CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103691/5015

Trade Name: Regranex

Generic Name: Becaplermin

Sponsor: OMJ Pharmaceuticals, Inc.

Approval Date: 5/18/2005

Indication: Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond, and have adequate blood supply.

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103691/5015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103691/5015

MAY 18 2005

OMJ Pharmaceuticals, Incorporated
Attention: Shirley Weisel
Senior Associate, Regulatory Affairs
Global Marketed Products
920 U.S. Highway Route 202
P.O.Box 300
Raritan, NJ 08869-0602

Dear Ms. Weisel:

Your request to supplement your biologics license application for Becaplermin to revise the Clinical Studies and Precautions sections of the package insert to include information regarding the treatment of venous stasis and pressure ulcers, to add a Geriatric Use subsection and to withdraw the 7.5 gram dose, has been approved.

This fulfills your commitment to submit final reports of clinical studies in venous stasis and pressure ulcers, as stated in commitment number 7 of the December 16, 1997, approval letter.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this supplement.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This information will be included in your biologics license application file.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosures: Package Insert
Patient Package Insert

CONCURRENCE PAGE

(b)(5)

(b)(5)

(b)(5)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103691/5015

LABELING

05-10-05-REVISED PI SUBMITTED BY OMJ-FINAL DRAFT

REGRANEX® GEL 0.01%

(becaplermin)

DESCRIPTION

REGRANEX® Gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 KD and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. Becaplermin Concentrate is produced by Chiron Corp. and supplied to OMJ Pharmaceuticals under a shared manufacturing arrangement. REGRANEX Gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of REGRANEX Gel contains 100 µg of becaplermin.

CLINICAL PHARMACOLOGY

REGRANEX has biological activity similar to that of endogenous platelet-derived growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue.

Pharmacokinetics

Ten patients with Stage III or IV (as defined in the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging, *J. Enterostomal Ther* 15:4, 1988 and *Decubitis* 2:24, 1989) lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a dose range of 0.32-2.95 µg/kg (7µg/cm^2) daily for 14 days. Six patients had non-quantifiable PDGF levels at baseline and throughout the study, two patients had PDGF levels at baseline which did not increase substantially, and two patients had PDGF levels that increased sporadically above their baseline values during the 14 day study period.

Systemic bioavailability of becaplermin was less than 3% in rats with full thickness wounds receiving single or multiple (5 days) topical applications of 127 µg/kg (20.1 µg/cm^2 of wound area) of becaplermin gel.

CLINICAL STUDIES

The effects of REGRANEX Gel on the incidence of and time to complete healing in lower extremity diabetic ulcers were assessed in four randomized controlled studies. Of 922 patients studied, 478 received either REGRANEX Gel 0.003% or 0.01%. All study participants had lower extremity diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond (Stages III and IV of the IAET guide to chronic wound staging). Ninety-three percent of the patients enrolled in these four trials had foot ulcers. The remaining 7% of the patients had ankle or leg ulcers. The diabetic ulcers were of at least 8 weeks duration and had an adequate blood supply (defined as $T_cpO_2 > 30$ mm Hg). In the four trials, ninety-five percent of the ulcers measured in area up to 10 cm^2, and the median ulcer size at baseline ranged from 1.4 cm^2 to 3.5 cm^2. All treatment groups received a program of good ulcer care consisting of initial complete sharp debridement, a non-weight-bearing regimen, systemic treatment for wound-related infection if present, moist saline dressings changed twice a day, and additional debridement as necessary. REGRANEX Gel 0.003% or 0.01% or placebo gel was applied once a day and covered with a saline moistened dressing. After approximately 12 hours, the gel was gently rinsed off and a saline moistened dressing was then applied for the remainder of the day. Patients were treated until complete healing, or for a period of up to 20 weeks. Patients were considered a treatment failure if their ulcer did not show an approximately 30% reduction in initial ulcer area after eight to ten weeks of REGRANEX Gel therapy.

The primary endpoint, incidence of complete ulcer closure within 20 weeks, for all treatment arms is shown in Figure 1. In each study, REGRANEX Gel in conjunction with good ulcer care was compared to placebo gel plus good ulcer care or good ulcer care alone.

In Study 1, a multicenter, double-blind, placebo controlled trial of 118 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.003% (n=61) was 48% versus 25% for placebo gel (n=57; p=0.02, logistic regression analysis).

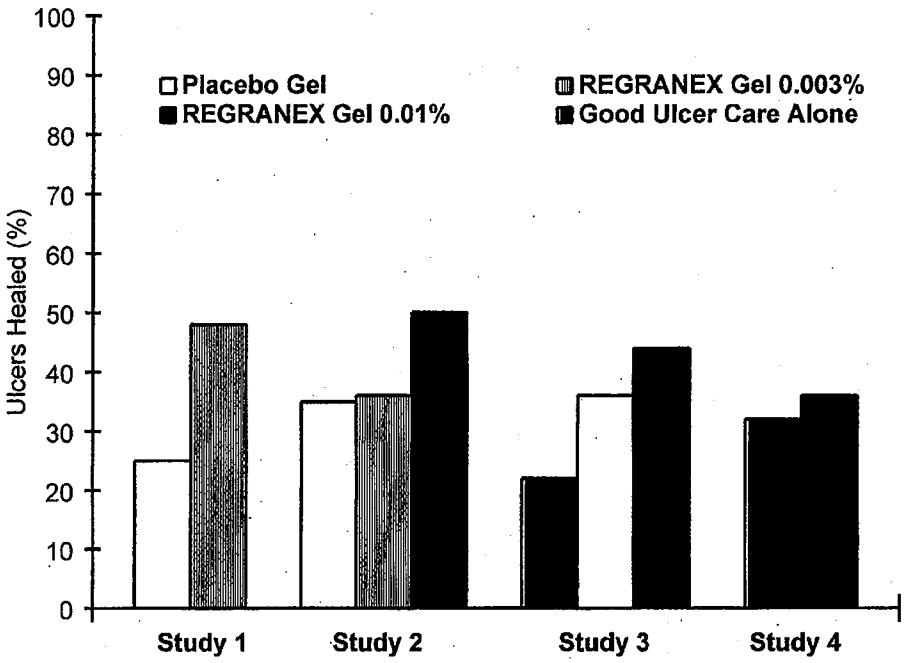
In Study 2, a multicenter, double-blind, placebo controlled trial of 382 patients, the incidence of complete ulcer closure for REGRANEX Gel 0.01% (n=123), was 50% versus 36% for REGRANEX Gel 0.003% (n=132), and 35% for placebo gel (n=127). Only REGRANEX Gel 0.01% was significantly different from placebo gel (p=0.01, logistic regression analysis).

The primary goal of Study 3, a multicenter controlled trial of 172 patients, was to assess the safety of vehicle gel (placebo; n=70) compared to good ulcer care alone (n=68). The study included a small (n=34) REGRANEX Gel 0.01% arm. Incidences

of complete ulcer closure were 44% for REGRANEX Gel, 36% for placebo gel and 22% for good ulcer care alone.

In Study 4, a multicenter, evaluator-blind, controlled trial of 250 patients, the incidences of complete ulcer closure in the REGRANEX Gel 0.01% arm (n=128) (36%) and good ulcer care alone (n=122) (32%) were not statistically different.

Figure 1: Incidence of Complete Healing



In general, where REGRANEX Gel was associated with higher incidences of complete ulcer closure, differences in the incidence first became apparent after approximately 10 weeks and increased with continued treatment (Table 1).

Table 1: Life Table Estimates of the Incidence (%) of Complete Healing Over Time for Study 2

	REGRANEX Gel 0.01% (%)	Placebo Gel (%)
Week 2	1	0
Week 4	6	2
Week 6	9	6
Week 8	16	14
Week 10	23	18
Week 12	34	25
Week 14	37	28
Week 16	43	33
Week 18	46	34
Week 20	50	37

In a 3-month follow-up period where no standardized regimen of preventative care was utilized, the incidence of ulcer recurrence was approximately 30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

~~The efficacy of REGRANEX Gel for the treatment of non-diabetic ulcers is under evaluation.~~

In a randomized, double-blind study of REGRANEX Gel (100mcg/g once daily for 16 weeks) in patients with Stage III or IV pressure ulcers, the incidence of complete ulcer closure was 15% (28/189) in the becaplermin group and 12% (22/190) in the vehicle control group. This difference was not statistically significant.

In two small, randomized, double-blinded studies of REGRANEX Gel (100mcg/g once daily for 16 weeks) in patients with venous stasis ulcers, the combined incidence of complete ulcer closure was 46% (30/65) in the becaplermin group and 39% (26/67) in the vehicle control group. This difference was not statistically significant.

INDICATIONS AND USAGE

REGRANEX Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel has not been established ~~demonstrated~~ for the treatment of pressure ulcers and venous stasis ulcers (see Clinical Studies), and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers. ~~has not been evaluated~~.

CONTRAINDICATIONS

REGRANEX (becaplermin) Gel is contraindicated in patients with:

- known hypersensitivity to any component of this product (e.g., parabens);
- known neoplasm(s) at the site(s) of application.

WARNINGS

REGRANEX Gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS

For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In preclinical studies, rats injected at the metatarsals with 3 or 10 μg/site (approximately 60 or 200 μg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

Information for Patients

Patients should be advised that:

- hands should be washed thoroughly before applying REGRANEX Gel;
- the tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use;
- a cotton swab, tongue depressor, or other application aid should be used to apply REGRANEX Gel;
- REGRANEX Gel should only be applied once a day in a carefully measured quantity (see Dosage and Administration section). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of REGRANEX Gel to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver;

Step-by-step instructions for application of REGRANEX Gel are as follows:

- Squeeze the calculated length of gel on to a clean, firm, non-absorbable surface, e.g., wax paper.
- With a clean cotton swab, tongue depressor, or similar application aid, spread the measured REGRANEX Gel over the ulcer surface to obtain an even layer.
- Cover with a saline moistened gauge dressing.
  - after approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without REGRANEX Gel);

- it is important to use REGRANEX Gel together with a good ulcer care program, including a strict non-weight-bearing program;
- excess application of REGRANEX Gel has not been shown to be beneficial;
- REGRANEX Gel should be stored in the refrigerator. Do not freeze REGRANEX Gel;
- REGRANEX Gel should not be used after the expiration date on the bottom, crimped end of the tube.

Drug Interactions

It is not known if REGRANEX Gel interacts with other topical medications applied to the ulcer site. The use of REGRANEX Gel with other topical drugs has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Becaplermin was not genotoxic in a battery of *in vitro* assays, (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells.

Carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX Gel.

Pregnancy: Category C

Animal reproduction studies have not been conducted with REGRANEX Gel. It is also not known whether REGRANEX Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REGRANEX Gel should be given to pregnant women only if clearly needed.

Nursing Mothers

It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when REGRANEX Gel is administered to nursing women.

Geriatric Use

Among the patients receiving any dose of REGRANEX Gel in clinical studies of diabetic lower extremity ulcers, 150 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients < 65 years of age and patients ≥ 65 years of age. The number of patients aged 75 and older were insufficient (n=34) to determine whether they respond differently from younger patients.

Pediatric Use

Safety and effectiveness of REGRANEX Gel in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS

Patients receiving REGRANEX Gel, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with REGRANEX Gel and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with REGRANEX Gel did not develop neutralizing antibodies against becaplermin.

DOSAGE AND ADMINISTRATION

The amount of REGRANEX Gel to be applied will vary depending upon the size of the ulcer area. To calculate the length of gel to apply to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer in either inches or centimeters. To calculate the length of gel in inches, use the formula shown below in Table 2, and to calculate the length of gel in centimeters, use the formula shown below in Table 3.

Table 2: Formula to Calculate Length of Gel in Inches to be Applied Daily

INCHES	
Tube Size	Formula
15 ~~or 7.5~~g tube	length X width X 0.6
2g tube	length X width X 1.3

Using the calculation, each square inch of ulcer surface will require approximately 2/3 inch length of gel squeezed from a 15g ~~or 7.5g~~ tube, or approximately 1 1/3inch length of gel from a 2g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1 1/4 inch length of gel should be used for a 15g ~~or 7.5g~~ tubes (1 X 2 X 0.6 = 1 1/4) and 2 3/4 inch gel length should used for a 2g tube (1 X 2 X 1.3 = 2 3/4).

Table 3: Formula to Calculate Length of Gel in Centimeters to be Applied Daily

CENTIMETERS	
Tube Size	Formula
15 ~~or 7.5~~g tube	length X width ÷ 4
2g tube	length X width ÷ 2

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will require approximately a 0.25 centimeter length of gel squeezed from a 15g ~~or 7.5g~~ tube, or approximately a 0.5 centimeter length of gel from a 2g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should

be used for a 15g ~~or 7.5g~~ tube [(4 X 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for a 2g tube [(4 X 2) ÷ 2 = 4].

The amount of REGRANEX Gel to be applied should be recalculated by the physician or wound care giver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of REGRANEX Gel from ~~7.5g and~~ 15g tubes is 0.65g per inch length and 0.25g per centimeter length.

To apply REGRANEX Gel, the calculated length of gel should be squeezed on to a clean measuring surface, e.g., wax paper. The measured REGRANEX Gel is transferred from the clean measuring surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The site(s) of application should then be covered by saline moistened dressing and left in place for approximately 12 hours. The dressing should then be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without REGRANEX Gel) for the remainder of the day. REGRANEX Gel should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with REGRANEX Gel should be reassessed. The step-by-step instructions for applying REGRANEX Gel for home administration are described under "Information for Patients".

HOW SUPPLIED

REGRANEX (becaplermin) Gel, supplied as a clear, colorless to straw-colored preserved gel containing 100µg of becaplermin per gram of gel, is available in multi-use tubes in the following sizes:

2g tubes	NDC 0045-0810-02
~~7.5g tubes~~	~~NDC 0045-0810-07~~
15g tubes	NDC 0045-0810-15

REGRANEX Gel is for external use only.

Storage

Store refrigerated, 2-8°C (36-46°F). DO NOT FREEZE. DO NOT USE THE GEL AFTER THE EXPIRATION DATE AT THE BOTTOM OF THE TUBE.

U.S. Patent #5,457,093

ORTHO-McNEIL

Distributed by:

OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869

Manufactured by:
OMJ Pharmaceuticals, Inc.
U.S. License No. 1196
San German, Puerto Rico 00683

Becaplermin Concentrate provided by: Chiron Corp.,
U.S. License No. 1106, Emeryville, CA 94608

OMP 1998 Revised ~~October 2004~~May 13, 2005 635-20-240-~~6~~X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103691/5015

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research

April 20, 2004

From: Louis Marzella, M.D., Ph.D. Medical Reviewer

Through: Marc Walton, M.D., Ph.D., Director,
Division of Therapeutic Biologic Internal Medicine Products,
Office of Drug Evaluation 6,
CDER, FDA

To: STN 103961/5015

Topic: Clinical Review of Labeling Supplement

BLA: STN 103961

Product: REGRANEX Gel (becaplermin)

Indication: Treatment of Chronic Diabetic Foot Ulcers

Sponsor: OMJ Pharmaceuticals

TABLE OF CONTENTS

RECOMMENDED REGULATORY ACTION

It is recommended that the labeling supplement be approved provided that the sponsor agrees with the agency's revisions to the package insert.

BACKGROUND

Becaplermin gel received approval for marketing in 1997 as an adjunct to good ulcer care for the topical treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply.

The sponsor committed to submitting to FDA the final study reports for clinical trials evaluating the efficacy of becaplermin gel in pressure ulcers and venous stasis ulcers (see commitment # 7 in the agency's December 16, 1997 license application approval letter).

The sponsor submitted the labeling supplement in January 2003. The agency requested additional data analyses to support the geriatric labeling revisions and issued a "completed review" letter. The sponsor resubmitted the supplement with the required additional data in November 2004.

This document contains the review of the data in the initial labeling supplement and the review of the data in the sponsor's response to the completed-review letter. In addition this document contains the review of the label changes proposed by the sponsor.

REVIEW OF LABEL CHANGES PROPOSED BY THE SPONSOR

In this prior approval labeling supplement the sponsor proposes the following four modifications to the becaplermin package insert.

1. "Clinical Studies" Section

The sponsor proposes deleting the present statement:
"The efficacy of REGRANEX Gel for the treatment of non-diabetic ulcers is under evaluation."

The sponsor proposes adding the following statement:

(b) (4)

[redacted]

This revision is based upon the sponsor's interpretation of results of four studies that were submitted to the FDA on January 14, 2002. Clinical study reports for PULC- 001 and 002 were submitted under IND (b) (4) Serial No.065 and clinical study reports for

VSLU-002 and 003 were submitted to IND 3486 Serial No: 253.

Reviewer's Comments

- *The efficacy studies of becaplermin in VPU and VSU are inconclusive. It is likely that a small treatment effect exists. The studies do not raise safety concerns. The sponsor stopped development of becaplermin in these two other major ulcer types. Some off-label use of the product is likely in these ulcer types. It is appropriate to inform health care providers of the existing information.*

- *The labeling statement proposed by the sponsor is not sufficiently informative. The reviewer recommends a brief mention of the principal PU study and of the combined VSU study in the Clinical Studies section of the PI and in the Indications and Usage Statement.*

- *The reviewer proposes that the following statements be added at the end of the Clinical Studies Section of the PI.*

  "In a randomized, double-blinded study of REGRANEX Gel (100µg/g once weekly for 16 weeks) in patients with Stage III or IV pressure ulcers, the incidence of complete ulcer closure was 15% (28/189) in the becaplermin group and 12% (22/190) in the vehicle group. This difference was not statistically significant."

  "In two small, randomized, double-blinded studies of REGRANEX Gel (100µg/g once weekly for 16 weeks) in patients with venous stasis ulcers, the combined incidence of complete ulcer closure was 46% (30/65) in the becaplermin group and 39% (26/67) in the vehicle group. This difference was not statistically significant."

- *The reviewer proposes that the reference in the Clinical Studies to ongoing studies in patients with Pressure Ulcers and Venous Stasis Ulcers be deleted.*

- *The reviewer proposes that the following wording be added to the existing second paragraph of the Indications and Usage Section statement.*

  "The efficacy of REGRANEX Gel *has not been established* for the treatment of *pressure ulcers and venous stasis ulcers (see* ***Clinical Studies****), and has not been evaluated for the treatment of* diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers. ~~has not been evaluated~~.

2. "Precautions" Section

(b) (4)

The sponsor proposes adding the following statement

(b) (4)

This revision is based upon the sponsor's interpretation of results of a final study report submitted to the FDA on January 17, 2003 under IND (b) (4) Serial No. 071.

Reviewer's Comments
The seven-patient imaging study of patients with exposed bone and tendons is not sufficiently informative due to small numbers and lack of quantitative assessments. The reviewer recommends that the precaution about the potential effects of becaplermin on exposed joints, tendons, ligaments and bone (b) (4)

3. "Geriatric Use" Subsection
The PI contains no "Geriatric Use" section. The sponsor proposes adding the following statement

(b) (4)

Reviewer's Comment
In the original submission, the sponsor provided no data analyses to support the labeling statement. Upon request by FDA, the sponsor provided the analyses on November 10, 2004. The analyses of the data support the labeling change. The reviewer recommends a more concise statement.

"Among the patients receiving any dose of REGRANEX Gel in clinical studies, 150 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients <65 years of age and patients ≥65 years of age. The numbers of patients aged 75 and over were insufficient (n=34) to determine whether they respond differently from younger subjects."

4. "Dosage and Administration" and "How Supplied" Sections
The sponsor proposes removing all references to the 7.5 gram tube since they have not marketed this dose and they do not intend to do so in the future.

Reviewer's Comment
The reviewer agrees that references to the 7.5 mg tube should be removed from the PI because the sponsor has not marketed this tube size and does not plan to do so.

REVIEW OF SUPPORTING DATA FOR PROPOSED CHANGES TO CLINICAL STUDY SECTION OF THE PACKAGE INSERT

The sponsor submitted four study reports. Two reports for pressure ulcers (PULC) and two reports for venous stasis ulcer (VSLU) studies. No data sets were submitted and none were requested by the agency. The studies are summarized below.

1. Study Protocol PDGF-PULC-001

Study Title
A Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Effective Dose Range and Safety of Recombinant Human Platelet-Derived Growth Factor (rhPDGF-B) in the Treatment of Chronic, Full- Thickness, Non-Healing, Pressure Ulcers

Study Period and Phase of Development
3 Mar 94 to 21 Nov 95; Phase 2.

Study Objectives
The primary objective of this study was to evaluate the safety and dose range of becaplermin applied topically for up to 16 weeks.

Study design
Double-blind, randomized (1:1:1:1, stratified by center), multicenter, placebo-controlled study of becaplermin (0, 100 mcg/g qd, 100 mcg/g bid, or 300 mcg/g qd) applied topically to for up to 16 weeks in 120 patients with non-healing pressure ulcers.

Concomitant therapy
Twice daily dressing changes, systemic antimicrobials as needed for diagnosis of ulcer infection. Sharp surgical debridement as necessary.

Diagnosis and Main Criteria for Inclusion
Adults (19-75 years of age) with chronic ($\geq$4 months), non-healing (<25% reduction in volume with $\geq$ 4 months of treatment) full-thickness (stage III-IV), pressure ulcers (10-150 ml in volume) with adequate blood flow (vascular assessment required for limb ulcers), lack of infection ($<10^6$ organisms/g tissue), adequate glycemic, nutritional, immunologic status. Etiologies other than pressure-ulcers (e.g burn, thermal, chemical etc) were excluded.

Criteria for Evaluation:
The primary efficacy criterion was the proportion of subjects with complete healing by 16 weeks. Additional efficacy criteria included the time to complete healing, the incidence and time to $\geq$90% healing, relative wound size (volume), wound evaluation score, and wound recurrence. Safety evaluations included pre-treatment to post-therapy differences in vital signs, hematology, blood chemistry, urinalysis, anti-becaplermin antibody determinations, and the incidence of adverse events.

Clinical assessments

Weekly visits were required. Assessments included ulcer tracings, jeltrate molds, photography, clinical laboratory assessments, QOL, anti-PDGF antibodies.

Statistical Methods

To analyze the incidence of complete healing (primary efficacy variable) a logistic regression model with study center and baseline ulcer volume were planned. The sample size was based on hypothesized 40% incidence of healing in placebo vs. 70% in 300 mcg/g. The study had 77% power alpha 0.5 one-sided to detect this difference.

In an amendment (#4) dated Feb 15, 1995 the primary analysis was a Cochran Armitage test for dose-response. The assumption for linear relationship between dose and complete healing would be tested using a chi square test for goodness of fit . If the linearity assumption would not hold or if there would be no evidence of trend the dose for further study would be selected by examination of point estimates and CI about the proportions for each group. The trend test was applied to two orderings of dosage regimens with the 100 mcg/g BID dose ranked either next to the highest (300 mcgg/g) or as the highest dose.

Study Results

A total of 124 patients were enrolled and assigned to the following dose groups (placebo n= 31; 100 qd n=31;100 bid n=30, 300 qd, n=32).

The table below shows no meaningful differences in demographics between the treatment groups.

Table 2: Demographic Characteristics
(Intent-To-Treat Subjects: Protocol PDGF-PULC-001)

Characteristic	Placebo (N=31)	Becaplermin 100 µg/g (N=31)	Becaplermin 300 µg/g (N=32)	Becaplermin 100 µg/g b.i.d. (N=30)	Total (N=124)
Sex					
Male	25 (80.6 %)	26 (83.9 %)	27 (84.4 %)	26 (86.7 %)	104 (83.9 %)
Female	6 (19.4 %)	5 (16.1 %)	5 (15.6 %)	4 (13.3 %)	20 (16.1 %)
Total	31	31	32	30	124
Race					
White	22 (71.0 %)	23 (74.2 %)	21 (65.6 %)	21 (70.0 %)	87 (70.2 %)
Black	8 (25.8 %)	7 (22.6 %)	6 (18.8 %)	8 (26.7 %)	29 (23.4 %)
Other	1 (3.2 %)	1 (3.2 %)	5 (15.6 %)	1 (3.3 %)	8 (6.5 %)
Total	31	31	32	30	124
Age (Years)					
N	31	31	32	30	124
Mean (SD)	50.2 (13.61)	47.5 (13.09)	48.5 (12.53)	50.8 (18.30)	49.2 (14.40)
Median	51.0	46.0	49.0	47.0	48.0
Range	(26, 77)	(20, 75)	(28, 71)	(21, 93)	(20, 93)
Weight (lb)					
N	28	30	31	28	117
Mean (SD)	162.3 (49.09)	152.0 (37.65)	164.2 (43.14)	151.5 (35.66)	157.6 (41.55)
Median	155.0	153.0	173.0	150.0	155.0
Range	(82, 350)	(90, 250)	(78, 250)	(88, 242)	(78, 350)
Height (in)					
N	29	27	31	28	115
Mean (SD)	68.7 (3.33)	68.9 (4.33)	69.7 (3.35)	68.1 (4.30)	68.9 (3.83)
Median	69.0	70.0	70.0	68.0	69.0
Range	(62, 75)	(53, 76)	(63, 76)	(54, 75)	(53, 76)

Cross-reference: Attachments 2.1 through 2.3

The table below shows that there were small differences in ulcer dimensions across treatment groups at baseline. The most prognostically significant paramater for ulcer closure (baseline median ulcer volume) appeared to favor slightly the active groups. Median and mean duration of ulcer was numerically higher in the placebo group compared to the active groups overall.

Table 3: Baseline Characteristics: Target Ulcer Evaluation
(Intent-To-Treat Subjects; Protocol PDGF-PULC-001)

	Placebo (N=31)	Becaplermin 100 µg/g (N=31)	Becaplermin 300 µg/g (N=32)	Becaplermin 100 µg/g b.i.d. (N=30)	Total (N=124)
Target Ulcer Area (cm²)[a]					
N	31	31	32	30	124
Mean (SD)	18.5 (18.47)	20.2 (17.23)	24.7 (26.53)	25.1 (24.56)	22.1 (21.98)
Median (IQR)	13.8 (22.02)	13.5 (18.83)	17.3 (20.14)[b]	16.8 (22.00)	15.6 (19.94)
Range	(0[b], 95)	(2, 57)	(1, 136)	(2, 100)	(0[b], 136)
Target Ulcer Volume (mL)[c]					
N	31	31	32	30	124
Mean (SD)	29.3 (24.94)	27.8 (30.44)	29.5 (30.64)	30.0 (25.79)	29.2 (27.78)
Median (IQR)	19.6 (21.86)	16.6 (15.13)	17.2 (19.73)	17.6 (33.81)	18.3 (24.03)
Range	(10, 112)	(4, 145)	(7, 143)	(1, 104)	(1, 145)
Target Ulcer Length[a] (cm)					
N	31	31	32	30	124
Mean (SD)	6.2 (3.19)	6.6 (2.72)	7.1 (4.05)	6.6 (3.19)	6.6 (3.31)
Median (IQR)	5.5 (4.00)	6.1 (4.40)	6.3 (4.42)	5.7 (4.52)	6.0 (4.16)
Range	(1, 17)	(2, 14)	(1, 21)	(2, 16)	(1, 21)
Target Ulcer Width[a] (cm)					
N	31	31	32	30	124
Mean (SD)	3.6 (1.59)	4.0 (2.29)	4.5 (2.80)	4.6 (2.40)	4.2 (2.32)
Median (IQR)	3.2 (2.35)	3.5 (2.60)	4.1 (2.75)	4.0 (2.95)	3.8 (2.86)
Range	(1, 7)	(1, 9)	(1, 14)	(1, 10)	(1, 14)
Total Wound Evaluation Score[d]					
N	31	31	32	30	124
Mean (SD)	1.5 (1.23)	1.5 (1.26)	1.4 (1.29)	1.6 (1.38)	1.5 (1.28)
Median (IQR)	1.0 (2.00)	2.0 (2.00)	1.5 (2.00)	2.0 (2.00)	2.0 (2.00)
Range	(0, 4)	(0, 5)	(0, 5)	(0, 5)	(0, 5)
Time Since Ulcer Onset to First Med (weeks)[e]					
N	31	30	32	30	123
Mean (SD)	76.0 (154.9)	39.2 (52.41)	44.8 (37.08)	37.2 (35.62)	49.4 (86.34)
Median (IQR)	30.1 (43.00)	22.0 (32.00)	33.4 (39.93)	21.5 (51.57)	27.6 (38.00)
Range	(6, 795)	(5, 263)	(6, 161)	(4, 137)	(4, 795)

[a] Area, length, and width are based on planimetry data. Length (major axis) is the longest axis across the ulcer surface and width (minor axis) is the longest axis perpendicular to the major axis.

[b] The smallest baseline Target Ulcer area was 0.41 cm².

[c] Derived by: weight of the feltrate mold/1.13 g/mL.

[d] It is calculated as 6 times the mean of the non-missing scores of 6 evaluation parameters. Each parameter was rated by a 4 point scale: 0=Absent, 1=Mild, 2=Moderate, 3=Marked.

[e] When the exact day was not available to determine the date of onset, 15 was substituted. When neither the month nor the day were available, June 30 was substituted. Only when the month, day, and year were missing on the CRF was the date of ulcer onset considered to be missing.

The overall proportion of patients discontinuing treatment was numerically higher in the active groups. Only one subject discontinued due to an adverse event.

Table 4: Number (%) of Subjects Who Completed/Withdrew from Study
(Intent-To-Treat Subjects: Protocol PDGF-PULC-001)

	Placebo (N=31)	Becaplermin 100 µg/g (N=31)	Becaplermin 300 µg/g (N=32)	Becaplermin 100 µg/g b.i.d. (N=30)	Total (N=124)
Complete	29 (94)	30 (97)	28 (88)	26 (87)	113 (91)
Withdrew	2 (6)	1 (3)	4 (13)	4 (13)	11 (9)
Subject Choice	1 (3)	1 (3)	3 (9)	1 (3)	6 (5)
Other*	0	0	1 (3)	2 (7)	3 (2)
Lost to Follow-up	1 (3)	0	0	0	1 (1)
Adverse Event	0	0	0	1 (3)	1 (1)

* "Other" includes: one subject who was withdrawn due to a physician's decision, one subject who was discontinued due to noncompliance with the dressing change and gel application regimens, and one subject who was discontinued due to a protocol violation (ulcer too small).

The proportion of study visits at which debridement was performed ranged from 3 to 7% in the active groups and was 3.4 % in the placebo group.

Study visits at which debridement of study ulcer was performed (% of total)			
placebo	100 mcg/g	100mc/g bid	300 mcg/g qd
3.4	3.1	7.2	4.6

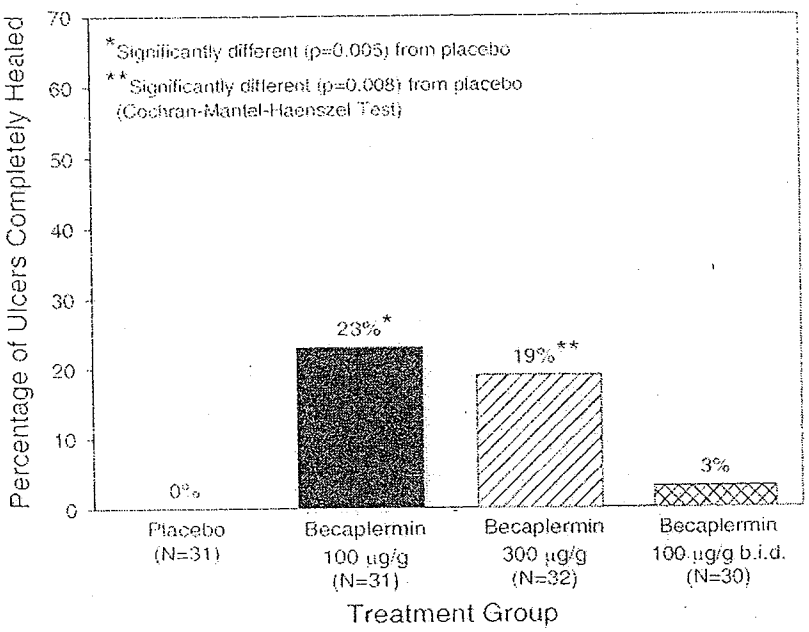
The proportion of ulcers that were too small to qualify for enrollment was higher in the active arms.

Table 5: Protocol Deviations Leading to Non-Evaluability for Efficacy
(All Enrolled Subjects: Protocol PDGF-PULC-001)

Treatment Group Subject	Investigator	Protocol Deviation (Value)	Healed at Endpoint?
Placebo			
1006	Filoreo	>21 days elapsed between visits (65 days)	No
Becaplermin 100 µg/g			
401	Eng	Volume out of 10-150 mL range (3.8 mL)	Yes
801	Read	Volume out of 10-150 mL range (8.1 mL)	No
606	Crum	Volume out of 10-150 mL range (8.0 mL)	No
1103	Lieberman	>21 days elapsed between visits (28 days)	No
Becaplermin 300 µg/g			
503	Read	Volume out of 10-150 mL range (9.1 mL)	No
608	Crum	Volume out of 10-150 mL range (8.8 mL)	No
910	Rees	Volume out of 10-150 mL range (6.7 mL)	No
Becaplermin 100 µg/g b.i.d.			
201	Binnde	Volume out of 10-150 mL range (7.4 mL)	No
502	Read	Volume out of 10-150 mL range (1.2 mL)	No
712	Nemchausky	Volume out of 10-150 mL range (9.2 mL)	Yes

An intent to treat analysis using CMH adjusted by center showed that the 100 mcg/g and 300 mcg/g were different from placebo (p=0.0005 and 0.0008 respectively)

Figure 1: Percentage of Treated Ulcers Completely Healed
(Intent-To-Treat Subjects: Protocol PDGF-PULC-001)



There was no evidence of dose relationship using either of the two dose orderings shown below.

1. placebo gel
2. becaplermin gel 100 µg/g
3. becaplermin gel 300 µg/g
4. becaplermin gel 100 µg/g b.i.d.

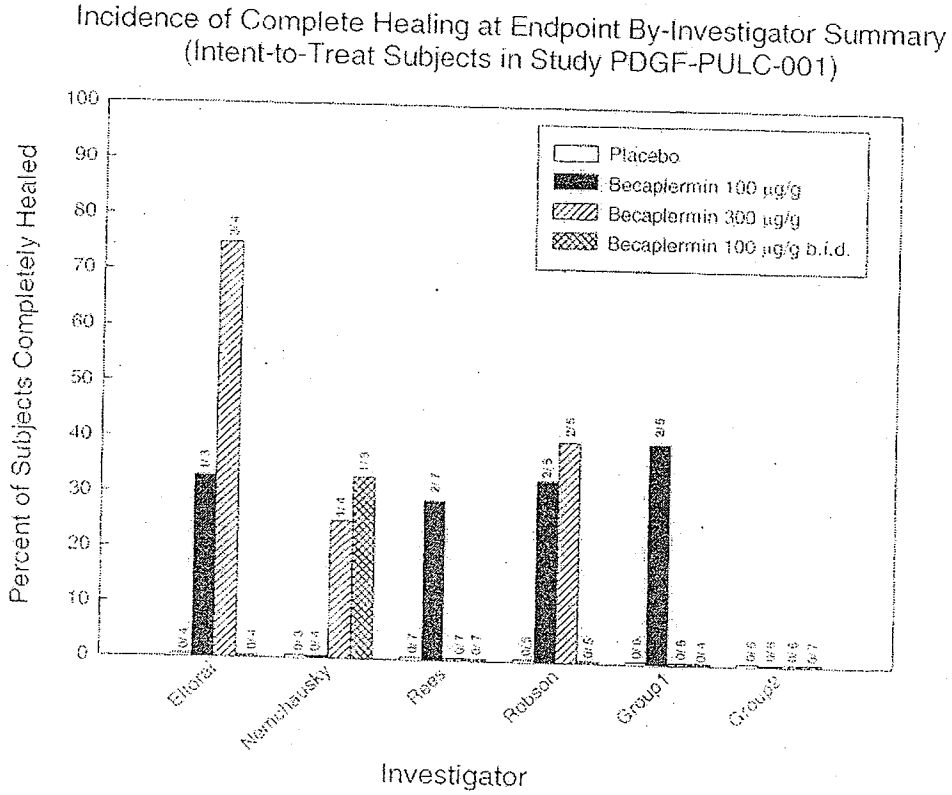
and

1. placebo gel
2. becaplermin gel 100 µg/g
3. becaplermin gel 100 µg/g b.i.d.
4. becaplermin gel 300 µg/g.

The Cochran-Armitage Trend test for increasing efficacy with increasing dose was not significant for either of the two tested dose-orderings.

Analysis of time to complete healing did not show any significant differences for all comparisons.

The numbers of patients per center were small and the incidence of complete healing was variable across centers.



Sponsor's assessments
Study met its primary endpoint. Becaplermin is active. Optimal dose selected for phase 3.

Reviewer's assessment

- Small, insufficiently powered dose-ranging study with inconclusive results. A second adequately powered dose-ranging study should have been carried out.

- Variables associated with more favorable outcome (lower baseline ulcer volume and shorter duration of ulcer) favored slightly the active arms.

- Enrollment of ineligible patients (baseline ulcer <10ml) higher in treated arms

- Surgical debridement somewhat higher in one treatment arm. The significance is unclear.

- Suggestive evidence of becaplermin treatment effect. However the incidence of closure observed in placebo (0%) is lower than expected.
- No evidence of dose-response.
- Pre-specified analysis method (logistic regression) could not be carried out, adjustment for pre-specified baseline variable (ulcer volume) not performed
- No safety signals. Two deaths post-therapy (placebo day 155, 100mg day 32).

2. Study Protocol PDGF-PULC-002

Study Title
A double-blind, placebo-controlled, parallel group, randomized study evaluating the effect of regranex (becaplermin) gel versus placebo gel in the treatment of full-thickness pressure ulcers (RWJ-60235)

Study Dates
The first subject began screening procedures on 05 February 1997. The last subject completed all study assessments on 8 May 2000.

Study Objective
The objective of this study was to evaluate the safety and efficacy of becaplermin gel in the treatment of full-thickness pressure ulcers.

Study Design
This was a randomized (1:1), double blind, parallel-group, placebo-controlled, multicenter (n=46), multinational (US and Canada) study of becaplermin gel 100mcg/g applied topically once daily for 16 weeks in the treatment of full-thickness pressure ulcers, planned in 380 subjects. Follow-up visits were to be scheduled at six weeks and at twelve weeks following study completion.

Enrollment Criteria
Eligible subjects included men and women of 18 years or older, who had a poorly-responding, Stage III or Stage IV (full thickness) pressure ulcer of the trunk of between 5 mL and 75 mL in volume; a total lymphocyte count of at least 1200/mcL; a serum albumin level no less than 2.5 g/dL; if diabetic, a glycohemoglobin A1c level less than 12%; $< 1 \times 10^6$ bacteria per gram of tissue and no beta-hemolytic streptococci.

Ineligible subjects met one or more of the following criteria: active malignant disease; osteomyelitis affecting the area of the target ulcer, active rheumatic or collagen vascular disease; serum creatinine level >3.0 mg/dL; more than three truncal full thickness ulcers;

received treatment with topical antibiotics or antiseptics within four days before randomization; used enzymatic debridement agents within seven days before randomization; received systemic corticosteroids, immunosuppressives, anticancer agents, or any radiation therapy within 30 days of randomization.

Study treatment

Study drug was applied topically each morning in an amount sufficient to form a continuous thin layer covering the target ulcer surface and was alternated with a dressing of saline-moistened gauze in the evening.

Endpoints

The primary efficacy criterion was the incidence of complete healing of the target ulcer after 16 weeks of treatment. Complete healing was measured as a functional assessment score of 1 (absence of a scab, not requiring a dressing and no drainage present). Secondary efficacy criteria consisted of the time to complete healing and 90% wound closure and the incidence of ≥90% wound closure. Safety was assessed by the nature, incidence, and severity of treatment-emergent adverse events; changes from baseline in clinical laboratory test (blood chemistry, hematology, and urinalysis) results, anti-PDGF antibody formation; discontinuation rates and ulcer recurrence rates.

Clinical Assessments

Subjects were evaluated weekly during the 16-week double-blind phase. Photo documentation was performed at every visit from baseline through the 12-week follow-up visit. Efficacy evaluations included the wound evaluation score, functional assessment score, Jeltrate-mold measurements, acetate tracing of the target ulcer, and prospective and retrospective evaluations of the ease of surgical closure of the ulcer for each visit. Additional efficacy evaluations included the reduction in wound volume and area, wound evaluation scores at endpoint, and changes in Health-Related Quality of Life. The final visit of the double-blind phase occurred at completion of the 16 weeks of study therapy, upon complete healing of the target ulcer, or upon discontinuation of study therapy due to a poor response to treatment (greater than 50% increase in the size of the target ulcer volume from baseline), subject choice, adverse event, lost to follow-up or for other reasons, whichever occurred first.

Follow-up visits were scheduled at 6 and 12 weeks after the final visit (or at ulcer healing or recurrence, whichever came first) to determine the target ulcer status (healed, not healed, or recurred) as compared with the status during the double-blind phase. Adverse events also were collected during the follow-up period to evaluate long-term safety.

Statistical analyses

Sample size. Using a one-sided alpha of 0.025, a sample size of 125 subjects per treatment group provided a power of 80% to detect a difference of 15% or more assuming that the healing incidence in placebo would be no higher than 16%.

Primary efficacy analysis. The proportion of subjects with complete healing to be

analyzed by logistic regression model with terms for treatment group, center, baseline ulcer volume as a covariates and ulcer size by treatment interaction. Treatment by center interaction would also be tested. An interim analysis was planned after 80% of subjects treated to resize the study.

Results

The demographic characteristics were well balanced in the two groups. The median age was 66 years overall; nearly 80% of patients were Caucasians and 60% were men.

Table 2: Demographic Characteristics
(Intent-to-Treat Subjects: Protocol PDGF-PULC-002)

Characteristics	Placebo Gel (N=190)	Becaplermin Gel 100 ug/g (N=189)	Total (N=379)
Sex			
Male	113 (59.5%)	111 (58.7%)	224 (59.1%)
Female	77 (40.5%)	78 (41.3%)	155 (40.9%)
Race			
White	146 (76.8%)	153 (81.0%)	299 (78.9%)
Black	37 (19.5%)	29 (15.3%)	66 (17.4%)
Asian	2 (1.1%)	4 (2.1%)	6 (1.6%)
Other	5 (2.6%)	3 (1.6%)	8 (2.1%)
Age (years)			
N	190	189	379
Mean (SD)	63.9 (20.28)	60.3 (20.30)	62.1 (20.34)
Median	69.0	62.0	66.0
Range	20 - 99	19 - 97	19 - 99
< 60	76 (40.0%)	88 (46.6%)	164 (43.3%)
≥ 60	114 (60.0%)	101 (53.4%)	215 (56.7%)
Weight (kg)			
N	183	182	365
Mean (SD)	66.88 (19.51)	66.17 (17.66)	66.53 (18.59)
Median	64.50	63.90	64.10
Range	26.8 - 145.5	29.5 - 115.3	26.8 - 145.5
Height (cm)			
N	172	177	349
Mean (SD)	170.09 (12.83)	169.23 (17.06)	169.66 (15.11)
Median	170.20	170.20	170.20
Range	104.1 - 193.0	86.4 - 195.6	86.4 - 195.6

The baseline ulcer characteristics ulcer volume and ulcer onset tended to favor the active treatment group.

Table 3: Selected Baseline Characteristics: Target Ulcer Evaluation and Identification
(Intent-to-Treat Subjects; Protocol PDGF-PULC-002)

Characteristic	Placebo Gel (N=190)	Becaplermin Gel 100 ug/g (N=189)	Total (N=379)
Target Ulcer Volume (mL)			
N	190	189	379
Mean (SD)	19.0 (14.60)	18.2 (14.26)	18.6 (14.42)
Median	15.0	12.9	13.5
Range	1.9 - 82.3	4.7 - 74.7	1.9 - 82.3
Target Ulcer Volume (mL)[a]			
< 5	4 (2.1%)	2 (1.1%)	6 (1.6%)
5 - 75	183 (96.3%)	187 (98.9%)	370 (97.6%)
> 75	3 (1.6%)	0	3 (0.8%)
Target Ulcer Area (cm^2)[b]			
N	190	189	379
Mean (SD)	14.0 (13.33)	15.6 (15.99)	14.8 (14.72)
Median	10.2	9.9	10.1
Range	0.8 - 103.7	1.0 - 108.3	0.8 - 108.3
Target Ulcer Length (cm)[b]			
N	189*	188*	377*
Mean (SD)	5.3 (2.43)	5.2 (2.47)	5.2 (2.45)
Median	4.9	4.7	4.8
Range	1.3 - 16.4	1.8 - 15.7	1.3 - 16.4
Target Ulcer Width (cm)[b]			
N	189*	188*	377*
Mean (SD)	3.3 (1.67)	3.4 (1.86)	3.3 (1.76)
Median	3.0	3.0	3.0
Range	0.6 - 9.3	0.6 - 10.5	0.6 - 10.5
Target Ulcer Depth (cm)			
N	188*	187*	375*
Mean (SD)	2.3 (1.30)	2.2 (1.43)	2.3 (1.36)
Median	2.0	2.0	2.0
Range	0.2 - 6.6	0.2 - 7.5	0.2 - 7.5
Ulcer Onset (Weeks)			
N	190	188*	378*
Mean (SD)	81.3 (248.80)	53.4 (98.82)	67.4 (189.93)
Median	27.6	24.1	26.4
Range	4.1 - 2633.3	4.6 - 724.7	4.1 - 2633.3
Location			
Left posterior trunk	1 (0.5%)	1 (0.5%)	2 (0.5%)
Right posterior trunk	0	1 (0.5%)	1 (0.3%)
Sacrum	77 (40.5%)	82 (43.4%)	159 (42.0%)
Left buttock	10 (5.3%)	5 (2.6%)	15 (4.0%)
Right buttock	9 (4.7%)	13 (6.9%)	22 (5.8%)

Note: One subject is excluded because she was deemed unevaluable.

* Reflects available data.

[a] Derived by: weight of the Jeltrate mold / 1.13 g/mL.

[b] Area, length, and width are based on planimetry data. Length (major axis) is the longest axis across the ulcer surface and width (minor axis) is the longest axis perpendicular to the length.

(Continued)

The incidence of study completion was similar in the two groups. A high proportion of patients withdrew due to adverse events in both study groups.

Table 4: Number (Percent) of Subjects Who Completed/Withdrew From Study
(Intent-to-Treat Subjects: Protocol PDGF-PULC-002)

	Number (%) of Subjects		
	Placebo Gel (N=190)	Becaplermin Gel 100 ug/g (N=189)	Total (N=379)
Completed	157 (82.6%)	157 (83.1%)	314 (82.8%)
Withdrew	33 (17.4%)	32 (16.9%)	65 (17.2%)
Adverse Event	23 (12.1%)	20 (10.6%)	43 (11.3%)
Subject Choice	6 (3.2%)	8 (4.2%)	14 (3.7%)
Other [a]	4 (2.1%)	4 (2.1%)	8 (2.1%)
Deaths	26 (13.7%)	27 (14.3%)	53 (14.0%)
Treatment Phase	18 (9.5%)	16 (8.5%)	34 (9.0%)
Post Treatment	8 (4.2%)	11 (5.8%)	19 (5.0%)

There was no difference in the incidence of complete healing at endpoint in the two treatment groups

Table 5: Incidence of Complete Healing at Endpoint
(Intent-to-Treat Subjects: Protocol PDGF-PULC-002)

Number (%) of Subjects Completely Healed	
Placebo Gel (N=190)	Becaplermin Gel 100 ug/g (N=189)
22 (11.6%)	28 (14.8%)

Logistic Regression Analysis	df	Wald Chi-Square	p Value
Overall Treatment Effect (rhPDGF-BB vs. placebo)	1	0.0038	0.9507
Covariate (Baseline Target Ulcer Volume)	1	0.5137	0.4735
Treatment by Covariate Interaction	1	2.5467	0.1105

The table below shows that of the ulcers that healed by the prespecified endpoint (16 weeks) the rate of recurrence was numerically higher in the becaplermin group (25%) compared to placebo (9%).

Table 14: Follow-up and Ulcer Recurrence Summary
(Intent-to-Treat Subjects Who Healed: Protocol PDGF-PULC-002)

Phase of Healing Events after Healing	Placebo Gel (N=190)	Becaplermin Gel 100 ug/g (N=189)	Total (N=379)
Ever Healed During Study [a]	28 (14.7%)	43 (22.8%)	71 (18.7%)
Time to First Healing (days) [c]			
N	28	43	71
Mean (SD)	100.4 (33.3)	111.7 (40.1)	107.2 (37.7)
Median	96.5	100.0	99.0
Range	50-164	45-183	45-183
First Healed in 16 Weeks double-blind Treatment Period [a]	22 (11.6%)	28 (14.8%)	50 (13.2%)
Ulcer Recurred by Week 6 Follow-Up Visit [b]	2 (9.1%)	7 (25.0%)	9 (18.0%)
Time to Recurrence (days) [d]			
N	2	7	9
Mean (SD)	27.5 (33.2)	25.3 (17.1)	25.9 (18.9)
Median	27.5	28.0	28.0
Range	4-51	1-45	1-51
First Healed in the follow-up Period [a]	6 (3.2%)	15 (7.9%)	21 (5.5%)
Time to Healing (days) [e] Since Last Double-Blind Dose			
N	6	15	21
Mean (SD)	41.5 (6.7)	48.3 (8.1)	46.4 (8.2)
Median	43.0	48.0	44.0
Range	29-49	39-72	29-72

Note: One subject is excluded because she was deemed unevaluable.
[a] Percentages are calculated using the number of intent-to-treat subjects.
[b] Percentages are calculated using the number of subjects achieving complete healing in the 16-week, double-blind period.
[c] Calculation includes subjects ever achieving complete healing in the study.
[d] Calculation includes subjects first achieving complete healing in the 16-week, double-blind period.
[e] Calculation includes subjects first achieving complete healing in the follow-up period.

Safety

The overall incidence of adverse events was similar 86 and 87% in the placebo and becaplermin groups. One hundred forty-two subjects (68 [36%] who received placebo gel and 74 [39%] subjects who received becaplermin gel) experienced serious treatment-emergent adverse events during the course of the study. There were 53 deaths in the study (34 during the double-blind treatment phase and 19 during the post-treatment period). In the treatment period there were 18 deaths (10%) in the placebo group and 16 deaths (9%) in the becaplermin group. In the post-treatment period there were 8 deaths (4%) in the placebo group and 11 deaths (6%) in the becaplermin group. The most common causes of death listed are respiratory failure, cardiac failure, and pneumonia. This mortality is consistent with the population studied.

Overall, the most common serious adverse events were urinary tract infections (17 subjects (9%) in the placebo gel treatment group and 14 subjects (7%) in the becaplermin gel treatment group) and pneumonia (16 subjects (8%) in the placebo gel treatment group and 11 subjects (6%) in the becaplermin gel treatment group). Serious adverse events, excluding death, led to early discontinuation from the study for eight subjects, four from the placebo gel treatment group and four from the becaplermin gel treatment group. These adverse events are consistent with the patient population studied.

Assessment

- Point estimates for primary endpoints similar for two groups. Becaplermin arm numerically higher than placebo with treatment difference of 3%.
- Ulcer volume numerically higher in placebo at baseline; volume non-significant in logistic regression model.
- Ulcer duration numerically higher in placebo group
- Validity of analysis model questionable when center effect included; therefore center effect excluded from final analysis.
- Ulcer recurrence lower in placebo than becaplermin group
- Typically severely affected patient population. No safety signals.

3. Study Protocol VSLU 002

Study Title
A double blind, randomized, study evaluating the safety and efficacy of becaplermin gel versus vehicle in the treatment of venous ulcers (RWJ-60235)

Study Duration and Phase
5 Feb 1998 to 25 Feb 1999; phase 2

Study Objective
The objective was to evaluate the safety and activity of becaplermin in venous stasis ulcers.

Study Design
Double-blind, randomized, multicenter (n=10) placebo-controlled (vehicle) study of becaplermin (100 mcg/g once daily for up to 16 weeks) in 60 patients with venous stasis ulcers. Post-treatment follow up at 6 and 12 weeks post-treatment for ulcer recurrence.

Concomitant Ulcer Treatments
Compression therapy (30-40 mm Hg) required. Other aspects allowed to be study-site specific. Topical antiseptics not allowed.

Enrollment Criteria
Eligible. Men and women 18 years of age or older with full thickness, chronic (>4 weeks duration) lower extremity (gaiter area) VSU between 2 and 20 cm^2 in size (post-debridement), ABI> 0.8, absence of infection, adequate glycemic control A1c <9.9%, adequate nutritional status (albumin > 3g/dl).
Ineligible. Presence of: malignancy, etiology other than venous stasis (burn, chemical etc.).

Study endpoints
Primary: Incidence of complete ulcer closure by 16 weeks. Subjects with >25% increase in ulcer size from baseline eligible to discontinue as treatment failures.
Secondary: time to complete closure, relative ulcer area, weekly wound closure rate

Clinical Assessments
History and physical examination, routine hematology and chemistry, anti-PDGF antibodies, adverse events

Statistical analyses
Sample size: No inferential analyses planned. Assumption of proportion of ulcer closure 0.5 for placebo and 0.7 for becaplermin. Width of CI around difference between two groups would be 0.48
Primary efficacy: Logistic regression model with terms for treatment group, center, treatment by center and baseline ulcer size. Odds ratio with 95% CI to be calculated.

Results

Of the 71 subjects enrolled in the study 70% were men, 73% were Caucasian, and the median overall age was 66 years.

There were no clinically significant differences in ulcer characteristics between groups at baseline.

Table 3: Baseline Characteristics: Target Ulcer Evaluation
(All Subjects Enrolled in Study PDGF-VSLU-002)

Characteristic	Placebo (N= 36)	Becaplermin (N= 35)	Total (N=71)
Planimetry Area (cm²)			
N	36	35	71
Mean (SD)	6.83 (6.09)	5.35 (3.41)	6.10 (4.98)
Median	3.94	4.05	3.99
Range	1.1-26.4	1.2-12.2	1.1-26.4
Target Ulcer Size (cm²)[a]			
N	36	35	71
Mean (SD)	10.20 (8.74)	8.88 (5.89)	9.55 (7.45)
Median	6.20	6.48	6.30
Range	2.0-40.5	2.1-19.6	2.0-40.5
Target Ulcer Length (cm)[b]			
N	36	34	70
Mean (SD)	3.86 (1.89)	3.55 (1.57)	3.71 (1.73)
Median	3.22	3.12	3.16
Range	1.4-8.0	1.5-7.2	1.4-8.0
Target Ulcer Width (cm)[b]			
N	36	34	70
Mean (SD)	2.20 (1.13)	2.14 (0.77)	2.17 (0.97)
Median	1.84	1.98	1.91
Range	0.8-4.9	0.6-3.7	0.6-4.9
Target Ulcer Depth (cm)			
N	36	35	71
Mean (SD)	0.28 (0.16)	0.25 (0.18)	0.26 (0.17)
Median	0.20	0.20	0.20
Range	0.1-0.8	0.1-0.8	0.1-0.8
Time Since Target Ulcer Onset to Baseline (weeks)			
N	36	35	71
Mean (SD)	46.15 (42.90)	51.64 (29.69)	48.86 (36.82)
Median	30.50	51.86	41.43
Range	5.7-180.6	8.3-146.9	5.7-180.6
Total Wound Evaluation Score[c]			
N	36	35	71
Mean (SD)	3.6 (2.30)	3.1 (2.26)	3.3 (2.28)
Median	3.0	3.0	3.0
Range	0-9	0-10	0-10

[a] Target Ulcer size (length times width) as measured by the investigator.
[b] Target Ulcer length and width measured by the longest/shortest cross-ulcer measurements from planimetry data.
[c] Total Wound Evaluation score was calculated as six times the mean of the non-missing scores of six evaluation parameters. Each parameter was rated by a four-point scale: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Marked.

SD = Standard Deviation

The rate of study completion was similar in the two treatment groups.

Table 4: Reasons for Discontinuation of Study Drug
(All Subjects Enrolled in Study PDGF-VSLU-002)

Reason for Discontinuation	Placebo (N=36)		Becaplermin (N=35)		Total (N= 71)	
	n	%	n	%	n	%
Completed Study	31	86.1	29	82.9	60	84.5
Discontinued Study	5	13.9	6	17.1	11	15.5
Lost to Follow-Up	1	2.8	2	5.7	3	4.2
Adverse Event(s)[a]	2	5.6	1	2.9	3	4.2
Subject Choice	2	5.6	3	8.6	5	7.0
Death	0	0	0	0	0	0

[a] Subject #1121 (placebo gel) discontinued due to a serious adverse event; subject #1033 (placebo gel) discontinued due to a greater than 25% increase in Target Ulcer size; and subject #1018 (becaplermin gel) discontinued due to development of three new ulcers on the target limb.

The incidence of complete closure was similar in the two treatment groups.

Table 5: Subjects Achieving Complete Healing at Endpoint
(Intent-to-Treat Subjects in Study PDGF-VSLU-002)

Variable	Placebo (N=35)		Becaplermin (N=33)	
Number (Percent) of Subjects with Complete Healing at End Point	12 (34.3)		12 (36.4)	
95% CI of Proportion Healed	(0.19, 0.50)		(0.20, 0.53)	
Treatment Difference[a] (95% CI)	0.02 (-0.21, 0.25)			
Conditional Logistic Regression Analysis[b]	df[c]	Wald Chi-Square		P-value
Overall Treatment Effect	1	0.782		0.376
Covariate (Baseline Area)	1	2.624		0.105
Treatment-by-Covariate Interaction	1	4.517		0.034

[a] Incidence in subjects receiving becaplermin minus incidence in subjects receiving placebo.
[b] Based on a conditional logistic regression model controlling center with terms of treatment, baseline area, and treatment-by-baseline interaction.
[c] df = degrees of freedom.
CI = Confidence Interval

The ulcer recurrence rate was similar in the two treatment groups.

Table 14: Follow-up and Ulcer Recurrence Summary
(Intent-to-Treat Subjects in Study PDGF-VSLU-002)

Variable	Placebo (N=35) n	%	Becaplermin (N=33) n	%
Healed During Treatment Phase	12		12	
Ulcer Recurrence Data Available[a]	11		12	
Ulcer Recurred[b]	0	0	1	8.3
Ulcer Did Not Recur[b]	11	100.0	11	91.7
Not Healed During Treatment Phase	23		21	
Ulcer Follow-Up Data Available[a]	18		19	
Ulcer Healed During Follow-Up[b]	3	16.7	4	21.1
Ulcer Did Not Heal During Follow-Up[b]	15	83.3	15	78.9

[a] Follow-up visit at either Week 6 or Week 12.
[b] Percentages are calculated as a percentage of those subjects with available data.

The percentage of subjects who experienced an adverse event was 72% (26/36) in the placebo group and 74% (26/35) in the becaplermin group. The most common adverse events were skin ulceration, infection, pruritus and skin disorder. Two patients in the placebo group discontinued for adverse events (one due to worsening of target ulcer and the other due to worsening of satellite ulcer); one patient in the becaplermin group discontinued due to development of new ulcers. There were no deaths. The incidence of serious adverse events was 17% (6/36 in the placebo group and 6% 2/35 in the becaplermin group (one episode of chest pain of moderate severity in a patient with CAD that resolved and one episode of drug abuse).

Assessment

- Sample size insufficient for inferential analyses.
- No statistical evidence of treatment effect, incidence of healing numerically higher in becaplermin group.
- No safety concerns

4. Study Protocol VSLU 003

Study design, entry criteria, endpoints, statistical analyses
Were identical to those of study VSLU 002

Results

Of the 64 subjects enrolled into the study 55% were men, 64% were white and the median age was 62 years.

The target ulcer characteristics (size, wound evaluation score) were less favorable in the placebo group than in the becaplermin group

Table 3: Baseline Characteristics: Target Ulcer Evaluation
(All Subjects Enrolled in Study PDGF-VSLU-003)

Characteristic	Placebo (N=32)[a]	Becaplermin (N=32)[a]	Total (N=64)[a]
Planimetry Area (cm^2)			
Mean (SD)	5.42 (3.75)	5.47 (5.26)	5.44 (4.53)
Median	4.29	3.03	4.06
Range	0.7 – 16.7	0.4 – 22.9	0.4 – 22.9
Target Ulcer Size (cm^2)[b]			
Mean (SD)	7.94 (5.29)	7.44 (6.15)	7.69 (5.70)
Median	7.41	4.96	6.19
Range	1.3 – 20.0	0.6 – 25.0	0.6 – 25.0
Target Ulcer Length (cm)[c]			
Mean (SD)	3.62 (1.32)	3.42 (1.90)	3.52 (1.63)
Median	3.76	2.91	3.39
Range	1.2 – 7.0	0.9 – 8.8	0.9 – 8.8
Target Ulcer Width (cm)[c]			
Mean (SD)	2.05 (0.86)	2.05 (1.19)	2.05 (1.03)
Median	1.92	1.72	1.81
Range	0.8 – 4.1	0.6 – 6.0	0.6 – 6.0
Target Ulcer Depth (cm)			
Mean (SD)	0.27 (0.16)	0.21 (0.12)	0.24 (0.14)
Median	0.30	0.20	0.25
Range	0.1 – 0.7	0.0 – 0.5	0.0 – 0.7
Time Since Target Ulcer Onset to Baseline (weeks)			
Mean (SD)	55.37 (49.76)	48.65 (44.75)	52.01 (47.07)
Median	35.64	35.71	35.64
Range	7.1 – 173.9	4.9 – 145.9	4.9 – 173.9
Total Wound Evaluation Score[d]			
Mean (SD)	3.9 (2.18)	4.0 (2.40)	3.9 (2.27)
Median	4.0	3.0	3.0
Range	1 – 10	1 – 12	1 – 12

[a] The N values for each treatment group were identical for each characteristic.
[b] Target Ulcer size (length and width) as measured by the investigator.
[c] Target Ulcer length and width measured by the longest/shortest cross-ulcer measurements from planimetry data.
[d] Total Wound Evaluation score was calculated as six times the mean of the non-missing scores of six evaluation parameters. Each parameter was rated by a four-point scale: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Marked.
SD = Standard Deviation

The rate of completion was similar in the two treatment groups. A total of three subjects discontinued for adverse events and there were no deaths.

Table 4: Reasons for Discontinuation of Study Drug
(All Subjects Enrolled in Study PDGF-VSLU-003)

Reason for Discontinuation	Placebo (N=32)		Becaplermin (N=32)		Total (N=64)	
	n	%	n	%	n	%
Completed Study	28	87.5	29	90.6	57	89.1
Discontinued Study	4	12.5	3	9.4	7	10.9
Lost to Follow-Up	1	3.1	0	0	1	1.6
Adverse Event(s)	1	3.1	2	6.3	3	4.7
Subject Choice	1	3.1	1	3.1	2	3.1
Other[a]	1	3.1	0	0	1	1.6
Death	0	0	0	0	0	0

[a] Subject #2024 discontinued because she moved out of state.

The difference in the incidence of complete healing (12%) during the 16-week treatment period favored becaplermin but was not statistically significant (p = 0.174)

Table 5: Subjects Achieving Complete Healing at Endpoint
(Intent-to-Treat Subjects in Study PDGF-VSLU-003)

Variable	Placebo (N=32)		Becaplermin (N=32)	
Number (percent) of Subjects with Complete Healing at Endpoint	14 (43.8)		18 (56.3)	
95% CI of Proportion Healed	(0.27, 0.61)		(0.39, 0.73)	
Treatment Difference[a] (95% CI)	0.12 (-0.12, 0.37)			
Conditional Logistic Regression Analysis[b]	**df[c]**	**Wald Chi-Square**	**P-value**	
Overall Treatment Effect	1	1.852	0.174	
Covariate (Baseline Area)	1	9.720	0.002	

[a] Incidence in subjects receiving becaplermin gel minus incidence in subjects receiving placebo gel.

[b] Based on a conditional logistic regression model controlling center with terms of treatment and baseline area.

[c] df = degrees of freedom.

CI = Confidence Interval

The incidence of ulcer recurrence was similar in the two treatment groups.

Table 14: Follow-up and Ulcer Recurrence Summary
(Intent-to-Treat Subjects in Study PDGF-VSLU-003)

Variable	Placebo (N=32) n	%	Becaplermin (N=32) n	%
Healed During Treatment Phase	14		18	
Ulcer Recurrence Data Available[a]	14		18	
Ulcer Recurred[b]	4	28.6	6	33.3
Ulcer Did Not Recur[b]	10	71.4	12	66.7
Not Healed During Treatment Phase	18		14	
Ulcer Follow-Up Data Available[a]	15		13	
Ulcer Healed During Follow-Up[b]	4	26.7	2	15.4
Ulcer Did Not Heal During Follow-Up[b]	11	73.3	11	84.6

a. Follow-up visit at either Week 6 or Week 12.
b. Percentages are calculated as a percentage of those subjects with available data.

The percentage of subjects with adverse events was 69% 22/32 in the placebo group and 78% 25/32 in the becaplermin group. The most common adverse events were infection, pruritus, skin disorder, skin ulceration and urinary tract infection. One subject in the placebo group and two subjects in the becaplermin group discontinued for worsening of the target ulcer; the subjects in the becaplermin group required hospitalization. There were no deaths. A total of four of 32 ubjects (13%) in the placebo group and 4 of 32 subjects (13%) in the becaplermin group experienced serious adverse events

Assessment

- Study design, endpoint similar to VSLU 002
- Sample size insufficient for inferential analyses.
- Incidence of closure favors becaplermin
- No safety concerns

Studies- PDGF-VSLU-002 and VSLU 003 Combined

Given the similarity in study protocols including study population, study treatment and concomitant treatment, and endpoints, the incidence of closure was examined for the two venous stasis ulcer studies combined (See statistical review by Dr. Koti).

Table 1. Subjects Achieving Complete Healing at Endpoint (Intent-to-Treat subjects in Study PDGF-VSLU-002 and PDGF-VSLU-003 Combined)

Variable	Placebo (N = 67)	Becaplermin (N = 65)
Number (percent) of subjects with complete healing at end point	26 (38.8%)	30 (46.2%)
Treatment difference (95% CI)	0.074 (-0.01, 0.16)	

The 95% confidence interval around the 7% treatment difference does not exclude 0.

2. REVIEW OF SUPPORTING DATA FOR PROPOSED CHANGES TO THE PRECAUTIONS SECTION OF THE PACKAGE INSERT

The sponsor submitted the report of a study entitled "A double-blind, placebo-controlled, parallel group, randomized study evaluating the safety of regranex (becaplermin) gel 0.01% versus placebo gel on exposed bony and fibrous tissue in the treatment of pressure ulcers." Patients with PU received daily becaplermin application for 16 weeks. Ulcer healing and radiographic images (X-ray, CT, MRI) of exposed bony or fibrous tissue in the ulcer bed were evaluated at baseline and 8 and 16 weeks of treatment. Radiographs were to be obtained at 8 and 16 weeks of follow up if changes were observed during study treatment. The sponsor did not develop a plan for standardizing or quantifying the collection and evaluation of the CT, MRI and radiographic images.

Ten patients were planned and seven were enrolled. Among the four placebo patients one experienced ulcer closure, one withdrew when treatment was unblinded. Among the three becaplermin patients, none healed. No unusual pathologic changes of the ulcer bed (e.g. calcification) were observed on visual inspection. No changes to bony or fibrous tissues were observed from baseline. Review of imaging interpretation in the three becaplermin patients shows no information on joint changes or ligamentous changes (listed as not applicable). Evaluation of tendons and bone are not sufficiently quantitative to be useful (e.g. listed as probably present, or probably absent).

It is concluded that no meaningful new information was obtained in this study and (b) (4)

(b) (4)

3. REVIEW OF SUPPORTING DATA FOR PROPOSED CHANGES TO THE GERIATRIC SUBSECTION OF THE PACKAGE INSERT

The submission provides data on the activity and safety of becaplermin in geriatric subjects, 65 years of age and older. Data from the four 20-week registration studies (92-22120-K, 90-22120-F, PDGF-DBFT-001, PDGF-DBFT-002) are summarized by:

- Age group
  <65 years of age and ≥65 years of age
  65 to 74 years of age and ≥75 years of age

- Treatment group
  standard therapy, vehicle, and becaplermin 100 µg/g

The submission contains

- Summaries of the results for the individual four 20-week efficacy studies
- Demographic, baseline characteristics, study completion, and extent of exposure data for the individual four 20-week efficacy studies
- Primary efficacy endpoint results and adverse event data by age group for the individual four 20-week efficacy studies;

Table 1 lists the four registration studies.

Table 1: Becaplermin Clinical Studies Included in the Geriatric Efficacy Summary

Protocol No./ (Description)	Investigator (Country)	Start Date	Study Design/ Duration	No. Subjects
92-22120-K (Phase 3 Efficacy and Safety)	Multicenter (U.S.)	Nov 92	Double-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily for up to 20 weeks.	127 - vehicle 132 - becaplermin 30 µg/g 123 - becaplermin 100 µg/g
90-22120-F (Phase 2 Efficacy and Safety)	Multicenter (U.S.)	Oct 90	Double-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily for up to 20 weeks.	57 - vehicle 61 - becaplermin 30 µg/g
PDGF-DBFT-001 (Phase 2 Vehicle Effect)	Multicenter (U.S.)	Mar 94	Third-party-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily or standard therapy for up to 20 weeks.	68 - standard therapy 70 - vehicle 34 - becaplermin 100 µg/g
PDGF-DBFT-002 (Phase 3 Efficacy and Safety)	Multicenter (U.S.)	Aug 94	Third-party-blind, randomized, parallel-group, controlled study. 20 weeks becaplermin gel or standard therapy plus 16 weeks standard therapy.	124 - standard therapy 128 - becaplermin 100 µg/g

The four 20-week efficacy studies were all randomized, multicenter, blinded studies designed to evaluate the effect of once-daily topical treatment with becaplermin

gel on the healing of chronic, full-thickness (Stage III or IV), lower extremity, diabetic ulcers. Study medication was administered in conjunction with good wound care. Subjects were diabetic men or women, 19 years of age or older, who had at least 1 chronic (duration being not less than 8 weeks from onset to dosing), Stage III or IV diabetic ulcer.

The four 20-week studies also were similar with respect to subject selection criteria, and primary efficacy measure (proportion of patients with complete healing). For all studies, the primary population for efficacy analyses was the ITT population, defined as all subjects randomized to receive study medication who received at least 1 dose of study medication and who had post-baseline data.

The studies enrolled a total of 925 subjects, 922 of whom were considered intent-to-treat (ITT) subjects. Subjects were enrolled into 1 of 4 treatment groups (standard therapy, vehicle, becaplermin 30 µg/g, or becaplermin 100 µg/g) as described in **Table 2.**

Table 2: Subject Enrollment and Evaluability (Becaplermin Gel Lower Extremity Diabetic Ulcer 20-Week Studies)

Study	Standard Therapy	Vehicle	Becaplermin 30 µg/g	Becaplermin 100 µg/g	Total
92-22120-K[b]	-	127 (127)	132 (132)	124 (123)	383 (382)
90-22120-F	-	57 (57)	61 (61)	-	118 (118)
PDGF-DBFT-001	68 (68)	70 (70)	-	34 (34)	172 (172)
PDGF-DBFT-002	124 (122)	-	-	128 (128)	252 (250)
Total	192 (190)	254 (254)	193 (193)	286 (285)	925 (922)

In general, subject demographic characteristics were consistent across treatment groups within studies and across studies. The majority of subjects enrolled into each of the four 20-week diabetic ulcer studies were men (67% to 75%) and white (80% to 86%). The median age across studies ranged from 57 to 61 years.

Key baseline characteristics included baseline ulcer area, time since ulcer onset (ulcer duration), and TcpO2 on the affected limb. In general, baseline characteristics were consistent across treatment groups within studies as well as across studies. However, the median baseline ulcer area by total subjects was larger in Study 90-22120-F (3.46 cm^2) than in the other 3 studies (1.36 cm^2 to 1.47 cm^2). Exposure to study treatment and study completion rates were similar across age subgroups.

Activity of Becaplermin in Geriatric Patients

For the purpose of the geriatric efficacy analyses only the studies including the recommended becaplermin dose (100 µg/g) will be considered.

Study PDGF-DBFT-001

In this small phase 2 study the incidence of closure was numerically higher in patients receiving becaplermin in the <65 years subgroup compared to patients in the ≥65 years subgroup. There was a numerical treatment difference favoring becaplermin in both age subgroups. Among the subjects in the becaplermin group none were > 75 years of age (**Table 3**).

Table 3: Complete Closure of Target Ulcer-Study PDGF-DBFT-001

Achieved Complete Healing of Target Ulcer	Standard Therapy (N=68)	Vehicle (N=70)	Becaplermin 100 µg/g (N=34)
All subjects, N	68	70	34
Yes, n (%)	15 (22.1)	25 (35.7)	15 (44.1)
Age <65, n	47	47	22
Yes, n (%)	10 (21.3)	19 (40.4)	11 (50.0)
Age ≥ 65, n	21	23	12
Yes, n (%)	5 (23.8)	6 (26.1)	4 (33.3)

Study PDGF-DBFT-002

In this phase 3 study, among patients receiving becaplermin, the incidence of closure was similar in patients <65 years compared to patients ≥65 years. A numerical difference favoring becaplermin was observed in both age subgroups (**Table 4**).

Table 4: Complete Closure of Target Ulcer-Study PDGF-DBFT-002

Achieved Complete Healing of Target Ulcer	Standard Therapy (N=122)	Becaplermin 100 µg/g (N=128)
All subjects, N	122	128
Yes, n (%)	39 (32.0)	46 (35.9)
Age <65, n	73	88
Yes, n (%)	24 (32.9)	32 (36.4)
Age ≥ 65, n	49	40
Yes, n (%)	15 (30.6)	14 (35.0)

Among the older (≥65 years of age) subjects, those 65 to 74 years of age treated with becaplermin 100 µg/g had an incidence of complete healing of 38%. Among the small number of subjects ≥75 years of age, 25% (2/8) of the becaplermin100 µg/g-treated subjects achieved complete healing.

Study 92-22120-K

For subjects receiving becaplermin 100 µg/g, the incidence of complete healing was similar for subjects <65 years of age and ≥65 years of age (49% and 50%, respectively) and was greater than the incidence for age-comparable subjects treated with vehicle (**Table 5**).

Table 5: Complete Closure of Target Ulcer-Study 92-22120-K

Achieved Complete Healing of Target Ulcer	Vehicle	Becaplermin 100 µg/g
	(N=127)	(N=123)
All subjects, N	127	123
Yes, n (%)	44 (34.6)	61 (49.6)
Age <65, n	92	89
Yes, n (%)	30 (32.6)	44 (49.4)
Age ≥ 65, n	35	34
Yes, n (%)	14 (40.0)	17 (50.0)

Among the older (≥65 years of age) subjects, those 65 to 74 years of age treated with becaplermin 100 µg/g had an incidence of complete healing of 63%. Among the small number of subjects ≥75 years of age, none (0/7) of the becaplermin100 µg/g-treated subjects achieved complete healing.

Overall, in the three studies that included becaplermin 100 µg/g as a treatment, more subjects experienced complete healing of the target ulcer with becaplermin than with vehicle treatment or standard therapy. In these three studies, the incidence of complete healing appeared to be generally similar for subjects <65 years of age, ≥65 years of age, and 65 to 74 years of age. A treatment effect was observed for all three age subgroups. In the oldest age group >75 years of age a numerically lower incidence of healing was observed and no treatment effect was observed. However this subgroup had too few subjects for meaningful comparisons.

Table 6 summarizes the efficacy data pooled across the three studies. There is no evidence in either vehicle or standard therapy arms that age influences ulcer closure. With the exception of the >75 years of age subgroup, the various other age subgroups show numerically similar becaplermin treatment effects.

Table 6: Complete Closure of Target Ulcer-Comparison of Age Groups (ITT Subjects in Blinded Diabetic Ulcer Studies 90-22120-K, 92-22120-F, PDGF-DBFT-001, and PDGF-DBFT-002)

Treatment	<65 Years	≥65 Years	65-74 Years	≥75 Years	Total
Vehicle					
N	177	77	51	26	254
Yes, n (%)	60 (33.9)	23 (29.9)	14 (27.5)	9 (34.6)	83 (32.7)
Standard Therapy					
N	120	70	48	22	190
Yes, n (%)	34 (28.3)	20 (28.6)	14 (29.2)	6 (27.3)	54 (28.4)
Becaplermin 100 µg/g					
N	199	86	71	15	285
Yes, n (%)	87 (43.7)	35 (40.7)	33 (46.5)	2 (13.3)	122 (42.8)

Assessment of Activity

As far as can be judged from the small number of patients ≥65 years of age (n=86) in the registration studies, the efficacy of the recommended becaplermin dose (100 µg/g) appears to be similar in geriatric patients compared to younger (<65 years) patients.

Safety of Becaplermin in Geriatric Patients

The table below shows the number of subjects exposed to becaplermin (100 µg/g and all doses) by study and by age group.

	Vehicle or Standard Care Controls	Becaplermin 100 µg/g	Becaplermin All Doses Combined	Total
All subjects	444	285	478	922
Study no.				
90-22120-F	57	0	61	118
92-22120-K	127	123	255[c]	382
PDGF-DBFT-001	138[d]	34	34	172
PDGF-DBFT-002	122	128	128	250
Age group (years)				
<65	297	199	328	625
≥65	147	86	150	297
65-74	99	71	116	215
≥75	48	15	34	82

The table below shows that the proportion of patients discontinuing from the study for adverse events and other reasons was not higher in the becaplermin group compared to placebo. The incidence of withdrawals for adverse events was similar in the <65 and ≥65 age groups.

	<65 Years (N=625)			≥65 Years (N=297)		
Reason	Control	Becaplermin 100 µg/g	Becaplermin All Doses Combined	Control	Becaplermin 100 µg/g	Becaplermin All Doses Combined
	(N=297)	(N=199)	(N=328)	(N=147)	(N=86)	(N=150)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse event	31 (10)	17 (9)	30 (9)	19 (13)	6 (7)	16 (11)
Lost to follow-up	8 (3)	4 (2)	7 (2)	7 (5)	1 (1)	1 (<1)
Subject choice	3 (1)	4 (2)	7 (2)	2 (1)	0	0
Other	11 (4)	7 (4)	14 (4)	5 (3)	1 (1)	4 (3)
Non-compliance	3 (1)	3 (2)	7 (2)	1 (<1)	0 (0)	1 (<1)
Protocol violation	3 (1)	1 (<1)	2 (<1)	0 (0)	1 (1)	2 (1)
Intercurrent medical problem	1 (<1)	0	2 (<1)	1 (<1)	0	0
Other reason	4 (1)	3 (2)	3 (<1)	3 (2)	0	1 (<1)
Total discontinuations	**53 (18)**	**32 (16)**	**58 (18)**	**33 (22)**	**8 (9)**	**21 (14)**
Total completing study	244 (82)	167 (84)	270 (82)	114 (78)	78 (91)	129 (86)

The overall incidence of death was approximately 3% (16/478) in the becaplermin group combined and 4% (18/444) in the placebo group. The causes of death were typical for patients with diabetes mellitus. Cardiovascular events (myocardial infarction, congestive failure) and infections (sepsis, pneumonia) were the principal causes. The incidence of death was higher in patients $\geq$ 65 years of age compared to patients < 65 years of age. In patients $\geq$ 65 years of age the incidence of mortality was numerically higher in the overall becaplermin group (6.6%) compared to placebo (5.4%).

The table below shows that the incidence of serious adverse events was similar across the study arms and across the two age subgroups.

	<65 Years (N=625)			65 Years (N=297)		
Body System	Control[a] (N=297)	Becaplermin 100 µ/g (N=199)	Becaplermin All Doses Combined[b] (N=328)	Control[a] (N=147)	Becaplermin 100 µg/g (N=86)	Becaplermin All Doses Combined[b] (N=150)
	%	%	%	%	%	%
Subjects with at least 1 SAE	28	27	27	25	24	25
Musculo-skeletal system disorders	9	9	7	6	7	5
Application site disorders	9	8	7	5	5	5
Resistance mechanism disorders	9	6	6	7	5	4
Metabolic and nutritional disorders	1	5	3	3	1	1
Respiratory system disorders	1	2	2	2	6	4
Body as a whole—general disorders	3	3	4	5	2	3
Vascular (extracardiac) disorders	4	3	4	3	2	7
Gastrointestinal system disorders	1	2	2	3	2	2
CNS and PNS disorders	1	2	1	0	1	1
Urinary system disorders	1	2	2	1	2	1
Cardiovascular disorders, general	2	1	1	1	2	3
Heart rate and rhythm disorders	1	2	1	5	1	1
Myo pericardial and valve disorders	2	0	<1	1	4	2
Neoplasms	1	1	1	1	2	1
Psychiatric disorders	0	1	1	0	0	0
Platelet, bleed/clotting disorders	1	1	<1	0	0	0
Red blood cell disorders	1	0	0	1	1	1
Skin and appendages disorders	1	1	1	1	0	1
Vision disorders	1	1	<1	0	0	0
Liver and biliary system disorders	<1	0	1	0	0	0
Reproductive disorders, male	0	0	0	1	0	0

Infections (including wound infection, osteomyelitis, cellulitis, abscess, pneumonia, and sepsis) were the most common serious adverse events followed by cardiovascular disorders (including myocardial infarction, cardiac failure, peripheral ischemia). The types of adverse events by treatment group and by age were similar.

Assessment of Safety
By criteria of treatment withdrawal for adverse events and incidence of serious adverse events including mortality, there is no evidence of increased risk attributable to becaplermin in patients with diabetic foot ulcers treated with topically applied becaplermin. There is no evidence of increased risk in geriatric patients.

Overall Assessment of Geriatric Data
Among the patients receiving becaplermin (any dose) in clinical studies, 150 patients were 65 years of age and older. Among these, 85 patients received the recommended dose of becaplermin and the assessment of activity in the geriatric patients focused on this subgroup. No overall differences in safety or effectiveness were observed between patients <65 years of age and patients ≥65 years of age.

The numbers of patients aged 75 and over receiving any dose or the recommended dose of becaplermin were insufficient (n=34, and n=15 respectively) to determine whether they respond differently from younger subjects.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103691/5015

ENVIRONMENTAL ASSESSMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: April 20, 2005

To: Administrative File, STN 103691/5015

From: Jianming Li, Facility Reviewer, CDER/OC/DMPQ/TFRB, HFD-328 4/20/05 JL

Through: Michael D. Smedley, Branch Chief, CDER/OC/DMPQ/TFRB, HFD-328 4/25/05

Subject: **Pre-Approval Supplement (PAS):** Revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to with draw an un-marketed dose, and to add a Geriatric Use subsection.

Review of the applicant's claim for categorical exclusion from environmental assessment requirement and compliance check are needed from TFRB.

Applicant: OMJ Phamaceuticals, Inc.

Product: Becaplermin

Indication: Treatment of diabetic ulcers.

Due Date: May 14, 2005

Recommendation: Information related to categorical exclusion has been reviewed and the submission is recommended for approval.

Review Narrative:
This PAS seeks to revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to with draw an un-marketed dose, and to add a Geriatric Use subsection.

The scope of this TFRB review is limited to the claim for categorical exclusion from environmental assessment requirement and compliance check. No other facility information

was included in the CMC section.

I. Categorical Exclusion

The firm claimed categorical exclusion based on 21 CFR 21.31(a). We found the applicant's request is acceptable under 21 CFR 25.15 (d) and 25.31(a), and the FDA guidelines provided in Section III.B. of Guidance for Industry—Environmental Assessment of Human Drug and Biologics Applications (Revision 1, July 1998).

II. cGMP Status

A Compliance Check was completed by the Investigations and Preapproval Compliance Branch on April 22, 2005. OMJ Pharmaceuticals was last inspected by Team Biologics on 1/22-29/04 and was found to be acceptable. There are no pending or ongoing actions that would prevent approval of STN 103691/5015.

CC:
HFD-328: Smedley
HFD-320: Famulare
HFD-109: Tyson-Medlock
HFD-328: TFRB Blue Files (STN 103691)

Date prepared: Li, 4/20/05

Archived File: S:\archive\BLAs|\103691\103691.5015.ctg.exc.04-20-05.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103691/5015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 103691/5015 Supplement Type (e.g. SE5): _____ Supplement Number: N/A

FDA Received Date: January 21, 2003 Action Date: May 14, 2005

HFM 109 Product and Proprietary names/dosage form: Becaplermin

Applicant: OMJ Pharmacueticals, Incorporated Therapeutic Class: N/A

Indication(s) previously approved:
treatment of diabetic ulcers

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _____

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ☐ Partial Waiver ☐ Deferred ☐ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☑ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children

☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

âââAâSOther: Þb ■ð ■ ÞcÛ ÞŠ ? @ â âûŸ? â c■ ¼û Þ ã Þ@ u?û â âÌû Þ
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Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments: Testing, testing, testing, testing, Testing, testing, testing, testing, Testing, testing, testing, testing, testing, Testing, testing, testing, testing, Testing, testing, testing, testing,

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Victoria Tyson-Medlock
Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

TELECONFERENCE SUMMARY

DATE: January 29, 2003

TIME: 12:30 pm EST

SPONSOR: Johnson & Johnson for OMJ Pharmaceuticals

PRODUCT: Becaplermin (Regranex®)

INDICATION: Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

TO: STN 103691/5015 File

FROM: Susan E. Giuliani, Regulatory Project Manager

SUBJECT: Request for additional information

PARTICIPANTS: CBER: (Initiated): Susan Giuliani
Johnson & Johnson: Shirley Wiesel (908-218-6519)

I called Ms. Wiesel and asked for electronic copies of the labeling changes both in PDF and in Word format, to be provided either on a diskette or a CD ROM. Ms. Wiesel agreed to do.

I also requested that Ms. Wiesel submit a more comprehensive table of contents (TOC) so that the reviewers could access the different volumes more quickly. Ms. Wiesel agreed to do so.

The telecon concluded.

BLA/NDA/PMA

Review Committee Assignment Memorandum

X Initial Assignment
❑ Change

STN: 103691/5015

Applicant: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin Gel

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
S. Giuliani	Reg. Coordinator	Admin/Regulatory	K Schneider	1/23/03
	Reviewer	Admin/Regulatory		
		Product		
		Product		
		Product		
L. Marzella	Chairperson	Clinical	Jeff Siegel	1/28/03
		Clinical		
		Clinical Pharmacology		
		Pharm/Tox		
		Biostatistics		
		BiMo		
		Epidemiology		
		Facility		
		Inspector		
		Labeling		
		Other		

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Susan Giuliani — Name Printed

Susan E. Giuliani — Signature

1/30/03 — Date

Memo entered in RMS by: DLS Date: 1/30/03 QC by: 1-30-03 Date: MB

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

TELECONFERENCE SUMMARY

DATE: January 30, 2003

TIME: 12:30 pm EST

SPONSOR: Johnson & Johnson for OMJ Pharmaceuticals

PRODUCT: Becaplermin (Regranex®)

INDICATION: Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, REGRANEX Gel increases the incidence of complete healing of diabetic ulcers.

TO: STN 103691/5015 File

FROM: Susan E. Giuliani SEG, Regulatory Project Manager

SUBJECT: Notification of arrears

PARTICIPANTS: CBER: (Initiated): Susan Giuliani
Johnson & Johnson: Shirley Wiesel (908-218-6519)

I informed Ms. Wiesel that this supplement is considered efficacy and is now in arrears due to non-payment of user fees.

Ms. Wiesel stated her understanding and added that the company deliberated about this issue before making their decision, knowing that it may need a user fee.

I stated that senior management also deliberated before making their final decision. I informed Ms. Wiesel that the company would be receiving an official letter from FDA acknowledging the supplement as well as describing more detail about the user fee.

The telecon concluded.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

OMJ Pharmaceuticals, Incorporated
C/O Cindy Chianese
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C
920 U.S. Highway 202, Box 300
Raritan, New Jersey 08869

FEB 03 2003

Dear Ms. Chianese :

SUBMISSION TRACKING NUMBER (STN) BL 103691/5015 has been assigned to your recent supplement to your biologics license application for Becaplermin, received on January 23, 2003, to revise the package insert to update the Clinical Studies and PRECAUTIONS sections regarding treatment of venous stasis and pressure ulcers, to delete an unmarketed dose, and to add a Geriatric Use subsection.

Under Section 736 (e) of the Prescription Drug User Fee Act of 1992 as amended by the Food and Drug Administration Modernization Act of 1997, an application is considered incomplete and will not be acceptable for filing until all fees owed have been paid. We note that you are in arrears with payment of fees, and therefore **review of your supplement referenced above will not commence until all outstanding fees have been paid**. Upon receipt of the outstanding fees we will start the user fee clock and commence review of your application.

All future correspondence or supportive data relating to this supplemental application should bear the above STN and be addressed to the Director, Division of Application Review and Policy, Office of Therapeutics Research and Review, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20852-1448.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need to discuss the technical aspects of this supplement, you may obtain the name of the chairperson of the review committee by contacting this division at 301-827-4358. Any questions concerning administrative or procedural matters should also be directed to this division.

Sincerely yours,

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: DARP BLA File, HFM-585
Libero Marzella, HFM-582
Susan Giuliani, HFM-588

OTRR/DARP:K.Townsend:1.28.2003
S:\STN 2002\103691.5015.PAS.doc

COMMUNICATION TYPE:

LETTER: Acknowledgment Letter (ACK)
Summary Text: STN Assignment – Pre Approval (PAS)

SS & RIS Data Check:

- If "Unacceptable for Filing (UN)" add under LETTER.
- Communication
- Verify inclusion of Option 1 paragraph for manufacturing supplmts *(if Alt. 6 is not used)*.

RIS Data Check:

- Submission Screen: In Arrears Box Is Checked
- Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match
- No Action Due Date
- STN Status – Unacceptable for Filing

Division	Name/Signature	Date
DARP	S. Giuliani	1/28/03
DARP	[illegible]	1-31-03
DARP	Dg for Toner	2-3-03
DARP	Kelly Townsend	2-5-03

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103691/5015

MAY 1 4 2003

OMJ Pharmaceuticals, Incorporated
C/o Cindy Chianese
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.
920 U.S. Highway 202, Box 300
Raritan, NJ 08869

Dear Ms. Chianese:

As you were notified in our letter of February 3, 2003 your supplement for Becaplermin was unacceptable for filing due to non-payment of fees required under the Prescription Drug User Fee Act of 1992.

This is to notify you that the Agency has received all fees owed at this time for this supplement. Effective May 2, 2003, the user fee clock has been started and review of this supplement will commence.

Should you have any questions regarding this matter please call the Regulatory Project Manager, Susan E. Giuliani, in the Division of Application Review and Policy at (301) 827-4358.

Sincerely yours,

Earl Deye

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: L. Marzella, HFM-582
DARP BLA file, HFM-585

CBER:DARP: S. Giuliani 5-6-03:K.Townsend:5.7.2003
(S:\Giuliani\BLS\103691_5015\ off arrears letter.doc)

COMMUNICATION TYPE:
LETTER: Notification/receipt of fees (AL)

SS & RIS Data Check:

- **Communication**
- **"Payment Received" date in Submission Screen User Fee box is listed as "Effective" Date in Letter**

RIS Data Check:

- **Milestone: Confirm New Action Due Date**
- **PAYMENT DATE: EFFECTIVE DATE OF LETTER, USER-FEE BOX , LATE USER FEE PAID IN MILESTONE CLOSED DATE SHOULD BE THE SAME**

Division	Name/Signature	Date
DARP	Giuliani	5/12/03
DARP	Schneider	5-12-03
DARP	Dye for Jones	5-14-03
DARP	Kelly Townsend	5-14-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: June 4, 2003

From: Susan Giuliani, DARP, TPPB, HFM-588

To: 103691/5015 file

Subject: First Committee Meeting Summary

Meeting Date: May 29, 2003 Time: 3:30 pm - 4:40 pm

Location: WOC 1, Conference Room 400S

Sponsor: OMJ Pharmaceuticals, Inc.

Product: Becaplermin (Regranex®)

Proposed labeling change: revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to delete an unmarketed dose, and to add a Geriatric Use subsection

Purpose: To discuss the milestones and strategies for meeting the deadlines and potential problems and deficiencies.

Discussion:

The need for a user fee for this efficacy BLS was discussed and the milestones were presented. Some members questioned the sponsor's rationale for deleting an unmarketed dose, however this issue would be dealt with in DARP. The clinical reviewer, Dr. Marzella stated that this label had not been changed for some time, and the goal was not to RTF this supplement, but to correct any deficiencies early. Dr. Koti, the statistical reviewer, stated that he might not need all of the actual datasets. The datasets he may need are from the studies in venous stasis ulcers and the Geriatric use section. He will verify and get back to the committee. Regarding the content of the labeling, Dr. Siegel stated that three of the studies showed varying degrees of efficacy and questioned how these studies could be applied to the sponsor's proposed labeling changes. Dr. Marzella will check into this; he has no intent for a contraindication. A suggestion was made for a possible disclaimer, the wording of

which could be drafted by the sponsor. The "deficiencies identified" (Day 74 letter) milestone was discussed and clarified.

The meeting adjourned.

Decision/Agreement Reached:

1. DARP will handle the unmarketed dose and this wording in the label. (Follow-up: Dr. Glen Jones stated that if they want to delete a dose from the PI, they will need to "withdraw" that dose from the approved BLA. If they again want to market it in the future, a supplement would be needed (if there had been no changes in the manufacturing of that dose, they could cross-reference the data that originally supported its approval).

2. This supplement will not go to the Advisory Committee.

3. An epidemiological consultant is not needed for this file.

Action Items:

4. RPM will check the RMS/BLA database for the last time the label was changed and get back to the committee.

5. RPM will find out from the sponsor as to why the particular dose is being deleted.

6. Dr. Koti will check to see what datasets he will need and get back to the team.

7. Dr. Marzella will check into the issue of varying degrees of efficacy from three of the studies.

8. Dr. Marzella will complete the filing memo and forward it to the RPM the week before the filing meeting.

FDA Attendees:

Lou Marzella
Jeffrey Siegel
Kallappa Koti
Kay Schneider
Susan Giuliani

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: June 13, 2003

From: Susan E. Giuliani, DARP, TPPB, HFM-589

To: 103691/5015 file

Subject: Filing Meeting Summary

Meeting Date: June 11, 2003 Time: 3:00 - 4:00 pm

Location: WOC 1, 400 North

Sponsor: OMJ Pharmaceuticals, Inc.

Product: Becaplermin (Regranex®

Proposed Label Changes: revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an unmarketed dose, and to add a Geriatric Use subsection

Discussion:

RPM stated that because of these efficacy trials, financial disclosure may be required. The clinical reviewer stated that only one trial (PULC-002) appeared to fall under financial disclosure requirements, and this depended on when the trial was completed. A question was raised as to whether or not enough Geriatric data was generated. Datasets will not be required for these studies, so the decision was made to file this BLS and to request any review deficiencies in the day 74 letter. The clinical reviewer discussed preliminarily the marginal and inconclusive results from the studies and the sponsor's proposed revisions in the PI. The question at this point is how the changes should be worded, and Toni Stifano and Marc Walton will be consulted to provide input from examples. Regarding the sponsor's response to the post marketing commitment, the group decided that these study results did not fulfill it, and that OMJ would be released from it. The group also decided to include the first labeling meeting with the mid cycle meeting on September 30, 2003.

Action Items:

1. RPM will find out when Study PULC-002 was completed, and if after February 2, 1999, will request financial disclosure documents from sponsor.

2. Clinical reviewer will check for adequacy of Geriatric data.

3. RPM will consult with Toni Stifano regarding products with similar clinical issues (marginal/inconclusive data) and request those labels.

4. Clinical reviewer will consult with Marc Walton regarding other similar clinical issues.

5. The RPM will check the status of the PMC in the database and will get back to the group.

6. The RPM will draft the filing letter.

FDA Attendees:
Lou Marzella
Jeff Siegel
Kallappa Koti
Kay Schneider
Susan Giuliani

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

SEB

From: Susan E. Giuliani, DARP, TPPB, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: June 23, 2003 Time: 8:30 am EDT

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becalpermin Gel (Regranex®)

Short Summary: Revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an unmarketed dose, and to add a Geriatric Use subsection

Purpose of call: To clarify official contact for OMJ Pharmaceuticals and to confirm decision about withdrawing 7.5mg dose.

Discussion:

Ms. Weisel of Johnson & Johnson returned my voice message of 6/20/03 confirming that Francisco Franco is the official contact for OMJ. I also advised Ms. Weisel that OMJ can either send a letter requesting withdrawal of the 7.5mg dose from the BLA, or they can keep this dose in the package insert (PI), even though it will not be marketed. However, if they choose to withdraw this dose from the BLA, they must submit a BLS if they decide to return this dose to the market in the future. FDA does not reconcile the gap of an unmarketed dose that remains in the PI. Ms. Weisel stated that she would take this advise to her colleagues and get back to me with their decision.

FDA Attendee: (Initiated) Susan Giuliani

Sponsor Attendee: Shirley Weisel (Ph. 908-218-6519)

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103691/5015

JUN 27 2003

Francisco Franco
OMJ Pharmaceuticals, Incorporated
Road 362, Km. 0.5, Box 367
San German, Puerto Rico 00683

Dear Mr. Franco:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your supplement dated January 24, 2003 for Becaplermin to determine its acceptability for filing. In accordance with 21 CFR 601.2(a) the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the supplement, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Susan E. Giuliani, at (301) 827-4358.

Sincerely yours,

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc: Cynthia Chianese
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.
920 U.S. Highway 202, P.O. Box 300
Raritan, N.J. 08869

CONCURRENCE PAGE

cc: DARP BLA file, HFM-585
L. Marzella, HFM-582
E. Dye, HFM-585
G. Jones, HFM-585

CBER:DARP:RPM:S. Giuliani:6-16-03, 6-20-03: K. Townsend: 6.23.2003: 6.26.2003
(S:\Giuliani\BLS\103691_5015\FilingLtr.doc)

COMMUNICATION TYPE:
LETTER: Filing Notification (FL)

SS Data Check:
- **Communication**
- **Milestone: Confirm Filing Action Entry & Closed Date**

Division	Name/Signature	Date
DARP	Giuliani	6/26/03
DARP	Schneider	6-26-03
DARP	Dep. for Toner	6-27-03
DARP	Kelly Townsend	6-27-03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUL 15 2003

Our STN: 103691/5015

Francisco Franco
OMJ Pharmaceuticals, Incorporated
Road 362, Km. 0.5, Box 367
San German, Puerto Rico 00683

Dear Mr. Franco:

Please refer to the supplement to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated June 27, 2003.

While conducting our filing review we identified the following potential review issues. Please provide the following information or specify the location of this information with your BLA supplement:

CLINICAL INFORMATION

1. Please provide Financial Disclosure information for study PULC-002. Please refer to the "Guidance for Industry, Financial Disclosure by Clinical Investigators" for specific details on this requirement as per 21 CFR Parts 54, 312, and 601.

2. What is your intention regarding the 7.5 gram dose in the **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the package insert (PI)? We remind you that withdrawal of this dose means withdrawal of an approved dose from the original BLA and requires sending a request letter as an official amendment to this supplement. If you decide to market this dose again in the future, you must submit a new BLA supplement. Alternatively, the 7.5 mg dose may remain in the PI without marketing it.

3. Please provide the efficacy and safety data of the product in the geriatric population. This data should include all relevant summaries and listings and be submitted in a format that can be adequately reviewed.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Susan E. Giuliani at (301) 827-4358.

Sincerely,

Susan E. Giuliani, R.N., M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

cc: Cynthia Chianese
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.
920 U.S. Highway 202, P.O. Box 300
Raritan, N.J. 08869

Concurrence Page

Letter Type: Deficiencies Identified (DI)

SS Data Check:
- **Communication**
- **Milestone: Confirm Deficiencies Identified Entry & Closed Date**

cc: Division BLA Files
L. Marzella, HFM-582 (Comments rec'd 7/9/03)
K. Koti, HFM-219
S. Giuliani, HFM-588

History: S. Giuliani-7.10.03: K. Townsend: 7.14.2003: 7.15.2003

File Name: (S:\Giuliani\BLS\103691_5015\Day74Ltr.doc)

Concurrence box

Office	Name/Signature	Date
DARP	Giuliani	7-15-03
DARP	Kelley Townsend	7-16-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, DARP, TPPB, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: July 28, 2003 Time: 11:30 am EDT

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becalpermin Gel (Regranex®)

Short Summary: Revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an unmarketed dose, and to add a Geriatric Use subsection

Purpose of call: To confirm decision about withdrawing 7.5mg dose.

Discussion:

Ms. Maybroda called regarding a different issue, and before this telecon concluded, I asked Ms. Maybroda the status of OMJ's decision regarding deleting the 7.5gm dose from the package insert (PI), item #2 in the 7/15/03 day 74 letter to both OMJ and J & J.
Ms. Maybroda replied that this dose would remain in the PI and would not be marketed. I replied to her that the only problem may be that the companies may get calls from the medical community as to why this dose remains in the label without being marketed. I reiterated that the FDA does not respond with a regulatory action in this situation.

The telecon concluded.

FDA Attendee: Susan Giuliani

Sponsor Attendee: (Initiated) Adrianna Maybroda (Ph. 908-704-4385)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, DARP, TPPB, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: July 31, 2003 Time: 11:30 am EDT

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becalpermin Gel (Regranex®)

Short Summary: Revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an unmarketed dose, and to add a Geriatric Use subsection

Purpose of call: To update status of items requested in FDA's 7/15/03 DR letter.

Discussion:

Ms. Weisel updated me with the following:

1. J & J & OMJ had decided to keep the 7.5gm dose in the PI and not market it. Ms. Wiesel was preparing a formal reply in a letter.

2. J & J is compiling all geriatric data and double-checking it for accuracy and format. This information will be submitted shortly.

3. The clinical group will be meeting next week to discuss the adequacy of the information compiled for financial disclosure. They are also double-checking this information for accuracy. The financial disclosure information will be the last item submitted to this supplement.

The telecon concluded.

FDA Attendee: Susan Giuliani

Sponsor Attendee: (Initiated) Shirley Wiesel (Ph. 908-218-6519)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: October 7, 2003

From: Susan E. Giuliani, RPM, ODEVI/ DRMP, HFM-588

Subject: September 30, 2003 Midcycle Meeting Summary

To: STN 103691/5015 file

Product: Becaplermin

Sponsor: OMJ Pharmaceuticals, Inc.

FDA Attendees: Lou Marzella, Kallapa Koti, Marc Walton, Susan Giuliani

REVIEW STATUS

Review of the data is ongoing. (Dr. Marzella)

DECISIONS REACHED/ACTION ITEMS

1. The sponsor has not submitted the geriatric data and financial disclosure. This submission will not be classified as a major amendment.

2. Dr. Marzella will obtain additional information regarding the clinical data from the sponsor.

3. A preliminary review of the package insert has been completed and Dr. Marzella plans to make changes to the text provided by the sponsor. Additional minor changes might also be made to other sections of the package insert.

4. Additional internal meetings will not be scheduled. All comments to the PI will be communicated via e-mail.

5. RPM will contact Dr. Stromberg regarding immunogenicity of the product and the possible need for an Immunogenicity section added to the PI.

6. RPM will obtain senior management input on the possible need for a consult to ODS.

7. RPM will ask the sponsor about a PPI and carton/package labeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, ODEVI, DRMP, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: January 30, 2004 Time: 11:30 am EST

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin Gel (Regranex®)

Short Summary: Revise the package insert (PI) to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an unmarketed dose, and to add a Geriatric Use subsection

Purpose of call: To clarify and update status of items requested in FDA's 7/15/03 deficiencies identified letter.

Discussion:

I informed Ms. Weisel via voice mail yesterday that FDA's plan at that point was to meet the March 1, 2004 PDUFA deadline, depending on when they could submit the required information from the 7/15/03 deficiencies identified letter. This plan, however, has changed, and the best approach, considering that the labeling changes have not begun to be negotiated, is for the FDA to issue a complete response (CR) letter. The clinical reviewer informed me that minimal geriatric data was needed from those patients up to 65 years of age. What were the status of financial disclosure and their initial plan of with withdrawing the 7.5 gm dose from the PI?

Ms. Weisel updated me with the following:

1. Regarding the geriatric data, J & J compiled all safety and efficacy data and double-checked it for accuracy and format. They discovered that this data was insufficient for the purpose intended. They decided to reanalyze the original database for those patients up to age 65, those patients 65 – 75 years of age, and those patients over 75 years of age, as specified in 21 CFR. They discovered that the clinical team supporting this product was also deficient, and had to out

source for this task. The process of reanalyzing the original database as such has just begun, and OMJ hopes that this process will be completed by the second quarter of 2004.

2. J & J & OMJ had decided to keep the 7.5gm dose in the PI and not market it. Ms. Wiesel was preparing a formal reply in a letter and would include a copy of the PI showing this dose as not deleted.

3. The financial disclosure information was being finalized and would be ready to submit soon.

Ms. Wiesel asked if OMJ could withdraw their request for a new geriatric use subsection and possibly approve the BLS from the data regarding venous status and pressure ulcers. I replied that I would take this question to my senior management and get back to her.

The telecon concluded.

FDA Attendee: Susan Giuliani (Initiated)

Sponsor Attendee: Shirley Wiesel (Ph. 908-218-6519)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, ODEVI, DRMP, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: February 2, 2004 Time: 11:30 am EST

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin Gel (Regranex®)

Short Summary: Revise the package insert (PI) to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an un marketed dose, and to add a Geriatric Use subsection

Purpose of call: To clarify required geriatric data and final action plans

Discussion:

I informed Ms. Weisel that if OMJ decided to withdraw the geriatric data portion of this BLS and approve it on the data submitted thus far was not acceptable to FDA due to the fact that FDA and the sponsor have not negotiated labeling yet. The review package must be completed 3 weeks ahead of the deadline in preparation for a tertiary review. The complete response letter would issue.

Regarding the geriatric data, I informed Ms. Weisel that Dr. Marzella had stated that the following information is required:

1. We would like the overall data analyzed by two groups: patients <65 years of age and patients $\geq$ 65 years of age.

2. We would like the data for patients ≥ 65 years of age further divided into two subgroups: patients aged 65-74 years and patients ≥ 75 years

Ms. Weisel stated her understanding.

The telecon concluded.

FDA Attendee: (Initiated) Susan Giuliani (Initiated)

Sponsor Attendee: Shirley Weisel (Ph. 908-218-6519)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, ODEVI, DRMP, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: February 9, 2004 Time: 2:30 pm EST

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin Gel (Regranex®)

Short Summary: Revise the package insert (PI) to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an un marketed dose, and to add a Geriatric Use subsection

Purpose of call: To clarify issues related to the required geriatric data

Discussion:

Ms. Weisel followed up from a fax transmitted from J & J on 2/2/04. The fax included statements of understanding from guidance conveyed by this writer from Dr. Marzella on 2/2/04 related to the Geriatric data required in this BLS. I informed Ms. Weisel that Dr. Marzella had an additional point of clarification in that a listing of all serious AE's would not be adequate. J & J would need to summarize this data and compare by age groups, just as they had done with the efficacy data.

Ms. Weisel stated her understanding and added that she would take this clarification to the clinical group at J & J.

The telecon concluded.

FDA Attendee: Susan Giuliani

Sponsor Attendee: (Initiated) Shirley Weisel (Ph. 908-218-6519)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Susan E. Giuliani, ODEVI, DRMP, HFM-588

To: 103691/5015 File

Subject: Telecon Summary

Teleconference Date: February 10, 2004 Time: 2:30 pm EST

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin Gel (Regranex®)

Short Summary: Revise the package insert (PI) to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, to withdraw an un marketed dose, and to add a Geriatric Use subsection

Purpose of call: To clarify definitions related to the primary endpoint

Discussion:

Ms. Weisel called me and asked the following question:

Regarding the rate of closures and non-closures, what is meant by the term "rate"? Does this term mean, "Time to achieve?"

I responded that I would check with Dr. Marzella and get back to her.

The telecon concluded.

Follow-up 2/11/04: After consulting with Dr. Marzella, I left a voice mail message for Ms. Weisel with Dr. Marzella's response as follows:

"We are interested in the proportion of patients who heal (achieve complete ulcer closure at endpoint."

FDA Attendee: Susan Giuliani

Sponsor Attendee: (Initiated) Shirley Weisel (Ph. 908-218-6519)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103691/5015

FEB 27 2004

OMJ Pharmaceuticals, Incorporated
Attention: Shirley Weisel
Senior Regulatory Associate, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Weisel:

This letter is in regard to the supplement to your biologics license application for Becaplermin to revise the package insert to update the Clinical Studies and Precautions sections regarding treatment of venous stasis and pressure ulcers, and to add a Geriatric Use subsection submitted under section 351 of the Public Health Service Act. Reference is also made to our July 15, 2003, discipline review letter, and your response dated February 9, 2004.

We have completed the review of your supplement, including all amendments received through February 9, 2004. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

You have proposed that the Geriatric Use subsection of the package insert be revised to state, (b) (4) (b) (4) However, you have not submitted data and analyses to support your proposed labeling change. Please submit the following additional information:

1. The safety and efficacy data relating to geriatric patients within the product's indicated population, including all relevant summaries and data listings.

2. Data from studies 90-22120-F, 90-22120-K, PDGF-DBFT-001, and PDGF-DBFT-002 which evaluated patients with diabetic foot ulcers:

   a. Listings by study and by treatment arm of the following:

      1) All serious adverse events.

      2) Patients experiencing complete ulcer closure.

   b. Incidence of serious adverse events and of ulcer closure in each study and treatment arm. Please provide analyses for the following:

      1) The overall population.

2) Age subgroups: <65 years, ≥ 65 years; ≥75 years; and 65-74 years.

We reserve comment on the proposed labeling until the supplement is otherwise acceptable.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

You may request a meeting or teleconference with CDER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; (3) withdraw the supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the supplement. In the absence of any of the above responses, we may initiate action to deny the supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

We acknowledge receipt of your amendments dated February 10, and 13, 2004. You may cross reference applicable sections of these amendments in your complete response to this letter and those sections will be reviewed as a part of your complete response.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 827-4358.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Complete Response (CR):

SS & RIS Data Check:

- **Communication**
- **Milestone: Confirm First Action Due Closed Date. Ltr. Date And CR Milestone Date Should Match**
- **Submission Screen: STN Status – Complete Response Ltr.**

cc: Rosenberg, HFM-535
B. Cherney, HFM-536
M. Walton, HFM-570
E. Unger, HFM-570
DARP BLA file, HFM-585
L. Marzella, HFM-576 (Comments rec'd 2/23/04)
K. Koti, HFD-711
A. Chakravarty, HFM-597
K. Weiss, HFM-500
E. Dye, HFM-585
V. Tyson-Medlock, HFM-588

History: S. Giuliani:2/23/04: K. Townsend: 2.26.2004: 2.27.2004

File Name: S:Giuliani\BLS\103691_5015\Complete Response Letter.doc

Division	Name/Signature	Date
ODE VI / DRMP	S. Giuliani	2/27/04
ODE VI / DRMP	Karen D Jones	2/27/04
ODE VI / DRMP	Vickey Thomas for Dye	2/27/04
ODE VI / DTBMP	MD for MKW	2/27/04
DRMP	Kelly Townsend	3/2/04

Review Committee Assignment Memorandum

STN: 103691/5015

☐ Initial Assignment
☒ Change

Applicant: OMJ Pharmacueticals

Product: Becaplerming

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
V. Tyson-Medlock	Reg. Project Manager	Admin/Regulatory	Kay Schneider	11-12-04
	Reviewer	Admin/Regulatory		
	Reviewer	Product*		
	Reviewer	Product*		
	Reviewer	Product		
	Reviewer	Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
		Labeling		
		Other		
	CHAIRPERSON			

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Susan Guiliani	Reg. Project Manager	Admin/Regulatory	Kay Schneider	11-12-04

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

V. Tyson-Medlock — Name Printed

V. Tyson-Medlock — Signature

11-12-04 — Date

Memo entered in RMS by: Kay Date: 4/6/05 QC by: LB Date: 4-7-05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: April 21, 2005

From: Victoria Tyson-Medlock, DRMP, HFD-109

To: The file-STN 103691/5015

Subject: Meeting type-Midcycle Meeting Summary

Meeting Date: April 20, 2005 **Time: 3:30-5:00**

Location: WOC 2 Conference Room D

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin [Regranex]

Proposed Use: Treatment of diabetic ulcers

Type of meeting: Midcycle Meeting

Meeting Purpose: to discuss the status of reviews for this efficacy supplement submitted to revise the Clinical Studies and Precautions sections of the package insert to include information on the treatment of venous stasis and pressure ulcers and to add a Geriatric Use subsection. Also, the 7.5 gram tube is being withdraw from the market. This is a prior approval efficacy supplement with a 10-month review cycle.

Agenda

- Overview-Vicky Tyson-Medlock-5 minutes

This supplement was submitted to revise the Clinical Studies and the Precautions sections of the package insert to include information on the treatment of venous stasis and pressure ulcers and to add a Geriatric Use subsection. This is a Prior Approval Efficacy Supplement (PAS) with a 10-month review clock and the Division of Therapeutic Biological Internal Medicine Products will take the lead on this supplement. Dr. Louis Marzella is the clinical reviewer and

the chairman and Dr. Kallappa Koti is the statistician assigned to this supplement. This supplement was submitted on January 23, 2003. However, the required user fee was not received until May 2, 2003, which started the regulatory clock. A complete response letter was issued on February 4, 2004. A Class 2 response was received on November 12, 2004 and the first action due date is May 14, 2005.

- Status of Clinical/Statistical Review- Dr. Louis Marzella and Kallappa Koti - 45 hour minutes

  Dr. Louis Marzella presented the results of his review and made recommendations and revisions to the package insert

- Labeling Review-45 minutes

- Action Items

  The claim for categorical exclusion needs to be reviewed and completion of the compliance check.

  Reivisions to the package insert were done and sent to Drs. Marzella and Walton for final concurrence. The FDAs proposal will then be sent to the sponsor.

FDA Attendees:

Louis Marzella, Marc Walton, Kallappa Koti, Catherine Gray, Boguang Zhen, and Victoria Tyson-Medlock

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Teleconference Date: May 10, 2005 **Time: 10:30 a.m.**

Sponsor: OMJ Pharmaceuticals, Incorporated

Product: Becaplermin [REGRANEX]

STN 103691/5015

Proposed Use: diabetic foot ulcers

Teleconference Purpose: Information request

DISCUSSION:

I called Ms. Shirley Weisel to discuss the proposed changes to the package insert submitted on May 10, 2005. After discussing the sponsors proposal with Dr. Louis Marzella I informed Ms. Weisel that the changes to the third paragraph, the second sentence on page 4 were unacceptable, because it is not factually correct, implies that there is a treatment effect and that the data from the venous statis ulcers should be regarded as different that the pressure ulcers:

(b) (4)

The sponsor agreed to delete this sentence and (b) (4)

This difference was not statistically significant.

The agency agreed to accept replacing demonstrated with established in the following sentence:

The efficacy of REGRANEX Gel has not been established for the treatment of pressure ulcers and venous stasis ulcers (see Clinical Studies), and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic ulcers.

I asked the sponsor to submit a revised copy of the PI that includes that changes discussed.

FDA Participants:

Victoria Tyson-Medlock

Sponsor Participants:

Shirley Weisel

LICENSING ACTION RECOMMENDATION

Applicant: OMJ Pharmcuetical, Incorporated STN: 103691/5015

Product:

Becaplermin

Indication / manufacturer's change:

to revise the Clinical Studies and Precautions sections of the package insert to include information regarding the treatment of venous stasis and pressure ulcers, to add a Geriatric Use subsection and to withdraw the 7.5 gram dose

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

■ Review of Environmental Assessment ☐ FONSI included ■ Categorical Exclusion

■ Review of labeling Date completed 5-10-05 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

☐ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____ Date: _____

Product Office's Responsible Division Director(s)*: _____ Date: 5/13/05

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: 4-25-05

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: 5-13-05

Responsible Division Director _____ Date: _____
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y (N)	Not required
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	Y (N)	Not required
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
▢ Biopharmaceutics and associated analytical methods	Y (N)	Not required
▢ Clinical pharmacology [includes immunogenicity]	Y (N)	Not required
▢ Clinical Efficacy [for each indication]	(Y) N	
▢ Clinical Safety	(Y) N	
▢ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y (N)	Not required
Tabular Listing of all clinical studies [5.2]	Y (N)	
Study Reports and related information [5.3]	(Y) N	
▢ Biopharmaceutic	Y (N)	Not required
▢ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y (N)	"
▢ Pharmacokinetics (PK)	Y (N)	"
▢ Pharmacodynamic (PD)	Y (N)	"
▢ Efficacy and Safety	(Y) N	
▢ Postmarketing experience	Y (N)	"
▢ Case report forms	Y N	
▢ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	Y (N)	"
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
▢ legible	(Y) N	
▢ English (or certified translation into English)	(Y) N	
▢ compatible file formats	Y (N)	Not applicable
▢ navigable hyper-links	Y (N)	"
▢ interpretable data tabulations (line listings) & graphical displays	(Y) N	

STN 103691/5015 Product Becaplermin

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	Y (N)	Not applicable
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y (N)	Not applicable
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	Not applicable
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y (N)	Not applicable
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y (N)	Not applicable

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	Y (N)	Not applicable
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y (N)	"
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	Not applicable
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
VSLV-002	(Y) N	Y N (NR)	Y (NR)	Y N (NR)
PULC-002	(Y) N	Y N (NR)	Y (NR)	Y N (NR)
VSLV-003	(Y) N	Y N (NR)	Y (NR)	Y N (NR)
PULCV-001	(Y) N	Y N (NR)	Y (NR)	Y N (NR)
PHI-009	(Y) N	Y N (NR)	Y (NR)	Y N (NR)
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

NO

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

Reviewer: L Margolis Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)
June 11 2003

Concurrence:

Branch Chief: Jeffrey N. Siegel Division. Director:
(signature/ date) (signature/ date)
6/17/03

STN 103691/5015 Product Becaplermin

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
☐ including list of all establishment sites and their registration numbers	Y N	
☐ If foreign applicant, US Agent signature.	Y N	
Comprehensive Table of Contents	Y (N)	Just for reports - not comprehensive ✓ done submitted 5/1/0
Debarment Certification with correct wording (see * below)	Y (N)	
User Fee Cover Sheet	(Y) N	
User Fee payment received	Y (N)	- off arrears on 5/9/03
Financial certification &/or disclosure information	Y (N)	- will need for studies completed after 2/2/99
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y (N)	N/A
Pediatric rule: study, waiver, or deferral	Y (N)	NA - not usually used in Peds patients
Labeling:	(Y)	
☑ PI –non-annotated	N	
☑ PI –annotated	(Y)	- will call sponsor for current unannotated PI, PPI, & carton labeling & electronic version on diskette unless has secure Email ✓ done submitted 5/1/
☑ PI (electronic)	Y (N)	
☐ Medication Guide	Y N	
☐ Patient Insert	Y N	
☐ package and container	Y N	
☐ diluent	Y N	
☐ other components	Y N	
☐ established name (e.g. USAN)	Y N	
☐ proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y (N)	Not comprehensive TOC - Sponsor to be called - ✓ done, submitted 5/1/03
☑ legible	(Y) N	
☑ English (or translated into English)	(Y) N	
☐ compatible file formats	Y N	
☐ navigable hyper-links	Y N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
☐ summary reports reference the location of individual data and records	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☑ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
☐ description and results of studies performed to evaluate the change	Y N	
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☑ changes in labeling clearly highlighted	(Y) N	
☑ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	Y N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo). No user fee.
The sponsor will need to supply a comprehensive mail TOC, unmanufactured current PI, PPI (if there is one), & carton/package labeling. The labeling also needs to be provided in electronic format, either by diskette or secure, e-mail. I believe these items can be provided very quickly as amendments & will not be a filing issue. No financial disclosure submitted and this is a 74 day letter issue. Sponsor to be notified

Has orphan drug exclusivity been granted to another drug for the same indication? No

If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? yes

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period: N/A

- Name: _____
- Dates: _____

Recommendation (circle one): (File) RTF

RPM Signature: S. Cavaliere Branch Chief concurrence: Schneider

6-11-03

Examples of Filing Issues	Yes?	If not, justification, action & status
☑ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
☑ ~~description and results of studies~~ performed to evaluate the change (not seen)	(Y) N	
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☑ changes in labeling clearly highlighted	(Y) N	
☑ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	Y N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

I will request an additional electronic copy of unannotated PI.

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? No

Does this submission relate to an outstanding PMC? yes

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one): (File) RTF

RPM Signature: S. Giuliani Branch Chief concurrence: