

**P060021**  
**Stryker Biotech**  
**OP-1 Putty**

**Restorative Devices Branch**  
**Division of General, Restorative**  
**and Neurologic Devices**  
**Office of Device Evaluation**  
**Center for Devices and Radiological Health**

# **Review team**

## **Panel presentations**

**Aric Kaiser, MS - lead reviewer - introduction**

**Kathy Lee, MS – CMC concerns**

**Susan Kirshner, PhD – immunology concerns**

**Ryan Kretzer, MD – clinical concerns**

**Jianxiong (George) Chu, PhD - statistical concerns**

# **Review team**

## **Additional review expertise**

### **CDRH**

- **Robert Betz**
- **Peter Hudson**
- **Tracey Bourke**
- **Martin Hamilton**
- **Mary Ann Wollerton**

### **CDER**

- **Harold Dickensheets**
- **Ennan Guan**
- **Gemma Kuijpers**
- **William Lubas**
- **Naomi Lowy**
- **Brenda Uratani**

# Product description

## combination product consisting of:

- recombinant human bone morphogenetic protein 7 (OP-1)
- Type I bovine collagen
- carboxymethylcellulose
- saline

# Product description

## proposed intended use/indication

autograft replacement as an aid to  
uninstrumented posterolateral fusion for  
treatment of grade 1 or 2 lumbar  
spondylolisthesis

# Previous FDA action

## letter outlining multiple deficiencies:

- key safety issues not adequately addressed
- did not meet primary endpoint (overall subject success at 24 months) approved in original IDE
- did not meet revised primary endpoint proposed in pre-PMA submission
- new issues resulting from additional revised primary endpoint provided in response to major deficiency letter
- inadequate responses to concerns associated with manufacturing, potency, dosing and immune response

# Previous FDA action

**specific requests outlined in letter:**

**request for modified protein manufacturing  
to address concerns associated with:**

**gamma irradiation**

**potency**

**stability**

**request for new data:**

**non-clinical and clinical dosing studies**

**clinical trial**

# Previous FDA action

**additional requests outlined in letter:**

**additional manufacturing information**

**improved antibody assays**

**additional repro/tox study**

# PMA vs. Humanitarian Device Exemption

## PMA

- approval based on demonstration of safety and effectiveness resulting from clinical data
- use in any patient meeting the approved use
- no limits on number of patients
- may be used without prior IRB approval

## HDE

- approval based on demonstration of relative safety and probable benefit → exempt from PMA effectiveness requirement
- only approved for populations consisting of <4000 patients/year
- fills unmet need
- IRB approval required prior to use

# OP-1 HDEs

## H010002 - OP-1 Implant

approved with conditions – October 17, 2001

“This device is indicated for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed.”

## H020008 - OP-1 Putty

approved with conditions - April 7, 2004

“This device is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.”

# Basis for approval of OP-1 HDEs

## HDE requirements

- identification of orphan population
- lack of treatment options for orphan population  
→ demonstration of unmet need

## non-clinical data

- description of proposed mechanism of action of OP-1
- animal models of bone formation or spinal fusion

## clinical data

- extrapolated probable benefit based on no/minimal clinical data from proposed use
- extrapolated safety profile from different use
- no antibody assay data

# Panel questions summary

## protein manufacturing and irradiation sterilization

- protein stability/potency
- biological activity
- immunological response

# Panel questions summary

## success definitions and statistical analyses

- **clinical relevance**
- **statistical soundness**

# Panel questions summary

## clinical performance - effectiveness

- general effectiveness discussion
- necessity of additional studies
  - human dosing study
  - clinical trial

# Panel questions summary

## clinical performance - safety

- general safety discussion
- clinical concerns of immune response
- safety concerns and impact on maternal and/or child health

# CMC summary and concerns

**Kathy Lee, M.S**

**Division of Therapeutic Proteins**

**Office of Biotechnology Product**

**Office of Pharmaceutical Sciences**

**Center for Drug Evaluation and Research**

# OP-1

## Recombinant human Osteogenic Protein 1 (OP-1), also known as BMP-7

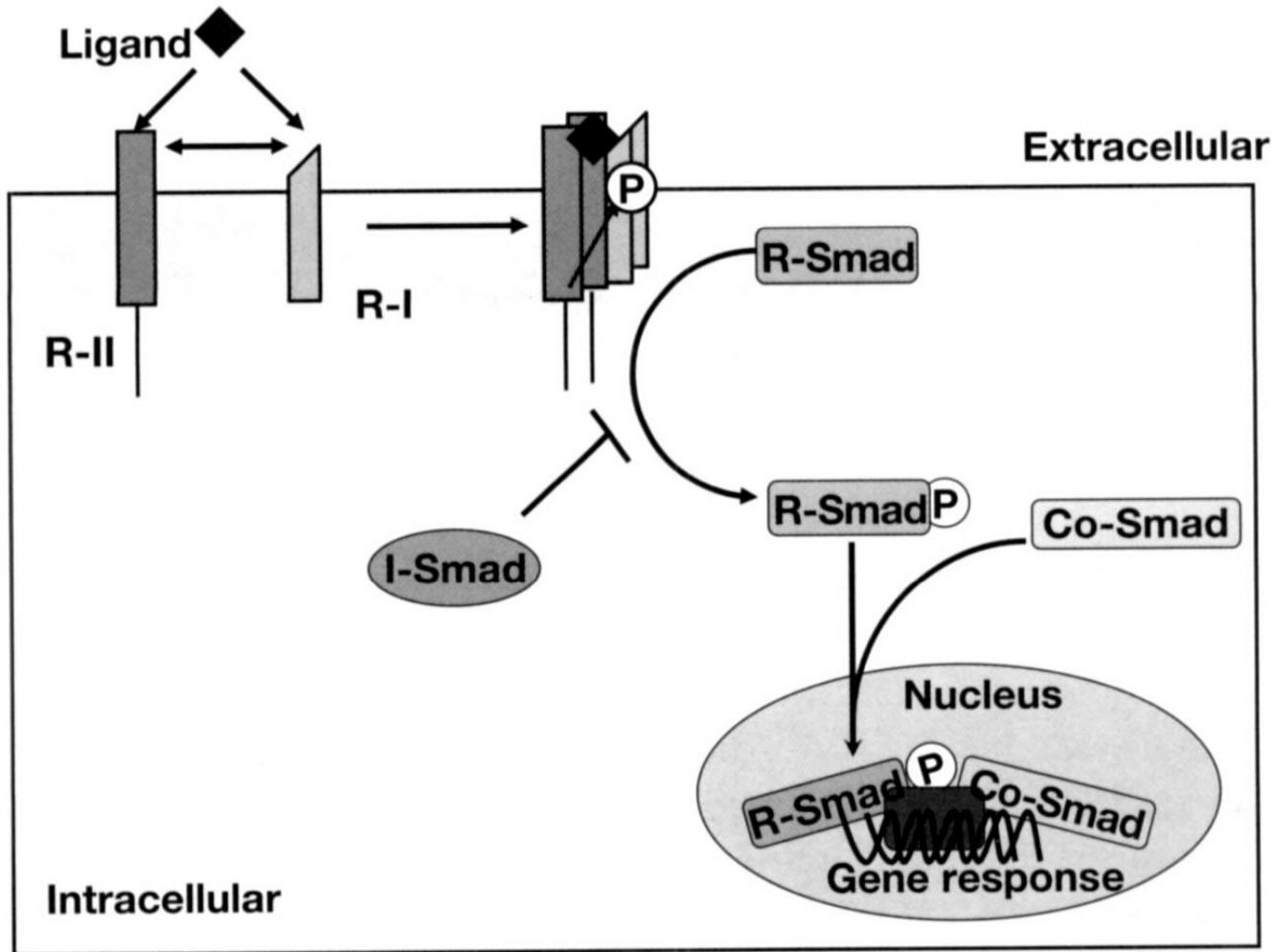
- Member of transforming growth factor-beta (TGF- $\beta$ ) superfamily
- Initiates a signaling cascade leading to recruitment and differentiation of mesenchymal stem cells
- Results in bone formation

# BMP-7 biology

**BMP-7 is critical in development and may have functions post-development**

- **Fetal kidney, eye and bone development**
  - **BMP-7 knock-outs are neonatally fatal due to kidney dysfunction**
- **In adult animals BMP-7 provides protection from post-ischemic reperfusion injury in kidney and brain**

**Recombinant human OP-1 is a dimer, is glycosylated and has N-terminal truncated forms**



# Manufacture of recombinant human OP-1

- 1. Produced in Chinese Hamster Ovary Cells**
  - Using recombinant technology, the OP-1 gene is inserted into the host DNA
  - CHO cells secrete the OP-1 protein into cell supernatant
- 2. The supernatant with the protein is then processed through a series of purification columns and stored**
- 3. The purified OP-1 is tested using a variety of assays to verify product quality**
- 4. Once released, the OP-1 is further processed as part of the OP-1 Implant**

# OP-1 Putty

**OP-1 Putty is a mixture of recombinant OP-1 protein and bovine collagen**

**These two components are produced separately, mixed, dried, terminally sterilized by high dose  $\gamma$  irradiation and then co-packaged with the sterile dried putty additive**

# **$\gamma$ -irradiation and proteins**

**Ionizing radiation is an effective method for elimination of microorganisms including bacteria and viruses**

**Used for surgical instruments and devices, as well as some pharmaceuticals and foods**

**25 kGy recommended dose to sterilize medical devices**

**OP-1 Putty is sterilized with 24.5 kGy – 31.5 kGy**

# **$\gamma$ -irradiation and proteins**

**$\gamma$  -irradiation is not typically used for biologic (protein) drugs, due to their general sensitivity to the effects of ionizing radiation**

- The typical sterilization method used for biologics are filtration and aseptic processing**

# Effects of ionizing radiation on proteins

## Direct effects on protein structure

- Breakage of covalent bonds randomly along the polypeptide chain, causing protein truncation and inactivation
- Larger molecules are more susceptible

## Indirect effects on protein structure

- Oxidation, deamidation, disulfide modification/shuffling, cross-linking

# Observed changes induced by $\gamma$ -irradiation on OP-1 protein and Putty

## Loss of activity

- 30% decrease in potency assay after extraction from OP-1 Implant

## Aggregation

- Increased levels of OP-1 aggregates, (~ 19-fold higher)

Increased amounts of truncated and oxidized variants

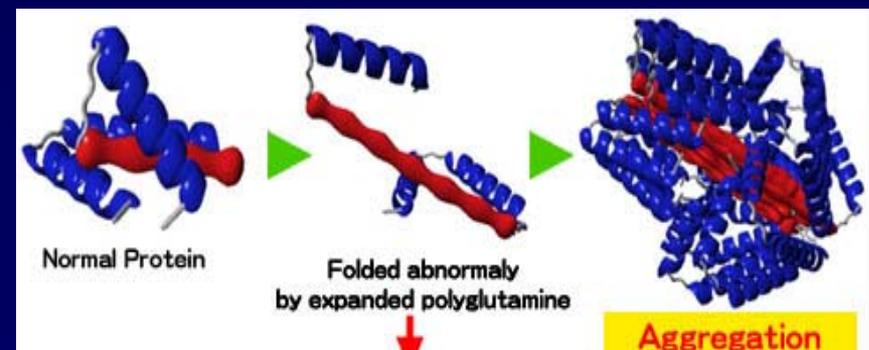
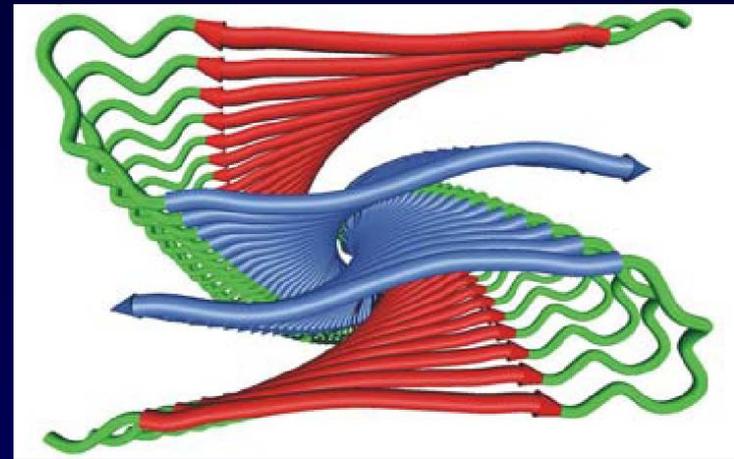
Increased Immune response to OP-1 Putty

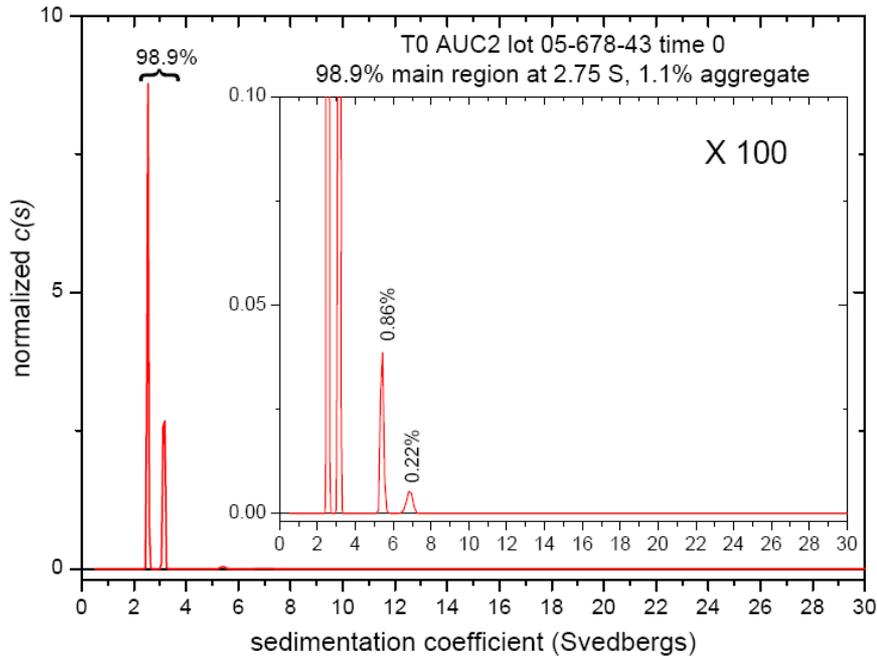
Development of neutralizing antibodies against OP-1 Putty and potential cross-reactivity on endogenous BMP-7

# Aggregate definition

Aggregates are high MW protein species composed of multimers of natively conformed or denatured protein

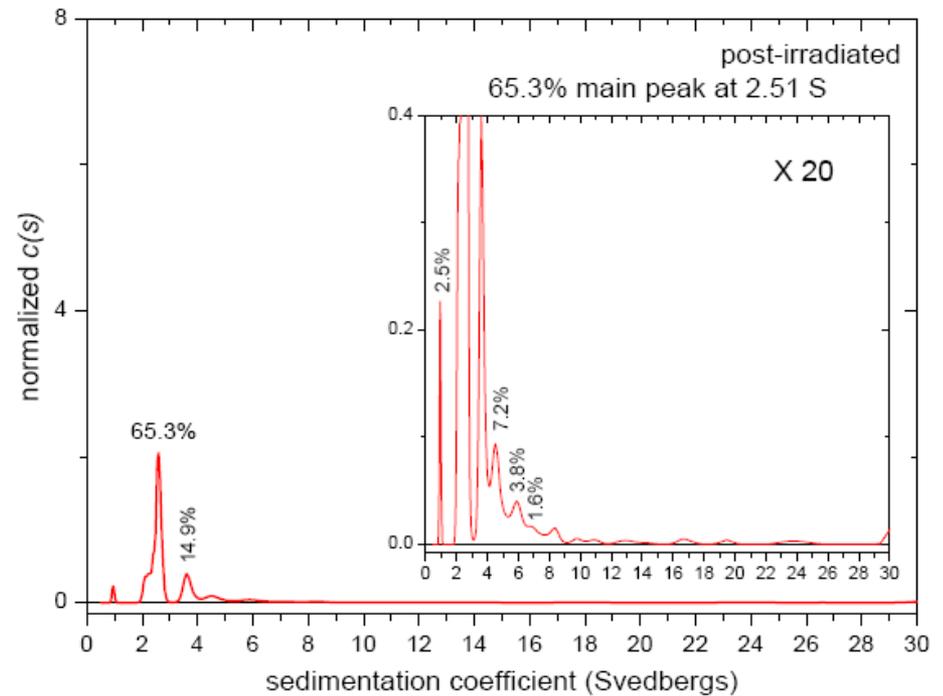
- soluble or insoluble
- reversible or irreversible within the given environment





**Non-irradiated OP-1 aggregate content as measured by AUC**

**Irradiated OP-1 aggregate content as measured by AUC**



# Reducing SDS-PAGE of OP-1 from OP-1 Implant Before and After Irradiation

Mol Wgt (kDa)

200

116.3

97.4

66.3

55.4

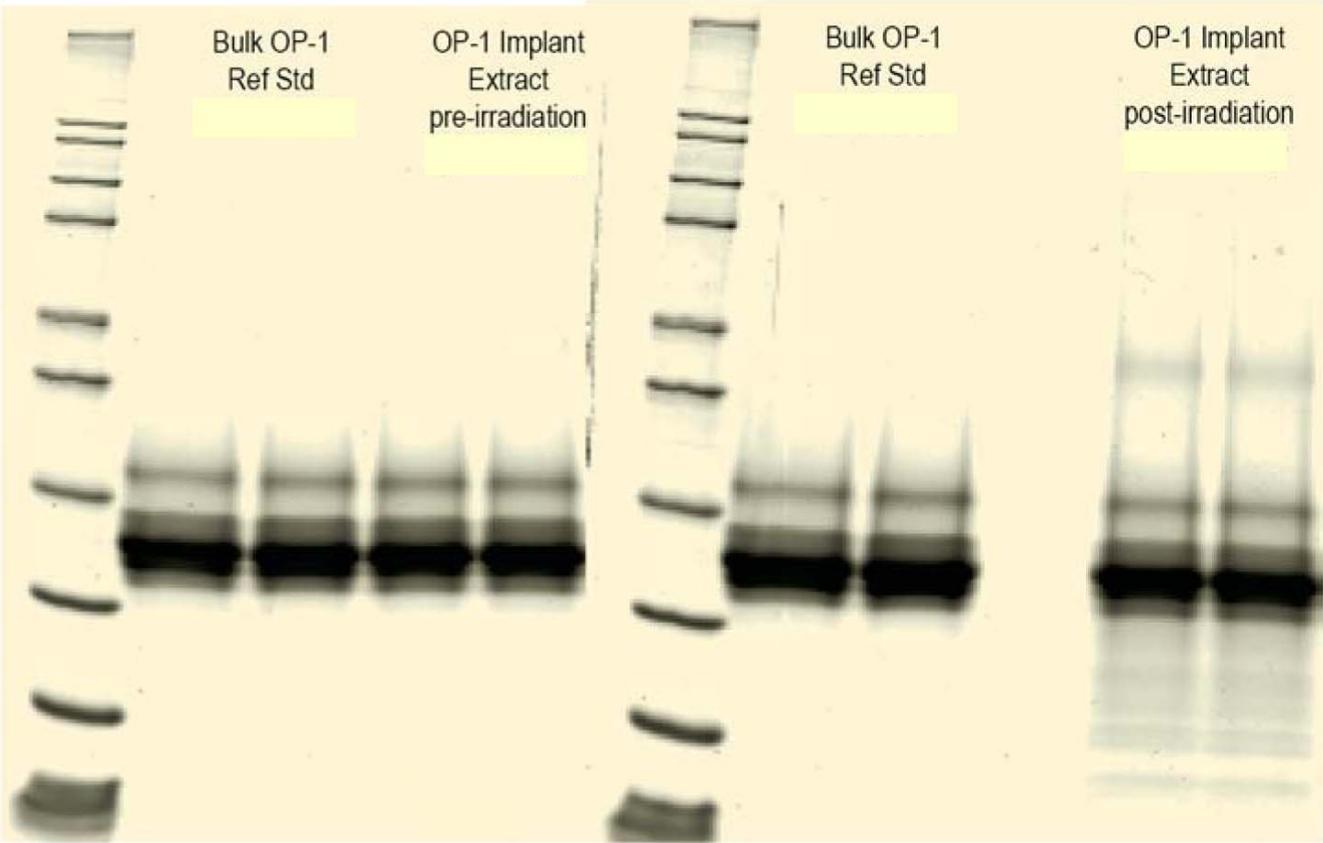
36.5

31.0

21.5

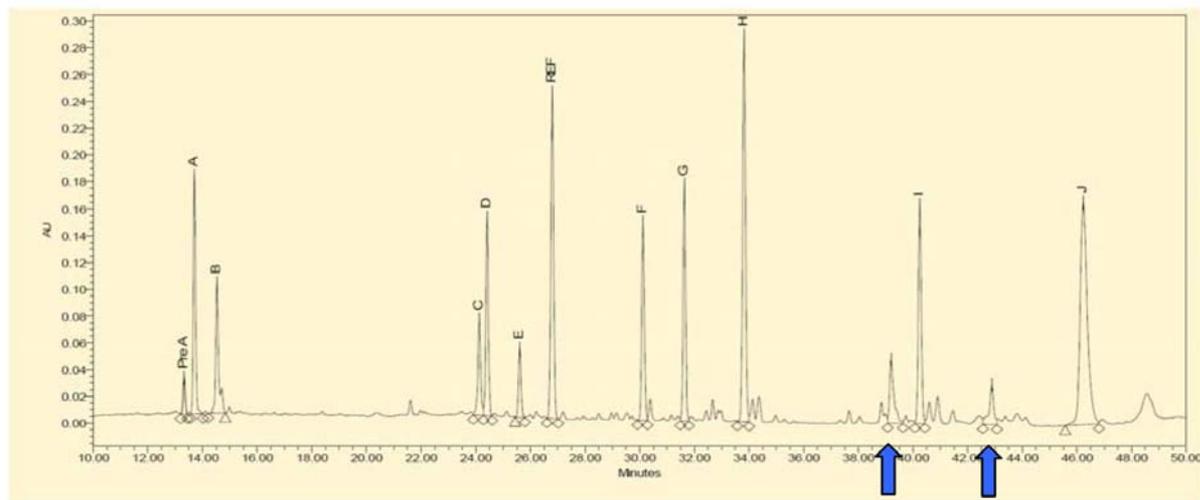
14.4

6.0

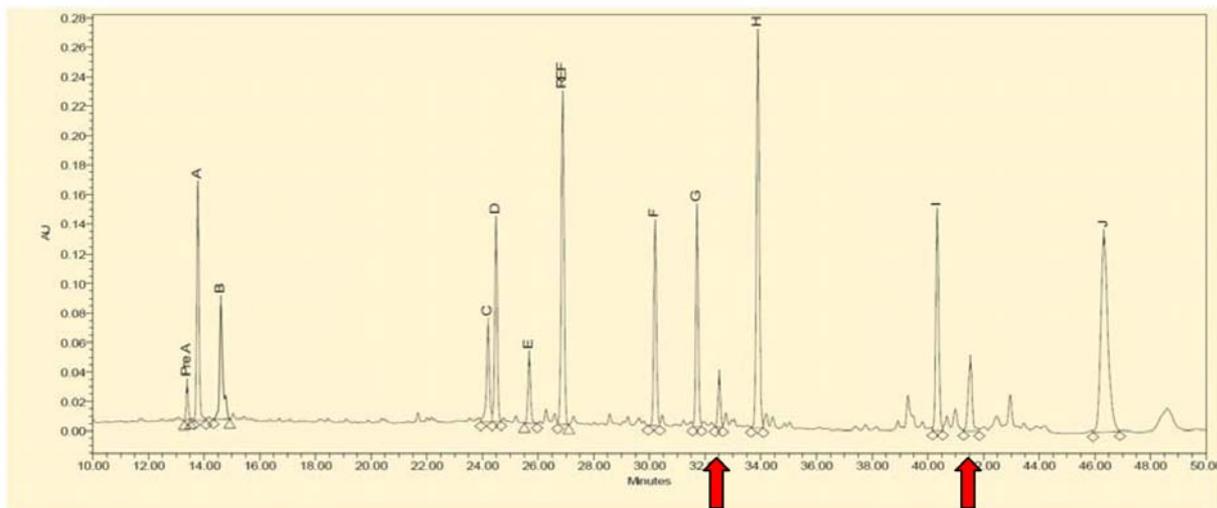


Peptide mapping with  
OP-1 from  
Putty  
before and  
after  
 $\gamma$ -irradiation

before Irradiation



after Irradiation



# Summary

**$\gamma$ -irradiation is used to sterilize OP-1 Putty**

**$\gamma$ -irradiation is not used for approved recombinant protein products**

**$\gamma$ -irradiation causes loss of biological activity, aggregation, truncation, and oxidation of recombinant human OP-1**

**A high incidence of immunogenicity is observed with  $\gamma$ -irradiated OP-1 Putty**

# **Immunology summary and concerns**

**Susan Kirshner, Ph.D.**

**Division of Therapeutic Proteins  
Office of Biotechnology Product  
Office of Pharmaceutical Sciences  
Center for Drug Evaluation and Research**

# Assessing immune responses: binding and neutralizing antibodies

**Binding antibodies (BAb)**– antibodies that specifically bind to the target molecule, in this instance OP-1.

**Neutralizing antibodies** – a subset of BAb that inhibit the activity of the target molecule (OP-1) in a bioassay.

- Indicates that at least some of the antibodies interfere with the receptor-ligand interaction
- Provides information on potential clinical impact

**Both BAb and NAb can interfere with drug function in vivo.**

# Concerns for antibodies in the clinic

<b>Clinical Concern</b>	<b>Clinical Outcome</b>
<b>Safety</b>	<ul style="list-style-type: none"><li>• Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome</li><li>• Hypersensitivity reactions</li></ul>
<b>Efficacy</b>	<ul style="list-style-type: none"><li>• Enhancing or decreasing efficacy by extending or decreasing half life.</li><li>• Decrease efficacy by altering biodistribution away from target</li></ul>
<b>Pharmacokinetics</b>	<ul style="list-style-type: none"><li>• Antibody production may dictate changes in dosing level due to PK changes.</li></ul>
<b>None</b>	<ul style="list-style-type: none"><li>• Despite generation of antibodies, no discernable impact</li></ul>

# Issues regarding anti-OP-1 Ab

## Cross-reactivity of anti-OP-1 antibodies on endogenous BMP-7

- To date no data have been provided to the FDA regarding antibody cross-reactivity

## In animal studies anti-OP-1 antibodies cross the placenta

## Studies indicate BMP-7 activities include

- Fetal kidney, eye and bone development
  - BMP-7 knock-out is neonatally fatal due to kidney dysfunction
- Protection from post-ischemic reperfusion injury in kidney and brain in adult animals

**We do not know how the presence of antibodies will impact the normal functions of BMP-7**

# Immunogenicity results

**There was a high incidence of binding (94%) and neutralizing (25.6%) antibodies developing in patients treated with OP-1 putty.**

**41% of subjects (71/173) still tested positive for binding antibodies 24 months post-treatment.**

**No patients tested positive for neutralizing antibodies after 12 months.**

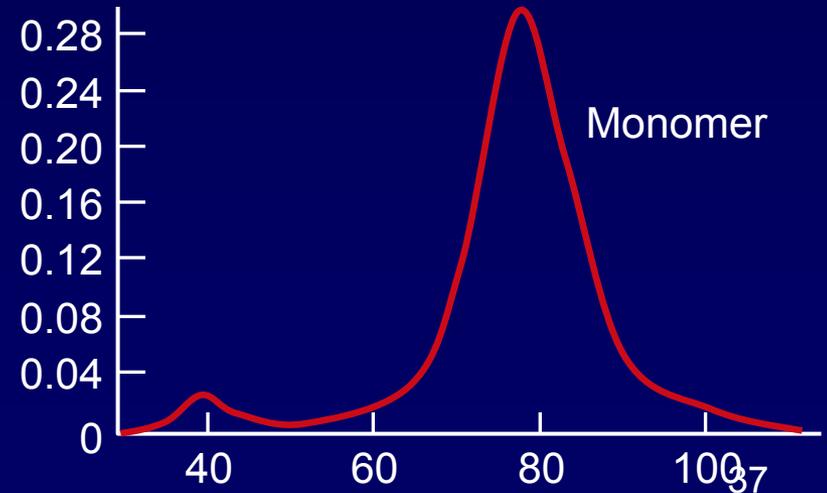
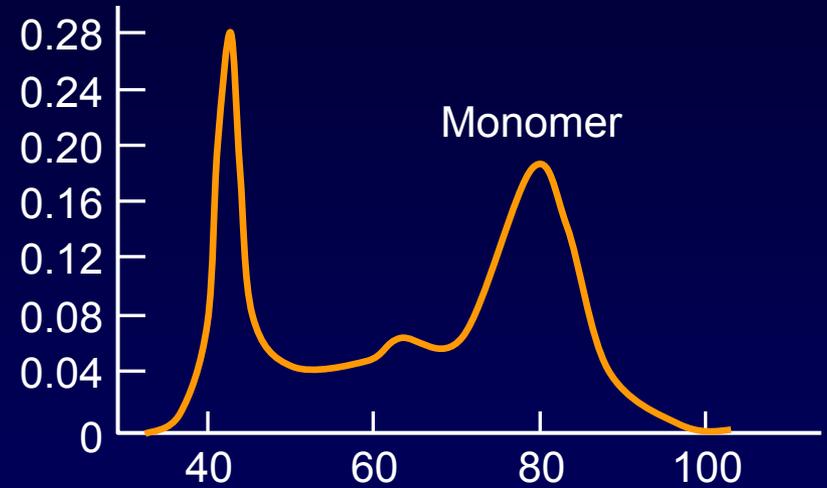
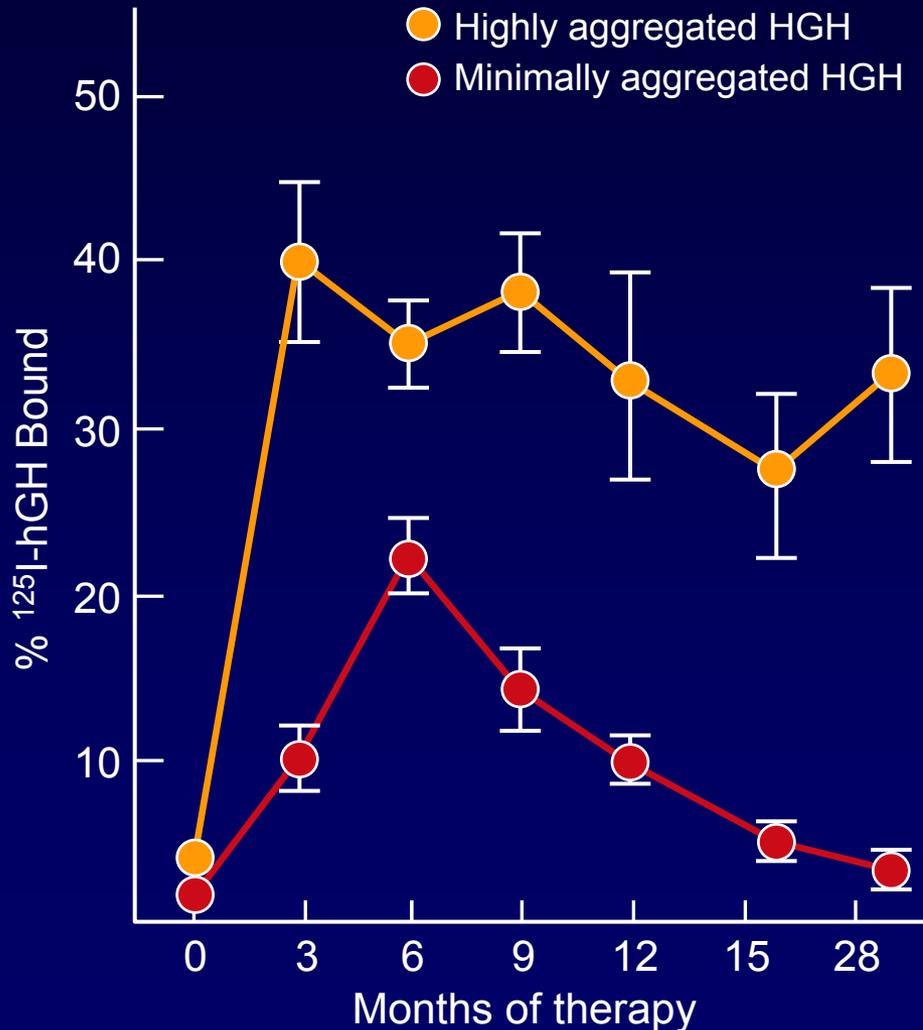
**36.7% of subjects (18/49) tested positive for binding but not neutralizing antibodies at 36 months.**

# Aggregates and immunogenicity

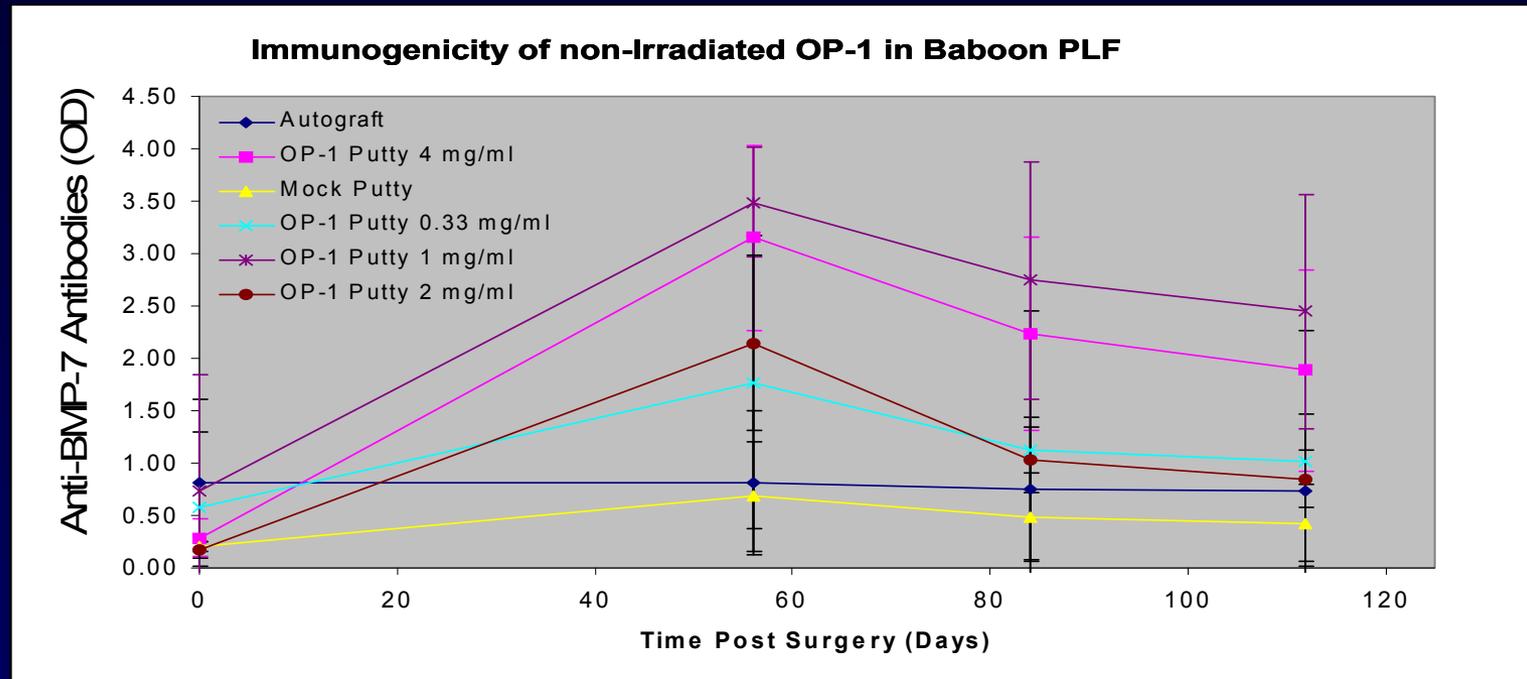
**Aggregated proteins tend to be more immunogenic than their non-aggregated counterparts**

**Protein aggregation may qualitatively and/or quantitatively impact the immune response**

# Case study on aggregates and immunogenicity: the amount of aggregates determines antibody persistence to HGH (Moore and Leppert 1980)



# There is insufficient data regarding OP-1 to understand the impact of aggregates on immunogenicity



The baboon data does not cover a long enough time span to evaluate its relevance to the human experience with OP-1, i.e. are some baboons sero-positive at 24 months.

# Immunogenicity summary

There was a high incidence of binding (94%) and neutralizing (25.6%) antibodies developing in patients treated with OP-1 putty.

41% of subjects still tested positive for binding antibodies 24 months post-treatment.

The impact of these antibodies on the long term health of those patients is not understood.

# **Clinical summary and concerns**

**Ryan M. Kretzer, MD**

**Division of General, Restorative, and  
Neurological Devices  
Office of Device Evaluation  
Center for Devices and Radiological  
Health**

# Summary of clinical studies

**1) Pilot Clinical Study: S99-01US**

**2) Pivotal Clinical Study: S01-01US**

**3) Extension Clinical Study: 06-UPLF-01**

# Indication for use

**“OP-1® Putty is indicated for posterolateral lumbar spinal fusion in patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment.”**

# Pilot clinical study: S99-01US

**Design:** Prospective, randomized, controlled, multicenter clinical trial

**Goal:** To evaluate the safety and effectiveness of OP-1 Putty both alone and as an adjunct to autograft in the augmentation of un-instrumented spinal fusion in patients with grade 1-2 degenerative spondylolisthesis with spinal stenosis at a single level from L3-S1.

# Treatment arms

**Initial protocol:** OP-1 Putty + autograft vs. autograft alone

**Protocol revision:** OP-1 Putty vs. autograft

# Blinding

**Due to the nature of second-site surgery for iliac crest bone harvest, patient/clinician blinding was not possible in relation to the OP-1 Putty only treatment group**

**Radiological assessments were performed by 2 independent, blinded radiologists with discrepancies resolved by a 3<sup>rd</sup> reviewer**

# Primary effectiveness endpoint

**Overall Treatment Success at 24 mo., defined as a composite of:**

- **$\geq 20\%$  improvement in ODI (Oswestry Disability Index)**
- **Radiographic spinal fusion**
  - **bridging bone on x-ray at the treated level AND**
  - **$\leq 5^\circ$  angular motion AND**
  - **$\leq 2$  mm translational motion**
- **Absence of reoperation intended to promote fusion at 24 mo.**

# Primary safety endpoint

**A comparison of complications and neurological status between groups**

# Secondary endpoints

**SF-36 Health Outcomes Survey scores**

**Leg/buttock pain measured by VAS**

**Donor site pain measured by VAS**

**Disc height on x-ray**

**Degree of angular and translational motion**

# Patients treated

## 48 patients treated:

- OP-1 Putty only: 24 patients
- OP-1 Putty + autograft: 12 patients
- Autograft: 12 patients

# Results - effectiveness

Outcome	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes
Overall success with LOCF	24	11 (45.8)	12	5 (41.7)	12	4 (33.3)
Overall success without LOCF	18	10 (55.6)	9	4 (44.4)	9	3 (33.3)
Radiographic success	19	11 (57.9)	10	5 (50.0)	10	4 (40.0)
Bridging Bone	19	15 (78.9)	10	7 (70.0)	10	9 (90.0)
Angulation Success	18	12 (66.7)	10	5 (50.0)	10	5 (50.0)
Translational Movement	18	16 (88.9)	10	6 (60.0)	10	7 (70.0)
ODI	18	17 (94.4)	9	8 (88.9)	10	6 (60.0)
No Retreatment	24	24 (100.0)	12	11 (91.7)	12	12 (100.0)

# Results - *safety*

## Pseudoarthrosis

- 30% (13/36) of patients treated with OP-1 Putty (2 patients required reoperation)
  - OP-1 Putty only: 42% (10/24) of patients
  - OP-1 Putty + autograft: 25% (3/12) of patients
- 0% (0/12) of patients treated with autograft

## Immunogenicity

- Antibody titers at 6 months:
  - OP-1 Putty only: 92% (22/24) of patients
  - OP-1 Putty + autograft: 83% (10/12) of patients
- Neutralizing antibodies at 6 weeks:
  - OP-1 Putty only: 29% (7/24) of patients
  - OP-1 Putty + autograft: 0% (0/12) of patients

## Pseudoarthrosis in patients with neutralizing antibodies

- 57% (4/7) of patients who developed neutralizing antibodies also experienced pseudoarthrosis

# FDA review

OP-1 Putty looked promising in terms of overall success compared to the other two groups

The autograft treatment group (control) showed the highest percentage of patients with bridging bone formation

OP-1 Putty showed high pseudoarthrosis and immunogenicity rates compared to control

Of note, there were **no concerns** regarding OP-1 Putty migration (medial vs. lateral) or the inadequacy of x-ray imaging for the quantification of bone/bridging bone formation

Although some questions existed, the results of the Pilot Study were felt to support a Pivotal Trial

# Pivotal clinical study: S01-01US

**Design:** Prospective, randomized, controlled, open-label, blinded radiographic assessment, multicenter clinical trial

**Goal:** To evaluate the safety and effectiveness of OP-1 Putty as a replacement for autograft in patients with single level (L3-S1) degenerative spondylolisthesis (Grade 1-2) and spinal stenosis undergoing decompression and un-instrumented posterolateral lumbar fusion.

# Treatment arms

**OP-1 Putty vs. autograft (autogenous iliac crest bone graft)**

**2:1 randomization scheme**

# Blinding

**Due to the nature of second-site surgery for iliac crest bone harvest, patient/clinician blinding was not possible in relation to the OP-1 Putty treatment group**

**Radiological assessments were performed by 2 independent, blinded radiologists with discrepancies resolved by a 3<sup>rd</sup> reviewer**

# **Overall treatment success – definition #1 (approved by FDA)**

**Overall Treatment Success at 24 mo., defined as a composite of:**

- **≥ 20% improvement in ODI (Oswestry Disability Index)**
- **Radiographic spinal fusion**
  - **bridging bone on x-ray at the treated level AND**
  - **≤ 5° angulation on flexion-extension x-rays AND**
  - **≤ 2 mm translational motion on flexion-extension x-rays**
- **Absence of a decrease in neurological status (muscle strength, reflexes, sensory, straight leg raise) unless attributable to a concurrent medical condition or to the surgical procedure**
- **Absence of retreatment**
- **Absence of treatment-related serious adverse events (SAEs)**

# Overall treatment success - *revised definitions (acknowledged but not approved by FDA)*

**Definition #2** (after all clinical data had been collected but prior to closure of the database):

- Radiographic criteria changed from “presence of bridging bone” to “presence of bone”
- Translational motion changed from “ $\leq 2\text{mm}$ ” to “ $\leq 3\text{mm}$ ”

**Definition #3** (based on *post hoc* analysis of the data):

- Radiographic criteria removed (i.e. “Overall Clinical Success”)

**Definition #4** (based on *extension study*):

- 24 month clinical outcome data
- 36+ month CT scan data
- Absence of retreatment based on 36+ month data

# Safety endpoints

**Adverse events**

**Clinical laboratory evaluations**

**Neurological status**

# Secondary endpoints

**Overall success at 12, 24, and 36 months without imputation of missing data**

**Components of overall success (ODI, absence of treatment-related SAEs, absence of retreatment to promote fusion, neurological success, and overall radiographic success at 12, 24, and 36 months without imputation of missing data)**

**Overall radiographic success at 24 months with missing data imputed**

# **Additional information**

**VAS results for pain assessment**

**Donor site pain (autograft only)**

**Medication use**

**Hospitalization data**

**General health survey (SF-36)**

# CT imaging

**CT imaging was performed on all patients at 9 mo. post-treatment in order to assess for bridging bone formation and pseudoarthrosis**

**This was not included as a criteria for patient success or as a study endpoint**

# Patients

**295 patients treated:**

- **OP-1 Putty only: 208 patients**
- **Autograft: 87 patients**

# Treatment

## Conservative care

- $\geq 6$  months prior to surgery

## Surgical procedure

- Posterior decompression and posterolateral intertransverse process arthrodesis
- Multi-level decompression was permitted but only 1 level could be fused
- 1 OP-1 Putty unit used on each side of the spine in each patient in the treatment group

## Bracing

- All patients braced in a lumbar corset for 3 months post-operatively

# Relevant demographics

**Patient age:** Mean 68 yrs. (36-84)

**Spinal level:** L4-5 treated in 86% of patients in both groups

**Spondylolisthesis grade:**

- **OP-1 Putty:** 93% of patients were grade 1
- **Autograft:** 92% of patients were grade 1

# Results – *overall treatment success*

OP-1 was not shown to be non-inferior to autograft in:

- Overall Treatment Success (using success definition #1 or #2)
- ODI Success
- Radiographic Success (using success definition #1 or #2)

OP-1 was shown to be non-inferior to autograft in:

- Absence of Retreatment
- Neurological Success

# Results – *safety (AEs)*

## AEs

- Similar rates of AEs, serious AEs, treatment-related AEs, and deaths were noted between the OP-1 and control groups
- Although not statistically significant, there was a trend towards a higher rate of treatment-related serious AEs in the investigational group (25/208 = 12%) compared to control (6/87 = 7%) (P = 0.22)

## Pseudoarthrosis

- OP-1 Putty: 11% of patients
- Autograft: 12% of patients

# Results – *safety (immunogenicity)*

## Immunogenicity

- Neutralizing Abs (peaked at 6 wks. – 3 mos.; resolved by 24 mos.; no correlation with AEs)
  - OP-1 Putty: 26% of patients
  - Autograft: 1% of patients

## Immunogenicity and the Relation to Study Success/Radiographic Success

- Overall Treatment Success in OP-1 Patients (no statistical significant difference)
  - Neutralizing Abs: 30%
  - Non-neutralizing Abs: 41%
- Overall Radiographic Success in OP-1 Patients (no statistical significant difference)
  - Neutralizing Abs: 42%
  - Non-neutralizing Abs: 56%

# Results – 9 month CT scan

## “Any bone” formation:

- OP-1 Putty: 85% of patients
- Autograft: 99% of patients

## “Bridging bone” formation:

- OP-1 Putty: 31% of patients
- Autograft: 54% of patients

# Concerns regarding alternate success definition #2

**Definition #2**: change from “bridging bone” to “bone” formation

- In order to prove radiographic fusion, a continuous column of bone should connect the two levels to be fused (irrespective of medial vs. lateral location of bone)
- In the absence of surgery to explore the fusion mass, bridging bone formation on radiographic imaging is the only surrogate available for the determination of the device’s ability to build new bone

# Concerns regarding alternate success definition #3

**Definition #3**: elimination of radiographic criteria from “Overall Treatment Success” (newly defined “Overall *Clinical Success*”)

- Based on *post hoc* analysis
- Radiographic criteria were the only blinded components of effectiveness in the study (due to second site surgery in the control group)
- Because the natural history of spondylolisthesis progression remains unclear, radiographic evidence of bone formation (esp. bridging bone) is the best indicator of bony fusion
  - Elderly population (mean age 68 years), low grade slip (93% grade 1)
  - Clinical success at 2 years may be more indicative of adequate operative nerve root/spinal canal decompression than of spinal fusion

# FDA review

OP-1 Putty was not shown to be non-inferior to autograft in “Overall Treatment Success” as prospectively defined at the beginning of the study (definition #1) and after subsequent revision of the definition of success (definition #2).

Although immunogenicity did not appear to play a role in AEs in OP-1 treated patients, there was a trend towards decreased “Overall Treatment Success” and “Radiographic Success” in patients who developed neutralizing Abs compared to those who developed non-neutralizing Abs.

# Extension clinical study: 06-UPLF-01

## i.e. “Overall Treatment Success” Definition #4

- 24 month clinical outcome data
- 36+ month CT scan data
- Absence of retreatment based on 36+ month data

**Sponsor attempted to collect longer term follow-up in the form of a single CT scan on study subjects, as well as a clinical assessment**

## **Based on the sponsor’s belief that:**

- 1) X-rays were inadequate to evaluate bone formation in OP-1 treated patients
- 2) The initial radiological reviewers were looking in the wrong location (lateral) for bone formation, because device migration after muscle closure led to more medial bone formation

# Patients

## 257 eligible patients

- 79% (202/257) were re-evaluated
  - OP-1 Putty: 79% (144/183) of patients
  - Autograft: 78% (58/74) of patients

Mean follow-up 4.4 years (range 3.7-5.5 yrs.)

# Results – overall treatment success

As reported by the Sponsor:

Overall Treatment Success (using “any bone” on CT):

- OP-1 Putty: 47% of patients
- Autograft: 47% of patients (P = 0.025 using a revised non-inferiority margin of 14% and multiple imputation for missing data)
- *Concerns regarding this analysis will be discussed by our statistician*

Overall Treatment Success (using “bridging bone” on CT):

- mITT analysis
  - OP-1 Putty: 26% (39/148) of patients
  - Autograft: 36% (21/58) of patients (P = 0.175; not non-inferior)
- SPP analysis
  - OP-1 Putty: 30% (39/131) of patients
  - Autograft: 40% (21/52) of patients (P = 0.221; not non-inferior)

# Results – *bridging bone formation on 36+ month CT*

## “Bridging bone” formation

- OP-1 Putty: 56% (68/122) of patients
- Autograft: 83% (35/42) of patients
- (P = 0.001)

# Concerns regarding alternate success definition #4

Implant migration had not been previously observed in either the non-clinical animal studies or the pilot study

What is the relevance of evaluating 36+ month CT scans given that...

- 1) The 9 month CT imaging (per radiologist reading in pivotal study and re-reading in extension study) showed less bone and less bridging bone in the OP-1 Putty group compared to control
- 2) Clinical practice generally dictates the need for an earlier evaluation of fusion (i.e. 12-24 months)

# FDA review

Using the originally approved radiographic definition of “bridging bone” formation, OP-1 was not found to be non-inferior to autograft in “Overall Treatment Success” (definition #4)

# Summary

Regardless of the definition of treatment success, OP-1 Putty was not found to be non-inferior to autograft in the treatment of single level (L3-S1) degenerative spondylolisthesis (Grade 1-2) in patients undergoing decompression and un-instrumented posterolateral lumbar fusion.

# **Statistical summary and concerns**

**Jianxiong (George) Chu, Ph.D.**

**General & Surgical Devices Branch**

**Division of Biostatistics**

**Office of Surveillance and Biometrics**

**Center for Devices and Radiological**

**Health**

# Outline

**Study Design:** Pivotal S01-01US + Extension 06-UPLF-01

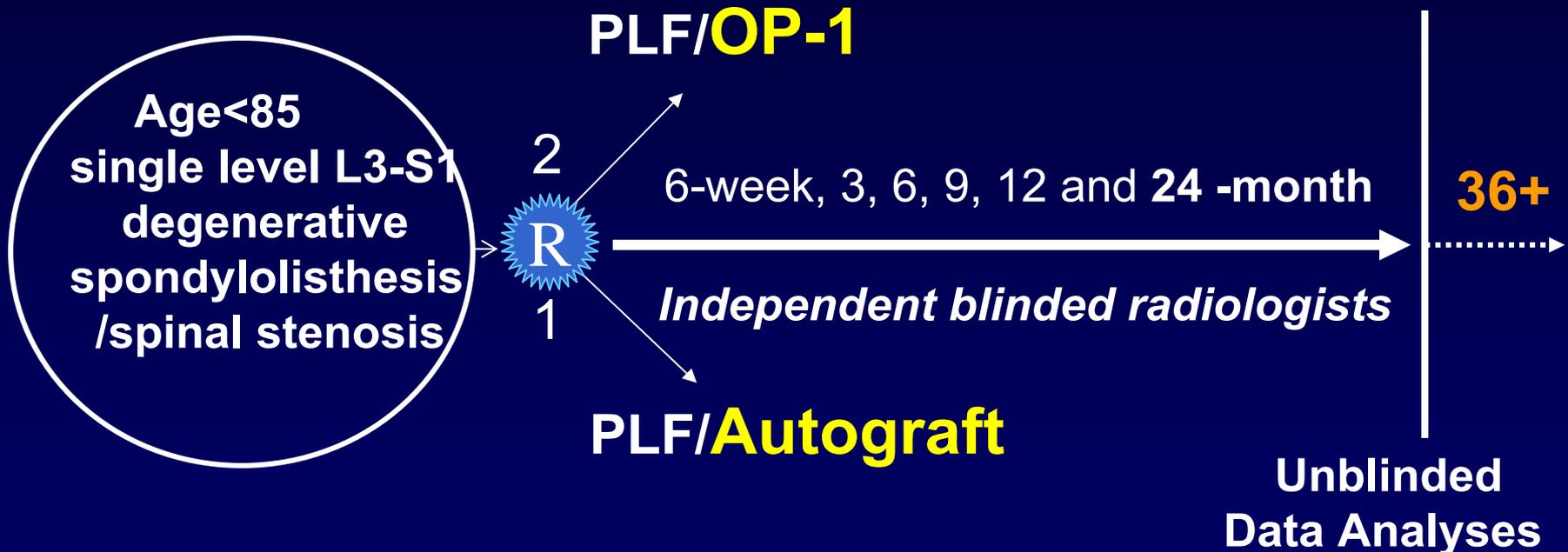
**Study Results: patient overall success**

- SAP in the original IDE protocol: Definition #1 (bridging bone)
- Revised SAP (when study nearly complete): Definition #2 (any bone)
- Post hoc Analysis: Definition #3 (no radiographic component)
- Analysis of the extended study: Definition #4 (“hybrid”: 24 months clinical outcomes plus the new 36+ months radiographic CT data or retreatment from the extension study)

**Summary**

# Study design

Prospective, multi-center, randomized (unmasked)



**Non-inferiority trial:** OP-1 Putty is **not unacceptably worse** than the active control

# Primary statistical hypotheses

$H_o: P_{auto} - P_{OP-1} \geq 10\%$  *OP-1 is worse than Autograft by at least 10%*

$H_a: P_{auto} - P_{OP-1} < 10\%$  *OP-1 is not worse than Autograft by more than 10%*

**Note:** **10%** is the non-inferiority margin as pre-specified in the **original approved IDE protocol**

Fixed sample size: OP-1 = 208 Autograft = 104

– *Statistical power of 80% at one-sided alpha=0.05*

– *Assume:  $P_{op-1} = 53\%$ ,  $P_{auto} = 47\%$  and non-evaluable = 15%*

if the upper bound of 90% CI ( $P_{auto} - P_{OP-1}$ )  $< 10\%$   
→ claim non-inferiority

# Original primary endpoint (definition #1)

A composite of both effectiveness and safety endpoints

Patient's overall success at 24 months: all need to be met

1. Radiographic fusion:

- Presence of bridging bone, and
- Angulation of  $\leq 5^\circ$ , and
- Translational movement of  $\leq 2$  mm)

2.  $\geq 20\%$  improvement in Oswestry Disability Index (ODI)

3. No revisions, removals, or supplemental fixations.

4. Absence of serious treatment-related adverse events.

5. No decrease in neurological status unless the decrease is due to a concurrent medical condition or to the surgical procedure by a blinded independent neurological reviewer

# Original Statistical Analysis Plan (SAP)

- **Intent-to-treat (ITT):** includes all randomized patients and analyzed as randomized. Patients with missing data were to be initially classified using the last observation carried forward approach (LOCF). A **sensitivity analysis** was then to be performed to examine the stability of the conclusions to alternative classification methods.
- **Per-protocol (PP):** excludes patients who violated the inclusion/exclusion criteria. Patients were also to be excluded if they were missing an ODI assessment at 24 months, if their 24 month radiographic results were missing or not evaluable, or if the patient was missing a neurological assessment.

# Patient Accounting

Total # Randomized  
N=336

OP-1  
N=228

Autograft  
N=108

*Withdrawal = 11*  
*Other = 9*

*Withdrawal = 8*  
*Other = 13*

OP-1 Treated  
N=208

Autograft Treated  
N=87

*Death = 6*  
*Withdrawal = 4*  
*Lost-to-follow = 3*  
*Other = 2*

*Death = 3*  
*Withdrawal = 9*  
*Lost-to-follow = 4*  
*Other = 4*

SAP Primary  
"ITT" N=205  
Per Protocol N=160

SAP Primary  
"ITT" N=84  
Per Protocol N=58

# Study results: original SAP

## Patient Overall Success at 24 months (Definition #1)

Sponsor Analysis	Autograft (N=87)	OP-1 (N=208)	P-value non-inferiority	Difference ( $P_{Auto} - P_{OP}$ )	90% CI ( $P_{Auto} - P_{OP}$ )
'ITT'-LOCF <sup>1</sup>	48% (40/84)	32% (65/205)	0.824	16%	[5%, 26%]
Per-Protocol	57% (33/58)	35% (56/160)	0.942	22%	[10%, 34%]

*Note: 1. patients without any post-operative data were excluded*

According to the original approved IDE, the pivotal trial failed to reject the null hypothesis.

Based on the 90% confidence interval, the OP-1 Putty could be worse than Autograft by up to 26%

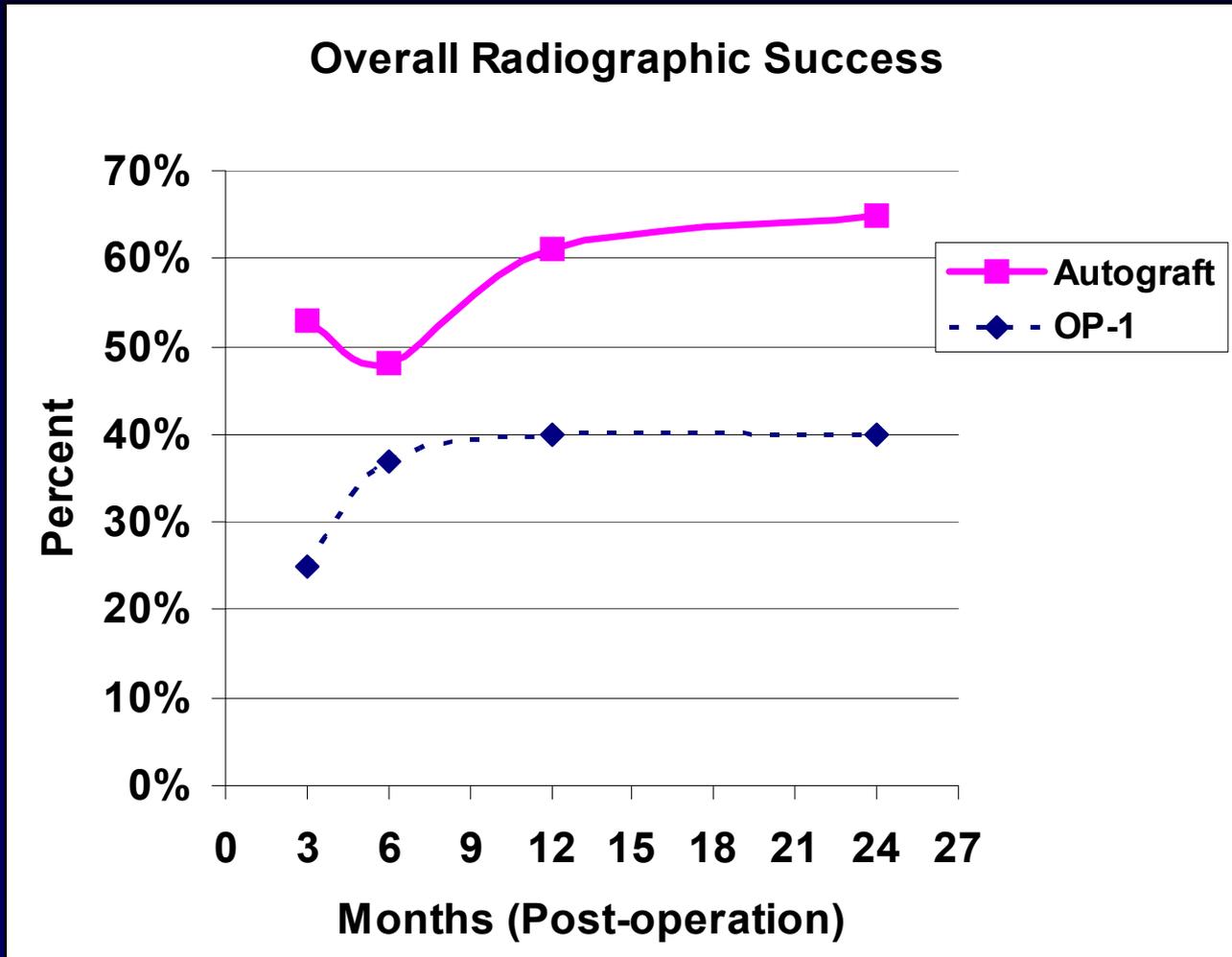
# Study results: original SAP (continued)

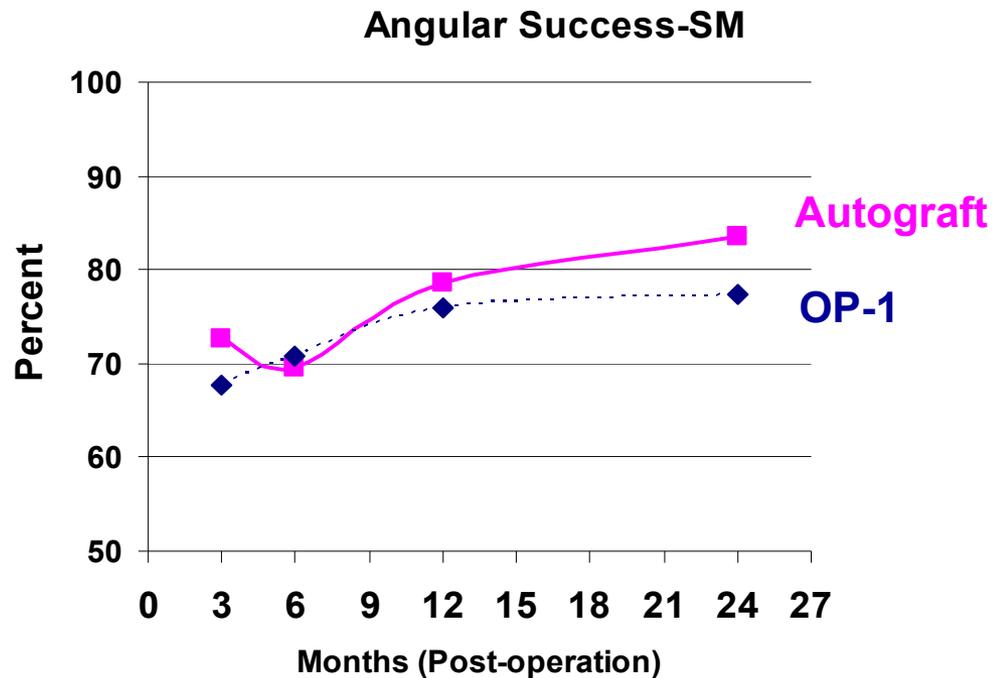
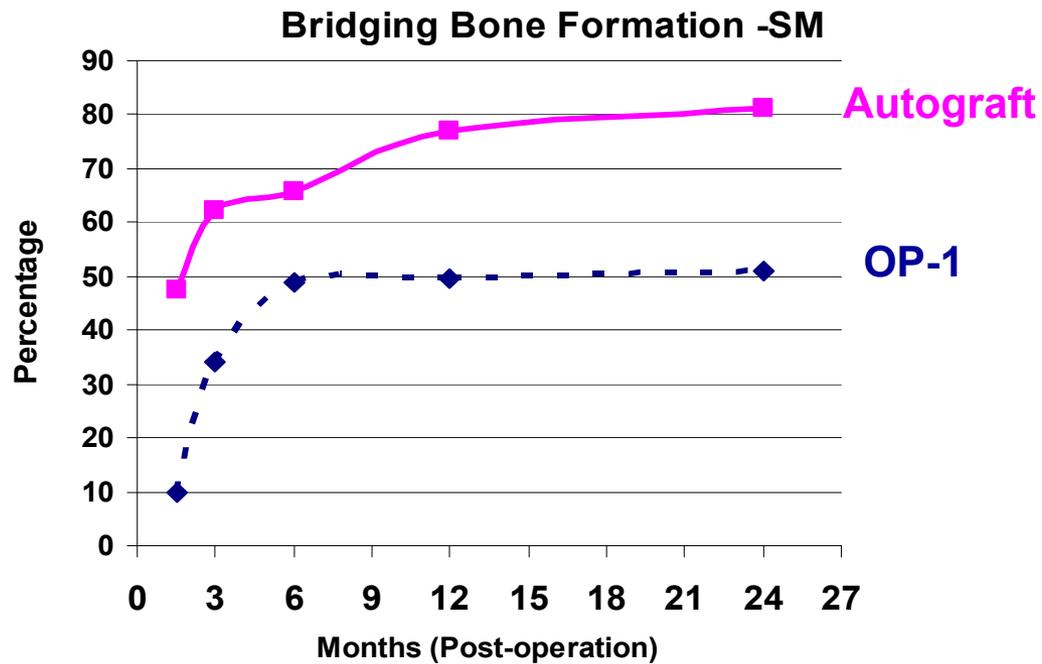
## Individual Components at 24 months:

Endpoint	Autograft (N=87)	OP-1 (N=208)	P-value non- inferiority	Difference (P <sub>Auto</sub> - P <sub>OP</sub> )	90% CI (P <sub>Auto</sub> - P <sub>OP</sub> )
<b>Radiographic</b>	<b>74%</b> <b>(43/58)</b>	<b>40%</b> <b>(64/160/)</b>	<b>1.000</b>	<b>34%</b>	<b>[23%, 46%]</b>
<b>ODI</b>	<b>85%</b> <b>(53/62)</b>	<b>80%</b> <b>(144/179)</b>	<b>0.180</b>	<b>5%</b>	<b>[-4%, 14%]</b>
<b>No serious treatment-AE</b>	<b>96%</b> <b>(64/67)</b>	<b>89%</b> <b>(172/193)</b>	<b>0.141</b>	<b>7%</b>	<b>[1%, 12%]</b>
<b>No retreatment</b>	<b>93%</b> <b>(62/67)</b>	<b>93%</b> <b>(179/193)</b>	<b>0.003</b>	<b>0%</b>	<b>[-6%, 6%]</b>
<b>Neurological</b>	<b>94%</b> <b>(62/66)</b>	<b>100%</b> <b>(189/189)</b>	<b>&lt;0.001</b>	<b>-6%</b>	<b>[-11%, -1%]</b>

**Radiographic component is the primary difference maker**

# Overall radiographic success through the post-operative follow-up





# Revised statistical analysis plan

Sponsor proposed a revised SAP dated Dec. 29, 2005 when the study nearly complete (the last patient reached 24-month on Nov. 14, 2005)

## Four major modifications:

1. The overall radiographic success was changed into:
  - *Presence of bone (rather than bridging bone), and*
  - *Angulation of  $\leq 5^\circ$ , and*
  - *Translational movement of  $\leq 3$  mm (rather than  $\leq 2$  mm)*
2. The fixed non-inferiority margin of 10% was modified to be variable, ranging up to approximately 14% depending upon the success rate in the control group
3. The efficacy populations for analysis were changed into a modified intent-to-treat population (mITT) which included all treated patients with at least one post-treatment follow-up visit.
4. For the overall success and overall radiographic success endpoints at 24 months, missing data imputation was changed from LOCF to multiple imputation.

# Revised SAP (continued)

## Concerns with the late-stage changes:

- **Significant changes (primary endpoint, non-inferiority margin) were proposed by the sponsor when the study was close to the end. Be aware that this is an open-label study.**
- **The sponsor's proposal to allow a larger non-inferiority margin is not justified from a statistical point of view since the close-to-maximum variability was already accounted for in the original sample size estimation, which assumed near 50% overall success rate for both groups (OP-1 = 53% vs. Auto= 47%).**

# Study Results: Revised SAP

## Patient Overall Success at 24 months (Definition #2)

Analysis	Autograft (N=87)	OP-1 (N=208)	P-value non- inferiority	Difference ( $P_{\text{Auto}} - P_{\text{OP}}$ )	90% CI ( $P_{\text{Auto}} - P_{\text{OP}}$ )
mITT	50% (43/86)	39% (80/207)	0.331	11%	[1%, 22%]
Per- Protocol	49% (34/70)	38% (69/180)	Not reported	11%	[-1%, 22%]

**According to the revised SAP,  
OP-1 Putty was not shown to be non-inferior to Autograft**

# Sponsor's Post-hoc Analysis

**Overall Clinical Success at 24 months: Definition #3  
Removal of the radiographic component**

Sponsor's completer analysis:  $P=0.029$  (unadjusted)  
OP-1 Putty: 71.2% (136/191)  
Autograft: 69.0% (49/71)

## **Issues with the sponsor's original claim of non-inferiority:**

- The inflation of Type I error rate due to the retrospective re-definition of the primary endpoint.
- Compromised study capability (assay sensitivity) to differentiate the two treatments since radiographic outcome is the sole blindly evaluated component.
- Potential bias in favor of OP-1 Putty due to the imbalanced exclusion: Autograft:  $15/86=17\%$  vs. OP-1:  $16/207=8\%$ .

# Extension Study (Definition #4)

Hybrid: 24-month clinical outcomes/36+ months CT & Retreatment

Sponsor's analyses:

OP-1		Autograft		Upper Bound of 90% CI	P-value <u>Non-inferiority</u> $\delta = 10\%$
Number of Patients	Success Rate	Number of Patients	Success Rate		
<b>Multiple Imputation (MI): ~ 30% of the total treated patients (N=293)</b>					
207	47.2%	86	46.8%	11.6%	0.076
No imputation for missing data					
146	37.7%	58	39.7%	14.4%	Not reported

## Issues with the sponsor's claim of non-inferiority:

- The P Value was not adjusted for the multiple changes of the primary endpoint (Definition #1 to Definition #4).
- The upper bound of the 90% CI exceeded the non-inferiority margin of 10% as pre-specified in the original approved IDE.
- The underlying assumption of missing at random for MI might not hold (the majority of patients without 24+ months data succeeded at earlier time points, especially for the Autograft group).

## Extension Study: Presence of Bone by CT 36+

### ➤ Sponsor's presented analysis:

CT-36+: Any Bone	OP-1 Putty (N=144)	Autograft (N=58)
Success Rate	74.8%*	77.4%*

\*Missing data or non-evaluable excluded

CT-9m Re-evaluation      80% (147/185)      100% (75/75)

### ❖ FDA Initial Review: Potential bias against Autograft ?

CT-36+: Any Bone	OP-1 Putty	Autograft
Completer Case	88% (108/123)	98% (42/43)
Missing=Success*	90% (129/144) <sup>1</sup>	98% (57/58) <sup>2</sup>

\*1. Most of OP-1 putty subjects (17/21) had bone by CT-9 months

\*2. All missing Autograft (n=15) had bone by plain film or CT-9.

----- More sensitivity analyses (Re-op = bone failure) -----  
without ignoring missing data due to other reasons showed  
the upper bound of 95% CI (Auto-OP)  $\geq$  15%

# Summary

According to the original protocol-defined SAP and the revised SAP, OP-1 Putty was not shown to be non-inferior to the control.

Concerns over the sponsor's claim of non-inferiority based on their post hoc analysis (unadjusted  $p=0.029$ ) and the analysis of the extended study (unadjusted  $p=0.025$ ):

- Type I error rate inflation
- Probably biased in favor of OP-1 Putty group

According to the pre-defined 10% non-inferiority margin, the sponsor's mITT analysis (with or without imputation for missing data) of the extended study still failed to support the non-inferiority claim even without any adjustment for the retrospective change of the primary endpoint.

# Panel Questions

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- **Protein manufacturing and irradiation sterilization**
- **Success definitions and statistical analyses**
  - **Clinical performance - effectiveness**
    - **Clinical performance - safety**

# **Protein Manufacturing and Irradiation Sterilization**

**Discuss the potential for irradiation sterilization to impact:**

- **protein stability and potency**
- **OP-1 Putty biologic activity**
- **immunological response of subjects and resulting clinical responses**

# **Success Definitions and Statistical Analyses**

**Discuss the various primary endpoint success definitions with respect to the following:**

- their clinical soundness**
- their statistical soundness**

# **Clinical Performance - Effectiveness**

**Comment on the clinical effectiveness of the combination product, including a discussion of the necessity for performing:**

- a human dosing study**
- a new clinical study**

# **Clinical Performance - Safety**

**Comment on the clinical safety of the combination product, including the potential for:**

- **clinical concerns associated with the observed immune response**
- **immune-associated adverse events that could potentially affect either maternal or child health**