

# InFuse<sup>®</sup> Bone Graft

## Agenda

- Call to Order and Introductory Remarks
- Open Public Hearing
- Presentations by Medtronic Sofamor Danek
- Break
- Presentations by FDA
- Lunch Break
- Panel Deliberations
- Break
- Open Public Hearing
- Summations by FDA and Sponsor
- Panel Recommendations and Vote



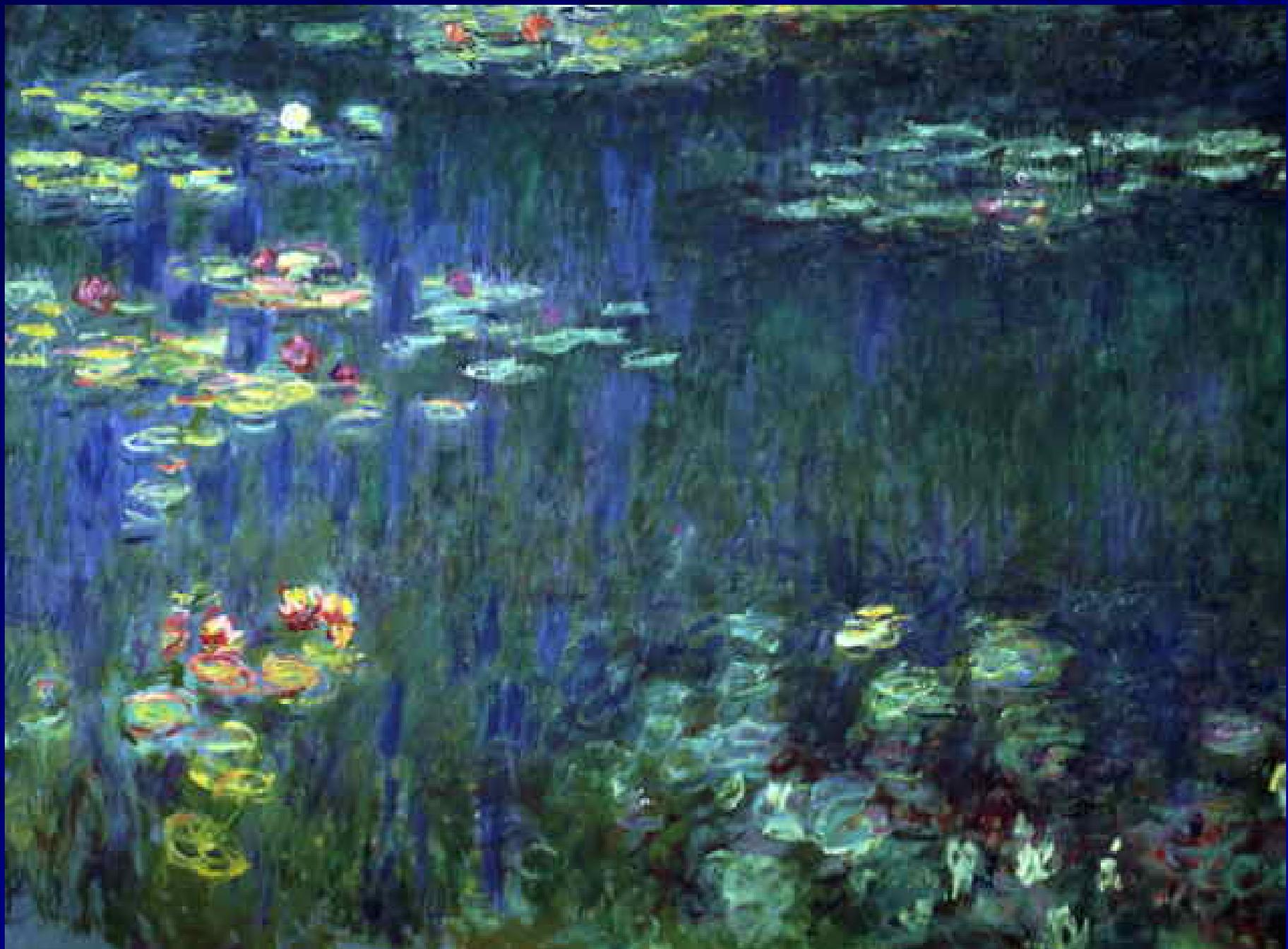
# InFuse<sup>®</sup> Bone Graft Dental Products Panel Meeting

November 9, 2006  
Gaithersburg, MD

# InFuse<sup>®</sup> Bone Graft

- Preclinical Studies – Dr. Peter L. Hudson
- Statistical Analysis – Dr. Zhiwei Zhang
- Clinical Studies – Dr. Robert S. Betz





# Pre-Clinical Data

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Food and Drug Administration

# Talk Outline

- Device Description
- Manufacturing
- Toxicology/Biocompatibility
- Preclinical Proof of Concept Evaluations
- Summaries – Effectiveness and Safety

# Device Description

## InFuse<sup>®</sup> Bone Graft

- Product consists of recombinant human bone morphogenetic protein – 2 (rhBMP-2) to be used with an absorbable collagen sponge.
- The product has been approved by FDA for spinal fusion and tibia repair procedures previously.
- This product is identical to the product reviewed for the spinal fusion and tibia repair indications in terms of the manufacturing process and the product itself, i.e., rhBMP-2 (1.5 mg/mL) on collagen sponge.

# Device Description

The INFUSE Bone Graft kits contain:

- Lyophilized rhBMP-2
- Absorbable collagen sponge (ACS)– Integra LifeSciences Corporation
- USP Grade Sterile Water for Injection for reconstitution
- Syringes and needles used in the reconstitution and application steps
- Four kits are available depending on the size of the implant site and the amount of bone repair required. The kits are designated as small, medium, large and large II

# Device Description

- Small: one vial delivering 4.2 mg rhBMP-2, **2 ACS**
- Medium: two vials delivering 4.2 mg rhBMP-2 each, **4 ACS**
- Large: one vial delivering 12 mg rhBMP-2, **6 ACS**
- Large II: one vial delivering 12 mg rhBMP-2, **1 ACS**

# Device Description

## Ingredients

- rhBMP-2
- L-glutamic acid
- Glycine
- Sucrose
- Polysorbate-80
- Sodium chloride

# Manufacturing

- rhBMP-2 is secreted from cultures of Chinese Hamster Ovary (CHO) cells encoding the human rhBMP-2 protein gene.
- Cell culture occurs in a production bioreactor with periodic harvesting of the conditioned cell culture medium.
- The conditioned medium is filtered to separate the cells away from the medium which then undergoes a purification process which includes column chromatography, a virus-retaining filtration step, an ultrafiltration step and a final filtration step.

# Manufacturing

- The sponsor has conducted a viral inactivation validation assessment of their manufacturing process.
- In addition, the sponsor conducted viral and microbial agent evaluations in accordance with the ICH guidance document regarding viral safety evaluation of human and animal cell lines.

# Manufacturing

- The testing included:
  - Mycoplasma
  - Sterility
  - Adventitious Viruses
  - In Vitro assay for the presence of bovine viruses
  - In Vitro assay for the presence of porcine parvovirus
  - In Vivo assay for viral contaminants
  - MAP, HAP and RAP testing
  - Retrovirus cocultivation assays
  - XC plaque or Mus dunni assays

# Preclinical Evaluations: Toxicology/Biocompatibility

- Acute single and multiple dose general toxicology expt.'s
- Chronic toxicity
- Intracutaneous toxicity
- Delayed contact sensitization
- Cytotoxicity
- Systemic toxicity
- In vitro hemolysis
- Implantation
- Mutagenicity
- Teratology and fertility studies

# Preclinical Evaluations: Post-approval studies

- Effects on human transformed cell lines
  - cell proliferation evaluations of tumor cell lines of interest, e.g., of osteogenic lineage and others
- Tumor cell line receptor studies
- Xenograft studies in nude mice

# Preclinical Proof of Concept Evaluations

- A number of preclinical evaluations have been conducted to investigate the safety and effectiveness of rhBMP-2/ACS
  - Models were predominantly dog but non-human primates were included
  - Studies were conducted in 2 phases: critical size defect repair alone, and defect repair with subsequent implant placement

# Preclinical Proof of Concept Evaluations

- First phase of testing
  - Critical sized mandibular defects of both acute or chronic standing
  - Guided bone regeneration investigated
  - Biomaterial potential enhancement of rhBMP-2 effect investigated
  - Space maintenance effect investigated
  - Non-human primate dosing study

# Preclinical Proof of Concept Evaluations

- 1<sup>st</sup> Phase results
  - Bone formation was demonstrated to include:
    - Neovascularization
    - Cellular differentiation
    - Woven trabecular bone formation
  - Bone formation in the canine jaw via an intramembranous osteogenesis pathway without involving chondrogenesis

# Preclinical Proof of Concept Evaluations

- 1<sup>st</sup> Phase results
- Guided Bone Regeneration (GBR)
  - Apparent interference with wound healing and bone repair; bone density of GBR/rhBMP-2/ACS less than rhBMP-2/ACS alone
  - Wound dehiscence, infection observed in GBR-treated dogs

# Preclinical Proof of Concept Evaluations

- 1<sup>st</sup> Phase results
- Biomaterial enhancement of rhBMP-2/ACS – chronic alveolar ridge defect model
  - Bioactive glass and DBM showed a 2 fold increase in rhBMP-2 induced bone formation, i.e., increased alveolar ridge height
  - 2<sup>nd</sup> chronic model, HA served as a space provider and enhanced rhBMP-2 effect

# Preclinical Proof of Concept Evaluations

- 1<sup>st</sup> Phase results
- Non-human primate evaluation (n = 3)
  - Critical size mandibular defect
  - Low (0.2 mg/mL) and High (0.8 mg/mL) doses evaluated
    - More bone formation observed with high dose
    - No excessive bone formation seen with high dose

# Preclinical Proof of Concept Evaluations

- 2<sup>nd</sup> Phase
- Implant fixation evaluation – canine, mandibular saddle-type, alveolar ridge defects were created
  - To evaluate bone formation and dental implant-bone contact at long-term of functionally loaded, dental implants placed into alveolar ridge defects treated with rhBMP-2

# Preclinical Proof of Concept Evaluations

- 2 stage implant dog study
- defect sites immediately treated with rhBMP-2, ePTFE or resorbable membranes were placed over defects, healing allowed to progress for 3 months
- Dental implants at 3 months, prosthetic reconstruction devices (bridges) placed after 4 months of osseointegration
- Functional loading for 12 months

# Preclinical Proof of Concept Evaluations

- Results
- A number of implants were lost due to wound failure or infection.
- Oval-shaped radiolucent voids within the newly formed bone were observed in several sites at 1 month but over time resolved; 13 of 24 defect sites were noted to have bone voids
- Comparable bone-contact osseointegration was observed for rhBMP-2 treated sites and control, resident bone implanted sites.

# Preclinical Proof of Concept Evaluations

- Results
- Model demonstrates that the device (rhBMP-2/ACS) can form new bone in critical size mandibular defects and that dental implants placed in these sites appear to be functionally effective
- Localized swelling correlates with rhBMP-2 treatment; bone voids or seromas noted but resolved over time
- GBR seen again to complicate wound healing and bone repair

# Preclinical Proof of Concept Evaluations

- Dog study – 2 endpoints: 1. evaluation of space-providing macroporous ePTFE device for alveolar augmentation, and 2. dental implant fixation with rhBMP-2/ACS
- Purpose: evaluation for alveolar bone induced by rhBMP-2/ACS used as an onlay (augmentation) and evaluation of effect of rhBMP-2/ACS on regeneration of alveolar bone, cementum, and a functionally oriented periodontal ligament (PDL)

# Preclinical Proof of Concept Evaluations

- Results
- rhBMP-2 plus the ePFTE barrier accounted for more bone formation (area) than with either rhBMP-2 alone or buffer alone
- Bone density was higher in sites receiving rhBMP-2 without the barrier membrane

# Preclinical Proof of Concept Evaluations

- Results
- Ankylosis was found irrespective of group
- Seroma formation was observed for rhBMP-2 treated sites but not in control sites
- Functionally oriented PDL fibers were commonly observed in controls but were rarely found among rhBMP-2 treated sites
- rhBMP-2 induced bone formation on the alveolar ridge and use of a macro-porous barrier enhanced new bone formation

# Preclinical Proof of Concept Evaluations

- Other investigations – sinus floor augmentation, extraction socket preclinical studies
- Sinus floor – goat model
- Subantral augmentation in nonhuman primate model – 2 stage: defect repair and implant fixation; equivalent results
- Cynomolgus monkeys were implanted in contralateral extraction socket sites treated with rhBMP-2

# Preclinical Proof of Concept Evaluations

- Results
- Goat study: New bone formation was observed at 4, 8 and 12 weeks in sinuses implanted with the device.
- Subantral non-human primate: Newly formed bone of similar quality and resulted in similar osseointegration as in the regional resident bone
- Extraction socket study: 7/8 rhBMP-2 sites exhibited evidenced of osseointegration compared to 4/8 controls.

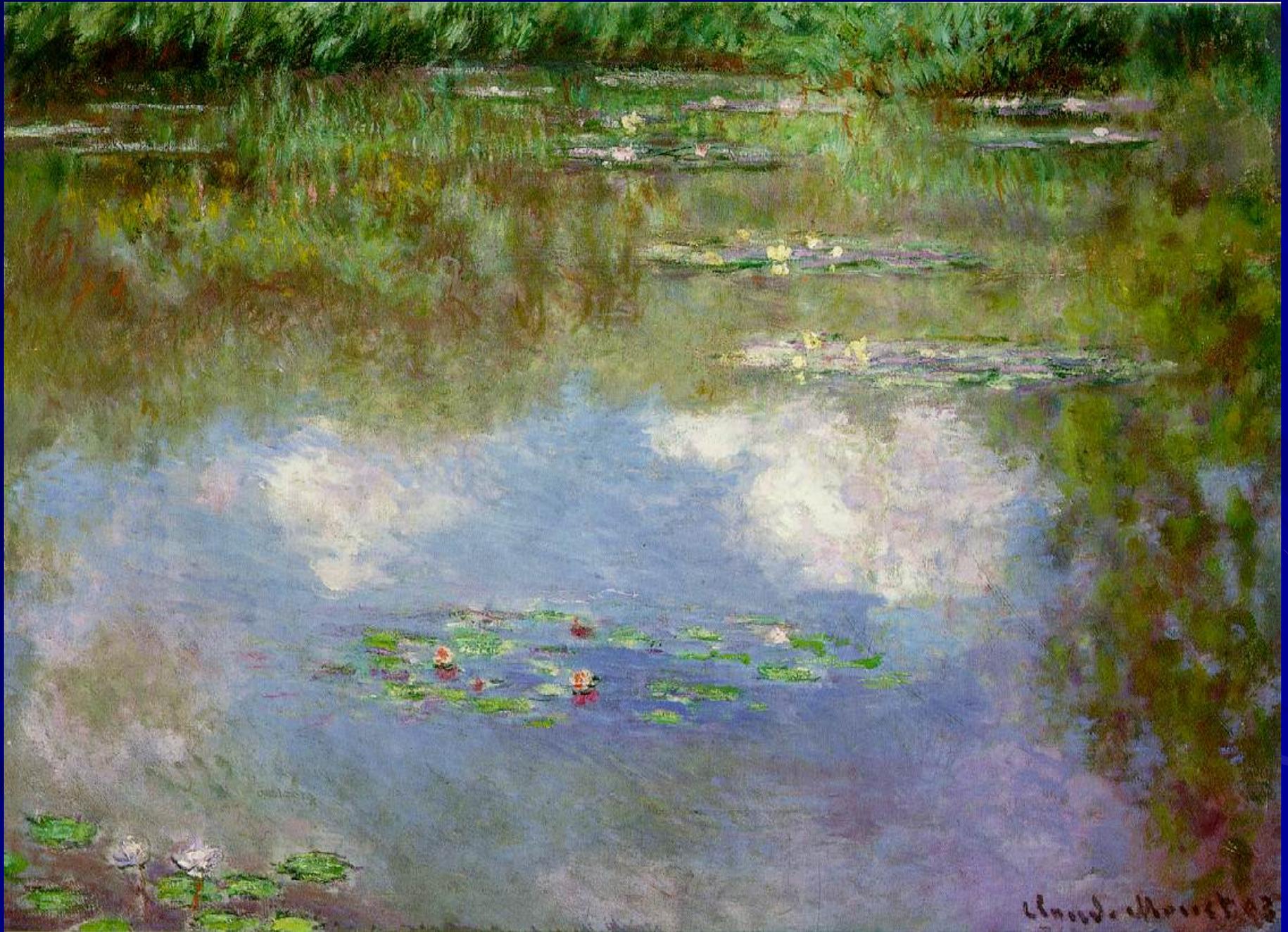
# Preclinical Studies Effectiveness Summary

- rhBMP-2 was found to cause bone formation in surgically-created mandibular alveolar ridge defects. This effect was seen across the animal models which included dogs and nonhuman primates.
- When endosseous dental implants were placed into alveolar ridge defects filled with rhBMP-2 induced bone, comparable bone-contact osseointegration was observed for rhBMP-2 treated sites, i.e., comparable to native, resident bone



# Preclinical Studies Safety Summary

- Results with GBR appear mixed; preservation of space may assist bone formation, however complications were also observed
- rhBMP-2 caused localized swelling at times
- seroma formation/bone voids were observed



# Statistical Analysis

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# Outline

- Device
- Sinus augmentation
  - Dosing study
  - Pivotal study
- Extraction socket augmentation
  - Dosing study

# Infuse Bone Graft

- Recombinant human bone morphogenetic protein-2 (BMP)
- Placed on an absorbable collagen sponge (ACS)
- Applied at a concentration of 1.5 mg/ml (default)

# Dosing Study for Sinus

- 48 patients were enrolled at 6 sites and randomized at a 1:1:1 ratio to receive
  - bone graft
  - 0.75 mg/ml BMP
  - 1.5 mg/ml BMP
- Treatment course (up to 48 months)
  - Initial surgery followed by bone induction phase
  - Dental implant placement followed by osseointegration phase
  - Functional loading followed by functional restoration phase

# Pivotal Study for Sinus

- Objective
  - To compare 1.5 mg/ml BMP with bone graft
- Population
  - Candidates for a two-stage bilateral or unilateral maxillary sinus augmentation procedure

# Design Parameters

- 160 patients at 20 sites
- Treatment (BMP or bone graft) assigned randomly at a 1:1 ratio
- Open label
- Treatment course similar to that of dosing study

# Primary Endpoint

- Proportion of BMP-treated patients with successful dental implant borne restoration at 6 months post-loading
- Protocol claims success if the above proportion exceeds 73%
  - Not based on statistical hypotheses
  - Does not involve a comparison to the control

# Patient Accountability

	Bone Graft	BMP
Completed <sup>1</sup>	69	57
Failed	7	18
Discontinued <sup>2</sup>	2	7
Total	78	82

1. Remained successful through 24 months after functional loading
2. Withdrawn or lost to follow-up

# Baseline Comparison

- No significant differences with respect to age, race, history of nicotine use, current alcohol consumption or menopausal status
- Significant differences
  - Higher proportion of subjects  $\geq 65$  years of age in the BMP group ( $p = 0.024$ , Fisher's exact test)
  - Higher proportion of male subjects in the BMP group ( $p = 0.003$ , Fisher's exact test)

# Pooling Studies

- The dosing and pivotal studies for sinus have
  - Similar inclusion/exclusion criteria
  - Similar baseline characteristics
  - Similar treatment courses except for timing of post-operative CT scans
  - Similar outcomes except for change in bone height ( $p > 0.05$ )
- No major statistical issues are noted in pooling the studies for analyses of functional restoration

# Patient Success Rates at 6 Months Post-Loading<sup>1</sup>

Data	Control	BMP	Difference
Pivotal only	90.8% (69/76)	79.0% (64/81) (68.5%, 87.3%) <sup>2</sup>	-11.8% (-22.8%, -0.8%) <sup>3</sup>
Pivotal + dosing	89.9% (80/89)	79.6% (78/98) (70.3%, 87.1%) <sup>2</sup>	-10.3% (-20.4%, -0.2%) <sup>3</sup>

1. Discontinued patients (2 control; 1 BMP) excluded from analysis
2. Exact 95% confidence interval
3. Approximate 95% confidence interval



# Summary – Sinus

- The success criterion in the protocol is met
- However, the data shows that BMP could be inferior to bone graft by as much as 20% in terms of successful functional restoration at 6 months

# Dosing Study for Extraction Socket

- Primary objectives
  - To estimate the proportion of patients in each treatment group that have adequate bone formation for dental implant placement
  - To determine the most safe and effective concentration for inducing bone formation
- Population
  - Candidates for a two-stage local alveolar ridge augmentation procedure for buccal wall defects

# Design Parameters

- 80 patients randomized evenly to receive
  - No treatment (for bone formation)
  - Placebo (ACS only)
  - 0.75 mg/ml BMP
  - 1.5 mg/ml BMP
- Treatment assignment blinded to patients and investigators in the last 3 groups
- Treatment course similar to those of sinus studies

# Issues in Analysis

- Prospective analysis plan is not available for evaluation of long-term effectiveness
- Retrospective analysis may not be rigorous enough to establish safety and effectiveness
- In a retrospective analysis, need to determine the appropriate control group and primary endpoint

# Control Group

- Prefer placebo over no treatment because
  - Unlike the other 3 arms, assignment to no treatment was known to the investigator, who decided how to proceed in the treatment course, and the patient, who could have been negatively impacted
  - Placebo helps distinguish the biological effect of BMP from any possible placebo effect, even though it is not normally prescribed as an alternative treatment

# Primary Endpoint

- Suggest using the patient success rate at 6 months post-loading
  - To reflect the long-term performance of the device
  - To be consistent with the evaluation for the sinus augmentation indication
  - To minimize appearance of arbitrariness

# At 6 Months Post-Loading

	Placebo	BMP
Succeeded	7	14
Failed	7	5
Discontinued <sup>1</sup>	3	2
Total	17	21

1. Withdrawn or lost to follow-up

# Methods for Missing Data

1. To count all discontinued patients as failures
2. To exclude discontinued patients from the analysis

# Primary Analysis – 6M Success

Method	Placebo	BMP	Diff	95% CI for Diff
1	41.2%	61.9%	20.7%	(-10.6%, 52.0%)
2	50.0%	72.2%	22.2%	(-11.2%, 55.6%)

- A positive effect may exist, but statistical evidence is insufficient
  - Uninformative confidence intervals
  - Lack of statistical significance ( $p \geq 0.19$ )

# Summary – Extraction Socket

- It appears difficult to conduct a rigorous retrospective analysis, as illustrated by the controversies over the control group and the primary endpoint.



# Clinical Studies

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Food and Drug Administration

# InFuse<sup>®</sup> Bone Graft

## Proposed Indications for Use:

As an alternative to autograft for:

- Sinus Augmentation and
- Localized alveolar ridge augmentation for defects associated with extraction sockets

# InFuse<sup>®</sup> Bone Graft

## PMA Clinical Documentation

- Clinical Studies – conducted under IDEs
  - Sinus Augmentation Dosing Study
  - Sinus Augmentation Pivotal Study
  - Extraction Dosing Study
- Adverse Events
- Risk Analysis

# InFuse<sup>®</sup> Bone Graft

## Sinus Augmentation Study Results

Data	Control	BMP	Difference
Pivotal only	90.8% (69/76)	79.0% (64/81)	-11.8%
		(68.5%, 87.3%)	(-22.8%, -0.8%)
Pivotal + dosing	89.9% (80/89)	79.6% (78/98)	-10.3%
		(70.3%, 87.1%)	(-20.4%, -0.2%)

# InFuse<sup>®</sup> Bone Graft

## Extraction Site Study Results

- Primary purpose – to determine most suitable dose of rhBMP-2 to use
- Designed as a dosing study; no pivotal study submitted
- Retrospective analysis of endpoints
- Ridge height maintained and ridge width increased as compared to no treatment.
- 18 of 21 patients with larger dose were successful
- No treatment control group demonstrated some gain in ridge width



# Adverse Events

- Adverse Events
  - Surgical
  - Antibody responses
  - Ectopic bone formation
- Serious adverse events

# Adverse Events

## InFuse vs. Autograft

	InFuse 1.5 mg/ml rhBMP-2 (n=120)	Bone Graft (n=91)	<i>P value</i>
<b>FACE EDEMA</b>	<b>81 (67.5)</b>	<b>52 (57.1)</b>	<b>0.1500</b>
<b>INFECTION</b>	<b>30 (25.0)</b>	<b>39 (42.9)</b>	<b>0.0076</b>
<b>ORAL EDEMA</b>	<b>81 (67.5)</b>	<b>59 (64.8)</b>	<b>0.7688</b>
<b>ORAL ERYTHEMA</b>	<b>57 (47.5)</b>	<b>56 (61.5)</b>	<b>0.0513</b>
<b>MOUTH PAIN</b>	<b>102 (85.0)</b>	<b>76 (83.5)</b>	<b>0.8489</b>
<b>ABNORMAL GAIT</b>	<b>0 (0.0)</b>	<b>37 (40.7)</b>	<b>&lt;0.0001</b>
ECCHYMOSIS	19 (15.8)	21 (23.1)	0.2157
HYPERGLYCEMIA	8 (6.7)	15 (16.5)	0.0270
ARTHRALGIA	14 (11.7)	24 (26.4)	0.0069
BONE DISORDER	14 (11.7)	11 (12.1)	1.0000
HYPESTHESIA	5 (4.2)	15 (16.5)	0.0036
SINUSITIS	11 (9.2)	15 (16.5)	0.1390
RASH	9 (7.5)	34 (37.4)	<0.0001
<b>SENSORY LOSS</b> (autograft donor sites)	—	<b>9% - 12%</b>	—



# Adverse Events

## Antibody Response

	InFuse	Autograft
Anti-rhBMP-2	2.2%	0.0%
Anti Bovine Type I Collagen	20%	31%
Anti-Human Type I Collagen	0.0%	0.0%

InFuse Risks	
Failure to induce bone in desired quantities	Potential hypersensitivity to components
Unknown effects on fetal development	Unknown effects on hepatic/renal systems
Potential Immunogenicity problems	Sensitization upon subsequent challenge
Unknown effects on mother's milk	Unknown effects on undiagnosed tumors

Autograft Risks	
Failure to induce bone in desired quantities	Sometimes limited supply of autogenous bone
Sensory Loss	Pain
Gait disturbance	Swelling



InFuse Benefits	
Bone formation	No second surgery site
No need for allograft or heterograft	Responds in manner similar to native bone
Lower incidence of adverse events	Lower incidence of surgical complications
No need to use a sometimes limited supply of autogenous bone	Lower incidence of surgical complications

Autograft Benefits	
No device related allergic reactions	Responds in manner similar to native bone
Bone formation	The standard of care



# In Summary

## Sinus Augmentation Study

- Less effective than autograft after 6 months of loading
- 73% Success criterion met
- Bone generated in sufficient quality and quantity to place and support dental implants

## Extraction Site Ridge Augmentation Dosing Study

- No pivotal study
- No active control group
- Maintenance of alveolar ridge height and width
- Capable of creating bone sufficient in quality and quantity to support endosseous implants

## Both Studies

- Decreased morbidity with InFuse
- rhBMP-2/ACS antibody response





# Panel Question #1

In light of the preclinical data and the adverse events presented for InFuse, please discuss the safety of using InFuse for each of the proposed indications:

1. Sinus augmentation
2. Ridge augmentation at extraction sites



# Panel Question #2

An analysis of the sinus augmentation studies indicates that InFuse may be up to 20% less effective than the standard of care, the autograft.

	Control	InFuse	Difference
Pivotal + Dosing	89.0% (80/89)	79.6% (78/98)	-10.3%
		(70.3%, 87.1%)	(-20.4%, -0.2%)

1. In light of the above statistics from the FDA statistical presentation, please discuss the clinical implications of the InFuse results presented in this PMA.
2. Based on the data presented in the PMA for this indication, please discuss whether the possible reduction in morbidity associated with InFuse outweighs the potential reduction in effectiveness when compared to autograft  
(Risks vs. Benefits).



# Panel Question #3

Given the data submitted for ridge augmentation at tooth extraction sites, please discuss whether there is sufficient valid scientific evidence for this indication, to arrive at a clinically meaningful conclusion with respect to device effectiveness?

1. Is the data submitted rigorous enough to support this Indication for Use?
2. Given the data provided, please discuss whether it is possible to evaluate the risks vs. benefits for this indication.



# Panel Question #4

Please discuss whether sufficient valid scientific evidence has been provided to demonstrate the safety and effectiveness of InFuse Bone Graft for the following indications requested by the sponsor:

1. Sinus augmentation
2. Extraction socket augmentation



# Safety – 21 CFR § 860.7(d)(1)

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.



# Effectiveness – 21 CFR § 860.7(e)(1)

There is reasonable assurance that a device is effective when it can be determined, based upon scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

# Valid Scientific Evidence – 21 CFR § 860.7(c)(2)

Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.



