MEMORANDUM

DATE: December 9, 1997

FROM: Louis Marzella M.D., Ph.D.

THROUGH: William Schwieterman M.D.,
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TO: Karen Weiss M.D.,
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Office of Therapeutics Research and Review,
Center for Biologics Evaluation and Research.

SUBJECT: Clinical review of BLA-96-1408

PRODUCT: REGRANEX (becaplermin) Gel 0.01%

SPONSOR: OMJ Pharmaceuticals

INDICATION: Treatment of lower extremity diabetic ulcers

REFERENCE NUMBER: BLA-96-1408

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OVERVIEW

Sponsor:	OMJ Pharmaceuticals, Inc.
Product:	REGRANEX (becaplermin) Gel 0.01%, recombinant human platelet-derived growth factor (*Saccharomyces cerevisiae*).
Proposed Indication:	"REGRANEX Gel is indicated to promote healing of full-thickness diabetic ulcers. REGRANEX Gel is safe and effective in increasing the incidence of complete healing and decreasing the time to complete healing. The most consistent benefit is seen in diabetic ulcers up to approximately 7 cm^2 (length x width). REGRANEX Gel should be used in conjunction with good wound care practices."
Proposed regimen:	100 μg PDGF/g CMC gel applied daily over the surface of the ulcer.

This Biological License Application (BLA) for Regranex is the result of a shared manufacturing agreement between Chiron Corporation, which produces the drug substance of yeast-derived recombinant human platelet-derived growth factor (PDGF-BB, USAN name, "Becaplermin") and OMJ Pharmaceuticals, Inc., which is responsible for formulating the PDGF-BB with Sodium Carboxy-methylcellulose (NaCMC) and preservatives into a low-bioburden, multi-use gel drug product.

INTRODUCTION

Platelet-Derived Growth Factor (PDGF) biology and biochemistry

PDGF-BB represents the first recombinant DNA-derived product submitted to the FDA for licensure for the topical treatment of chronic ulcers. Native PDGF is a growth factor derived from blood platelets that mediates tissue repair via 1) mitogenesis of mesenchymal cells including dermal fibroblasts, smooth muscle cells and also perhaps wound capillary endothelial cells, 2) chemoattraction of fibroblasts, smooth muscle cells, monocytes, and neutrophils, 3) induction of extracellular matrix components in fibroblasts, including collagen, fibronectin and hyaluronic acid, and 4) induction of metalloproteinases involved in wound remodeling.

PDGF is composed of "A" and "B" chains, each of approximately [redacted] molecular weight.
[redacted]

8 lines

(b)(4)

[redacted]

Biochemically, PDGF-BB is a highly basic [redacted] disulphide-bonded dimer with [redacted] PDGF resides in alpha-granules of blood platelets (principally PDGF-AA and AB), and upon agglutination is released into the immediate wound environment. Protease cleavage occurs naturally to yield "clipped" PDGF isoform ligands [redacted] which nonetheless bind PDGF RTKs to remain biologically active.

(b)(4)

Drug substance

OMJ Pharmaceuticals's "Regranex" consists of PDGF-BB in a nearly aqueous gel of carboxymethyl cellulose. Chiron, Inc. obtains PDGF-BB by DNA recombinant technology using a strain of the yeast *Saccharomyces cerevisiae*, genetically modified with a [redacted] yeast expression plasmid that includes a gene [redacted] PDGF-BB. Becaplermin is the USAN designation for human recombinant PDGF-BB. Becaplermin is purified to homogeneity.

Drug formulation

Becaplermin is formulated by OMJ Pharmaceuticals, Inc. at 100 µg/g in a low percentage of Sodium Carboxymethylcellulose (NaCMC) as a gel containing anti-microbial preservatives. This drug product, "Regranex", is characterized by SDS-PAGE under reducing and non-reducing conditions. The biological potency of Regranex is assessed with a human fibroblast mitogenesis assay. The manufacture of Regranex has been demonstrated to be highly consistent and the material used in the clinical trials is comparable with the product intended to be marketed.

Regranex is a low bioburden (non-sterile) product. A microbial specification of bioburden of less than 10 colony forming units/g of Regranex has been established using the Microbial Limits Test. The bacteriocidal and fungicidal capacity of the preservative in Regranex is confirmed using the Preservative Effectiveness Test. Further, *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans* , and beta-hemolytic streptococci are absent in the finished product. Lower extremity diabetic ulcers are naturally contaminated by polymicrobial flora, even when not considered by clinical judgment to harbor an active infection. The gel is proposed to be applied as a thin layer the thickness of a dime to diabetic ulcers in conjunction with

good wound care practices.

Shared manufacturing

Chiron, Inc. is responsible for production of Becaplermin and mitogenic assay of drug substance and drug product for biological potency. OMJ Pharmaceuticals, Inc. is responsible for formulation of Regranex Gel Product and for adverse experience monitoring (RWJ PRI), microbiology and engineering support (OrthoBiotech). Product distribution and product complaints are handled through McNeil Pharmaceuticals. These four companies, associated with the drug product itself, are members of the Johnson and Johnson family of companies.

Pharmacology of becaplermin

Bioassay of cultured cells revealed no evidence of inverted U-shaped dose-response curve. For example mouse Balb/c 3T3 fibroblasts show half maximal growth at 15-30 ng/ml, maximal growth at 80 to 160 ng/ml and no change in the dose response curve at a concentration of 50,000 ng/ml. This latter concentration is close to concentrations used clinically (30 and 100 µg/g). This information is relevant to the safety/efficacy assessment of becaplermin because of the large (individual and overall average) excess becaplermin usage in the clinical studies.

In the various wound models tested, enhanced formation of local granulation tissue was noted within approximately one week of application of PDGF-BB. This granulation tissue fills the wound, and provides an extensive vascular matrix for the forming epidermis. The quantity of granulation tissue decreases as the wound becomes epithelialized and remodels. Little/no effect of PDGF-BB on contraction, epithelialization, or incisional wound strength was observed in the animal wound models. In certain models PDGF appears to inhibit both wound contraction and epithelialization. It is postulated that the primary action of PDGF-BB is to increase granulation tissue due to migration and proliferation of cells, followed by extracellular matrix deposition.

No clear dose response pattern was observed in the numerous studies performed in the guinea pig partial thickness skin excision model.

Rats injected at the metatarsus with PDGF levels up to 10 μg/site (200 μg/kg) every other day for 13 days displayed morphologic changes indicative of accelerated bone remodeling [periosteal hyperplasia, subperiosteal bone resorption and exostosis], reflective of PDGF's ability to stimulate connective tissue growth. This information is relevant to the safety assessment of becaplermin because in the clinical studies becaplermin could be applied to Stage IV diabetic ulcers with exposed periosteum.

Bioavailability of becaplermin

In animal models, the bioavailability of topically applied PDGF was less than 3% with no measurable systemic accumulation of PDGF.

In study #PHI-007, ten patients with Stage III or IV diabetic ulcers received 100 µg/g becaplermin topically at 7.0 $\mu g/cm^2$ daily for 14 days. No consistent elevation in PDGF levels above baseline plasma PDGF levels was observed.

This information is relevant to the safety assessment of becaplermin because of the potential activity of becaplermin on: a) vasculature in pathologically affected organs (e.g. myocardium, kidney, brain, ocular fundi) in subjects with diabetes and b) neoplastic cells.

Diabetic foot ulcers

Diabetic ulcers of the lower extremity are reported to occur in 10-15% of the approximately 15-16 million patients with diabetes in the US. The etiological triad of diabetic ulcers is considered to be loss of pressure and pain sensation due to diabetes-induced neuropathy, ischemia from angiopathy, and increased prevalence of foot deformities. The principal treatment modalities for the ulcers are sharp debridement, control of infection, pressure relief, and daily dressing changes. The use of plaster casting, in the form of either half casts or total contact casts appears to be particularly beneficial for ulcers on the heel or over the metatarsal heads. With standard care of neuropathic ulcers there is complete healing after initial treatment in about two thirds of patients. In the remainder of cases, the ulcers are considered chronic; about one third of these will heal with further treatment. The incidence of ulcer recurrence after complete healing is approximately 30% within 12 months.

CLINICAL STUDIES

Overview of the studies

Six controlled, randomized, blinded studies of becaplermin in neuropathic, chronic, cutaneous ulcers of the lower extremity in subjects with diabetes mellitus are discussed in this application. The objectives of the six studies were as follows. Three studies were designed to assess product safety as well as efficacy (90-22120**F**, 92-22120**K**, PDGF-DBFT-**002**). One study (PDGF-DBFT-**001**) was designed to test the safety of the drug vehicle. Study 92-22120-**M** was a dose-ranging study. Study PDGF-WFA-001 was designed to test the stability of the product in wound fluid. These six studies constitute the primary safety database. See Table 1 below for a listing of the characteristics of the six studies.

Efficacy was established after analysis of data from four studies (in short-hand designation "**F**", "**K**.", "**001**", and "**002**") of similar design and dosing regimens. Efficacy was established by the measurement of 100% wound closure (primary endpoint), time to 100% wound closure, and relative ulcer area at 20-weeks or earlier.

TABLE 1. CHARACTERISTICS OF THE SIX STUDIES

PROTOCOL NUMBER (Description)	STUDY DESIGN	NUMBER OF SUBJECTS ENROLLED	TREATMENT
Integrated Efficacy Studies			
90-22120-F (Phase 2 Efficacy and Safety)	Double-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily for up to 20 weeks	57	vehicle
		61	becaplermin gel 30 µg/g
92-22120-K (Phase 3 Efficacy and Safety)	Double-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily for up to 20 weeks.	127	vehicle
		132	becaplermin gel 30 µg/g
		124	becaplermin gel 100 µg/g
PDGF-DBFT-001 (Phase 2 Vehicle Effect)	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 gel 100 µg/g
PDGF-DBFT-002 (Pharmacoeconomic/QoL Study)	Third-party-blind, randomized parallel-group, controlled study. Once daily topical dosing or standard therapy only for up to 20 weeks followed by 16 weeks of standard therapy.	128	becaplermin gel 100 µg/g
		122	standard therapy
DOSE-RANGING STUDY			
92-22120-M (Phase 2)	Third-party-blind, randomized, parallel-group, vehicle-controlled study. Topical treatment once daily for 28 days.	21	vehicle
		19	becaplermin gel 30 µg/g
		19	becaplermin gel 100 µg/g
		18	becaplermin gel 300 µg/g
WOUND FLUID STUDY			
PDGF-WFA-001 (Phase 1, safety only)	Double-blind, randomized, parallel group, vehicle-controlled study. Single treatment.	3	vehicle
		3	becaplermin gel 100 µg/g

The PDGF-WFA-001 study was a randomized controlled study of the effect of chronic wound fluid on the structure and function of becaplermin. Only safety data are available from this study and the data support the safety of becaplermin; this study will not be discussed further.

In the sections that follow, the small "M" study and each of the four major studies are summarized and the efficacy and safety data in each are discussed. Finally the integrated efficacy of the four major studies and the integrated safety of the six studies and of the complete database are discussed.

STUDY 92-22120M

PROTOCOL

Study title

"A 28-day dose-ranging study evaluating three doses of recombinant human platelet-derived growth factor (becaplermin; RWJ 60235) in the healing of chronic, lower extremity diabetic ulcers (protocol 92-22120-M; phase 2)"

Study design

This was a randomized, third-party blinded, parallel study comparing formulations of 0, 30, 100, and 300 μg/g (2.1, 7 and 21 $\mu g/cm^2$). The primary efficacy criterion was relative ulcer area at endpoint, (area at given visit/area at baseline). The study was powered (based on an earlier pressure ulcer study) to detect a 15% difference between active arm(s) and placebo with 20 subjects per group.

PROTOCOL MODIFICATIONS

The sponsor at a meeting with the Agency (May 1993) proposed to do an analysis of the data after 54 subjects were treated and to terminate the study to determine the appropriate dose to be used in the remainder of the development program. However after the analysis the sponsor decided to continue the study and did not discuss the findings with the study investigators. The results were reported to the IND in July and later again in revised form in September of 1993; the latter report is included in the BLA. At interim analysis the sponsor concluded that the 100 μg/g dose was equivalent to the 300 μg/g dose and was superior to placebo and to the 30 μg/g dose.

RESULTS

The relative ulcer area at endpoint in intent to treat subjects is shown in Table 2.

TABLE 2. RELATIVE ULCER AREA AND INCIDENCE OF CLOSURE AT ENDPOINT (4 WEEKS)

	Becaplermin (μg/g)			
	0	30	100	300
Number of Subjects	21	19	19	18
Relative Ulcer Area				
Median	0.40	0.49	0.57	0.30
Mean	0.39	0.50	0.65	0.41
Incidence of Complete Ulcer Closure	0.05	0.11	0.11	0.00

The sponsor concludes in the July 1996 report that measurable therapeutic benefit was not seen due to short duration of treatment.

REVIEWER'S COMMENTS

The design of this study is compatible with that of other studies with the following important exceptions:

- duration of study treatment was only 4 weeks;
- third party (evaluator) blinding was used due to opacity of the 300 μg/g formulation;
- range of ulcer area was 3-15 cm^2;
- during the course of the study the formulation was changed to add lysine.

The study is not informative because the treatment period (4 weeks)) was too short. The treatment period was chosen on the basis of estimates of time to healing and incidence of healing data from a different patient population namely subjects with pressure ulcers. The pathophysiology of the ulcers and a number of variables that affect ulcer healing differ between subjects with pressure ulcers and subjects with diabetes.

Interestingly the descriptive statistics (see table above) for relative ulcer area and incidence of closure seem to suggest that healing in the 30 μg/g group is numerically lower when compared to the 100 μg/g group. Also to be noted is the numerically lower values for healing in the 300 μg/g group. A similar suggestion of lesser activity of doses higher than 100 μg/g comes from a subsequent dose-ranging study in subjects with pressure ulcers.

CONCLUSIONS FOR STUDY "M"

•This was a small trial with short duration of treatment.

•There were no statistically significant differences in outcome measures among the treatment groups .Therefore, no conclusions could be made regarding the active dose of drug.

•This study will not be used in the efficacy analysis.

STUDY 90-22120-F

PROTOCOL

Study title
"Clinical evaluation of platelet-derived growth factor (becaplermin; rwj 60235) for the treatment of lower extremity diabetic ulcers (protocol 90-22120-F)"

Study objectives
Evaluate the safety and efficacy of becaplermin 30 μg activity/g gel in the treatment of lower extremity diabetic ulcers.

Study design
Randomized, double-blind, parallel group, vehicle-controlled, multicenter study conducted to evaluate the therapeutic efficacy and safety of topically applied becaplermin 30 μg/g gel in the treatment of chronic Stage III or IV nonhealing lower extremity cutaneous ulcers (1-100 cm^2) in subjects with diabetes mellitus. Twenty subjects were to be enrolled at each of 6 different centers.

Dosing
•Subjects were dosed once daily for a maximum period of 20 weeks, or until the ulcer had completely healed without drainage or the need for a dressing, or until they

exited the study as treatment failures.
•Ulcer measurements were made at each visit and the dosage of study medication was calculated.
•Becaplermin was formulated at a concentration of 30 μg/g in a sodium carboxymethylcellulose gel with parabens and m-cresol added as preservatives.
•Vehicle contained only sodium carboxymethylcellulose with parabens and m-cresol.

Standard care
•Non-weight bearing was required.
•Ulcers were to be cleansed with saline-moistened gauze changed twice daily; study drug was applied in the morning.
•Sharp surgical debridement was allowed before entry into the study.
•Antimicrobial agents were allowed orally or parenterally.

Enrollment criteria
The criteria are similar to those of the K study (See page 17).

Outcome measures
The primary efficacy outcome was the comparison of the incidence of complete healing (functional score of 1) of the target ulcer between the two treatment groups at endpoint or after 20 weeks of treatment.

The secondary efficacy outcomes were:
• Time to healing.
•Ulcer area at each study visit.
•Endpoint values for total wound evaluation score.
•Investigator's overall assessment of effectiveness.

Safety outcomes included assessment of the incidence of treatment-emergent adverse events, clinical laboratory values, and vital signs.

Efficacy analyses
The primary efficacy analysis was a logistic regression with treatment as an independent variable. Fisher's exact test was to be used to compare the functional wound assessment scores (proportions of subjects with complete ulcer closure) between the two study groups. Time to complete closure was to be analyzed with a Kruskal-Wallis test. With 60 subjects per group the study was powered to show a 25% absolute difference between groups (e.g. 50% vs 75%) with a power of 0.8 at the 0.05 level of significance.

PROTOCOL MODIFICATIONS

•An interim administrative analysis was planned after 60 subjects.

Reviewer Comment:
The justification for the analysis was not strong. The analysis was extensive. No evidence of efficacy was seen because of insufficient power. However trends towards activity of the study drug were seen. The efficacy analysis was done at a 0.05 level of significance and no provision was made for conserving the α .

• Ulcer Recurrence. Subsequent to the completion of subject enrollment, and in response to an Agency request, a post-study followup questionnaire was sent to the investigators requesting followup information for all subjects.

•A number of covariates and interactions terms were defined at a later time and are summarized by the sponsor as follows. The baseline wound area was included as a covariate in the regression analysis. The Functional Assessment Score was first analyzed by a logistic regression model with treatment effect, investigator effect, the baseline wound area as a covariate, and terms for treatment-by-investigator interaction and treatment-by-covariate interaction. The interaction terms were dropped if not significant at the α=0.10 level. In the absence of interaction terms, the logistic regression model contained terms for the baseline wound area as the covariate, treatment effect, and investigator effect.

•The analysis of wound size and wound evaluation scores was changed from each visit to only the last observation with an adjustment for the baseline as a covariate. These two variables were analyzed by an analysis of covariance model with the terms: treatment effect, investigator effect, baseline covariate, treatment-by-investigator interaction, and treatment-by-covariate interaction. For the analysis of wound size, the response variable was the relative area, i.e., the ratio of the final wound area to the baseline wound area, and the covariate was the baseline area. The response variable and the baseline covariate for analyzing Wound Evaluation Scores were the Total Wound Evaluation Score and the baseline Wound Evaluation Score.

•As suggested by the Agency, Cox's proportional hazard model was used to analyze time to closure, with the baseline wound area as a covariate.

• The protocol planned for testing for comparability of demographic variables and baseline ulcer dimensions. This comparability test was replaced by adding baseline wound area as a covariate to all efficacy analyses: functional assessment, time to wound healing and wound size. This covariance analysis addressed potential differences between the two treatment groups with respect to comparability in

baseline ulcer size. No other inferential demographic or baseline comparisons were performed.

•The initial healing assessment allowed for three outcomes: 1) complete healing, 100% closure and no drainage or dressing; 2) partial healing, 100% closure with drainage present; 3) non- healed, < 100% closure with drainage present. This assessment was later dichotomized to healed and non- healed.

RESULTS

Of the 118 subjects enrolled into the study, 89 (75%) were men, 102 (86%) were white and the mean age of all subjects was 61 years. There were no clinically meaningful differences in demographic characteristics between the two treatment groups. The median baseline ulcer areas in the vehicle and becaplermin groups were 4.9 cm^2 and 3.1 cm^2, respectively. The percentage of subjects with adequate infection control in vehicle and becaplermin were 58% and 82% respectively.

Reviewer Comment:
As will be discussed in more detail in the review of the K study, an analysis of sixteen covariates was carried out by the sponsor. Significant ($p<0.1$) covariate effects were found for baseline serum creatinine (0.0016), infection control ($p=0.013$) and baseline ulcer area ($p=0.056$).

The addition of infection control as a factor in the model decreased the apparent treatment effect of 30 μg/g becaplermin leading to loss of significance; addition of baseline ulcer area also decreased the apparent treatment effect of 30 μg/g becaplermin ($p=0.134$). Taken together an imbalance in bacterial control and in ulcer area may possibly account for the activity of becaplermin in this study.

Discontinuation/completion information
Eighty percent of the 118 subjects enrolled completed the study. Of the 24 subjects who discontinued prematurely, 14 did so due to an adverse event. There was no apparent difference between the treatment groups in the number of subjects discontinuing due to adverse events, or other reasons.

Dosing of study drug and of other drugs
Subjects receiving vehicle were treated for a somewhat longer period (median, 18.1 weeks) than were subjects receiving becaplermin (median, 14.0 weeks), in part due to the higher proportion of subjects who healed in the becaplermin treatment group. There was a somewhat higher incidence of systemic antibiotic use in the vehicle group (32%) than in the becaplermin group (20%).

Deviations from protocol

The most common significant protocol variation (five subjects in the becaplermin group, two subjects in the vehicle group) was having an ulcer with dimensions outside of the stipulated 1 to 100 cm^2 range. Two subjects in the vehicle group had an abnormal baseline wound evaluation score and did not heal within the 20-week study period. Two subjects (one becaplermin, one vehicle) had a time since ulcer onset to baseline visit of less than eight weeks. Two subjects (one becaplermin, one vehicle) received concomitant medications on study which were prohibited by the protocol (topical antibiotics at the target ulcer, oral corticosteroids).

EFFICACY ANALYSES

The primary efficacy analyses were based on the intent-to-treat population, defined as all subjects randomized to receive study medication who received at least one dose and had postbaseline data. All 118 randomized subjects fulfilled the intent-to-treat criteria.

Also defined was an evaluable for efficacy population, for secondary analyses. The evaluable for efficacy subset included those subjects with a full thickness chronic diabetic ulcer at baseline (area of 1.0 to 100.0 cm^2, inclusive), with a $TcpO_2 < 30$ mm Hg at study entry, not receiving any interfering concomitant treatments and who received at least seven days of treatment with study medication. There were 109 subjects evaluable for efficacy (55 becaplermin, 54 vehicle). Data from the evaluable for efficacy population were also summarized and analyzed.

To assess the effect of study center on efficacy, subjects from smaller centers were pooled into a separate group such that the total number of subjects in this group did not exceed the total number of subjects enrolled at the largest center. All 118 subjects enrolled in the study were evaluable for safety.

Incidence of ulcer closure

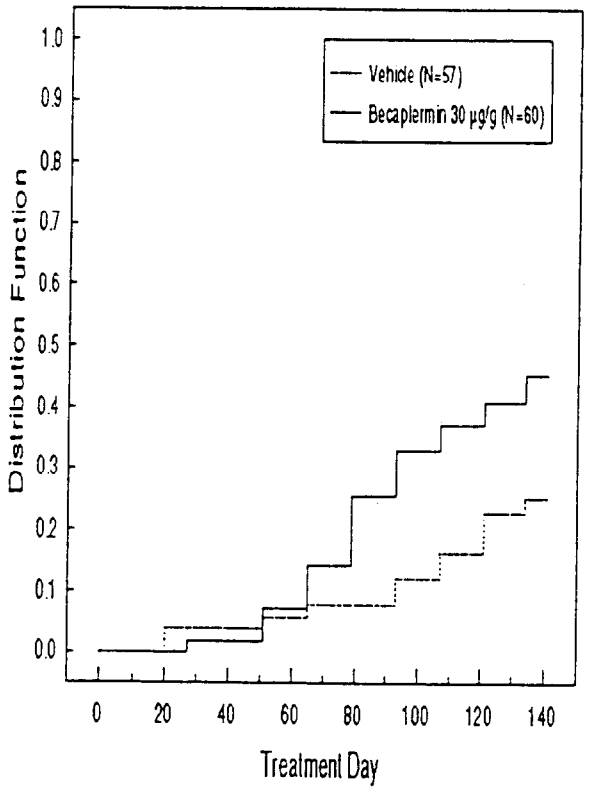
In the ITT analysis, twenty-nine (48%) of the 61 becaplermin subjects achieved complete closure (p=0.016) compared with 14 (25%) of 57 vehicle subjects. Baseline ulcer area was not a significant covariate and there was no significant investigator effect or treatment-by-investigator interaction indicating that the results were consistent across centers. The treatment-by-baseline wound area interaction was also found to be nonsignificant, indicating that the efficacy of becaplermin in healing ulcers was similar for ulcers of various sizes. The incidence of wound closure in the efficacy evaluable subjects was also greater in the becaplermin arm (46%; p=0.038) compared to placebo (26%). By Fisher's Exact Test, a significant (p=0.013) between-treatment group difference was confirmed in the ITT group.

Reviewer comment:
Since only one subject was given a functional score of two, the primary efficacy analyses in the ITT group are essentially the same whether three outcomes (100% closed; 100% closed but draining; not closed) or the dichotomized outcome (100% closed; not closed) are used.

Time to ulcer closure

Analysis of the time to healing using Cox's Proportional Hazards model indicated a statistically significant (p=0.036) between-treatment group difference for the intent to treat subjects, and a marginally significant (p=0.074) difference for the subjects evaluable for efficacy. The Kaplan-Meier estimate of the number of days to healing (25th percentile, an arbitrarily chosen cutpoint) was 78 days in the becaplermin treatment group and 141 days in the vehicle group. Baseline area was not a significant covariate in these analyses. A life table plot of the wound closure data (See Figure 1) shows that the probability of ulcer closure does not differ for the first 10 weeks. Separation of the curves at about Week 10 suggests that the healing effects of becaplermin begin to manifest at that time.

FIGURE 1. LIFE TABLE PLOT OF COMPLETE ULCER CLOSURE IN STUDY "F"



Relative Ulcer Area

The parameter was defined as the ratio of the endpoint area to the area at baseline. The mean relative area for subjects in the becaplermin group (0.4) was smaller than that for subjects in the vehicle group (0.7), but the difference was not significant (p=0.259). Relative area at each visit was examined descriptively. Between-group differences in relative area were apparent after Week 2 (Visit 4) and were maintained throughout most of the study. By Week 20 (Visit 14), becaplermin subjects exhibited a 64% reduction in relative area compared with a 33% reduction for vehicle subjects.

Wound evaluation score

There was no significant difference in final total wound evaluation score between the becaplermin (mean, 1.3) and vehicle groups (mean, 2.0; p=0.131). With regard to the investigator's evaluation of effectiveness, 48% of subjects in the becaplermin group received a rating of maximal effectiveness (score of 3) compared with 28% of vehicle subjects. More vehicle than becaplermin subjects received ratings of intermediate or minimal effectiveness (scores of 2 or 1, respectively).

The main efficacy outcomes in Study "F" are summarized in Table 3.

TABLE 3. EFFICACY OUTCOMES IN INTENT-TO-TREAT SUBJECTS IN STUDY "F"

	VEHICLE	BECAPLERMIN 30 µg/g	P
Incidence of ulcer closure (percentage)	14 (25%)	29 (48%)	0.01
Time to ulcer closure (days)[b]	141	78	0.03
Relative ulcer area[d]	0.7	0.4	0.26
Ulcer evaluation score[f]	2	1.3	0.13

a. Logistic regression analysis;
b. Kaplan-Meier estimate, 25th percentile.
c. Cox Proportional Hazards Model with treatment group and baseline wound area as covariates.

d. Ratio of area at endpoint/area at baseline.
e. Analysis of covariance.
f. Sum of six parameters indicative of infection, rated on a scale from 0 = absent, to 3 = marked.

Covariate analyses indicate that factors known to influence wound healing were reasonably well distributed Significant ($p<0.1$) covariate effects were found for baseline serum creatinine (0.0016), infection control ($p=0.013$) and baseline ulcer area ($p=0.056$). The addition of infection control as a factor in the model decreased the apparent treatment effect of 30 μg/g becaplermin leading to loss of significance; ($p=0.104$). The post-hoc analysis suggested that relatively small imbalances may be sufficient to account for some of the effectiveness of becaplermin over placebo.

Reviewer's comments:
•Several of the efficacy outcomes are consistent in showing activity of becaplermin.
•As could be expected from a small study, there were imbalances in wound variables/wound management in the two study arms.

SAFETY ANALYSES

The population evaluable for safety is identical to the intent-to-treat subject population. The adverse events observed were largely those expected for the subject population enrolled. There was no notable difference between the treatment groups in discontinuations due to adverse events, and none of the seven reported deaths was attributable to study medication. Laboratory values were in general consistent with the clinical condition of the subject population and no notable changes in vital signs were observed on study. No becaplermin antibodies were detectable.

Serious adverse events
After examination of all safety data by the medical monitor, 36 subjects (16 becaplermin, 20 vehicle) were identified as experiencing serious adverse events during the course of the study or follow-up period. Of the 36 subjects with serious adverse events, 11 (five becaplermin, six vehicle) experienced events which were related to infection of the Target Ulcer, including cellulitis, osteomyelitis, skin ulceration, and gangrene. Other events included myocardial infarction, pneumonia, peripheral edema, non-study ulcer related infections, and pain. While most of these events are related to the presence of lower extremity ulcers (e.g., wound infections requiring hospitalization), other events (e.g., renal and/or cardiac abnormalities) are related to the fact that these subjects are long-term diabetics with macro- and micro-angiopathy.

Deaths or discontinuations due to adverse events
Of the 118 subjects enrolled in the study, 14 (6 becaplermin, 8 vehicle) discontinued the study prematurely due to an adverse event. Seven subjects (three becaplermin, four vehicle) died

during the study followup period. Five of the deaths were apparently the result of myocardial infarction, one was due to multiple organ failure, and the cause of one death was unknown. In all cases, the death was either considered unrelated to the study medication or its relationship to study medication was unknown.

Other data

The mean changes in clinical laboratory values (serum chemistry, hematology, or urinalysis) from baseline to post-therapy were generally comparable between the treatment groups and were not clinically meaningful. There were no clinically relevant mean changes from baseline to post-therapy in any of the vital signs measured and vital signs at baseline and posttherapy were comparable between the two groups. None of the study subjects exhibited a positive antibody titer.

ULCER RECURRENCE

Followup questionnaires were returned for 109 of the 118 enrolled subjects. The median time of followup was 21.6 weeks for the 14 vehicle subjects who healed and 17.2 weeks for the 29 becaplermin subjects who healed. Forty-three percent (43%) of vehicle subjects reported that their study ulcer recurred sometime during the followup period, compared with 26% of becaplermin subjects. For the three subjects (two becaplermin, one vehicle) with available dates of recurrence, ulcers recurred in 24 to 30 weeks after healing.

Reviewer's comments:

- The ulcer recurrence data indicates that the clinical benefit, ulcer closure, is sufficiently durable (same as control) and therefore the quality of healing induced by the drug can be considered to be satisfactory.

- This information is important because it indicates that following healing, the skin and soft tissue have not become more resistant to break-down. Therefore, good preventive care remains an essential aspect of diabetic foot management.

CONCLUSIONS FOR STUDY "F"

- The primary efficacy outcome indicates that becaplermin 30 μg/g is superior to placebo.

- The evidence of efficacy is supported by several outcome measures.

- The ulcer recurrence data also lends general support to the evidence of efficacy.

- Post-hoc analyses showed the presence of an imbalance favoring the becaplermin arm in the

proportion of subjects with infection control; although the effect of this covariate was significant, it cannot be determined if it contributed to the treatment effect.

STUDY 92-22120-K

PROTOCOL

Study title

"A phase III, double-blind, placebo-controlled clinical evaluation of recombinant human platelet-derived growth factor (becaplermin; RWJ 60235) in the healing of chronic, lower extremity, diabetic ulcers"

Study objectives

The primary objective of this pivotal study was to evaluate the efficacy of two different doses of becaplermin gel (30 and 100 µg/g) compared to vehicle gel, applied topically to chronic, lower-extremity, diabetic ulcers for up to 20 weeks. An additional objective of this study was to collect safety information including adverse events and clinical laboratory abnormalities.

Study design

Randomized, double-blind, parallel group, vehicle-controlled, multicenter (minimum of 15 centers) study of becaplermin gel (30 or 100 µg/g) topically applied to Stage III or IV chronic, nonhealing lower extremity cutaneous ulcers in 300 (changed later to 360) subjects with diabetes mellitus. If more than one ulcer was present (not more than 3 ulcers of 100 cm^2 combined area were allowed) the ulcer presumed to take the longest to heal would be selected. If the ulcer had not healed at 20 weeks or if the ulcer had not changed or worsened after 8 weeks of study treatment, the subjects were deemed to have completed the study and were eligible to enter a 20-week open label extension study of becaplermin gel.

Dosing

The study drug was applied once daily preferably during the evening dressing for a maximum period of 20 weeks, until the study ulcer had healed, or until the study subject exited the study as treatment failure. Subjects began receiving study medication at Visit 2 (baseline visit) and were seen weekly for Visits 2 through 6, and every other week after Visit 6.

The surface area of the ulcer was estimated at each visit in the following manner. Length is the longest edge-to-edge measurement of the ulcer, width is taken from a perpendicular axis to the length; depth is the deepest vertical measurement using a sterile swab; subsequent measurements are obtained using the same orientation. The surface area (width x length) of the ulcer divided by 4 gives the length of gel (in cm) to be applied daily to the ulcer. Based on these measurements and calculations, the dosage (µg/cm^2) of study medication was adjusted at

each visit. The amount of becaplermin applied to the wound was approximately 2.1 μg/cm^2 and 7.0 μg/cm^2 for subjects in the 30 and 100 μg/g treatment groups, respectively.

Inclusion criteria

•Men or women age 19 or older with diabetes mellitus (Type I or II) who have a cutaneous [neuropathic] ulcer ranging in size between 1 and 40 cm^2 post debridement, present for at least 8 weeks and classified as stage III or IV (as defined by the Association of Enterostomal Therapy guide to chronic wound staging).

•The study ulcer should show "infection control" (defined as a rating lower than "3 "or lower than "marked", for each component of a wound scoring system) should be free of all necrotic and infected soft and bony tissue.

•Subjects should be able to adhere to non-weight bearing regimen.

Exclusion criteria

•Ulcers caused by venous or arterial insufficiency, osteomyelitis.
•Poor nutritional status (albumin < 3g/dl).
•Treatment with corticosteroids, immunosuppressive or chemotherapeutic agents, radiotherapy.
•Presence of necrosis, purulence or sinus tracts that cannot be removed by debridement.
•Presence of connective tissue disease, renal failure (serum creatinine > 3mg/dl) liver failure, malignancy.
•Revascularization surgery performed <8 weeks before entry in the study.

Standard care

•Sharp surgical debridement (including resection of necrotic soft tissue and bone, sinus tracts, fistulae, undermined borders, callus) to produce viable wound margins was to be performed before randomization and was repeated as needed during the study.
•Ulcer care included dressings changes twice daily; the skin around the ulcer was cleansed with mild soap and water, the wound was cleansed with a gauze pad. Study drug was applied to form a continuous film over the entire ulcer surface including the margins. Wet to dry saline dressing was to be alternated with the application of study drug.
•Oral and intravenous antimicrobial agents were allowed for treatment of presumed infection; topical antimicrobials and agents known to affect wound healing were not allowed.
•Unweighting or offloading was required using a variety of methods and devices.

Reviewer's comment:
There is no indication that wet to dry dressings were actually used. A moist wound environment appears to have been the actual standard of care.

Outcome measures

The primary efficacy outcome was the incidence of complete ulcer closure. Complete closure

is defined as 100 % closure with no dressing required and no drainage present (functional score of 1).

The secondary efficacy outcomes were time to ulcer closure and change and percentage change in ulcer size. Additional outcome measures were incidence and time to graftability of ulcer and ulcer recurrence after closure.

Monitoring

Clinical laboratory measurements, serum anti-PDGF antibodies. Ulcer assessments: date of onset; anatomic location; staging; dimensions; acetate tracings for planimetry; photographic documentation; wound evaluation score, graftability, $TcpO_2$; X-rays. Study drug compliance, adverse events, concomitant medications.

Follow-up

Cosmetic index for scar assessment. Ulcer recurrence.

Efficacy Analyses

- Comparisons were to be tested at the 0.05 alpha level. The primary comparison would compare placebo with either of the two PDGF groups in the ITT population and in the evaluable population. Both one way ANOVA with factor of treatment and two-way ANOVA with treatment, center, and their interaction and with baseline wound area used as a covariate
- Incidence of wound closure to be analyzed with a one-way logistic regression model with treatment group as independent variable. Estimates of healing time distribution were to be obtained using Kaplan-Meyer methods and tested with a Wilcoxon test.
- No subset analyses were proposed in the protocol. Closure by treatment group was to be summarized for sex and for age (using age 60 as a cut point).
- Sample size calculations:
  An incidence of closure of 28.3% in placebo and 48.3% in active drug with 100 study subjects per group would have 80% power with two-tailed α of 0.05 to detect a significant difference between groups.
- Definition of intent-to-treat subjects:
  All subjects who received at least one dose of study drug and had any post-baseline data.
- Definition of efficacy evaluable subjects:
  ITT subjects who had followed the protocol.

Safety analyses

The safety assessments were based on the incidence of adverse experiences, discontinuation due to adverse event, clinical laboratory data including becaplermin antibody titers, and vital signs.

The incidence of selected adverse events was compared statistically among the three treatment groups by a two-sided extended Fisher's exact test. These adverse events included those occurring on or near the target ulcer, all serious systemic infections, and tumors. Adverse

events within these categories were included in the analysis regardless of the investigator's assessment of study drug relatedness. Treatment-emergent adverse events are summarized by body system, primary term, and severity. Adverse events are coded according to the World Health Organization Adverse Reaction Terminology (WHOART) dictionary.

All laboratory data collected are presented as descriptive summaries, and changes from normal to marked abnormalities in hemoglobin, AST, ALT, albumin, creatinine, glucose, BUN, and urine protein are also presented. Scatter plots were generated for the quantitative laboratory variables.

Quality-of-Life

Change scores between the baseline and Week 20 assessments were compared between each of the becaplermin gel groups (30 μg/g and 100 μg/g) and the vehicle group using an analysis of covariance (ANCOVA) model; a separate model was used for each variable. Independent variables in these models included treatment group, age, gender, and study center; wound area at baseline (covariate) and a center-by-treatment-group interaction term were assessed and included in the model if they were significant at the 0.10 level. Primary analyses of all measures were conducted on the population of intent-to-treat subjects with completed baseline quality-of-life assessments.

Subject discontinuations

The following criteria were used. Withdrawal of consent, adverse event, treatment failure (ulcer not progressively healing or worsening), non-compliance with study medication (by comparing actual usage with prescribed dose) on two successive visits, missing two scheduled study visits.

PROTOCOL MODIFICATIONS

Efficacy evaluable subjects

To be evaluable subjects had to adhere to protocol. Adherence to protocol (previously undefined) was defined as subjects having at least seven days of treatment, with a Stage III or IV diabetic ulcer at baseline, a baseline ulcer area of 1 to 40 cm^2 inclusive, with a $TcpO_2 > 30$ mmHg at study entry, and not receiving any interfering concomitant medications or procedures (e.g., topical antibiotics, hyperbaric oxygen). Excluded from the evaluable-for-efficacy subjects were those subjects who were non-compliant with study procedures.

The definition and duration of non-compliance was changed as follows. Compliance had to extend over four or more study visits and consisted of receiving <50% of the prescribed dose of study medication, of missed visits, or violation of the non-weight bearing requirements.

Statistical analyses

To preserve the α, a Bonferroni procedure was agreed upon for the primary efficacy analysis.

Subsequently the Step-Down Multiple Testing Procedure described by Tamhane, Hochberg, and Dunnett was agreed upon. This procedure assumes that the becaplermin effect is a non-decreasing function of dose within the 0 to 100 µg/g range. Therefore, the comparisons of each becaplermin group to vehicle were one-sided. The becaplermin 100 µg/g dose was first compared with vehicle at the 0.025 significance level (one-sided). If this test was significant, then the becaplermin 30 µg/g dose was compared with vehicle, also at the 0.025 significance level (one-sided). All other tests were two-sided at the 0.05 significance level, with the exception of interactions which were tested at the 0.10 level of significance.

Demography and baseline characteristics

Instead of statistical testing for comparability of demographic variables and baseline ulcer dimensions, baseline ulcer area was added as a covariate to the efficacy analyses for the functional assessment score, time to wound healing, relative ulcer area at endpoint, and weekly healing rate. This covariance analysis addressed potential differences among the three treatment groups with respect to baseline variables.

Time to 100% wound closure

The statistical method for estimating the time to 100% wound closure was changed from the Kaplan-Meier method and Wilcoxon test to Cox's Proportional Hazards model; this change was suggested by the Agency. Life table plots were used to display the probabilities of healing at each visit window.

Ulcer area

Relative ulcer area (the ratio of the final ulcer area to the baseline ulcer area) was used as a response variable instead of ulcer area in order to take into account ulcer area at baseline. Endpoint relative ulcer area and weekly healing rate were used as response variables rather than change and percent change in target ulcer size. The *t*-test for within-treatment changes in ulcer size and by-week analysis of ulcer size were not done.

Total wound evaluation score

Total wound evaluation score was analyzed using analysis of covariance, with total baseline wound evaluation score as a covariate, rather than by two-way analysis of variance. This covariance analysis addressed potential differences among the three treatment groups with respect to total baseline wound evaluation score.

RESULTS

Subjects evaluable for intent to treat analysis

The study was terminated by administrative decision at one clinical center and the Agency concurred with the decision. All the study subjects at that center were considered unevaluable for all analyses; one subject in the 100 µg/g group developed a serious adverse event, namely osteomyelitis.

The efficacy data for the study center are shown in Table 4.

TABLE 4. INCIDENCE OF 100 % CLOSURE

	Vehicle	Becaplermin 30 µg	Becaplermin 100 µg
Visit #	4-8	3-8	6-8
Incidence of closure	1/4	0/4	0/4

The study subjects at this site will not be considered further.

With the exception of the subjects listed above, only one of the 383 subjects who were randomized was excluded from the intent to treat analysis. This subject was lost to follow up after visit 2, the time when treatment with study drug begins and this is in accordance with the ITT definition.

Study completion and withdrawal

The majority (81%) of the 382 intent-to-treat subjects completed the study, i.e., received 20 weeks of treatment or completed prior to 20 weeks either because of treatment failure or complete ulcer healing. Of the 73 subjects who discontinued prematurely, 43 did so due to an adverse event. There were no differences among the treatment groups in the number of subjects discontinuing due to adverse events, or any other reason.

Subjects evaluable for the efficacy analysis

Twenty-six subjects are not eligible for the efficacy analysis. The total number of evaluable subjects is 356. An ulcer area at baseline <1 cm^2 was the major reason for non-eligibility (13 subjects), followed by non-compliance and use of non-allowed treatments. For the purpose of determining eligibility, the ulcer area was calculated by multiplying the maximum width of the ulcer by the maximum length; this calculation overestimates the actual area. When the ulcer area was measured by the sponsor by planimetry of the tracing of the ulcer edges, the number of subjects with baseline ulcer area <1cm^2 is even greater. No major problems with the definition of the intent to treat and efficacy evaluable population.

Table 5 of the sponsor's summary shows subjects with significant protocol violations. The following subjects were discontinued due to noncompliance [b] or protocol violation [c] Vehicle: b 416, 815, 1407; c 501, 504, 1505; Becaplermin 30: b 715, 730, 1514; c 1207, 1526; becaplermin 100: b 713, 813, 1906; c 808, 1510.

Reviewer's comment:

Additional significant violations in the patient listings are unallowed treatment (e.g. oral corticosteroids, topical antiseptics or antimicrobials, hyperbaric oxygen), ineligibility due to duration of ulcer and baseline ulcer size. Not all these subjects were declared unevaluable for efficacy because they did not meet the pre-specified criteria for exclusion from the evaluable-for-efficacy population. Table 5 (see below) shows that there is a disproportionate number of subjects with a functional score of 1 at endpoint in the subjects with protocol violations in the

becaplermin 100 µg/g group. The significance of this observation is not clear and was not further evaluated because the primary efficacy analysis was done in the ITT population.

TABLE 5. FUNCTIONAL WOUND SCORES IN ALL SUBJECTS WITH PROTOCOL VIOLATIONS AND IN SUBJECTS WITH PROTOCOL VIOLATIONS DEEMED TO BE GROUNDS FOR EXCLUSION FROM THE EFFICACY-EVALUABLE SUBGROUP

DOSE GROUP	FUNCTIONAL SCORE 1		FUNCTIONAL SCORE 2	
	Sponsor	Reviewer	Sponsor	Reviewer
Vehicle	0	1	6	10
becaplermin 30 µg	0	1	6	10
becaplermin 100 µg	0	9	5	8

Subjects who withdrew early due to treatment failure were not counted as discontinuations. They were considered as completing the study with an unsuccessful treatment outcome.

Demographic and baseline characteristics

Of the 382 intent-to-treat subjects enrolled into this study, 255 (67%) were men, 309 (81%) were white and the mean age of all subjects was 58 years (Table 2). The median target ulcer area at baseline (based on planimetry)was similar among the three treatment groups (range of medians: 1.3 to 1.5 cm^2). No clinically meaningful differences in baseline or demographic characteristics were observed among the treatment groups. A total of 383 were randomly assigned to be treated once daily with either becaplermin 100 µg/g (124 subjects), becaplermin 30 µg/g (132 subjects), or a visually identical vehicle (127 subjects).

In order to assess the comparability of the treatment groups, the Agency and the Sponsor agreed on an analysis of sixteen factors and variables generally believed to have an impact on wound healing (See BLA amendments 1 and 2). The factors were examined by treatment group at baseline and/or over the course of the study for each individual study and for all studies combined. The intent-to-treat population was of primary interest to the Agency, the sponsor also analyzed these factors in population subsets based on baseline ulcer area (<10 cm^2 and < 5 cm^2).

The factors examined are: duration of ulcer at enrollment, baseline serum albumin, baseline serum creatinine, baseline calculated creatinine clearance, baseline hemoglobin A_{1c}, hemoglobin A_{1c} at 20 weeks, baseline T_cpO_2, infection control, location of study ulcer, non-weight bearing compliance, depth of target ulcer at baseline, baseline ulcer stage, debridement (percent of visits with debridement), baseline ulcer area, percent drug compliance (amount used/amount prescribed), average daily drug amount (µg/cm^2). The effect of the sixteen factors and variables on outcomes was also examined. Logistic regression analyses were performed to determine the significance of any imbalance at baseline.

Descriptive examination of average values of each variable by treatment and outcome (healed vs non-healed) showed that all the values were positively or negatively associated (numerically higher or lower) with outcome based on the expected biologic actions of each

variable. For example ulcers that healed were more likely to have been present for shorter time and to show no clinical signs of infection, were less likely to have been subjected to trauma as shown in Table 6 below.

TABLE 6. DESCRIPTIVE STATISTICS OF FOUR VARIABLES BY TREATMENT GROUP AND BY PRIMARY OUTCOME

	VEHICLE		BECAPLERMIN			
			30μg/kg		100μg/g	
	Healed	Non-healed	Healed	Non-healed	Healed	Non-healed
Duration of ulcer (wks)	30	54	41	63	42	50
Percentage of subjects with infection control	44	24	43	28	64	33
Non-weightbearing compliance (%)	36	27	40	21	52	25
Baseline ulcer area (cm^2)	2.6	3.0	2.1	2.9	2.1	3.1

There was no relationship between the amount of drug applied to the ulcer and outcome. Of specific interest was the finding that neither percent compliance above 100% nor daily use beyond 10 $\mu g/cm^2$ was associated with poor outcome.

In order to determine if a baseline imbalance existed in these variables and to statistically assess its influence on the magnitude and significance of the treatment outcome, logistic regression data were analyzed. For these analyses, terms for treatment, study or investigator, baseline ulcer area and the covariate of interest were included as well as all two-way interaction terms including treatment. The following covariates showed significant interactions ($p \leq 0.1$) with treatment: duration of target ulcer ($p = 0.018$), infection control ($p=0.0001$), location of target ulcer ($p=0.07$), non-weight bearing compliance (0.0001), baseline ulcer area ($p=0.07$). Examination of the treatment main effect from the final model showed that for this study the significance of the treatment contrasts was not affected.

Treatment compliance

The tube of medication was weighed when it was dispensed and when it was returned. In this manner the amount of drug applied could be estimated and compared to the amount the subject was directed to apply until the next visit. By this criterion the average percent compliance (amount used/amount prescribed) for the vehicle control, the 30 and the 100 μg groups were 353%, 319% and 341%. A considerable range of under- and over-utilization was seen for individual subjects and at different visits. Higher percent compliance for example occurred in the mid to late portion of the study. The variability of quantity of drug applied to the ulcer is another factor to be considered in assessing the safety and activity of the drug.

Drug compliance. Listing of individuals and compliance to daily treatment assessed at each visit.

In the individual subject listings occasional extreme values are seen e.g # 2012 ranges from 304% to 2850% with mean of 1053%. Some subjects showed a tendency to increased amount

of drug applied to the ulcer towards the end of the study. Very few subjects underdosed for a variety of reasons e.g noncompliance (#1512 73%, 69%, and 112% on three successive visits in which he was listed as non-compliant). In one subject (# 606, becaplermin 100 μg/g) there was suggestion of a learning curve with the percent compliance gradually moving towards acceptable range starting from the first visit as follows: 25%, 23%, 63%, 81%, 47%, 111%, 100%, 97% ...; the subject was listed as compliant for all visits.

As predicted from the data on drug usage, individual subject listings show that there were no major problems with compliance to the daily treatment schedule. It is not clear what the range of deviation from the daily schedule was. The following individuals were non-compliant for the following number of visits:

TABLE 7: SUBJECTS NONCOMPLIANT TO DAILY TREATMENT

Number of Visits	Subject Number
1 Visit	1212 1211 1313 1623 2036 2404 2405 2402 813 1613 720 1905 1903 623 621 1802 2108 1510 1519 218 1703 205 2011
2 Visits	1901 604 1506 210
>2 Consecutive Visits	620 1512

Reviewer comments:
Items for consideration for the instructions for use section of an eventual label are as follows.

•Might the variability of amount of drug applied in actual clinical usage be even more extreme than what was observed in the clinical trials, and might this variability influence efficacy?
•What proportion of the excess amount of drug applied is bioavailable?
•How convincing is the evidence that the amount of drug applied does not influence healing?

These considerations suggest that it would be desirable to instruct patients to apply a measured quantity rather than an estimated quantity of drug to the ulcers. The calculation of ulcer length times ulcer width divided by four (used in the trial) yields a reasonable estimate of the length of the ribbon of gel to be applied daily to the ulcer. This calculation is preferable to the qualitative estimation the sponsor is recommending.

Standard care
The use of good ulcer care in a standard manner (as specified in the protocol) across study sites is a critical aspect of the conduct of the trial. This aim appears to have been achieved.

• There is no evidence of major imbalance among the treatment groups with respect to adherence to non-weight bearing and off-loading.

•The second most important aspect of good ulcer care is debridement. Thorough surgical debridement was applied initially and as needed. There is no evidence of imbalance in the application of debridement among study arms.

•The clinical appearance of the wound was scored at endpoint; no differences were apparent between groups.

Individualized approach to non-weight bearing

There is consensus that non-weight bearing is essential to achieve healing of neuropathic ulcers. However the standard of care for achieving this goal in the community varies and the incidence of healing with various modalities varies. For example it has been proposed that total contact casting may be the most efficacious means of achieving off-loading and there is evidence that this modality is associated with higher incidence-of and shorter-time-to closure than other modalities for non-weight bearing. However total contact casting is not compatible with daily application of study drug and with maintenance of a moist wound environment and is contraindicated in the presence of edema, copious ulcer discharge etc. It is not clear if devices such as bivalved casts, total contact sandals and posterior splints achieve results comparable to those with total contact casting.

One of the possible explanations for the reported good outcome of the contact cast is that it ensures compliance to non-weight bearing. In this study any means for off-loading were deemed acceptable. Review of listings shows that the following were used alone or in various combinations simultaneously and/or sequentially: wheel chair; crutches; walker; shoes and orthotic devices of several types; bed-rest. Assessment of compliance to weight bearing was done at each visit. At selected investigative sites where a wide variety of approaches to non-weight bearing were used, the outcomes in each treatment group for the three modalities were compared. Treatment outcome did not appear to be related to the non-weight bearing procedure employed.

Reviewer's comments:

•The question of whether the quality of the non-weight bearing regimens was optimal for all study ulcers irrespective of anatomic location must be considered. The relatively low incidence of ulcer closure in the placebo group when compared to the incidence of closure reported in studies that have utilized contact casting suggests that it might not have been. However direct evidence of this is lacking.

•The use of contact casting is not compatible with daily application of a topical drug and the question of whether contact casting alone might outperform the drug plus other means of offloading remains open.

EFFICACY ANALYSES

Incidence of closure

Sixty-one (50%) of the 123 becaplermin 100 µg/g subjects had a functional assessment score of one (100% wound closure without dressing or drainage) at endpoint compared with 44 (35%) of 127 vehicle subjects. This between-treatment group difference was statistically significant (p=0.007; one-sided) after adjusting for the effect of baseline ulcer area, in accordance with the step-down multiple testing procedure used. There was no difference between the becaplermin 30 µg/g group (36%) and the vehicle group (35%) in the proportion of subjects having a functional assessment score of one. There was no significant treatment-by-investigator or treatment-by-baseline ulcer area interaction, indicating that the treatment group differences were consistent across study centers and the range of baseline areas included. The p-value for the effect of the covariate (baseline ulcer area) was 0.083 and the parameter estimate was 0.065, suggesting that smaller wounds have a greater probability of healing during a 20-week treatment period.

Reviewer's comments:

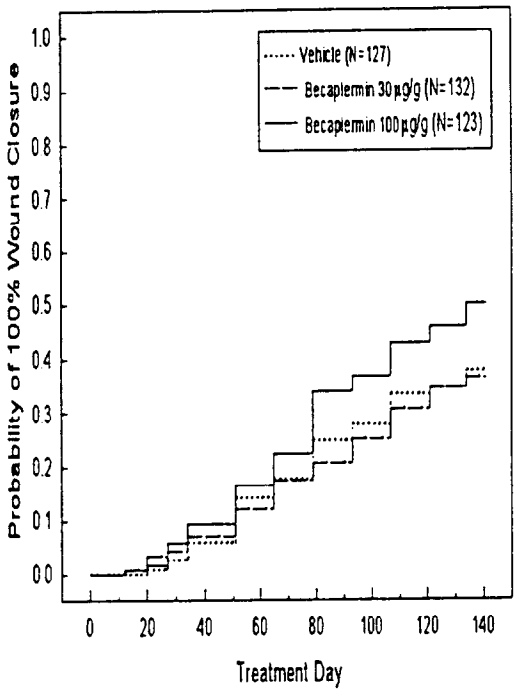
- The study might be considered a failure in the sense that it did not reproduce the finding of the F study, namely that the 30 µg/g formulation is effective. The study was powered for efficacy of the lower dose however the incidence of closure was higher than expected in placebo and lower than expected in the 30 µg/g arm. The 100 µg/g arm had initially been added as a dose-ranging measure.

- The Sponsor and the Agency agreed (only after the completion of the study) on a change in the analytical plan that is perhaps slightly less conservative than the original plan. However, the difference in ulcer closure between the 100 µg/g arm and placebo remains significant even after the originally proposed Bonferroni's correction for multiple comparisons is applied.

Time to healing

Analysis of the time to healing using Cox's Proportional Hazards model indicated a statistically significant treatment effect (p=0.046). The number of days to healing was significantly (p=0.013; one-sided) different in the becaplermin 100 µg/g group compared with the vehicle group (Kaplan-Meier 25th percentile; 71 days and 79 days, respectively). The number of days to healing for subjects in the becaplermin 30 µg/g treatment group was not significantly different from that in the vehicle treatment group (p=0.401). Baseline ulcer area was found to be a significant covariate in these analyses; for all treatment groups, smaller wounds were estimated to heal sooner than larger wounds. A Life Table plot of the time to complete closure is shown in Figure 2 . By day 80 there is separation between the 100 mg/g and the vehicle groups.

FIGURE 2. LIFE TABLE PLOT OF TIME TO ULCER CLOSURE IN STUDY "K"



Relative ulcer area at endpoint

The mean ratio of ulcer area at endpoint relative to baseline was similar among all groups and no significant treatment effects were observed.

Reviewer's comments

The results of this outcome would have been expected to be fully consistent with those of incidence-of and of time-to closure. It is not clear why no trends at all in favor of the drug were observed using relative ulcer area as an outcome measure.

Total wound evaluation score

At the end of the study, the mean (SD) Total Wound Evaluation Score was 1.3 (2.11) for the vehicle group, 1.6 (2.51) for the 30 µg/g becaplermin group and 1.1 (1.72) for the 100 µg/g becaplermin group. The total wound evaluation score was reduced from baseline to endpoint by 0.8, 0.9, and 1.1 for the vehicle, becaplermin 30 µg/g and becaplermin 100 µg/g groups, respectively.

A significant (p=0.005) treatment-by-investigator interaction was observed in this analysis. The treatment-by-covariate interaction was also significant (p=0.001). These interactions make the interpretation of treatment group differences with respect to total wound evaluation

score difficult. A by-subject listing of final total wound evaluation score is provided in Appendix 3.6.5 of the submission.

In order to better understand the treatment-by-investigator interaction, total wound evaluation score at endpoint was examined separately for each investigator (Attachments 9.1 and 9.2 of the submission). For investigators Brill, Corson, and Small Center Grouping 3, the mean total wound evaluation score was consistently smaller (i.e., more favorable) in the becaplermin treatment groups than in the vehicle treatment group (Attachment 9.2). In contrast, for investigators Hebert and Kroeker, the mean total wound evaluation score was larger (i.e., less favorable) in the becaplermin treatment groups than in the vehicle group. The results for the other centers revealed less of a consistent pattern.

Reviewer's comment
One possible explanation for these findings is that assessment bias is present in this subjective score. However there is no evidence of bias in favor of a particular study arm.

Investigator's evaluation of overall effectiveness
Investigators rated the overall effectiveness of study medication at endpoint for each subject. Forty-nine percent of subjects in the becaplermin 100 µg/g group received a rating of Excellent (score of 1) compared with 34% of subjects in the vehicle group. No differences were seen between the lower dose group of 30 µg/g becaplermin (34%) and the vehicle group (34%).

Weekly wound healing rate
There was no statistically significant difference among the treatment groups in the weekly wound healing rate ($p=0.157$).

Subjects Evaluable for Efficacy
Fifty-four (48%) of the 112 subjects in the 100 µg/g becaplermin group had a functional assessment score of one, compared with 42 of 119 (35%) vehicle subjects. This difference was statistically significant ($p=0.018$; one-sided) after adjusting for the marginally significant ($p<0.1$) covariate (baseline ulcer area), with no significant investigator effect, treatment-by-investigator interaction, or treatment-by-baseline ulcer area interaction. There was no significant difference between the 30 µg/g becaplermin group (37% achieving 100% closure) and the vehicle group (35%).

Reviewer's comment:
In general the efficacy of the 100 ug/g dose is supported by the secondary endpoints.

A summary of the efficacy data is shown in Table 9.

Table 9. EFFICACY OUTCOMES IN INTENT-TO-TREAT SUBJECTS IN STUDY "K"

	Vehicle	Becaplermin 30µg/g	Becaplermin 100µg/g	p[a]
N	127	132	123	
Incidence of ulcer closure (percentage)	44(35%)	48(36%)	61(50%)	0.007[b]
Time to ulcer closure (days)[c]	79	91	71	0.013[d]
Relative ulcer area[e]	0.5	0.6	0.5	0.47[f]
Ulcer evaluation score[g]	1.3	1.6	1.1	----[h]

a. Becaplermin 100 µg/g vs vehicle with step-down multiple testing procedure (0.025 level one-sided);
b. Logistic regression analysis;
c. Kaplan-Meier estimate, 25th percentile;
d. Cox Proportional Hazards Model with treatment group and baseline wound area as covariates;
e. Area at endpoint/Area at baseline;
f. Analysis of covariance;
g. Sum of six parameters indicative of infection;
h. Analysis of covariance, significant (p=0.005) treatment-by investigator interaction present.

Validation of efficacy data

In an April 28, 1997 BLA amendment, the sponsor in response to the Agency request, sent photographs of the study ulcers at the following three time points: baseline, penultimate and last visit for six investigators. The investigators' professional qualifications were: Orthopedic Surgery, Podiatry, Vascular Surgery, and General Surgery. The investigators/centers were selected without knowledge of their professional qualifications on the basis of the following criteria: numbers of subjects enrolled; evidence of efficacy (four centers) or no efficacy (two centers) of the 100 µg/g formulation of becaplermin; evidence of of protocol violations. The efficacy data for three of the investigators (77 subjects) was to be validated by site inspection by the Agency and would be reviewed by the medical officers if questions of interpretation arose. The efficacy data for the other three investigators (65 subjects) was reviewed by the medical officers.

For the purpose of this analysis the consistency between the following information and parameters were assessed (where applicable) at baseline, at the visit before endpoint and at endpoint: ulcer location; date of medication stop; consistency of dates and visit numbers; wound debridement; amount of missing data; wound closure as determined by clinical assessment of 100% closure, wound evaluation score, ulcer relative area, acetate tracings of ulcer, photograph of ulcer.

The data were judged to be uniformly consistent and valid except for the cases listed below.

There was some missing data (primarily tracings and photographs) but except for one case listed below, this did not affect the validation of the efficacy data. On the basis of photographic appearance (photographs were assumed to be taken after debridement as per protocol) wound care was judged to be excellent or satisfactory at two sites and on occasion suboptimal at one site. The reviewers noted that the investigators appropriately declared as failures ulcers that showed considerable improvement (90-95% closure) by endpoint and the reviewers interpreted this as a sign of data integrity.

The proportion of ulcers that according to the sponsor and reviewers were closed at endpoint is shown in Table 10. If the evidence of closure was questionable, the reviewers judged the subject not to have healed.

TABLE 10 : INCIDENCE OF 100% ULCER CLOSURE AT ENDPOINT AT THREE STUDY CENTERS

	Vehicle	Becaplermin 30 µg/g	Becaplermin 100µg/g
Site1			
100% closure: sponsor	3/6 (50%)	4/6 (67%)	4/5 (80%)
reviewer	*NC*	*NC*	*NC*
Site2			
100% closure: sponsor	1/7 (14%)	4/6 (66%)	3/5 (60%)
reviewer	*0/7 (0%)**	*NC‡*	*NC‡*
Site3			
100% closure: sponsor	5/10 (50%)	2/10 (20%)	4/10 (40%)
reviewer	*NC*	*1/10 (10%)***	*NC*

NC: No Change in incidence of closure by assessment of reviewers.

* Missing ulcer tracing and photographic evidence of closure in a subject classified by the sponsor as healed.

** The photographic evidence of closure in a subject classified by the sponsor as healed was judged to be questionable by the reviewers

‡ Diagnosis of neuropathic ulcer was questioned (? VSU) in subjects 404, 407. Both subjects were treatment failures and one misdiagnosis is confirmed by the sponsor.

According to a preliminary verbal report from inspectors there is no evidence of questionable efficacy data at the sites inspected. Taken together on the basis of the observations in 142 subjects there is little evidence of problems with the assessment of wound closure at endpoint. The questionable calls made by the reviewers all work against the demonstration of efficacy in the becaplermin 100 µg/g group.

Reviewer's comment:
The efficacy data is of good quality.

QUALITY-OF-LIFE ASSESSMENTS

Change scores between the baseline and Week 20 assessments differed somewhat among treatment groups, but these differences were not large relative to the standard errors of the measures; no consistent patterns were noted. In multi-factor analyses, the effects of becaplermin gel treatment on the measures evaluated were not statistically significant. Significant differences in mean change scores between treatment groups were not expected, based on power calculations that were performed on the population used in a validation study conducted on the quality-of-life component of Protocols 92-22120-K and PDGF-DBFT-001.

Reviewer's comment:
The use of QOL as important outcome criteria for chronic ulcers does not appear to be promising due to apparent low sensitivity.

ULCER RECURRENCE

A follow-up questionnaire was to be completed three months after healing, or three months after the last visit for subjects who did not heal. Multiple follow-up questionnaires were allowed by the protocol. For healed subjects with multiple follow-up questionnaires, the first questionnaire indicating a recurrence was used. For healed subjects without recurrence, the latest follow-up questionnaire was used to determine the follow-up date. Using these questionnaires, the follow-up date and date of ulcer recurrence (if any) were collected, and ulcer recurrence rates were calculated. Twenty-four percent of healed vehicle subjects had recurrences during the three-month post-treatment follow-up period, compared with 31% and 30% of the 30 μg/g becaplermin and 100 μg/g becaplermin subjects, respectively.

Data listings 3.14: these data were not discussed in the summary; the stage of the ulcer was not captured.

Table 11 shows the time to target ulcer recurrence is for the subjects who healed at or before 20 weeks and recurred within the protocol-defined follow up time of 3 months.

TABLE 11. TIME TO ULCER RECURRENCE (WEEKS) IN SUBJECTS HEALED AT ENDPOINT

Number of weeks:	**≤1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**≥ 13**
Number of subjects:	7	4	4	3	0	1	1	0	3	1	4	4	7

* time of follow up per protocol

Table 12 shows the duration of follow up for subjects who healed and had no recurrence.

TABLE 12. TIME OF FOLLOW UP OF SUBJECTS WHO HEALED AT ENDPOINT AND HAD NO RECURRENCE

Number of weeks:	≤10	11	12*	13	14	15	16	17	18	19	20	≥25
Number of subjects	6	4	4	13	14	5	8	10	4	5	10	23

These data were not collected in a standard fashion and are incomplete (144 subjects were counted who had ulcer recurrence data). The data have not been analyzed by group. The data show some evidence of durability beyond the 12 week follow up period.

Reviewer's comments:
•The evaluation of recurrence tests the quality and durability of the ulcer healing.

•The Agency requires that recurrence be no worse in the active arm of the study than in control and this condition was satisfied in the study.

•The relatively high recurrence rate is likely to be attributable to underlying pathophysiology of the ulcers and suboptimal ulcer prevention care after the conclusion of a patient's participation in the trial.

•The incidence of ulcer recurrence nevertheless has a negative impact on the overall clinical benefit that can be expected from the use of this drug in the management of diabetic foot ulcers. The quality of the tissue repair is not enhanced by the drug.

SAFETY ANALYSES

Safety was evaluated for all 382 intent-to-treat subjects (127 subjects in the vehicle group, 132 in the 30 µg/g becaplermin group and 123 in the 100 µg/g becaplermin group). Routine adverse events were monitored during the 20-week course of the study or until a subject healed. Serious adverse events were monitored through the follow-up visit.

Extent of exposure to study drug
Subjects in the vehicle group received treatment with study medication for a median time of 15.0 weeks. Those in the becaplermin 30 µg/g group received a median of 13.7 weeks and those in the becaplermin 100 µg/g group received study drug for a median period of 11.9 weeks. The shorter time on study drug in the becaplermin 100 µg/g group is due in part to the higher proportion of subjects healing in this group.

Many of the adverse events reported in the study were related to the subjects' lower extremity ulcer(s) and their underlying disease state and age. Among the most common treatment-emergent adverse events reported (infection, cellulitis, skin ulceration, osteomyelitis), the incidences were similar among the three treatment groups.

Deaths, other serious adverse events, and other significant adverse events

Deaths:

Seven subjects (three in the vehicle group, three in the becaplermin 30 μg/g group and one in the becaplermin 100 μg/g group) died during the study or three-month follow-up period. The death were due to intercurrent conditions and were not judged to be related to study medication.

Other Serious Adverse Events:

After examination of all safety data by the medical monitor, 100 subjects (30 vehicle, 33 becaplermin 30 μg/g, 37 becaplermin 100 μg/g) were identified as experiencing serious adverse events during the course of the study and follow-up period. The most commonly reported serious adverse events were cellulitis, osteomyelitis, and infection. For seven of the 100 subjects, the adverse events led to death. For 35 of the 100 subjects, the adverse events led to early discontinuation from the study.

Examination of CRF from subjects who experienced adverse events

The CRF for fifteen subjects was sampled to assess the quality of the conduct of the trial by looking for internal inconsistencies in the data, for protocol violations and for the type and number of clinical data correction done by the sponsor's monitor as indicated by the data correction forms. As a result of drug compliance findings six additional cases were subsequently examined to assess drug compliance only. The listing of the fifteen cases is shown below and the relevant hard copy of the CRF documentation is in the reviewer's notes. Vehicle (page 34A): 303, 409, 419, 1104, 2110; becaplermin 30mg (page 34B): 208, 809, 304, 602, 709; becaplermin 100mg (page 34C)

No discrepancies or corrections related to the primary efficacy data were found. There was evidence of missed adverse events such as infections which were captured on review of concomitant medications by the monitor and were subsequently added to the data base. The following inconsistencies were noted: the severity of an adverse event (anxiety/restlessness) was rated as mild and was treated with a major tranquillizer, an antidepressant and an anxiolytic drug; inadequate wound closure at endpoint (25% and 0%) in two subjects was rated respectively as good and excellent outcomes; data was entered on days when visits were missed (subject 409); the presence of peripheral vascular disease by history and examination in a subject (709) with very borderline T_cPo_2 was not detected and the subject later underwent amputation of the hallux. The measurement of the ankle/brachial index is listed in the CRF but is not required in the protocol and was not done by the investigators.

The major issue was the overuse of the study drug (up to 34-fold). The investigators per

protocol were required to assess compliance weekly by measuring the weight of the tube of study drug . While there was a requirement for discontinuation of subjects for consistent underdosing (<50 %), there was no requirement for correcting overdosing; there is no comment from investigators or monitors on this point. The extent of drug overuse was confirmed by reviewing the section entitled "Prospective drug compliance".

In summary by the criteria indicated above and in this small sample, the quality of the data appears to be acceptable.

Review of sponsor's summary descriptions of the serious adverse events
All the sponsor's summaries of the serious adverse events were reviewed. All are consistent with wound-related and/or systemic complications expected in these study subjects.

Target Ulcer-Related Adverse Events
The incidence of target ulcer-related adverse events (as assessed by the medical monitor) was similar among the three treatment groups, (35%, 27% and 35%) in the vehicle, becaplermin 30 μg/g and becaplermin 100 μg/g groups, respectively.

Reviewer's comment:
An important question is whether a low-bioburden preserved formulation is safe for use in chronic diabetic ulcers. While the design of this study does not allow a direct examination of this question, these data indicate that there is no imbalance between treatment groups in the incidence of infections. Comparison of these these data with the incidence of infections in the standard care arm of the other studies confirms the safety of the low bioburden formulation.

Laboratory data
No indication of risk due to study drug

Anti-PDGF antibodies
No clinically significant findings.

CONCLUSIONS OF "K" STUDY

•The efficacy of the 100 μg/g dose is supported by the observed differences in the primary endpoint and in the main secondary endpoint.

•The efficacy of the 30 μg/g dose (efficacious in the F study) was not confirmed in this study. There is no apparent explanation for this finding.

•While it appeared that several covariates influenced healing, the effect of 100 μg/g becaplermin appeared in general to remain constant over the range of values of the covariates that were examined.

STUDY PDGF-DBFT-001

PROTOCOL

Study title
"A clinical evaluation of recombinant human platelet derived growth factor (becaplermin, RWJPRI 60235), carboxymethylcellulose, and standard therapy in the healing of chronic, lower extremity, diabetic ulcers (protocol PDGF-DBFT-001; phase 2)"

Study objective
The primary objective was to evaluate the safety of the drug vehicle when applied to chronic, full thickness, diabetic foot ulcers by comparing it to standard therapy. A secondary objective was to compare the efficacy of the vehicle compared to the active drug formulation. A third objective was to examine the effects of active drug versus standard therapy or placebo on health-related quality of life.

Study design
Parallel group, randomized, evaluator (third-party) blinded, multi-center, study comparing the efficacy and safety of drug vehicle, standard therapy and 100 μg/g of becaplermin in 160 subjects randomized 2:2:1 and treated for 20 weeks.

The sponsor developed a SOP for maintaining the blind of the investigator to the standard care arm. This was accomplished by requiring all study related activities that were not associated with the study ulcer evaluation and functional assessment to be performed only by the study coordinator or nurse including removing the dressings and cleansing the ulcer before the investigator evaluated the ulcer. The source document was to document the individuals responsible for each of the above activities. No blinded study gel application on the satellite ulcers was permitted. The definition of standard therapy was the application of wet-to-dry saline gauze dressings in conjunction with sharp debridement, non-weight bearing status, and use of systemic antimicrobials as needed. The definition of standard therapy was the application of wet-to-dry saline gauze dressings in conjunction with sharp debridement, non-weight bearing status, and use of systemic antimicrobials as needed.

Reviewer's comment:
It is not clear if wet to dry dressings were in fact applied in this or other studies. In a summary of this study the sponsor states that these dressings were "in practice, wet-to-moist". Since surgical debridement is allowed, one questions the need for additional mechanical debridement by wet to dry dressings. Their use, if applied indiscriminately, would have interfered with wound closure.

Open-label extension of the study
A subject participated in the randomized period for a maximum of 20 weeks or until the

wound was 100% resurfaced, whichever occurred first. If the target ulcer had not healed after 20 weeks, subjects had the option of participating in a 12 week open-label extension of this study and of receiving becaplermin.

Entry criteria

The entry criteria are similar to those of other studies with the following two exceptions.

•The allowable size of the ulcer was defined as > 1 cm^2 and ≤ 10 cm^2.

•In the summary of the protocol the depth of the diabetic ulcer is defined as "full thickness" without reference to the usual staging criteria. However in the original protocol the stage of the ulcer required for entry in the study is specified as III and IV.

Evaluation of peripheral nerve involvement to document neurologic deficit and measurement of segmental pressures were required.

Efficacy outcomes

The primary efficacy variable was the incidence of 100% wound closure at endpoint.

The main secondary variables were the time to complete wound closure, and percent reduction in wound size from baseline to endpoint. Quality-of-Life assessments were done at baseline and study weeks 10 and 20.

Study drugs

rhPDGF-BB gel, 100 µg/g containing carboxymethylcellulose (CMC) as a base with lysine as a stabilizer, and parabens and m-cresol as preservatives; CMC gel (placebo) with lysine, parabens and m-cresol. Gel was applied once daily to the ulcer for up to 20 weeks in a pre-determined amount sufficient to form a continuous thin film.

Reviewer's comment:

Instructions for measuring the amount are included in the protocol.

Standard care

The method used to relieve pressure was individualized for every subject and noted in the case record form. All subjects who achieved 100% wound closure were instructed in the correct foot care and footwear to prevent ulcer recurrence and were required to return to the study site for a follow-up visit 3 months after the discontinuation date.

Efficacy analyses

Efficacy criteria were incidence of closure, time to closure, and percent reduction in wound area. The primary efficacy analysis was to be the comparison of drug vehicle with standard therapy; for the Quality-of-Life Assessment, the efficacy analysis was to be a comparison of rhPDGF-B with placebo.

The definition of wound closure, intent to treat and efficacy evaluable subjects were congruent with previously used definitions. The ITT population was the primary population and was

defined as all subjects randomized who received at least one dose of study therapy and had any data after baseline.

There would be up to 12 investigators who started the study. However, the intent was to end with 8 centers enrolling 160 subjects. To achieve this, the 4 slowest enrollers were to be dropped from further participation in the study prior to their enrollment of approximately 30 subjects amongst them. The primary analysis was to include only the 8 largest centers. Analyses were also to be conducted including the subjects from the 4 slow enrollers by combining them into one group, and treating them as a 9th center in the analyses.

The primary method of determining differences between treatment groups was proposed to be by examination of the pattern of proportions, medians and means, and their appropriate 95% confidence intervals on the pairwise difference between groups. The assessment of the drug vehicle's effect on response was to be made by the examination of these confidence intervals, especially the difference between the standard care and drug vehicle treated groups on the proportion of 100% wound closure. The confidence interval approach was to be supplemented by log-linear analysis controlling for the effects of treatment center and baseline wound area.

The null hypothesis was that the 100% healing rate for standard care minus the 100% healing rate for drug vehicle is greater than 22.5 percentage points. The alternative hypothesis was that the healing rate difference is 22.5% or less. Assuming a 100% healing rate at week 20 in 25% of drug vehicle subjects, the estimated sample size of 64 subjects per treatment group resulted in 80% power to detect a standard care response rate of 47.5% or greater, using a one-sided Fisher-Exact test with alpha of 0.05.

The secondary efficacy parameters were time to wound closure, percent change in target ulcer size, Quality-of-Life Assessment and the rate of ulcer recurrence.

Statistical power was calculated for the score on the Instrumental Activities of Daily Living scale, which is part of the quality-of-life questionnaire. Assuming the mean scores (standard deviations) would be 34.35 (20.0) and 21.85 (20.0) for the rhPDGF-B and placebo groups respectively and that 64 subjects in the placebo group and 32 in the rhPDGF-B group would complete the baseline and week-20 quality-of-life questionnaires, the study was calculated to have 81% power to detect a statistically-significant difference between rhPDGF-B and placebo therapy, using a two-tailed test to maintain an alpha level of 0.05.

PROTOCOL MODIFICATIONS

The following are significant modifications to the protocol.

•The Agency required that the sponsor evaluate the effect of vehicle on wound healing in

order to exclude a harmful effect by any of the constituents. The sponsor added a becaplermin (100 μg/g) treatment arm to the study on the advice of the investigators to enhance recruitment and to provide an opportunity for active gel treatment; a comparison of efficacy variables was not intended.

•The Agency asked the sponsor to provide supporting data (including 001) for the efficacy of the 100 μg/g formulation and the sponsor agreed.

•Primary efficacy analyses. The provision for limiting the primary analysis to the eight largest centers was dropped. The stipulation that log-linear analysis with model factors treatment, center, and baseline wound area be an additional efficacy analysis was dropped. Baseline wound size would be incorporated into the analyses as appropriate.

• Secondary efficacy analyses. Percent change in target ulcer size "from baseline to endpoint" was specified as an endpoint; the change was made to maintain consistency with the analysis of becaplermin in other protocols. It was specified that time to closure would be analyzed using Cox proportional hazards model with baseline ulcer size as a covariate.

•In contrast to the assertions in the original protocol, the sponsor informed the Agency on August 7, 1995 that the study did not have statistical power to detect differences in QoL measures, and statistical comparisons between the treatment groups would not be performed.

•A preliminary analysis of efficacy variables was performed upon completion of the double-blind study prior to the three-month follow-up before finalization of the database. The results of these analyses are in agreement with those in the final results.

•Study completion (withdrawal) was allowed for poor response to treatment.

RESULTS

Demographic and baseline characteristics

Of the 172 subjects enrolled into the study, 127 (74%) were men, 146 (85%) were white and the mean age of all subjects was 58 years. There were no clinically meaningful differences in demographic characteristics between the standard therapy and vehicle treatment groups.

The following covariates showed significant effects: baseline serum creatinine, infection control, non-weight bearing compliance, debridement, baseline ulcer area. None of these covariates when added to the model cause a loss of significance of the treatment effect. The intent-to-treat population included all subjects enrolled into the study (N=172). The population evaluable for efficacy was comprised of 162 subjects (60 standard therapy, 68 vehicle, 34 becaplermin). The subject evaluability status and reasons for exclusion from efficacy analysis were confirmed by the review.

Protocol deviations

The majority of protocol deviations (seven of eight subjects) involved study ulcer areas which were above or below the upper limit specified in the study protocol based on length x width measurements performed by investigators. One subject used a prohibited medication. During this study, the blind was broken in three cases and possibly compromised in six others.

EFFICACY ANALYSES

Incidence of complete closure

Of the 68 intent-to-treat subjects in the standard therapy group, 15 (22%) had complete closure at endpoint compared with 25 (36%) of 70 vehicle-treated subjects. The 95% confidence interval for the difference in proportions (standard therapy minus vehicle) was -29% to 1%. This interval was within the criterion stipulated in the protocol to establish that the vehicle was no worse than standard therapy. Of the 34 subjects enrolled into the becaplermin treatment group, 15 (44%) achieved closure at endpoint. There were no differences in the results of analyses for 100% wound closure for intent-to-treat and evaluable for efficacy populations examined.

Time to complete closure

Analysis by Cox's proportional hazards model indicated no statistically significant differences between the standard therapy and vehicle or the vehicle and becaplermin treatment groups. The number of days to healing (arbitrarily chosing the 25th percentile as cutpoint) was 141 days for the standard therapy group 98 days for the vehicle group and 85 days for the becaplermin treatment groups. A Life Table plot of the time to 100% wound closure data (Figure 3). shows that subjects in both the vehicle and standard therapy groups were comparable with respect to ulcer closure. For the subjects in the becaplermin group separation the healing curve over time appeared to separate from the other groups at about 14-15 weeks.

FIGURE 3. LIFE TABLE PLOT OF TIME TO ULCER CLOSURE FOR STUDY "001"

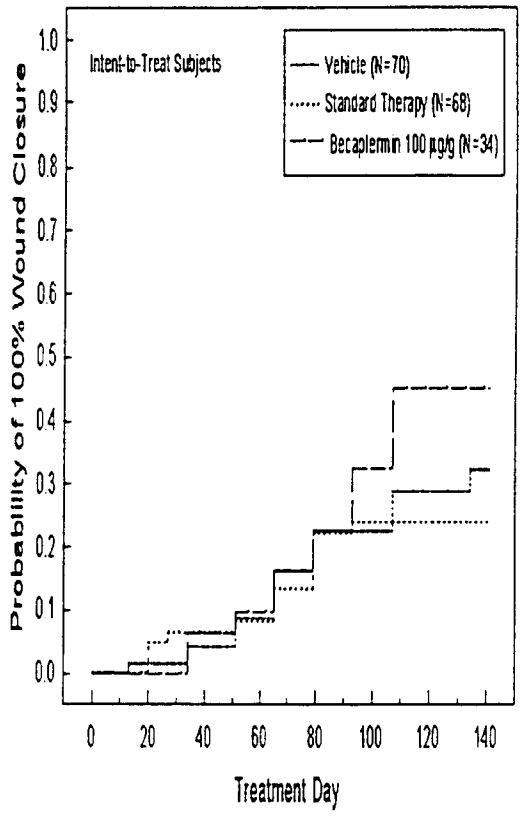


Table 13 shows the primary and the principal secondary outcome data.

TABLE 13. EFFICACY OUTCOMES IN ITT SUBJECTS FOR STUDY "001"

	Standard Care	Vehicle	Becaplermin 100µg/g	p[a]
Number of subjects	68	70	34	
Incidence of ulcer closure (percentage)	15 (22%)	25 (36%)	15 (44%)	0.48[b]
Time to ulcer closure (days)[c]	141	98	85	0.30[d]

a. Becaplermin 100 µg/g vs vehicle;
b. Logistic regression analysis; c. Kaplan-Meier estimate, 25th percentile;
d. Cox Proportional Hazards Model with treatment group and baseline wound area as covariates.

Relative ulcer area

Median relative ulcer areas at endpoint were comparable for the standard therapy and vehicle treatment groups (0.28 versus 0.31, respectively) with the becaplermin group having the smallest median relative area at endpoint (0.13). However mean data showed a trend in the opposite direction with values of 0.84 and 0.76 for standard therapy and vehicle and 1.26 for becaplermin.

Reviewer's comment:

As seen in previous studies, the results of relative ulcer area measurements are not consistent with the results of the other two main outcomes (incidence-of and time-to complete ulcer closure). This inconsistency is unexplained.

Total wound evaluation score

Total wound evaluation scores were calculated for all subjects at endpoint and the change from baseline in these scores were summarized for each treatment group. The median of the change was identical (-1.0) across the three groups and negative, indicating that, on average, wound evaluation scores had improved compared to baseline values. When the means were examined, all scores were again negative; however, mean scores for the standard therapy group were less negative than for either the vehicle or becaplermin groups, indicating the least amount of improvement for the standard therapy group.

Weekly healing rates

The weekly healing rates showed very large variability and are not interpretable.

Quality of Life

Although the statistical significance of differences between treatment groups was not examined, a trend toward greater improvement in QOL was noted among subjects in the becaplermin gel 100 μg/g group, particularly with respect to basic and intermediate activities of daily living, social functioning, and bed disability.

Reviewer's comment:

These data were not reviewed.

Covariate analyses

The following covariates showed significant effects: baseline serum creatinine ($p=0.003$), infection control ($p=0.0001$), non-weight bearing compliance (0.011), debridement (0.0045) baseline ulcer area (0.060). None of these covariates when added to the model altered the results.

SAFETY ANALYSES

The treatment groups were similar with respect to the incidence of adverse events. A total of 131 (76%) subjects completed the study; 41 (24%) withdrew. Of the 41 subjects who withdrew, 29 did so due to an adverse event. Slightly more subjects from the standard therapy group (24%) discontinued due to adverse events than subjects in either the vehicle (11%) or becaplermin (15%) groups. Four deaths (two standard therapy, one vehicle, one becaplermin) were reported, none of which were attributable to study therapy.

Forty-nine subjects (21 standard therapy, 17 vehicle, 11 becaplermin) experienced serious adverse events, a majority of which were considered unlikely to be related to study therapy. Fourteen subjects experienced changes to markedly abnormal laboratory values which were unlikely to be related to study therapy; otherwise, no clinically relevant changes from baseline values were observed in routine laboratory tests. No clinically relevant changes from baseline were observed in vital sign measurements or physical examination abnormalities.

Subjects were frequently treated with antibiotics during the course of this study. Most antibiotics were Administered systemically and were prescribed for treatment of a variety of infections, both associated and not associated with the study ulcer.

The CRF of all deaths were reviewed; no new findings emerged.

The narratives of patients with other significant adverse events were reviewed. There are no unexpected events.

All the clinical summaries of the serious adverse events were reviewed. The events are for the most part compatible with infectious, cardiovascular, or metabolic complications of diabetes mellitus. Serious adverse events attributable to other pathophysiologic processes do not appear to be confined to any specific treatment group.

It was not possible to assess the rationale for the use of antimicrobials because the antimicrobials were not used in a standard fashion and the diagnosis of infection not well documented. It was not meaningful to assess the incidence or severity of infections based on antimicrobial use.

There was no increase in the incidence of infection in the groups treated with study gel. All infection-related adverse events showed incidences of 37, 27, and 21 percent in the standard care, vehicle, and becaplermin arms. Three different lots were used.

Reviewer's comments:
•This study allows the conclusion that the low bioburden preserved formulation is not harmful.

•The placebo gel appears to outperform standard care. Hypotheses to explain this finding (in addition to a placebo effect) are as follows:

-The preservatives in the formulation are topically active and their antimicrobial action contributes to healing.
- Other constituents in the formulation influence the ulcer milieu (e.g. by influencing moisture content), promote wound closure and secondarily decrease the risk of ulcer infection.

ULCER RECURRENCE AT 3 MONTHS

In general, subjects from the becaplermin and vehicle groups had fewer ulcers recurrences than did subjects in the standard therapy group. The numbers are too few to draw any meaningful inferences.

CONCLUSIONS FOR STUDY "001"

•The drug vehicle appears to be safe

•Becaplermin appears to be safe and active.

STUDY PDGF-DBFT-002

PROTOCOL

Study title
"A randomized, clinical evaluation of recombinant human platelet-derived growth factor (becaplermin; RWJ 60235-000) versus standard therapy in the healing of chronic, lower-extremity, diabetic ulcers (protocol PDGF -DBFT-002; phase 3)"

Study objectives
The primary objective of this study was to compare health-related quality-of-life and wound-related resource utilization between subjects who were treated with becaplermin gel 100 µg/g and standard therapy during 20 weeks followed by an additional 16 weeks of standard therapy for all subjects. An additional objective was to evaluate the efficacy of becaplermin compared to standard therapy when applied topically to chronic, lower extremity diabetic ulcers for up to 20 weeks.

Study design
Randomized, third-party (evaluator) blind, parallel group, controlled, multicenter study to assess the efficacy and safety of topically applied (once daily) becaplermin gel 100 μg/g in the treatment of nonhealing lower extremity cutaneous wounds in 240 subjects with diabetes mellitus. Randomization was stratified based on presence of single or multiple ulcers. Random permuted block sizes of 4 and 2 were used for the single and multiple ulcer strata. The treatment assignments were to remain unknown to the investigator evaluating the study ulcer, but were known to other study site personnel.

Dosing
Becaplermin was to be administered in conjunction with standard wound care for a maximum period of 20 weeks, or until the study ulcer had completely healed or until they were switched to (or continued on) standard therapy due to poor response.

The subjects randomized to receive rhPDGF-B gel were instructed to apply study medication gel to the ulcer(s) to form a continuous film covering the entire surface of the ulcer, extending to the ulcer margins. A sufficient quantity was to be applied on the ulcer so that a film of gel approximately 1 mm (about the thickness of a dime) in thickness, was applied to the entire ulcer area.

Reviewer's comment:
An important difference in this protocol is that subjects were not asked to measure the dose of study drug to be applied to the ulcer.

Entry criteria
Differences from other protocols were the following:
•Allowable ulcer area for each ulcer (1-40 cm^2) and for all ulcers (60 cm^2) in each subject.
• Exclusion of ulcers with exposed bone.

Endpoints
Primary efficacy analyses were based on the comparison of the incidence of 100% wound closure of the target ulcer between the becaplermin gel 100 μg/g group and the standard therapy group. Also examined were the time to complete closure, the wound area at each visit and wound evaluation scores.

STATISTICAL PLAN

Sample size calculations
The assumptions for calculating sample size in the original protocol were as follows.
The sample size of 120 subjects per group was based on assuming the incidence of healed wounds at 36 weeks in the standard therapy group to be 48% and the incidence of healed wounds in the rhPDGF-B group at 36 weeks to be 64%. These data were based on the results

of the Phase 2 study. Using a one-sided α level of 0.05, the sample size of 120 subjects per group would provide 80% power to see this difference.

The assumptions stated in the summary report are as follows. Assuming a standard therapy healing incidence of 26% and a becaplermin gel 100 µg/g group healing incidence of 48%, Using a two-sided α level of 0.05, a sample size of 240 subjects (120 per treatment group) provides approximately 90% power to detect such a difference. Efficacy analyses were based primarily on the intent -to-treat population, defined as all subjects randomized to receive study medication who received at least one dose and had post-baseline data.

Efficacy analyses

The primary analysis of this primary efficacy parameter was to be a comparison of proportion of subjects with 100% wound closure at 36 weeks in the two treatment groups using a Cochran-Mantel-Haenzsel approach with investigators as strata. In addition, a logistic regression model was to be used in order to assess the effect of covariates such as demographic and baseline variables (e.g. initial wound size) and treatment group on the probability of "success" (i.e. a functional assessment grade score of 1).

Patients were stratified prior to randomization according to whether they had single or multiple ulcers. Data was to be pooled in all analyses unless a statistically significant quantitative interaction was found between treatment group and number of ulcers (single/multiple). Secondary efficacy parameters were the time to 100% wound closure and the percent change in ulcer size.

PROTOCOL MODIFICATIONS

The most common significant protocol deviation was having a target ulcer with dimensions (length x width) outside of the stipulated 1.0 to 40.0 cm^2 range at the screening visit. Thirteen subjects (five standard therapy, eight becaplermin gel 100 µg/g) fell into this category. All had study ulcers smaller than the lower limit. Two subjects had received concomitant medications prohibited by the protocol.

RESULTS

Of the 252 randomized subjects, 250 fulfilled the intent-to-treat criteria; subjects #1919 and #2151 were assigned to the standard therapy group and did not proceed further than signing the informed consent form. The majority of subjects (71%) were men and 201 (80%) were white. The mean age of subjects was comparable between treatment groups (standard therapy, 60 years; becaplermin 100 µg/g, 59 years). The median study ulcer areas for the two groups were comparable (standard therapy, 1.3 cm^2 becaplermin 100 µg/g, 1.5 cm^2). Excluded from the evaluable-for-efficacy population were those subjects who were non-compliant with study

procedures for four or more study visits (received <50% of the prescribed dose of study medication, missed visits, or violated the non -weight bearing requirements). There were 227 subjects evaluable for efficacy (113 standard therapy, 114 becaplermin 100 μg/g).

Of the 252 subjects enrolled into the study, 223 (88%) completed the 20-week treatment phase. Nearly twice as many standard therapy subjects (15%) as becaplermin gel 100 μg/g subjects (8%) discontinued from the study prematurely. Discontinuation due to adverse events was comparable between the two treatment groups (4% in each group).

EFFICACY ANALYSES

Ulcer closure

Forty-six (36%) of the 128 becaplermin-treated subjects healed at endpoint, compared with 39 (32%) of 122 standard therapy subjects (p=0.26). Baseline ulcer area was a significant covariate. Treatment by investigator interaction due to one center was handled by pooling the data from the center involved with another small center.

Time to ulcer closure

Using Cox's proportional hazards model no difference (p=0.994) between the becaplermin and standard therapy treatment groups. The Kaplan-Meier estimates of the number of days to healing (25th percentile) in the two treatment groups were similar (standard therapy, 89 days; becaplermin, 85 days). The life table plot of days to closure shows no significant separation between the treatment groups (See Figure 4 on page 50).

Relative ulcer area

The relative ulcer area at endpoint was similar between the two treatment groups, with mean (SD) values equal to 0.5 (1.12) in the standard therapy group and 0.6 (1.53) in the becaplermin gel 100 μg/g group.

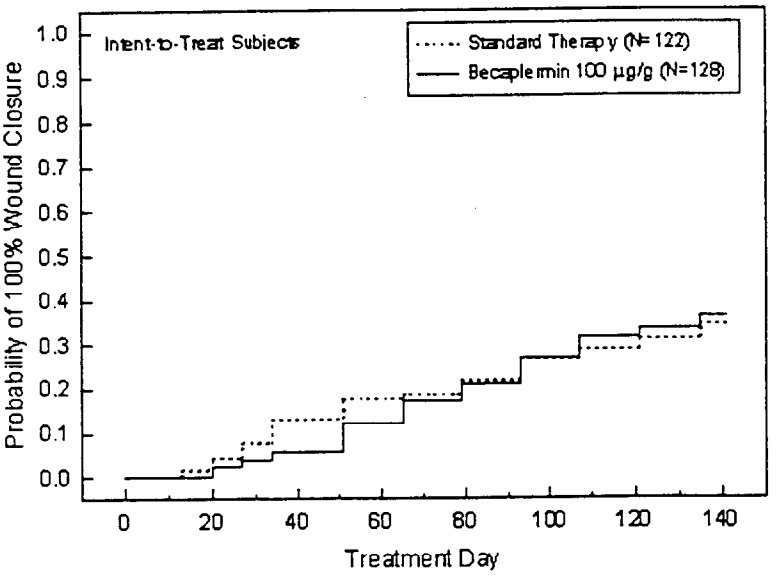
Ulcer evaluation score

The score was reduced from baseline to endpoint by 0.8 and 0.6 in the standard therapy and the becaplermin gel 100 μg/g groups, respectively. Baseline wound evaluation score was a significant (p=0.002) covariate in this analysis.

Quality of life

The results of the QOL analysis were not available at the time of the BLA submission.

FIGURE 4. LIFE TABLE PLOT OF ULCER CLOSURE OF STUDY "002



Summary of efficacy data

Table 14 shows the overall lack of efficacy in this study as demonstrated by all the major outcome measures.

TABLE 14. EFFICACY OUTCOMES IN INTENT-TO-TREAT SUBJECTS IN STUDY "002"

	Standard care	Becaplermin 100µg/g	p
Number of subjects	122	128	
Incidence of ulcer closure (percentage)[a]	39 (32%)	46 (36%)	0.26
Time to ulcer closure (days)	89	85	0.99
Relative ulcer area	0.5	0.6	0.44
Ulcer evaluation score	1.7	1.7	0.96

For definition of terms see previous tables; a. Significant treatment by investigator interaction.

The presence of investigator interaction for the primary outcome was found to be due to one center in which a large disproportion in outcome was seen between becaplermin and the standard care groups. These data were pooled with those from another center to allow the logistic regression analysis to be performed.

Post-hoc subgroup analyses

In the subgroup with baseline ulcer area < 5 cm^2 a more pronounced between -treatment group difference was observed (standard therapy, 33%; becaplermin , 42%), although the difference was not significant (p=0.129). When the analysis of 100% wound closure was limited to the 194 evaluable for efficacy subjects with baseline ulcer area <5 cm^2 a significant (P=0.040) between-treatment group difference was observed (standard therapy, 33%; becaplermin, 45%). There were no significant interactions in this analysis.

Analysis of covariates known to influence healing showed that the following had a significant effect on outcome: baseline hemoglobin A_{1c} (p= 0.09), baseline T_cpO_2 (p= 0.0001), infection control (p=0.0002), non-weightbearing compliance (p=0.023), debridement (p=0.04), and baseline ulcer area (0.001). When the T_cpO_2 was added to the model the treatment effect changed to p=0.053.

Reviewer's comment:
The magnitude of the effect of T_cpO_2 is not very large and mean differences between healed and non-healed subjects with respect to this covariate are small. It is not clear why the apparent effect of T_cpO_2 on healing is so pronounced.

Drug usage

The mean total usage (g/cm^2) of becaplermin was 40.6 in subjects who healed and 52.5 in subjects who did not heal.

Reviewer's comments:
•Drug usage was greatest in this study (mean usage 7-10 fold greater than usage calculated based on ulcer area) probably because the design of the study called for non-measured applications of the drug by the patients.

•There did not appear to an imbalance in the use of drug in subjects who healed compared to subjects who did not heal in study "002".

•It is important to note that in study "002" the greatest amount of drug was used of all the four studies, yet the overall efficacy of the drug was poorest in study "002".

SAFETY ANALYSES

Many of the adverse events reported in the study were related to the subjects' lower extremity

ulcer(s) and their underlying disease state and age. Among the most common treatment-emergent adverse events reported (skin ulceration, infection, cellulitis, osteomyelitis, pain), the incidences were similar between the two treatment groups, although the incidence of osteomyelitis among becaplermin treated subjects (21%) was greater than among standard therapy subjects (14%).

The percentage of subjects with one or more wound infection during the 20 -week treatment phase was comparable between the two treatment groups (standard therapy, 47%; becaplermin, 51%). In addition, cardiac failure occurred more frequently among becaplermin treated subjects (12%) than among standard therapy subjects (7%), but other cardiovascular events occurred with generally similar incidence between the two groups.

CONCLUSIONS OF STUDY "002"

•This study failed to show efficacy of the drug.

•A number of features in this study (e.g. aims, use of third-party blinding) are different. However it is not likely these factors account for the lack of efficacy in the study.

INTEGRATED SUMMARY OF EFFICACY USING FOUR STUDIES

Comparability of the four studies

The data from an additional 250 intent-to-treat subjects enrolled in the supplemental PDGF-DBFT-002 study was pooled together with the data from the three primary to test the efficacy of becaplermin 100 μg/g treatment.

All four studies enrolled subjects with diabetes who had chronic, stage III or IV, lower-extremity cutaneous ulcers. The studies enrolled a total of 925 subjects, 922 of whom were considered intent-to-treat. Subjects were enrolled into one of four treatment groups (standard therapy, vehicle gel, becaplermin gel 30 μg/g, or becaplermin gel 100 μg/g; not all groups were present in each study).

The major similarities in the four studies include enrollment criteria (with particular reference to factors and variables known to affect healing), standard care, (with particular reference to debridement and requirement for non-weight bearing), duration of becaplermin treatment (up to 20 weeks of once-daily topical application) and efficacy criteria (incidence and time to complete ulcer closure). The major differences among the four studies included the combinations of active arms and control (vehicle and/or standard care) arms which were used, allowable ulcer area at baseline, and manner of application of becaplermin, namely as

measured dose (μg/cm²) in studies "F", "K "and "001", and un-measured dose (uniform layer, about the thickness of a dime) in study "002" .

Efficacy analyses on ITT population

Simple, unadjusted statistical analysis of the crude proportions of completely healed subjects across the four 20 -week studies suggests a statistically significant (p=0.017) difference between the becaplermin gel 100 μg/g (43% healed) and vehicle (33% healed) treatment groups. However the difference between the becaplermin 30 μg/g group and the vehicle is not significant (p=0.135).

Efficacy analyses on subgroup defined by baseline ulcer area

The sponsor argues that the ITT group is not appropriate for the meta-analysis because of the presence of non-homogeneities in the data that he has determined can be decreased and ultimately resolved by excluding subjects with larger baseline ulcer area (he proposes two main cut points of > 5 and >10 cm²).

When the complete healing rates for each treatment within each study are stratified by baseline ulcer area (classified into successive 1 cm² increments) the following are noted.

•Over successive 1 cm² baseline ulcer area intervals through 5 cm², there is apparent homogeneity of treatment contrasts of healed proportions across the four studies;

•Over successive 1 cm² baseline ulcer area intervals from 5 cm² through 10 cm² there was decreasingly less evidence of homogeneity;

•Above 10 cm², the combined crude incidences and corresponding treatment contrast p - values are even more difficult to interpret.

Rationale for subgroup analysis:

When subjects in the four 20 week studies with baseline ulcer areas <10 cm² are included in the analysis (95% of the 922 intent to treat subjects), the analysis revealed only marginally significant study-by-treatment (p=0.126) and baseline ulcer area -by-treatment (p=0.140) interactions.

Based on the final model including the baseline ulcer area-by-standard therapy term, the estimated probability of 100% wound closure was significantly (p=0.007) higher in the becaplermin gel 100 μg/g group than in the vehicle group, and marginally significantly higher in the becaplermin gel 100 μg/g group than in the standard therapy group (p=0.066). While the estimated probability of 100% wound closure in the becaplermin gel 30 μg/g group was not significantly different than in the vehicle group (p=0.299), it was numerically greater than that in the vehicle group. This suggests that once-daily becaplermin treatment increases the probability of 100% wound closure in a dose-related fashion. No statistically significant heterogeneity can be demonstrated in the analysis of the ≤ 5 cm² pooled group. The sponsor

concludes that combining results in a meta-analytic approach for 5 cm^2 or less is fully statistically justifiable and meaningful.

Reviewer's comments:
•The subgroup analyses performed by the sponsor based on baseline ulcer size are to be considered exploratory. It is not clear why there should be a differential effect of becaplermin based on arbitrary cut-points for baseline ulcer size. These post-hoc analyses exclude subjects with larger ulcers and increase the apparent estimate of the treatment effect.

•The statistical significance of a straightforward comparison of incidence of closure across the four studies was confirmed by the Agency's statistical reviewer.

•Another approach used by the statistical reviewer was to analyze the data from two or more studies in which becaplermin and control arms were the same. Such data were combined by the Mantel-Haenszel method to obtain an estimate of common odds ratio; these analyses were also supportive of activity of the drug.

•Evidence of consistency and reproducibility in efficacy results between the four randomized and controlled studies:
The central issue in the evaluation of the efficacy of becaplermin is whether or not the primary outcome variable (incidence of complete closure) showed consistent and reproducible clinical benefits in the four well- and comparably-designed studies.

Table 15 summarizes the incidence of complete ulcer closure by treatment group across the four studies separately and across the four studies combined.

TABLE 15. INCIDENCE OF COMPLETE ULCER CLOSURE IN FOUR RANDOMIZED, CONTROLLED STUDIES

Study	Standard care		Placebo gel		Becaplermin 0.003% gel		Becaplermin 0.01% gel	
F	-----	-----	14/57[a]	(25)[b]	29/61	(48)	-----	-----
K	-----	-----	44/127	(35)	48/132	(36)	61/123	(50)
001	15/68	(22)	25/70	(36)	-----	-----	15/34	(44)
002	39/122	(32)	-----	-----	-----	-----	46/128	(36)
Four studies combined	**54/190**	**(28)**	**83/254**	**(33)**	**77/193**	**(40)**	**122/285**	**(43)**

a. For all the fractions, the numerator is the number of subjects with complete ulcer closure; the denominator is the number of subjects in the study arm.
b. Numbers in parentheses indicate the percent incidence of complete ulcer closure.

•Efficacy of 30 and 100 μg/g becaplermin: reproducibility and consistency across individual studies

30 µg/g becaplermin:

-In the "F" study , 47.5% of the 30 μg becaplermin patients had 100% closure as compared with 24.6% in the control (vehicle) patients. This absolute difference of 22.9% was significant (P=0.013).

-In the "K" study only 36.4% of the 30 μg becaplermin patients had 100% closure as compared with 34.7% in the vehicle-treated patients. The observed absolute difference of 1.8% was not significant. Thus, the significant difference observed in the "F" study was not confirmed in the "K" study.

100 μg becaplermin:

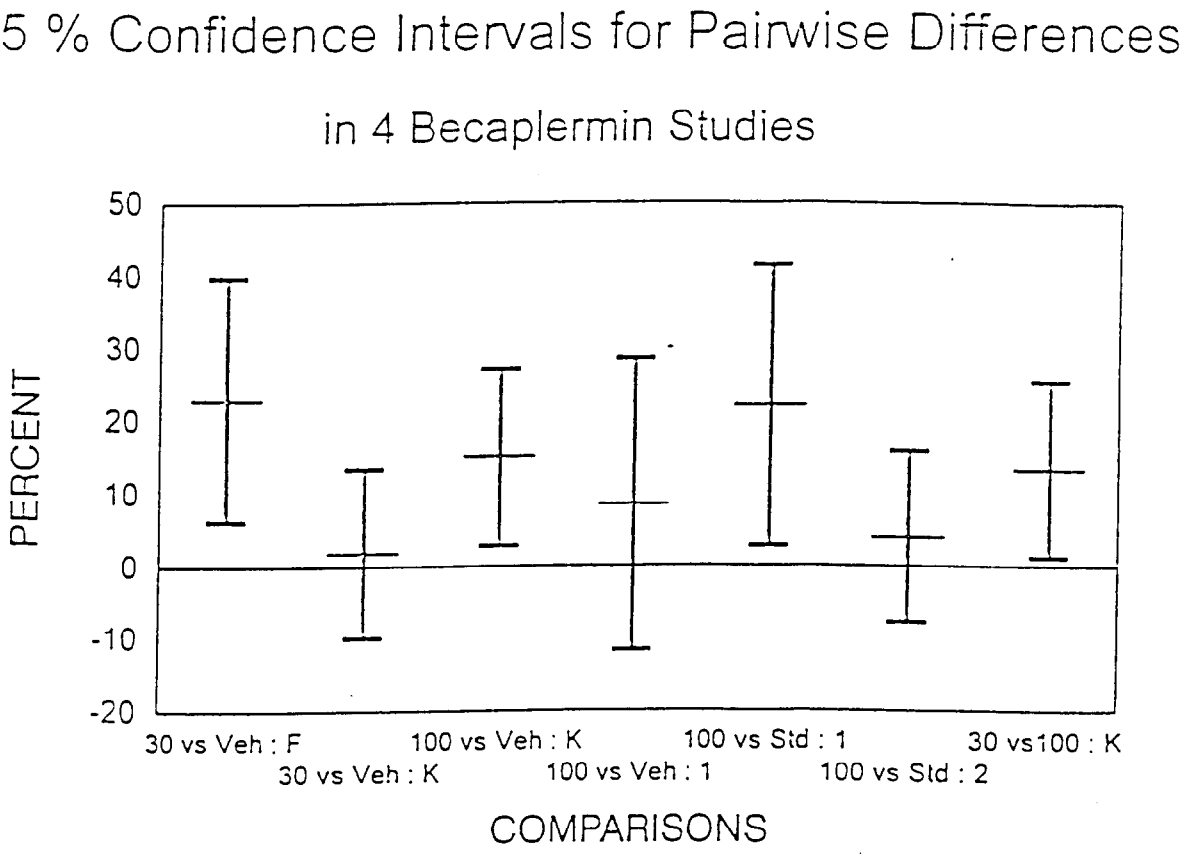
-In the "K" study, 49.6% of the 100 μg becaplermin-treated patients showed 100% closure. The efficacy in this high-dose group was significantly different from the vehicle group (an absolute difference of 15.0%, P=0.021). The 30 μg becaplermin group was also significantly different from the 100 µg/g becaplermin group (13.2% absolute difference, P=0.043).

-In the 002 study the observed frequencies of 100% wound closure in the standard and 100 μg becaplermin arms were 32.0% and 35.9%, respectively. This difference of 3.9% was not significant (P=0.593). Here again, the statistical significance observed in one study could not be reproduced. Nevertheless, the percentage of 100% wound closure was higher in the becaplermin arm. In the "001" study the 100 µg/g becaplermin arm was not significantly better than the standard arm.

•While not statistically reproducible, some evidence of consistency was shown in that the point estimates were always positive in favor of the drug. Figure 5 further illustrates this point.

Figure 5 (see page 57) shows the 95% confidence intervals around the pairwise differences in the incidence of ulcer closure in the various treatment groups. Even when crossing zero, the confidence intervals extend more to the positive side of the scale suggesting that the true difference between treatment and control is more likely to be positive.

FIGURE 5.



Legend to the figure

•Notations for the study arms. Becaplermin gel 30µg/g: 30; Becaplermin gel 100µg/g: 100; Placebo gel: Veh[icle].

•Notations for the studies. Study F: F; Study K: K; Study 001: 1; Study 002: 2.

Likelihood of response to treatment

For subjects who were randomized to treatment with becaplermin gel 100 µg/g during the blinded phase and possibly continued with this treatment into the open-label phase, the incidence of 100% healing was 56-57%. These incidences are similar to those observed during the blinded phase alone (shown in individual study reports).

In contrast, for those subjects who did not heal during the blinded phase and either continued treatment with becaplermin gel or switched from control treatment to becaplermin gel in the

open-label phase, a smaller proportion (18-39%) eventually healed, suggesting that some subjects are resistant to healing regardless of the therapy employed. According to the sponsor, these findings support the recommendation that treatment should be discontinued if the ulcer has not decreased in area by at least 30% by 8 weeks.

Reviewer's comments:

- It cannot be determined if continued treatment with becaplermin beyond 20 weeks is beneficial because there is no control group to which the 56% incidence of closure can be compared.

- The only direct way of testing the hypothesis that subjects who do not respond sufficiently after eight weeks of becaplermin treatment will not heal after 12 additional week of treatment, is to treat all study subjects for 20 weeks irrespective of initial response.

Becaplermin usage

Application of study medication in most of the clinical studies was based on the surface area of the target ulcer. After ulcer measurement, a formula was used to determine the length of gel to apply as a thin, even layer. However, in study PDGF-DBFT-002, the instructions were to apply an unmeasured amount sufficient to cover the entire surface of the target ulcer. Subjects enrolled in study PDGF-DBFT-002 used more becaplermin gel (mean [SD] = 0.65 [0.45] g/day or 48.2 [73.6] g/cm^2 than subjects enrolled in the other three 20-week studies combined (mean [SD] = 0.38 [0.30] g/day or 21.9 [25.7] g/cm^2).

The mean drug compliance for 0.01% becaplermin in studies "K", "001" and "002" was 380%, 500% and 840% respectively. Time on study medication was comparable between the measured dose studies and Study PDGF -DBFT-002. This suggests that unmeasured dosing will allow application of an adequate amount of becaplermin gel to the ulcer.

Reviewer's comments:

- There is no evidence that applying more drug is harmful.

- There is no evidence that applying more drug is more beneficial.

- These data are consistent with the notion that drug concentration at the ulcer site is a more important determinant of bioavailability than drug amount due to the presence of a local barrier to diffusion.

Exploratory analysis of clinically relevant factors affecting healing

To explore possible factors that can affect the likelihood of 100% wound closure, a number of further exploratory analyses were undertaken. Eight variables were defined based on factors thought to be possibly clinically relevant to the wound healing process: These eight variables are: duration of target ulcer, baseline serum albumin, baseline hemoglobin A_{1c}, baseline creatinine, baseline creatinine clearance, T_cpO_2 measured on the dorsum, infection

control, location of ulcer.

Analyses were conducted based upon the analytical statistical model framework employed for the integrated analyses and included baseline ulcer area as a covariate. Terms for each of the eight variables noted above were added individually to the model for the integrated analysis, and the additional explanatory effect of each variable was examined in each of the eight analyses. For those variables significant at the 0.05 level, further analyses were done to examine both the possible differential effects of each variable with regard to treatment and, then to examine, if found, the effects of these individually significant variables upon the probabilities of 100% wound closure.

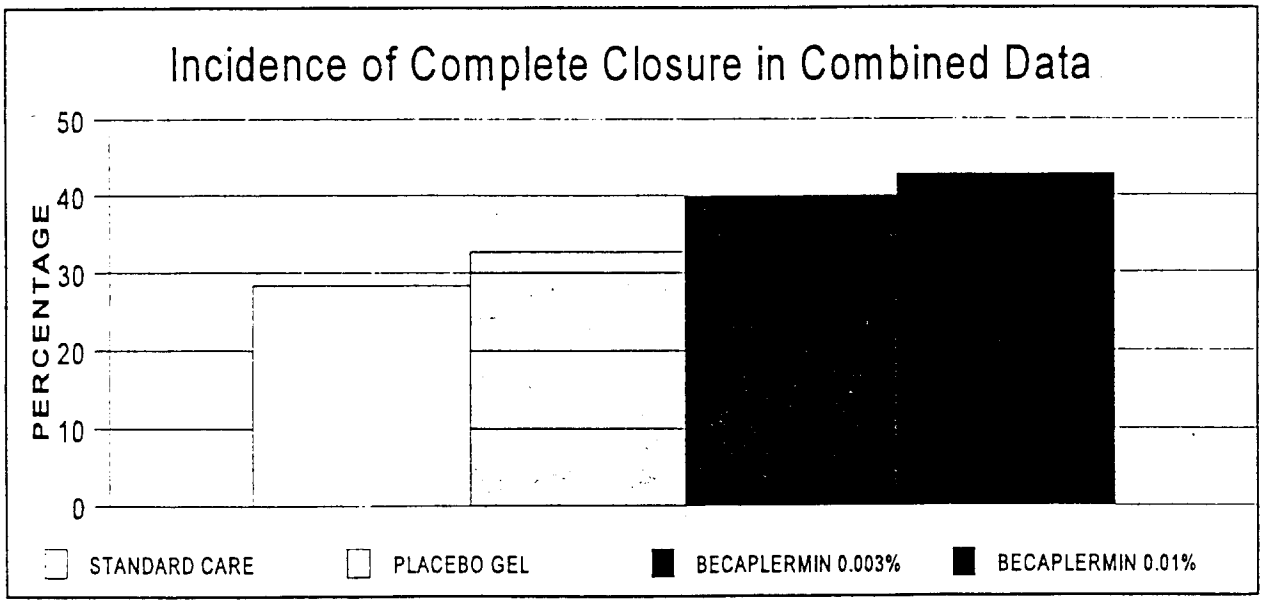
Reviewer's comments:
•These analyses were carried out on a population subgroup (< 5 cm^2). In a subsequent BLA amendment the sponsor provided an exploratory analysis of the intent-to-treat population.

•Based on these analyses it was determined that some of these variables were not balanced at baseline. Including these factors singly in the analysis of efficacy could significantly affect the magnitude of treatment effect (either increase or decrease). An analysis that included all these factors simultaneously in the model was not performed.

Magnitude of clinical benefit

Figure 6 graphically displays the combined incidence of closure from the four studies. The incidence of closure in the becaplermin 100 µg/g arm across the four studies was 42.8% compared to an incidence of 32.7% in the vehicle arm. The absolute difference is 10% in favor of becaplermin. If the incidence of ulcer recurrence is taken into account (about 30%), the magnitude of the durable benefit is even lower.

FIGURE 6.



UPDATED INTEGRATED SUMMARY OF SAFETY

The four-month safety update presents data from 1016 safety-evaluable subjects with lower-extremity diabetic ulcers (697 of whom received treatment with becaplermin gel) and 288 subjects with pressure ulcers (218 of whom received treatment with becaplermin gel) in a total of 14 studies that were completed as of June 15, 1996. The original BLA included safety data from 760 subjects with diabetic ulcers and 158 subjects with pressure ulcers who participated in 11 completed clinical studies. The 256 new subjects with diabetic ulcers and the 130 new subjects with pressure ulcers were part of three, ongoing studies in the original BLA that were completed as of June 15, 1996, the cutoff date for this update.

Reviewer's comments:
The safety profile of becaplermin was assessed by comparing numerically the incidence of target ulcer related adverse events and the incidence of serious adverse events across treatment groups by searching the electronic data base provided by the sponsor. Particular emphasis was placed on infections and on cardiovascular adverse events. The conclusions drawn by the sponsor were confirmed.

DEFINITION OF PATIENT GROUPS

Group 1a: Six blinded, randomized, controlled, diabetic ulcer studies
The four-month safety update to the BLA contains all safety data collected from the six primary safety studies. This group is designated Group 1a and consists of the double-blind or third-party (evaluator) -blind periods of six completed, well-controlled, randomized, lower-extremity diabetic ulcer studies.

These six studies include three efficacy and safety studies (90-22120-F, 92-22120-K, and PDGF-DBFT-002), one vehicle effect study (PDGF-DBFT-001), one dose-ranging study (92-22120-M), and one wound fluid stability study (PDGF-WFA-001). Safety comparisons of becaplermin gel therapy (30 µg/g, 100 µg/g, or all doses combined), to control therapy (vehicle treatment combined with standard therapy) were performed. Demographic characteristics for the 1006 subjects evaluable for safety in the Group 1a were similar across treatment groups and did not differ substantially from the Group 1 population studied in the original integrated summary of safety.

Reviewer's comment:
There are no clinically meaningful differences with regard to baseline characteristics.

Group 2a: All completed lower-extremity diabetic ulcer studies, becaplermin-treated subjects only

This group consist of all subjects who received becaplermin in completed lower-extremity diabetic ulcer studies. This group consists of ten studies, including the six studies that were part of Group 1A, as well as three open-label studies (90-22120-H, 92-22120-K-OL, and PDGF-DBFT-001-OL) that were extensions of three of the blinded, vehicle-controlled studies (i.e., 90-22120-F, 92-22120-K, and PDGF-DBFT-001, respectively), and one absorption study (PDGF-PHIO-005). The four-month safety update contains safety data collected from these studies. Safety data from the studies in this group are combined and summarized both for all subjects who received becaplermin gel at any time during the blinded or open-label (becaplermin treatment) parts of these trials and separately for each treatment grouping.

Group 3a: Completed blinded pressure ulcer studies

This group consists of the double-blind, vehicle-controlled, randomized portions of three completed pressure ulcer studies. These include one efficacy and safety study (90-22120-G), one dose-ranging study (PDGF-PULC-001) and one wound fluid stability study.

Group 4a: All completed pressure ulcer studies - becaplermin-treated subjects only

This group consists of all subjects who received becaplermin in completed pressure ulcer studies. In addition to the studies described in Group 3a, this group consists of one absorption study (90-22120-E) and the open-label extension (90-22120-I) of Study 90-22120-G.

Group 5a: Ongoing studies in subjects with diabetic ulcers

This group includes two studies: a Phase 3 study in subjects with diabetic ulcers (PDGF-DBFT-003) conducted in the U.K. and a Phase 1, open-label, absorption study in subjects with diabetic ulcers (PDGF-PHI-007). A sterile, single-dose, non-preserved formulation, rather than the preserved multidose formulation is being used in the U.K. study only. Both studies were ongoing and remained blinded as of August 30, 1996.

Safety summaries for study Group 1a (completed, well-controlled, blinded, lower-extremity diabetic ulcer studies) form the primary basis for conclusions regarding the safety of becaplermin in the treatment of lower-extremity diabetic ulcers. The extent of exposure to becaplermin and safety results on the overall population of subjects who received becaplermin in all completed blinded and open-label, lower-extremity diabetic ulcer studies (Group 2a) provide supportive information. Safety data from all pressure ulcer studies (Groups 3a and 4a) and ongoing studies (Group 5a) also provide supportive information.

SAFETY ANALYSES

Demographics

The 1006 subjects in Group 1a were treated with either becaplermin (538 subjects), vehicle (278 subjects), or standard therapy (190 subjects). Of the 538 subjects treated with any

concentration of becaplermin gel in Group 1a, 308 received the concentration of the proposed commercial dose of 100 µg/g. Among the 538 subjects treated with becaplermin gel in Group 1a, the majority (67%) were men, 82% were white, 12% were black, and 6% were of other racial groups.

Discontinuations

Discontinuations were approximately balanced across treatment groups. However, a slightly higher percentage of subjects who received becaplermin (87%, 100 µg/g; 85%, all doses combined) completed these studies than did subjects treated with vehicle (82%) or standard therapy (80%).The main reasons for discontinuation were adverse events (8-11% across treatment groupings) and loss to follow-up (standard therapy, 5%; all other treatment groupings, 1-2%).

Adverse events

The overall incidence of subjects experiencing at least one adverse event was slightly higher for subjects treated with standard therapy (81%) than it was for those treated with vehicle (67%) or becaplermin 100 µg/g (70%). Body systems with the highest incidence of adverse events were skin and appendages, resistance mechanisms, and body as a whole and the incidence of adverse events in these systems was somewhat higher (up to 18% higher than vehicle) for the standard therapy group than it was for the other groups.

Wound infection-related adverse events associated with the target ulcer, neoplasms and application site reactions, adverse events related to the cardiovascular system were of particular interest because of theoretical risks associated with a low bioburden product, and potential cardiovascular and tumorigenic effects of becaplermin. There was no evidence that becaplermin treatment increased infections or neoplasms; despite a higher proportion of subjects in the becaplermin group having suffered previous cardiovascular events, there was no overall evidence of increased cardiovascular risk in the becaplermin-treated subjects.

Adverse events associated with study ulcer

The most commonly reported adverse events in Group 1a studies were infection, cellulitis, skin ulceration, and osteomyelitis. The incidence of overall infection was numerically higher in the standard therapy group (18%) than in the vehicle (15%) or becaplermin 100 µg/g (15%) groups; subjects treated with any dose of becaplermin had a 12% incidence of infection. With regard to adverse events specifically associated with the study ulcer, Table 17 (see page 63) shows that the incidence of cellulitis ranged from a low of 7% for subjects treated with becaplermin (all doses combined) to a high of 11% for subjects treated with standard therapy. The incidence of osteomyelitis ranged from a low of 5% for subjects treated with vehicle to a high of 8% for subjects treated with standard therapy.

Reviewer's comments:

Table 17 indicates the following:

•The adverse events related to necrosis and/or infection of the study ulcer are numerically

lower in the arms receiving study drug (becaplermin gel or placebo gel).

•The numerically greater number of subjects experiencing rashes in the arms receiving study drug might be an indication of the irritation potential of the preservatives in the gel.

TABLE 17: INCIDENCE OF WOUND INFECTION-RELATED ADVERSE EVENTS ASSOCIATED WITH THE TARGET ULCER

	Treatment Grouping			
	Standard Therapy	Vehicle	Becaplermin 100μg/g	Becaplermin All Doses Combined[a]
	(N =190)	(N=278)	(N=308)	(N=538)
	%	%	%	%
Infections (total)	18	15	15	12
Bacterial Infection	3	1	2	1
Abscess	1	1	<1	<1
Fungal Infection	<1	<1	0	0
Cellulitis	11	7	8	7
Osteomyelitis	8	5	6	4
Fever	1	<1	0	0
Erythematous Rash	0	2	2	1
Gangrene	1	0	0	<1
Sum of Incidence of AEs	43	32	33	26

[a] Treatment groups are becaplermin 30μg/g and becaplermin 100μg/g

Of the 538 subjects treated with becaplermin (30, 100, or 300 μg/g) in the six studies primary for safety (Group 1a), seven (1%) subjects experienced application site reactions. Similar incidences were reported for subjects treated with standard therapy (<1%) or vehicle (1%). This incidence of application site reactions is consistent with that reported for all 566 diabetic ulcer subjects treated with becaplermin in the original BLA (1%).

The differences in incidence of infection-related adverse events associated with the target

ulcer by preferred term between control therapy (standard therapy plus vehicle treatment groups) and becaplermin treatment groupings in Group 1a were compared by Fisher's exact test. These comparisons revealed statistically significant lower overall incidences of adverse events of this nature in the becaplermin 30 μg/g (p=0.003) or all becaplermin doses combined (p=0.011) treatment groupings, but not in the becaplermin 100 μg/g (p=0.326) treatment grouping.

Lower incidences, by preferred term, that were statistically significant were: becaplermin 30 μg/g, infection (p=0.018) and all becaplermin doses combined, peripheral edema and skin ulceration (p=0.047, both). Kaplan-Meier 25th percentile estimates (days of treatment required for 25% of subjects to have experienced a first occurrence of a wound infection-related adverse event) for each treatment grouping is as follows: standard therapy, 69; vehicle, 86; becaplermin 100 μg/g, 95; and all becaplermin doses combined, 110.

Neoplasms

Although systemic absorption of topically applied becaplermin gel is negligible, the comparison between becaplermin and other treatment groups of treatment-emergent benign or malignant neoplasms of any type is nonetheless thought to be clinically relevant owing to the mitogenic characteristics of PDGF in mesenchymal cells.

As reported in the ISS of the original BLA, there were a total of 11 occurrences of neoplasms in 11 of 750 subjects while participating in the blinded phase of well-controlled diabetic ulcer studies (Group 1a). The neoplasms were varied in nature and origin and none were associated with a lower extremity. Moreover, they were evenly balanced between standard therapy or vehicle (6) and becaplermin-treated (5) subjects.

Cardiovascular adverse events

The possibility that local production of growth factors such as PDGF may contribute to the pathogenesis of atherosclerosis raises concern of whether the incidence of thrombotic and vascular adverse events may be increased in diabetic ulcer subjects treated with becaplermin. Abnormalities of repair of vascular lesions are known to occur in subjects with diabetes. Moreover, abnormalities in the coagulation system, including enhanced platelet aggregation and thrombus formation, are also known to occur in diabetics. Numerous factors including PDGF are involved in these processes.

Although this appears to be a theoretical risk due to the very low absorption of topically applied becaplermin and the demonstrated rapid metabolism of parenterally administered becaplermin in animal models, the incidence of cardiovascular disorders, specified by preferred term by the sponsor's medical monitor (e.g. arterial thrombosis, cerebrovascular disorder), was examined. Comparisons by preferred term revealed a higher incidence of cerebrovascular disorders in the becaplermin 30 μg/g group (2%) than in the control (<1%) group. This difference was statistically significant by Fisher's Exact test (p=0.033); however, the incidence in the becaplermin 100 μg/g group (<1%) was similar to that in the control

group (p=0.651). A higher incidence of cerebrovascular disorders in the becaplermin 30 µg/g group (2%) than in the control (<1%) group was statistically significant by Fisher's exact test (p=0.033); however, the incidence in the becaplermin 100 µg/g group (<1%) was similar to that in the control group (p=0.651); 70% (23 of 33 subjects) of the control group and 82% (37 of 45 subjects) of becaplermin-treated subjects had experienced cardiac or vascular disorders before entering the studies.

Reviewer's comments:
•Taken together with the bioavailability data discussed in a previous section and with the serious event data discussed below, these results do not suggest the presence of an imbalance in cardiovascular events in the study arms.

•The incidence of cardiovascular events in the ongoing studies (in subjects with diabetic foot ulcers and in subjects with pressure ulcers will be followed for additional data on this safety aspect.

Deaths, serious adverse events, and discontinuations due to adverse events
The total deaths in completed diabetic ulcer studies (Groups 1a and 2a) is 37 for this update. This includes 21 (4%) subjects treated with becaplermin, nine (3%) treated with vehicle, and seven (4%) treated with standard therapy. The majority of deaths were apparently related to the subjects' underlying diabetes and none were considered by the investigator to be related to study medication.

Among the 37 deaths associated with all completed diabetic ulcer studies, four occurred during the blinded phase of treatment: one due to an unconfirmed myocardial infarction (vehicle), one due to cardiac arrest secondary to myocardial infarction, one from multisystem failure due to congestive heart failure, and one due to sepsis and aspiration pneumonia (all three in the standard therapy group). All other deaths occurred up to 340 days posttherapy. Most of the deaths were a result of disorders commonly experienced by diabetic subjects such as myocardial infarction, cardiac arrest, and congestive heart failure and none were considered by the investigator to be related to study medication.

In the blinded phases of the diabetic ulcer studies (Group 1a), 24% of becaplermin-treated subjects, 25% of vehicle-treated subjects. and 28% of subjects treated with standard good wound care reported serious adverse events. Most of the subjects enrolled in the blinded diabetic ulcer studies completed treatment with either becaplermin or control therapy. Among the subjects in Group 1a, 9% of becaplermin-treated (all doses combined), 11% of vehicle-treated, and 11% of standard therapy-treated subjects discontinued treatment because of adverse events.

The nature and incidence of adverse events which led to discontinuation of therapy among becaplermin-treated subjects in all completed diabetic ulcer studies (Group 2a), 77 (11%) of 697 subjects, was similar to what was observed for becaplermin-treated subjects in Group 1a.

Pressure ulcer studies: Groups 3a and 4a

Median baseline ulcer volume was higher for becaplermin, all doses combined (11.0 ml) compared with vehicle (4.9 ml). These differences are related to differences in entry criteria for target ulcer volume across studies. In the blinded, vehicle-controlled, pressure ulcer studies (Group 3a), 129 (79%) of 164 subjects treated with becaplermin and 78 (73%) of 107 vehicle-treated subjects reported at least one treatment-emergent adverse event.

ANTIBODIES TO BECAPLERMIN

The original ISS showed two of 303 becaplermin-treated subjects in this group with an apparent antibody response to becaplermin; however, these antibodies appeared to be of very low affinity or reflected non-specific binding in the assay. Of the 172 subjects in the newly completed diabetic ulcer study (PDGF-DBFT-002) who had both baseline and poststudy plasma samples, none met the criteria for a positive antibody response to becaplermin.

DISCUSSION AND SUMMARY

1. Consistency of efficacy data

   Data from BLA # 96-1408 are variable with respect to effects of dose concentration and the magnitude of treatment benefit; the data are consistent with respect to the superiority of treatment over placebo effects. All clinical trials showed becaplermin to heal wounds more often than did either vehicle or placebo. However, only some of the trials showed this treatment benefit to be statistically significant.

   There are many possible explanations for these clinical data. Variability might be related to the following: differences in trial design; patient inclusion criteria and co-morbidities that affect healing; variations of standard of care; chance effects secondary to relatively small sample sizes in the studies. Differences in trial design, for example with respect to the use of controls, sample size and blinding techniques, were present among trials and may have contributed to the variability of efficacy data from various trials.

   Many variables affect healing of neuropathic diabetic ulcers, including infection control, ulcer location, ulcer duration, baseline ulcer area, T_cpO_2, non-weight bearing status, nutritional status, and patient glycemic control. There is evidence in the four major clinical studies suggesting that some of these variables were not balanced at baseline. Including these factors in the analysis of becaplermin's efficacy can affect significantly the magnitude and direction of treatment effects.

The observed incidence of complete healing between similar treatment arms among the four efficacy trials consistently varied by about (an absolute) 10%. It is likely that this degree of variation would be seen between study arms in most trials of this size given that data from relatively small number of patients are likely to be more associated with chance variation.

To overcome "noise" induced by chance or by covariates the trial size must be made relatively large to detect a statistically significant difference between becaplermin and control arms. For example, a trial designed to confirm (with 80% power) the observed finding that becaplermin is about 10% better than standard therapy (assuming a 30% incidence of ulcer closure in the control arm) would require approximately 800 subjects. A trial with 500 subjects (250 per arm) has only 65% power to detect a 10% difference. In the combined efficacy data from BLA 96-1408 there are 475 subjects total (190 in the standard care arm and 285 in the 100 µg/g becaplermin arm).

Despite the variable results reviewed above, there is some consistency between all four major clinical trials. In all studies, for example, the percentage of complete ulcer closure in the becaplermin groups is higher than in the placebo control or standard care groups. In addition, there is a suggestion that increased incidence of ulcer closure decreases other complications including soft and hard tissue infections at the ulcer site.

In the combined analyses the absolute percentage of subjects who benefited by the use of becaplermin was observed to be 10% (43% incidence in the 100 µg/g becaplermin and 33% in the placebo control). It is recognized that combined estimates of efficacy are limited by: a) the differences in the design of the trials (for example differences in: combinations of active arms and control arms; concentration and manner of application of becaplermin; sample size); and b) use of post-hoc assumptions about the data.

Given that about 30% of healed ulcers recurred within three months, only about seven percent of subjects experienced a durable benefit from treatment with becaplermin compared to placebo-treated patients. The rate of recurrence of the diabetic ulcers was about that expected from the clinical literature. The incidence of recurrence, however, was not greater in the becaplermin arm and this satisfies the current requirements for functionally adequate healing for this indication. There was also no evidence of pathologic (e.g. hypertrophic) healing. The recurrence rate suggests that underlying pathology either structural (e.g. foot deformities, vascular insufficiency) or infectious, may affect the durability of the clinical benefit. Alternatively, inferior wound care after the end of the treatment period of the study may also explain the ulcer recurrence rate.

2 A. Efficacy of drug product and vehicle.

The data submitted for all the studies support the Sponsor's claim that becaplermin is effective in the treatment of neuropathic diabetic ulcers of the lower extremity.

The drug vehicle alone did not adversely affect healing but rather outperformed standard care.

2 B. Optimal concentration and administration of becaplermin

Data from the trials presented in BLA 96-1408 are inconsistent with respect to optimal dose, perhaps due to design problems. In addition, preclinical dose ranging studies have not been useful to predict an optimal dose and suggest that there is a broad range of concentrations (from 10 to 300 µg/g) where the drug is active.

The concentration that is applied to ulcers clinically is several orders of magnitude in excess of that found to be mitogenic *in vitro* for relevant mesenchymal cells. However, the local drug concentration at the active sites is not known. Furthermore, any concentration of drug in the range mentioned above is believed to be safe.

The efficacy data for the 30 and 100 µg/g becaplermin formulations is not consistent in the different trials. In addition a comparison of drug usage and clinical outcome in the only trial in which dose was not measured (trial "002") showed excessive and variable usage about 8-fold more ($\mu g/cm^2$) on average than the required amount, and efficacy was not demonstrated. Moreover, the proportion of subjects treated with 100 µg/g becaplermin that had complete healing was the lowest of all the major trials. The sponsor believes that there is no advantage to measured dosing of becaplermin, though the potential exists for dose applications even in excess of that which occurred in the "002" trial.

A study is underway in 60 subjects with diabetic foot ulcers using the 100 µg/g formulation and comparing three treatment schedules (every other day for 20 weeks, daily for 8 weeks or daily for 20 weeks). The study is exploratory and is prompted by findings that PDGF appears to be stable in the wound environment (support for every-other-day dosing) and by the hypothesis that PDGF may initiate a self-sustaining cytokine cascade (hypothesis for the shortened eight week treatment interval).

In conclusion in the range of concentrations used clinically the drug appears to be safe. Application of excess amounts of drug does not appear to be more beneficial nor is it harmful. In view of excessive and variable amounts of drug used in the trials, directions for measured dosing will be necessary. In view of the uncertainties regarding optimal drug concentration, adequately powered studies to further explore these issues seem warranted.

3. Safety of drug product and vehicle

The following are the salient conclusions from the data: becaplermin is not systemically bioavailable; theoretical concerns raised by the biology of PDGF (i.e. increased vascular events or neoplasms) have not been confirmed by the clinical studies; the drug is in general well tolerated; product discontinuations, infectious adverse events,

tumorigenicity, cardiovascular problems, and deaths were similar between standard care, vehicle and product treatment arms; no neutralizing antibodies have been detected in studies of subjects with diabetes.

4. Definition of target population

With regard to ulcer pathophysiology, the ulcers treated in the trials are neuropathic ulcers and should be so defined in the label. Confirmation of adequate blood supply is necessary before initiating topical therapy.

With regard to depth of the ulcer at baseline, the definition of full-thickness ulcer is not adequate because it blurs the distinction between stage II and stage III ulcers. An anatomic description is needed with the important distinction that the ulcer must extend deeper than the dermis (into the subcutaneous layer or deeper). In addition to the lack of data on the efficacy of becaplermin for superficial ulcers, there is scant biologic rationale (PDGF is not likely to be effective in shallow ulcers because it does not directly promote re-epithelialization) and clinical rationale (superficial ulcers are expected to heal rapidly with standard care alone).

With regard to area of the ulcer at baseline, the finding that there is a greater activity of becaplermin in ulcers ≤ 5 cm^2 is the result of a post-hoc subgroup analysis and cannot be used to define the ulcer size that is indicated for treatment with becaplermin.

5. Low bioburden manufacture of the drug product

Regranex is manufactured as a preserved, multi-use, low bioburden product with the absence of specified objectionable microbes. The following data and observations support the microbial safety of this product. There is no difference in the incidence of infection-related adverse events in clinical trials between product, placebo, or standard care arms. No bacteria, fungi or yeast have yet been detected in tubes of the finished product using the Microbial Limits Test (the limit of detection is 10 CFU/g of gel product). The preservative system is bacteriocidal and fungicidal in the Preservative Effectiveness Test, which challenges the product with individual microbes of 10^5 each per gram of product. Lower extremity diabetic ulcers are inherently contaminated by microbes, and are considered to be in "bacterial balance" even if they contain up to 10^5 CFU per gram of ulcer tissue.

CONCLUSIONS

1. EFFICACY OF BECAPLERMIN

Becaplermin is effective for the treatment of lower extremity diabetic neuropathic ulcers

that extend through the dermis into, or through subcutaneous tissue and have an adequate blood supply. When used as an adjunct to, and not a substitute for, optimal ulcer care (including surgical debridement, non-weight bearing, control of infection) becaplermin increases the incidence of complete healing of the ulcers. The absolute difference in incidence of ulcer closure between placebo and becaplermin is 10%.

The inconsistency of the treatment effects of becaplermin in the four studies is likely due to chance variation and covariate effects caused by the relatively small size of the studies, and the relatively small magnitude of the treatment effect.

The data support the functionality and durability of the tissue repair in patients experiencing ulcer closure. Becaplermin must be used in conjunction with optimal ulcer care. In the absence of optimal care the benefit of becaplermin may decrease.

2. SAFETY OF BECAPLERMIN

No serious or clinically significant adverse effects have been observed thus far in subjects treated with becaplermin. Topically applied drug appears to be absorbed systemically in very small amounts if at all. Drug vehicle does not adversely affect ulcer closure. There is no evidence of adverse outcomes related to the low bioburden formulation.

RECOMMENDATION

It is recommended that this product be approved for marketing given the data supporting the product's safety and efficacy.