DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 17 2001

Amy J. LaForte, Ph.D.
Director, Regulatory Affairs
Stryker Biotech
35 South Street
Hopkinton, MA 01748

Re: H010002
OP-1™ Implant
Filed: May 29, 2001
Amended: May 29, June 28, July 5 and 23, and October 9, 11, and 17, 2001

Dear Dr. LaForte:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the OP-1™ Implant. 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. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

In addition to the postapproval requirements in the enclosure, you have agreed to provide:

1. a preclinical plan for assessing the effects of OP-1™ on tumor promotion;
2. a plan for addressing the preclinical and clinical immunological commitments that you have made; and
3. a plan to collect pregnancy outcomes that will be reported in your annual report.

Please submit the study plans for the first two items within 45 days of receipt of this letter. You may submit your response to the third item within 3-6 months of receipt of this letter. The results of these postapproval studies may require modifications to be made in the labeling (via a supplement) when the studies are completed.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/ode/hdeinfo.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.
Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at (301) 594-2018.

Sincerely yours,

Daniel G. Schultz, M.D.
Deputy Director for Clinical and Review Policy
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure
"Conditions of Approval"

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These

changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless

otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

(1) may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. If you have MDR regulation questions, please send an e-mail to RSMB@CDRH.FDA.GOV or call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (http://www.fda.gov/cdrh), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers International
and Consumer Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration

7

1350 Piccard Drive
Rockville, Maryland 20850

Summary of Safety and Probable Benefit

9

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Osteogenic Protein 1
Device Trade Name:	OP-1 Implant
Applicant's Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Humanitarian Device Exemption (HDE) Number:	H010002
Date of Humanitarian Use Device Designation:	May 4, 2001
Date of Panel Recommendation:	The HDE was not taken to the Orthopedic and Restorative Devices Panel for review (refer to Section XII for discussion).

Date of GMP Inspection:

West Lebanon, NH: August 9, 2001

Wilder, VT: August 9, 2001

Hopkinton, MA: August 15, 2001

Date of Notice of Approval to Applicant: October 17, 2001

II. INDICATIONS FOR USE

OP-1 Implant 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.

III. CONTRAINDICATIONS

- OP-1 Implant should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen.
- OP-1 Implant should not be applied at the site of a resected tumor which is at or near the vicinity of the defect/fracture or in patients with a history of malignancy.
- OP-1 Implant should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).

10

- OP-1 Implant should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

IV. WARNINGS AND PRECAUTIONS

See Warnings and Precautions in the final labeling (Package Insert). A patient brochure is available for use in counseling the patient.

V. DEVICE DESCRIPTION

OP-1 Implant is an osteoinductive bone graft material containing recombinant human Osteogenic Protein 1 (OP-1) and bovine bone derived collagen (ratio is 3.5mg OP-1 to 1g collagen). (OP-1 is also known as bone morphogenetic protein-7 or BMP-7.) OP-1 Implant is provided in a glass vial as a sterile, dry powder in the amount of one gram. The glass vial is sealed with a stopper and a crimp. Each vial is packaged in a thermoform tray and supplied in a box for convenient storage.

Storage: 2-8°C
Shelf-life: 18 months when stored at recommended temperature.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The following are possible alternative procedures or treatments for long bone nonunion.

- Autograft - when bone is taken from one part of the body and placed at the site of injury
- No treatment - some nonunions may be left untreated.
- Bone Growth Stimulators - devices that apply electrical energy to fracture sites to promote healing
- Amputation - the removal of a part of the body with surgery.

VII. MARKETING HISTORY

OP-1 Implant received market authorization in Australia on April 4, 2001 and in the European Union through a centralized approval application on May 17, 2001 under the regulations governing pharmaceuticals.

OP-1 Implant has not been withdrawn from marketing for reasons related to the safety and effectiveness of the product.

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VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events relevant to an orthopedic procedure occurring in >1% of 122 patients who participated in a multicenter trial of OP-1 Implant are listed in Table 1. No deaths were reported during the 24 month study period. Nearly all adverse events were classified as mild or moderate. Only three patients (2 Autograft; 1 OP-1 Implant) experienced a severe event during the 24 month study period. In the autograft group, these events were fracture of the cervical spine, and pain and decreased mobility. One patient experienced clinical depression in the OP-1 Implant group. None of these three events were recorded as being related to study treatment.

Adverse events that were clearly relevant to an orthopedic procedure for the treatment of nonunion or whose incidence was of significant interest to an orthopedic surgeon are reported in Table 1. Adverse events listed below the table typically occurred in only a few patients.

Table 1: Summary of Adverse Events for All Treated Patients in the Tibial Nonunion and Long Bone Nonunion Studies

Adverse Event Description	Tibial Nonunion Study		Long Bone Nonunion Study
	OP-1 Implant n=61	Autograft n=61	OP-1 Implant n=29
Musculoskeletal			
Hardware Complication	28/61	40/61	6/29
Nonunion	7/61	4/61	5/29
Osteomyelitis	6/61	15/61	7/29
Malunion	3/61	0/61	1/29
Injury Resulting from Fall	3/61	3/61	2/29
Hardware removal	2/61	1/61	0/29
Tendonitis (patellar, Achilles)	2/61	1/61	0/29
Contracture	1/61	3/61	1/29
Fracture (other)	1/61	3/61	0/29
Fracture (tibia, fibula)	1/61	3/61	1/29
Skin and Wound			
Wound Infection	18/61	14/61	5/29
Local Inflammation, rash, redness, itching	12/61	10/61	0/29
Swelling (ankle, foot, leg)	7/61	8/61	2/29
Blisters, skin abrasions	5/61	0/61	0/29
Neural			
Pain (ankle, knee, leg)	27/61	22/61	12/29
Neuralgia (numbness)	5/61	6/61	3/29
Pain (other)	3/61	3/61	3/29
Nerve Injury	2/61	2/61	0/29
Cardiovascular			
Hematoma	4/61	8/61	3/29
Anemia	4/61	5/61	1/29
Gastro-Intestinal			
Nausea, vomiting	18/61	19/61	3/29
Gastro-intestinal upset (indigestion, constipation, diarrhea)	7/61	5/61	1/29
Systemic and Other Complications			
Fever	31/61	29/61	0/29
Normal Surgical Complications	10/61	8/61	0/29
Drug Allergy (morphine, antibiotics)	2/61	5/61	1/29

Other events include: amputation of toe, aortocoronary bypass with valve replacement, arthritis, arthroscopy, arthrosis, athlete's foot, bruising, burning sensation, cardiac complications following surgery, chondrectomy, chondromalacia, cold symptoms/upper respiratory infection, death-unrelated causes, depression, dizziness, ear infection, fatigue, gangrene, headache/migraine, incontinence, insomnia, meniscal tear, muscle spasm, muscular herniation, myositis ossificans, nosebleeds, pancreatitis, peptic ulcer, plantar fascial fibromatosis, post operative bleeding, sciatica, skin graft, short term memory loss, shortness of breath, slow or decreased urination, stiffness, sweating, thrombophlebitis, thrombosis, urinary tract infection, weight loss, wound dehiscence, yeast infection.

12

In addition, adverse event data has been collected from over 500 patients treated with OP-1. These patients were from clinical U.S. investigational device exemptions studies and international clinical studies and compassionate use information.

In total, five patients reported the occurrence of cancer. Four of the 5 events reported non-osseous cancers of varying type and location occurring in elderly patients. One patient had a mantle cell lymphoma of the colon which lead to death in a 76 year old female and an 83 year old male had a pancreatic tumor with multiple metastases which led to death. Of the other two patients, a 60 year old male had a right occipital basal cell carcinoma and the other a 79 year old male had gastric carcinoma both of whom recovered. A fifth patient was in the study with a history of recurring chondrosarcoma who had resection arthroplasty in 1985 followed by a hip revision in 1991 and fracture of the prosthesis in 1999; OP-1 was used with allograft in a total hip revision. The treating physician believes the recurrence may have presented on a thalium scan prior to treatment with OP-1. Recurrence and disease progression were considered normal for this type of cancer. An additional patient had a nonunion of a pathologically fractured femur after radiotherapy to the site of lymphoma 7 years prior to treatment with OP-1; the patient had no adverse events or recurrence. In addition, there have been four reports of heterotopic bone formation reported, with no subsequent report of a cancer related events.

Eight out of more than 500 patients treated with OP-1 experienced 10 events related to urinary or renal systems. All 10 events were considered by the treating physicians as unrelated to study treatment and were mild to moderate in severity. No severe adverse events of this nature were reported. Events included urinary tract infection (5), slow urination (1), decreased urine output (1), urinary retention (1) and retrograde ejaculation (2). Many of these events were reported immediately post-treatment and can be attributed to catheterization during and after surgery.

One patient in the long bone nonunion study had a history of renal failure secondary to an allergic reaction to penicillin 2.5 years prior to treatment with OP-1. After treatment with OP-1, the patient had no adverse events related to renal function. One patient treated under the compassionate use in Australia was on kidney dialysis at the time of treatment with OP-1; no adverse events related to renal function were reported following treatment with OP-1 in this patient. Decreased urine output was reported in one patient in the long bone study 11 months after surgery with OP-1 but resolved in 8 days.

IX. SUMMARY OF PRECLINICAL STUDIES

The safety of OP-1 Implant was evaluated in accordance with tests described in ISO 10993. Extensive biocompatibility and safety testing has been performed using OP-1 Implant, including cytotoxicity, sensitization, genotoxicity, hemocompatibility, implantation and systemic toxicity and biodistribution. Additional studies, including safety pharmacology, reproductive toxicity, pharmacokinetics, and tissue distribution studies have been performed using the OP-1 protein alone. The results of this extensive biocompatibility and safety testing, performed in a range of *in vitro* cell-

13

based studies and *in vivo* animal studies (Table 2), suggest the safety of OP-1 Implant for bone repair.

Table 2: Safety Tests for OP-1 and OP-1 Implant

Test	Study	RESULTS
Sensitization	Modified Buehler Technique	Negative
	Epicutaneous Maximization Test	Negative
	Murine Collagen Type 2 Arthritis Model	Negative
Genotoxicity	Ames *Salmonella E. Coli* Reverse Mutation assay	Negative
	Chromosomal aberration test in CHO cells with OP-1 Implant	Negative
Cytotoxicity	L929 Agar Overlay Assay	Negative
	CHO Mammalian Cell Cytotoxicity Assay on OP-1 (OP-1 Implant)	Invalid: Test system incompatible with OP-1 Implant. Results inconsistent with known biocompatibility with CHO cells.
Hemocompatibility	Hemolysis Test	Negative
Implantation & Systemic Toxicity	Rat Acute Subcutaneous Implantation Study	No adverse toxic effects observed.
	Rat 22 Day Subcutaneous Implantation Study	No adverse toxic effects observed.
	Rat 13 Week Subcutaneous Implantation Study	No adverse toxic effects observed.
	Dog Tibial Implantation Study – Healing Timecourse	No adverse toxic effects observed.
	Hamster Submucosal Implantation Study	Negative.
	Healing of Tibial Segmental Defects in Dogs: Long Term Implantation	No adverse toxic effects observed. Presence of anti-OP-1 and anti-collagen antibodies did not correlate with clinical observations. No evidence of neoplastic or pre-neoplastic abnormalities long term (18 months).
	104 week Carcinogenicity Study in Rats with Subcutaneous Implantation with 52 week Toxicity Study	Tumors were found at the site of implantation in OP-1 treated animals. These results are believed to be consistent with the solid state carcinogenesis phenomenon observed when objects are implanted in rats.
	Comparative 4-week Toxicity Study in Cynomolgus Monkeys	Paravascular fibrosis and subintimal vasculopathy occurred at the injection sites in the saphenous veins; related to intravenous administration of OP-1 and not considered relevant to intraosseous implantation.
Implantation & Systemic Toxicity Continued	28 Day Repeat Dose Intravenous Study in Rats	Negative
	Acute Intravenous Study in Rats	Negative
	OP-1 Acute Intravenous Toxicity Test in Mice	Negative
Reproductive Toxicity	Development Toxicity Dose Range with OP-1	Negative
	Placental Transfer in Rat following Single Intravenous Administration	Placental transfer of ^{125}I-OP-1 to rat fetal tissue was <1%.
	OP-1 administered intravenously on embryo-fetal development in rabbits	No observable effect determined at 0.4 mg/kg/day.
	OP-1 administered intravenously on embryo-fetal development in rats	No observable effect level determined at 0.4 mg/kg/day.
Pharmacokinetics/ Biodistribution	Pharmacokinetics Following Single Intravenous Administration to Male Rats	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed in to deep compartments in the tissues.
	Pharmacokinetics Following Single Intravenous Administration to Male Cynomolgus Monkeys	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed into deep compartments in the tissues.
	Pharmacokinetics and Tissue Distribution of OP-1 Protein	Elimination of OP-1 from serum was rapid. Results suggest uptake of OP-1 from blood by liver. Results suggest OP-1 is not distributed into tissues. Uptake into thyroid considered associated with free ^{125}I.
	Rat Subcutaneous Implantation Study – Biodistribution of I-OP-1 Labeled Implant	No significant quantity of OP-1 is detected systemically. OP-1 eliminated from implantation site by 21 days.
	Rabbit Intraosseous Implantation Study – Biodistribution of ^{125}I-OP-1 Labeled Implant	No significant quantity of OP-1 is detected systemically.
Safety Pharmacology	Effect of OP-1 in the Irwin test in rats	Negative
	Cardiovascular effects of OP-1 in conscious telemetered rats.	Transient observations of increased blood pressure, bradycardia, tachycardia, and slight increase in body temperature to excess dose of intravenously administered OP-1 not considered cause for concern regarding intended use of intraosseous implantation.

Pharmacokinetic studies following intravenous administration of OP-1 suggest that any OP-1 which may become systemically available following intraosseous

14

application of OP-1 Implant would be quickly cleared. These studies performed in rats and primates establish that OP-1 is cleared from the blood in a biphasic manner ($t_{½\ elimination} < 12$ hours). The OP-1 is not distributed into deep tissue compartments. Pharmacokinetic data suggests that OP-1 is quickly removed from the blood through the kidneys. It is excreted from the body through the urine.

In addition, several animal studies were performed which support the probable benefit of OP-1 Implant in a range of evolutionary divergent species from rats to non-human primates. The studies were performed in a wide range of orthotopic sites, including long bone, cranial and maxillo-facial applications (Tables 3 and 4).

The results obtained from these studies show that OP-1 Implant is bioresorbable, osteoinductive, and osteoconductive. The product also provides a physical scaffold in the form of collagen particles to support bone formation. The preclinical data demonstrate that new bone is formed as a direct consequence of surgical implantation of OP-1 Implant in either a bony site defect or a void. Mechanical testing data shows that the natural mechanical strength of the treated defects can be restored. Comparisons between autograft bone and OP-1 Implant show that, in some of the animal models, defects treated with the OP-1 Implant had increased mechanical strength.

Table 3: Summary of preclinical studies: Bioactivity of OP-1 Implant (Long Bone Fracture Models)[1,2,3,4]

Study	Species	Evaluations	Findings
Ulna Segmental Gap Defect	Rabbit	Radiographs Histology Mechanical (torsion) testing	OP-1, in a collagen matrix, can be implanted effectively.
Ulna Segmental Gap Defect	Dog	Radiographs Histology Mechanical (torsion) testing	A dose of 3.5 mg/gm collagen matrix is effective in healing critical size defects in a large mammal species.
Ulna Defect (Enhancement of autograft or allograft)	Dog	Radiographs Histology Mechanical (torsion) testing	OP-1, in combination with either allograft or autograft was effective in healing critical size defects.
Ulna Defect (20 weeks)	Monkey	Radiographs Histology Mechanical (torsion) testing	OP-1 was more effective in healing a nonunion gap in a non-human primate model.
Ulna Defect (time-course study)	Monkey	Radiographic analysis Computed Tomography MRI Bone mineral density measurement Mechanical testing Histology	New bone formation was seen on x-rays at three weeks. CT and MRI showed increased mineralization of the new bone by twelve weeks. A significant increase in bone mineral content was observed from three to twelve weeks. Histologic sections at twelve weeks showed calcifying tissue, chondrocytes and osteoblasts and immature woven bone. At twenty weeks, the new bone was continuing to mature.
Tibial Segmental Gap Defect	Monkey	Radiographs Histology Mechanical testing	OP-1 completely restored the bone bridging of the critical size defect. Mature bone was generated faster in the OP-1 treated defects. There was good bone formation in close opposition to the intramedullary rod.
Tibial Segmental Gap Defect (time-course study)	Dog	Radiographs, Duel Energy Xray Absorption (DEXA) scans, Nondestructive biomechanical test, Acoustic impedance imaging, Histology	All specimens showed new bone on radiographs. At 2 weeks, there was extensive formation of immature bone. By 4 weeks, mature bone was seen in the periphery, and early bridging was seen. Evidence of union was seen at six weeks. By 8 weeks the new bone had matured and remodeled. At 12 weeks, radiographic union with bridging bone throughout the defect was observed. DEXA showed all specimens had bone formation.

Table 4: Summary of Preclinical Studies: Bioactivity of OP-1 Implant (Models other than Long Bone Fracture Repair)

Study	Species	Evaluations	Findings
Cranial Defect	Baboon[5,6]	Histomorphometry	Histology showed new bone formation from the periphery to the central core after rapid angiogenesis and mesenchymal cell migration in apposition to the collagenous matrix. New bone filled with fully differentiated bone marrow elements as early as day 15, even with the 0.1 mg dose of OP-1. At one year, restoration of the internal and external cortices of the calvaria was seen. Exuberent and ectopic bone formation was observed with the highest dose displacing the temporalis muscle.
Sinus Augmentation	Chimpanzee[7,8]	Radiography (CT scan) Histology (of lateral biopsies)	Radiographic analysis: dose-dependent increased mineralization rate (also, the height from sinus floor was dose-dependent). Histomorphometric analysis showed mature, remodeled bone at 7.5 mos. Controls showed poor resorption and the matrix showed partial bony growth.
Dental-Implant Fixation	Dog[9]	Radiographs Histology	At 12 weeks: extraction sites treated with OP-1 completely filled. New bone in untreated sites showed less density, remodeling, and incorporation.

X. SUMMARY OF CLINICAL INFORMATION

Two clinical studies were performed under Investigational Device Exemptions which included patients with long bone nonunions.

U.S. Tibial Nonunion Study[10]

A prospective, randomized, controlled, multi-center study was performed to evaluate the ability of OP-1 Implant to safely heal tibial nonunions. Study entry required that each patient failed to heal following conventional treatment. Therefore, healing could be attributed solely to the investigational treatment. All patients received intramedullary nailing (IM rod) to standardize mechanical stabilization of the fracture. Patients having tibial nonunions acquired secondary to trauma and requiring autograft and IM rod fixation were enrolled. Each patient was required to have a nonunion for at least 9 months, without surgical intervention or signs of healing for at least 3 months prior to the investigational treatment. Subgroup analysis was performed for those patients who had failed prior autograft before being enrolled into the study. This analysis is presented below.

Blinding: Because of the requisite donor site surgery associated with the control group, it was not possible to blind patients and physicians to treatment type. However, blinding was used for the independent review of all study radiology. Three radiologists were blinded to treatment group, site, patient history and study time point. (Confidentiality of patient identification was maintained.)

Patient Population: Patients were randomized equally between OP-1 Implant (up to 2 units) and autograft (amount determined by surgeon). The study included 18 investigational sites, with a total of 122 skeletally mature patients with 124 tibial nonunions. There were 61 patients with 61 nonunions in the autograft treatment

16

group and 61 patients with 63 nonunions in the OP-1 Implant treatment group (one patient had bilateral nonunions of the tibia; another had a proximal and distal nonunion in the same leg).

Of the 122 patients enrolled in the study, there were 26 OP-1 Implant and 19 autograft patients who had failed autograft prior to being enrolled in the study.

Baseline Demographics:
The OP-1 Implant group was 73% male (19/26), and the autograft group was 79% male (15/19). Height was comparable for both treatment groups. The nonunions included in this study began as fractures caused by high energy trauma (e.g. motor vehicle accidents), which are more likely to lead to nonunion. National Highway Traffic Safety Administration statistics report that 75% of all motor vehicle accidents occurring in the U.S. in 1998 involved male drivers. Therefore, the likelihood of men sustaining this type of injury is higher than that of women.

Table 5: Demographics and Risk Factors

Risk Factor	OP-1 Implant n=26 patients (27 nonunions)	Autograft n=19 patients (19 nonunions)
Nonunion Duration (Months) Median Mean ± Std. Dev.	 28 40 ± 34	 26 40 ± 35
Atrophic Nonunion	11/27	8/19
Comminuted Fracture at Injury	18/27	11/19
Grade III (a-c) Fracture at Injury	13/27	6/19
Open Fracture at Injury	20/27	9/19
Prior Autograft	27/27	19/19
Prior IM Rod	18/27	11/19
Tobacco/Nicotine Use (based on # of patients)	17/26	13/19
Age (Years) Median Mean ± Std. Dev.	 33 38 ± 17	 32 32 ± 7
Weight (Pounds) Median Mean ± Std. Dev.	 158 161 ± 37	 192 200 ± 46

Study Endpoints: Radiographic success was based on evidence of bridging in 3 of 4 views, as evaluated at 9 months post-treatment by consensus of two out of three independent radiologists. Clinical success was determined by the level of weight-bearing and the amount of pain experienced by the patient upon weight bearing. Full weight bearing with less than severe pain was considered a clinical success. Patients who received additional surgical interventions to promote healing at the nonunion site were considered failures for all analyses. Both the clinical and radiographic success parameters were required for classification as a comprehensive success in the study

Safety was assessed from medical events, treatment related events, laboratory tests, medication use and blood loss.

17

Success Rates:
Success was analyzed utilizing the radiographic and clinical outcomes. Both the radiographic and clinical success parameters were required for classification as a comprehensive success in the study. Data from the subset of 14 patients who had a history of failed prior autograft, who met the protocol criteria, and who had data at 9 months post-treatment with OP-1 Implant, are presented in Table 6.

Table 6: Patients with Prior Failed Autograft Meeting Success Criteria at 9 Months Follow-up

	OP-1 Implant N=14	Autograft N=13
Comprehensive	7/14	11/13
Clinical	12/14	12/13
Radiographic (Bridging in 3 views)	8/14	12/13

Safety Analyses:
Safety data is presented for the subset of patients with prior autograft, however, further confirmation of safety in all patients enrolled in the study is also provided as this is relevant to the safety of OP-1 Implant in humans.

Analysis of the subset of patients with history of prior failed autograft is presented to confirm safety in the proposed indication. Following this, analysis of safety data for all treated patients (regardless of history of prior autograft) is presented in order to give a comprehensive profile of all safety data relevant to the exposure to OP-1 Implant.

Safety Data for Prior Failed Autograft Patients:
All patients reported at least one adverse event. Table 7 summarizes adverse events reported by the physician as related to treatment for each of the two groups.

Table 7: Summary of Treatment Realated Adverse Events (AEs) for Patients with Prior Failed Autograft

	OP-1 Implant N=26		Autograft N=19	
Treatment Related Events	Swelling	N=1	Donor site pain	N=4
	Persistent Nonunion	N=1	Hematoma at Donor Site	N=1
	Drainage	N=1	Ecchymosis at Donor Site	N=1
			Infection at Donor Site	N=1
Total	**3 events (2 patients)**		**7 events (5 patients)**	

Safety Data for All Treated Patients:
As previously seen in Table 1, all 122 treated patients reported at least one adverse event. Table 8 summarizes adverse events reported by the physician as related to treatment for each of the two groups.

18

Table 8: Summary of Treatment Related Adverse Events (AEs) for All Treated Patients

	OP-1 Implant N=61		Autograft N=61	
Treatment Related Events	Persistent Nonunion	N=3	Donor site pain	N=5
	Erythema/swelling	N=2	Hematoma at Donor Site	N=1
	Drainage	N=1	Seroma at Donor Site	N=1
			Ecchymosis at Donor Site	N=1
			Numbness at Donor Site	N=1
			Infection w/drainage at Donor Site	N=1
			Persistent Nonunion	N=1
			Broken IM rod	N=1
			Stress Fracture at original fracture site	N=1
Total	**6 events (5 patients)**		**13 events (11 patients)**	

Very low titers of circulating antibodies to OP-1 developed in 23/61 (38%) patients treated with OP-1 and 8/61 (13%) patients treated with autograft. Three (5%) OP-1 Implant patients developed circulating antibodies to type 1 collagen. All but one of these patients had a very low titer response. Review of the individual patient records revealed no direct correlation between medical events or treatment success and the presence of anti OP-1 or anti collagen type I activity in the blood.

U.S. and Canadian Treatment Study of OP-1 Implant in Long Bone Nonunions

This prospective, non-randomized, multicenter study evaluated the ability of OP-1 Implant to safely heal long bone nonunions utilizing the patient as his own control. The inclusion criteria included only those patients with long bone nonunions who required autograft, but had failed prior autograft attempts or were not eligible for autograft. Mechanical stabilization of the fracture was allowed to vary as appropriate for the individual fracture. Each patient was required to have a nonunion for at least 9 months, without surgical intervention or radiographic/clinical evidence of healing for at least 3 months prior to the investigational treatment.

Study Design: All patients received OP-1 Implant (average of 2 units, maximum of 4 units). No control treatment was performed.

Study Centers and Randomization: Six investigational sites (5 U.S. and 1 Canadian) enrolled patients. Twenty-nine patients were treated and are eligible for analysis, 25 in the U.S. and 4 in Canada. Treated fractures included 17 of the tibia, 8 of the femur, and 4 of the humerus. Table 9 below summarizes the risk factors for healing in this patient population and the incidence of these factors for all treated patients.

19

Table 9: Demographics and Risk Factors

Risk Factor and Demographics	N = 29
Nonunion Duration (months) Median Mean ± S.D.	 38 67 ± 81
Atrophic Nonunion	14/29
Comminuted Fracture at Injury	16/29
Open Fracture at Injury	11/29
Grade III, IIIa, IIIb, or IIIc Fracture at Injury	10/29
Prior Autograft	24/29
Tobacco/Nicotine Use	23/29
Age (years, mean ± S.D.)	49 ± 18
Weight (pounds, mean ± S.D.)	191 ± 53

Study Endpoints: Success was based on no further retreatment of the surgical site, clinical evaluation of function and pain at the nonunion site, and radiographic evidence of bridging in 3 out of 4 cortices as determined by consensus of two independent radiologists. Safety was assessed from adverse events and laboratory tests.

Success Rate Analysis:
Success was evaluated based on radiographic and clinical outcomes without further surgical intervention. The criteria for success were:

1. Less than severe pain;
2. In lower extremity treatments, full weight bearing; or in upper extremity treatments, normal activities or slight restriction in normal activities only; and
3. $\geq$ 75% bridging callus, or 3 out of 4 cortices bridged by radiographic assessment; and

Both the radiographic and clinical success parameters were required for classification as a comprehensive success in the study. Data from the subset of 10 patients who met the protocol criteria, and who had data at 9 months post-treatment with OP-1 Implant, are presented in Table 10.

Table 10: Patients Meeting Success Criteria at 9 Months Follow-up

	OP-1 Implant N=10
Comprehensive	1/10
Clinical	7/10
Radiographic (Bridging in 3/4 cortices)	2/10

20

Safety Analysis:
Evaluation of safety parameters indicated 26 (87%) reported adverse events, with 21 patients reporting at least one serious adverse event. Two adverse events, both of mild severity, were suspected as related to OP-1 Implant: one patient reported myositis ossificans presenting as bone forming in the free flap, and one patient reported suspected immune response presenting as erythema and ecchymosis. The patient with a suspected immune response did not exhibit an increase in antibody level in the blood. Both events resolved without treatment and sequelae.

Five patients (17%) tested developed circulating antibodies to OP-1 and three patients (10%) developed antibodies to Type 1 collagen. All positive titres were considered relatively low. The observed low titres to both OP-1 and collagen were similar to the types of responses observed in the Tibial Nonunion Trial. Serum levels of anti OP-1 and anti Type I collagen did not indicate any untoward effect on healing. Evaluation of serum samples for anti OP-1 and anti collagen antibodies indicated no correlation with adverse events and no inhibition of bone formation. However, none of the 5 patients in the Long Bone Nonunion Study who were positive for anti-OP binding antibodies achieved a successful outcome.

XI. RISK/PROBABLE BENEFIT ANALYSIS

The results of the preclinical studies in animals demonstrate that OP- Implant:

- is capable of generating bone that fully bridges a critical size defect
- induces bone formation in a variety of long bones and animal species
- generates bone that is mechanically and histologically normal

Based on two clinical studies in human, OP-1 Implant has demonstrated probable benefit as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed, thus providing patients with a treatment for nonunion where the alternatives are either amputation or no treatment. This should allow the patient to regain some mobility and may decrease their pain on ambulation.

The use of autograft in treating long bone nonunions requires a donor site, often leading to pain and morbidity to the patient. Some nonunions may be left untreated, however, this can lead to pain, limited movement, deformity, and paralysis. Amputation of the affected limb is associated with physical and psychological disability to the patient. OP-1 Implant has the potential to eliminate the risks and complications associated with these treatment alternatives.

The pre-clinical and clinical data suggest that it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

21

XII. PANEL RECOMMENDATION

This HDE was not reviewed by the Orthopedic and Restorative Devices Advisory Panel. However, the review of this HDE was done as collaboration between scientists in the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER). In addition, a review was done as a homework assignment by an outside pathology expert.

XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in this HDE application, the OP-1 Implant will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on October 17, 2001. All facilities involved in the manufacture of this device have been inspected and found to be in compliance with the Quality System Regulation.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the physician's labeling.

Hazards to Health from Use of the Device: See Indications, Contraindication, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

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23