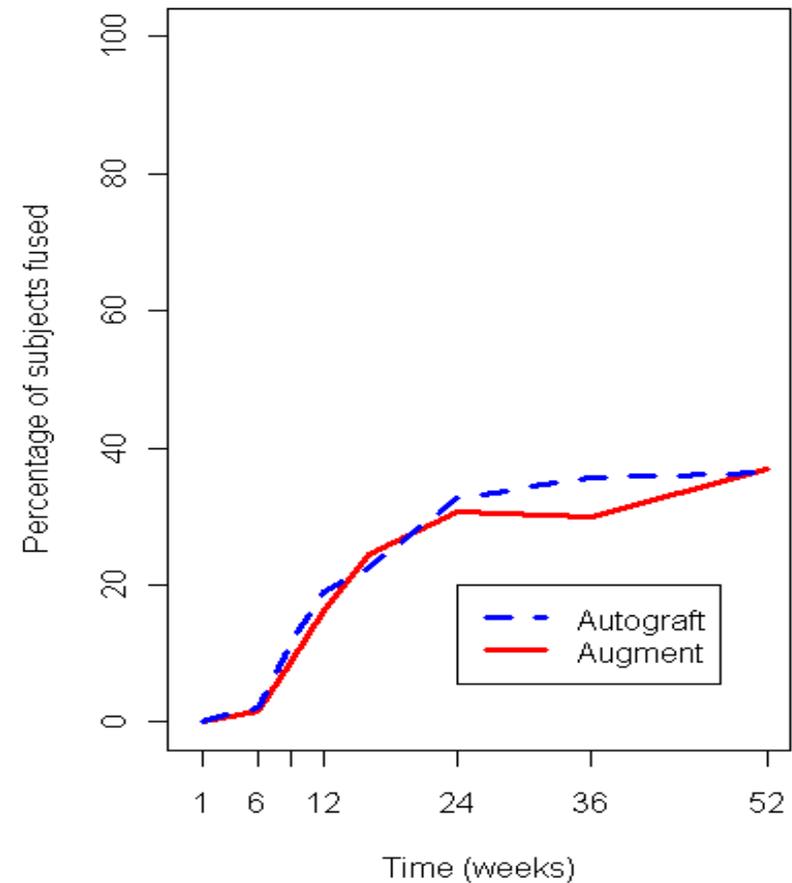
Wilcoxon-Gehan p-value = 0.1047

# Radiographic fusion rates over time (mITT)

Radiographic - 2 aspects



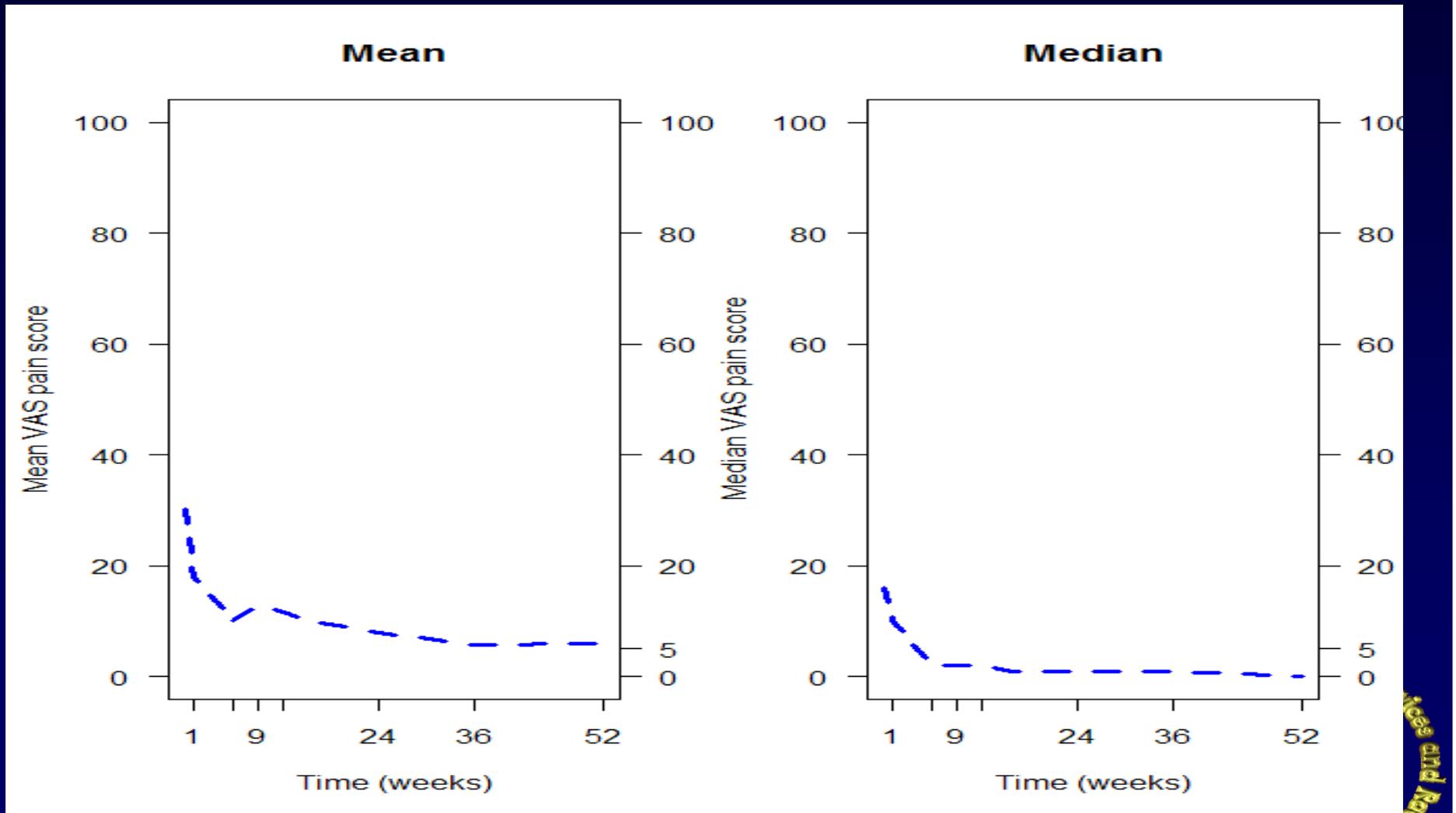
Radiographic - 3 aspects



# Graft harvest site pain over time (100 mm VAS): Autograft subjects only (mITT)

Visit	N	% with $\geq 20$	Mean	Median
Surgery	119		30.2	16
Day 7-21	144	35.8%	17.9	10
Week 6	144	19.0%	10.1	2
Week 9	134	21.9%	12.8	2
Week 12	139	24.1%	11.6	2
Week 16	141	14.6%	9.9	1
Week 24	143	12.4%	7.9	1
Week 36	138	7.3%	5.8	1
Week 52	142	8.8%	5.9	0

# Graft harvest site pain over time (mITT)



# Missing data (primary effectiveness endpoint)

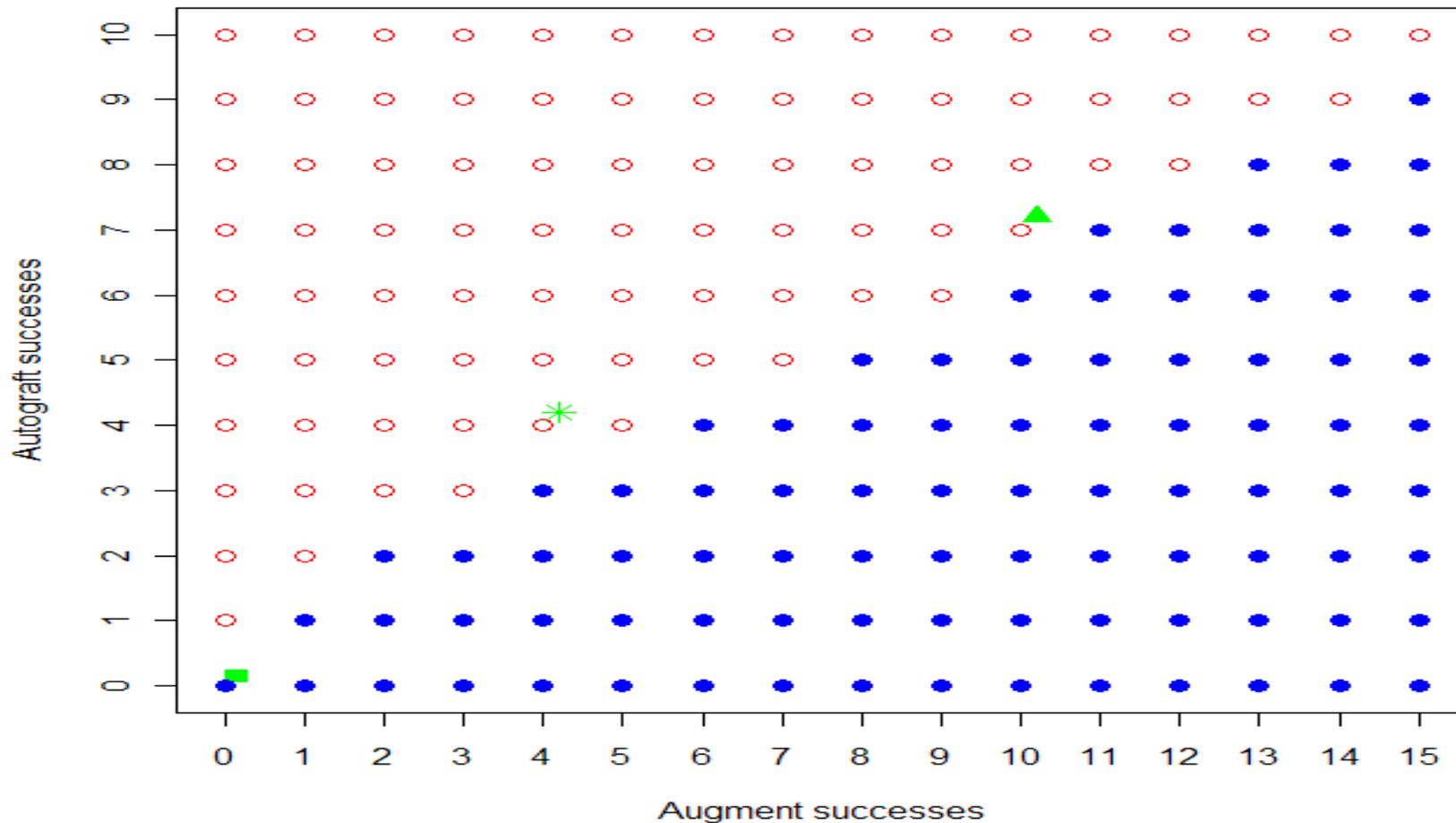
Analysis population	Augment	Autograft
<b>mITT</b> (N=397)	5.8% (15/260)	7.3% (10/137)
<b>ITT</b> (N=434)	10.2% (30/285)	10.1% (16/149)

# Sponsor sensitivity analysis to missing data (mITT)

Model	Augment (n=260)	Autograft (N=137)	Difference (Augment – Autograft)	1-sided 95% lower bound	Non-inferiority p-value
Primary: Impute missing to failure	61.2% (159/260)	62.0% (85/137)	-0.9%	-9.3%	0.038
1: Last observation carried forward (LOCF)	62.7% (163/260)	65.0% (65/137)	-2.3%	-10.6%	0.063
2: Impute missing to success	66.9% (174/260)	69.3% (95/137)	-2.4%	-10.5%	0.061
3: Assuming best case for Augment	66.9% (174/260)	62.0% (85/137)	4.9%	-3.5%	0.002
4: Assuming worst case for Augment	61.2% (159/260)	69.3% (95/137)	-8.2%	-16.4%	0.358
5. Observed / complete case	64.9% (159/245)	66.9% (85/127)	-2.0%	-10.5%	0.062

# Tipping point analysis (mITT)

Tipping point graph (mITT analysis population)



95 All as failures \* Last observation carried forward (LOCF) Missing completely at random (MCAR)

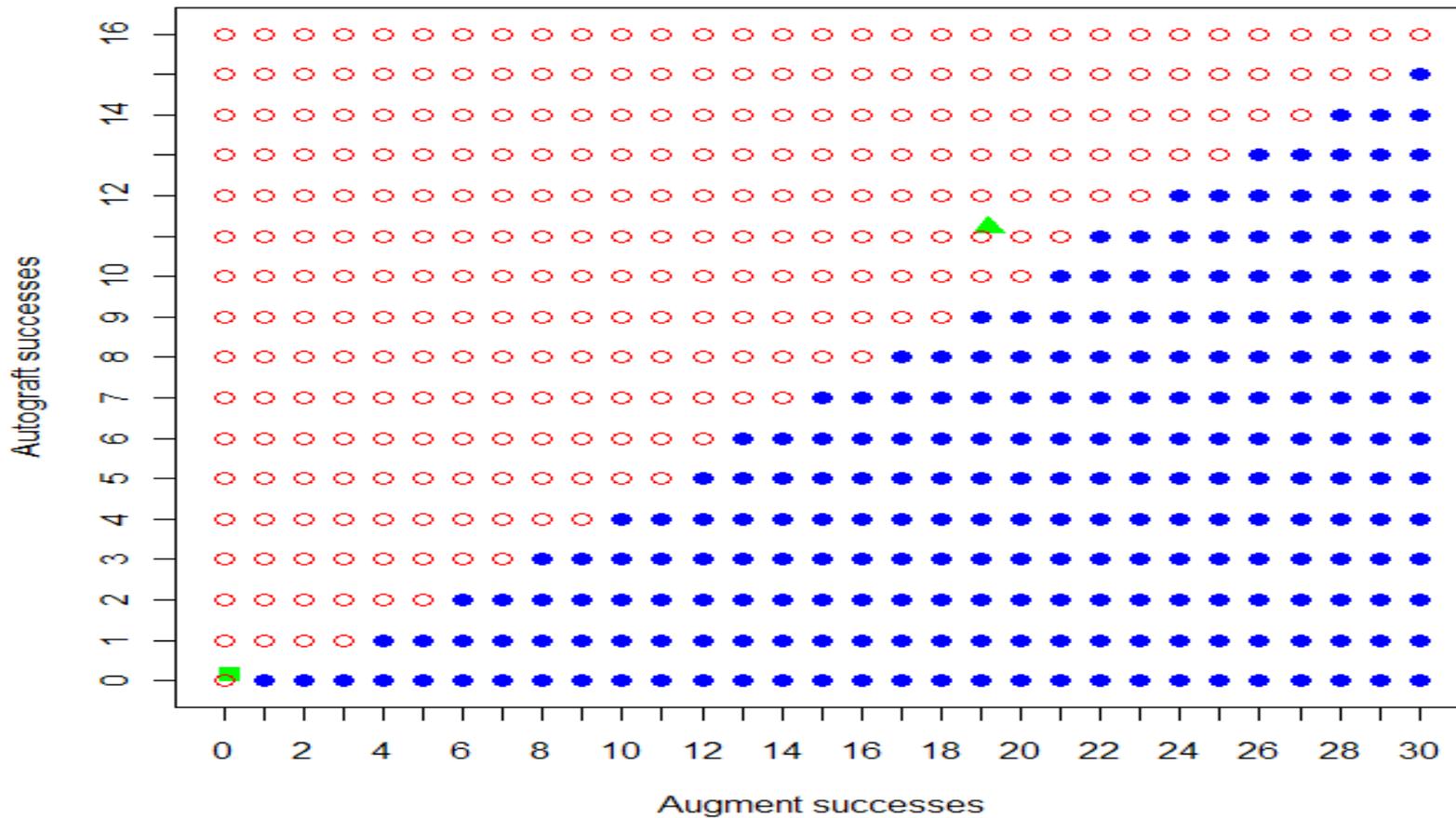
# Sensitivity analysis to missing data (ITT)

Model	Augment (n=285)	Autograft (N=149)	Difference (Augment – Autograft)	1-sided 95% lower bound	Non-inferiority <i>p</i> -value
Primary: Impute missing to failure	57.9% (165/285)	60.4% (90/149)	-2.5%	-10.7%	0.065
2: Impute missing to success	68.4% (195/285)	71.1% (106/149)	-2.7%	-10.3%	0.061
3: Assuming best case for Augment	68.4% (195/285)	60.4% (90/149)	4.7%	0.02%	<0.001
4: Assuming worst case for Augment	57.9% (165/285)	71.1% (106/149)	-13.2%	-21.0%	0.742
5. Observed / complete case	64.5% (165/256)	67.2% (90/134)	-2.7%	-11.0%	0.074



# Tipping point analysis (ITT\*\*)

Tipping point graph (ITT analysis population)



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# **Post-Approval Study Considerations for BioMimetic's Augment™ Bone Graft**

**Hong Cheng, MD, PhD, MPH**

**Division of Epidemiology**

**Office of Surveillance and Biometrics /  
CDRH**

**Orthopedic and Rehabilitation Devices  
Panel**

**May 12, 2011**

# Reminder

- The discussion of a post-approval study (PAS) prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance

# General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness
- Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness



# Need for Post-Approval Studies

- **Gather postmarket information**
  - » Long-term performance including effects of re-treatments & device changes
  - » Real-world device performance (patients and clinicians)
  - » Effectiveness of training programs
  - » Sub-group performance
  - » Outcomes of concern (safety and effectiveness)
- **Account for Panel recommendations**

# Post-Approval Study Components

- **Fundamental study question or hypothesis**
- **Safety endpoints and methods of assessment**
- **Acute and chronic effectiveness endpoints and methods of assessment**
- **Duration of follow-up**

# Important Postmarket Concerns

- Possible risk of developing neoplasms
- Long term evaluation of immunogenicity
- Long term effectiveness

# Outline for the Sponsor Proposed PAS

<b>Study Design</b>	Continue follow-up of the IDE patients out to five years post implant
<b>Sample Size</b>	Of the 414 IDE participants, who return to clinical visits (N<414)
<b>Safety Endpoints</b>	Evaluation of the long-term safety will utilize the patient physical examination findings and adverse events collected at 36, 48 and 60 months post-surgery
<b>Effectiveness Endpoints</b>	None

# Outline for the Sponsor Proposed PAS: Safety Endpoints

- Non-unions
- Therapeutic failures
- DVT/PE associated with the fusion site procedure
- Neoplasms and other SAEs
  - Infections and infestations
  - Musculoskeletal and connective tissue disorders
  - Neoplasms, benign
  - Neoplasms, malignant and unspecified
  - Complications related to bone graft harvest
- Death, regardless of relationship to the study device
- Clinically significant device related adverse events

# FDA Assessment - PAS Outline

- The proposed study does not have specific hypotheses.
- The proposed study may lack generalizability to a broader patient population treated in the postmarket setting (real world experience).
- It is not clear how the follow-up length of 5 years is determined and whether it is sufficient.
- The rationale of the clinical visit at only 36 months is not described.

# FDA Assessment - PAS Outline

- The sample size is not determined by specific study hypotheses. The power of the study to draw a clinically meaningful conclusion is undetermined.
- The proposal only includes a list of safety endpoints, but there is no specific hypotheses associated with the listed endpoints.
- Additionally, there is no plan to collect long-term effectiveness data.

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# Panel Question 1

**In the clinical study for Augment™ Bone Graft, the patient population included various diagnostic groups (i.e. osteoarthritis, rheumatoid arthritis, and traumatic arthritis) for the Augment treatment group and the autograft control group. The patient population was also heterogeneous with respect to specific joint(s) fused (ankle, subtalar, calcaneocuboid, etc.), total number of screws utilized in the procedure, and estimated amounts of graft material used.**

# Panel Question 1a

**Please comment and provided feedback on the appropriateness of the sponsor's proposed indications for use:**

**“ as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions.”**

# Panel Question 1b

Is it appropriate to pool the patient population with respect to diagnostic groups, joint (s) to be fused, number of screws utilized, and amount of graft materials used to determine safety and effectiveness?

## Panel Question 2

Taking into consideration the response to question 1, please comment and provide feedback on the appropriateness of the sponsor's primary/secondary study endpoints in consideration of the following points:

- a. There was no predefined secondary endpoint of successful fusion defined as CT evidence of greater than 50% osseous bridging and involving a “full complement of joints.”
- b. There was no predefined secondary composite clinical endpoint that included pain and function of the treated joint. Instead the sponsor used pain at the graft donor site in the control group.

# Points to consider for Question 2

**2c. The sponsor's CT radiographic method of analysis did not include validation information with respect to traditional radiographic methods.**

# Panel Question 3

Please comment on the appropriateness of the statistical analyses of each of the following points:

- a. The mITT analysis was not identified in the IDE as the primary analysis dataset for the premarket application. Rather it was the ITT analysis that had been identified in the IDE.
- b. Statistical significance was attained only in the mITT analysis population and not in the ITT analysis population.

## Points to consider for Panel Question 3 cont.

- c. While the results were statistically supportive for non-inferiority at 24 months in the mITT analysis population, statistical significance was not retained at 36 months.
- d. The results of the tipping point sensitivity analysis suggest that the results are extremely sensitive to the potential impact of missing data.
- e. FDA has concerns that the patient accounting table provided by the sponsor is inaccurate.

## Panel Question 4

Please discuss any potential concerns with adverse events, rates, and/or reporting, including the following:

- a. The seven subgroup analyses of adverse events categorized by the sponsor. FDA and the study's DSMB have previously expressed concern that only certain adverse events were being documented with this method.
- b. The sponsor defined "Therapeutic Failures" to capture safety events not related to delayed or non-union and its substitution for a complete categorization of secondary surgeries.

## Panel Question 5

**Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to carcinogenicity, and its potential effect on undetected transformed cells in the patient's body, i.e., tumor promotion. Please be as specific as possible on the type of testing needed. Please consider the following:**



# Points to consider 5a. & 5b.

- 5a. The sponsor has evaluated the product via an *in vitro* mutagenicity assessment and has conducted a one year, femur-onlay evaluation of the device for its carcinogenic potential. The assessments were negative for any indication of carcinogenicity.
- 5b. There is a potential for implanted or injected cytokines to promote or stimulate transformed cell growth, i.e., cancers not detected or diagnosed prior to the product usage. There may be a risk for tumor promotion with use of the product. This concern is based on epidemiologic findings regarding rhPDGF-BB used for the treatment of diabetic foot ulcers . These findings and concerns for rhPDGF-BB led to an FDA public health advisory.

## Panel Question 5 cont.

**5c. FDA has asked this sponsor to conduct a more standard drug type of tumor promotion assessment, i.e., the Rat Liver Foci Bioassay, where foci of altered hepatocytes (FAH) or preneoplastic lesions due to chemical carcinogenesis are assessed with respect to whether rhPDGF-BB can promote their growth and development. Do you believe this assessment should be completed prior to marketing the product?**

# Panel Question 6

**Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to reproductive toxicology/teratogenic potential. Please be as specific as possible on the type of testing needed. Please consider the following:**

# Points to consider 6a.

The sponsor has conducted a standard reproductive toxicology assessment to investigate the potential of rhPDGF-BB to influence reproduction and reproduction outcomes, e.g., fetal growth and development. The study found changes in rates of ossification of certain bones in the fetus, i.e., the sponsor does acknowledge that the changes in ossification parameters, i.e., indication of a minor transitory change in the rate of ossification, were likely attributable to rhPDGF-BB.

## Points to consider 6b.

The sponsor is in the process of conducting a 2nd reproductive toxicology evaluation which will investigate the effect of anti-rhPDGF-BB antibodies on developing fetuses. These results are not available at this time. This experimental paradigm investigates the consequences of “knocking-out” PDGF-BB during embryonic development, i.e., interference with the protein’s normal roles in embryonic tissue growth and development as could occur in a pregnant woman exposed to the implanted product.

# Panel Question 7

**Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to its' potential ability to elicit an immune response. Please be as specific as possible on the type of testing needed. Please consider the following:**

## Points to consider 7a.

There were differences noted in antibody events in patients treated with Augment™ Bone Graft, as compared to the control. An acceptable neutralizing assay has not yet been performed and therefore the incidence of neutralizing antibody formation is unknown.

Accordingly, there is a concern that antibody formation could interfere with normal PDGF-BB signaling.

# Points to consider 7b.

**Antibodies elicited to rhPDGF-BB could cross react with endogenous PDGF-BB and cause an autoimmune syndrome.**

# Reminder

- The discussion of a PAS prior to FDA determination of product approvability should not be interpreted to mean FDA is suggesting that the product is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for product approval.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

# Question 8

If the product is deemed approvable by FDA, the sponsor has provided a post approval study to continue following the IDE patients for 5 years. FDA is concerned that the proposed plan lacks critical key components of a PAS, including specific study hypothesis, the target study population, justification of the study powder, and comprehensive endpoints for the evaluation of safety and effectiveness in the post-market setting. In your discussion please address the following:



# Question 8 continued

- a. Whether a PAS is needed if the product is found to be approvable?
- b. If a PAS is recommended, whether the proposed safety endpoints are adequate to assess the long-term safety? If not, please recommend the major safety endpoints.
- c. If a PAS is recommended, what are the long-term effectiveness endpoints you would recommend?
- d. If a PAS is recommended, what type of study design you would recommend to evaluate the study questions?

# FDA Summation



# Cancer

- **Neoplastic safety concerns with product use**
- **FDA Black Box warning for same molecule (rh-PDGF-BB), different application (Regranex)**
- **Safety signal supported by biological plausibility and observations of a clinical trial cohort**
- **Any dose-response relationship unknown**

# Heterogeneous Patient Population

- **Proposed use in multiple anatomical areas**
  - Varying technical difficulties and surgical approaches
  - Varying numbers of supplemental pins and screws in the fusion
  - Varying historical outcomes rates by surgical site
- **Proposed use in different patient population**
  - Patients with OA, RA, trauma, diabetes, osteoporosis
  - Varying historical outcomes by comorbidity

# Primary and Composite Endpoint(s)

- Device effectiveness without clinically meaningful parameters in both the primary endpoint and the secondary composite endpoints
- Outcome measures without pre-defined validated determinants of success fail to capture clinically meaningful differences
- Overall low success rates

# Risk/Benefit

- **Risks**
  - Molecular potential for cancer promotion
  - Production of anti-PDGF antibodies with unknown neutralizing activity
  - Incomplete understanding of device related risks
- **Benefit**
  - Based on Primary radiographic effectiveness, not clinical effectiveness
  - Limited time course (6 months) to declare beneficial fusion success
  - Incomplete understanding of the intended population
  - Majority of graft harvest is from low morbid sites
- **Comparator (autogenous bone graft)**
  - Known performance
  - Risk well characterized

# Statistical Considerations

- Questionable non-inferiority
- Sensitivity to Missing Data

# Thank You

