# Integrating the Results of Phase IV (Postmarketing) Clinical Trial With Four Previous Trials Reinforces the Position that Regranex (Becaplermin) Gel 0.01% Is an Effective Adjunct to the Treatment of Diabetic Foot Ulcers

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## ABSTRACT

**Background:** Platelet-derived growth factor (PDGF) has been demonstrated in pre-clinical studies to promote granulation tissue and stimulate cutaneous ulcer healing. Becaplermin gel 100 µg/g is the commercial preparation of the PDGF-BB homodimer and has been approved by the FDA as Regranex Gel 0.01% for use in diabetic foot ulcers.

**Materials and Methods:** A Phase IV (Postmarketing) investigator-blinded, randomized, parallel group, multicenter trial was performed comparing once daily application of Regranex Gel 0.01% plus standardized wound therapy to standardized therapy alone. Meta-analyses were performed on the results of the Phase IV trial integrated into the pooled results of 4 previous trials using becaplermin gel evaluating incidence of

complete healing, time to healing, and relative ulcer size at endpoint.

**Results:** In the Phase IV trial, 42% of the Regranex Gel treatment group healed versus 35% for the standardized therapy alone ($P = 0.316$). Of the subjects who achieved complete healing, there was evidence for preferential healing of ulcers with baseline areas less than 1.46 $cm^2$ for Regranex Gel treatment ($P = 0.0286$). The integrated analysis showed that becaplermin 100 µg/g was superior to vehicle gel ($P = 0.015$) and standardized care ($P = 0.002$) in achieving complete healing. In the ulcers less than or equal to 10 $cm^2$ in area, the becaplermin gel 100 µg/g was also superior to vehicle gel ($P = 0.011$) and standardized care ($P = 0.006$). Significant differences were seen among treatment groups ($P = 0.010$; Cox's Proportional Hazards Analysis). The Kaplan-Meier estimate of the 35th percentile for the time to complete healing was 99 days for becaplermin gel 100 µg/g versus 141 days for the vehicle.

**Conclusion:** The results of the pooled integrated analyses are consistent with those reported from the 4 preapproval studies showing that Regranex Gel 0.01% significantly increases the incidence of complete healing and reduces the time to complete closure of diabetic neuropathic ulcers. These results reinforce the position that Regranex Gel 0.01% is a useful adjunct for the treatment of diabetic foot ulcers.

## INTRODUCTION

Platelet-derived growth factor (PDGF) stimulates the proliferation of a variety of mesenchymal cells, including fibroblasts.[1,2] PDGF has been demonstrated in preclinical studies to promote the formation of granulation tissue in ulcers and thus stimulate cutaneous ulcer healing.[3,4]

Recombinant human (rh) PDGF-BB (becaplermin) has been prepared and purified for use in clinical studies of wound healing. The BB homodimer was chosen for clinical study because it was known that fibroblasts are more responsive to it than to the AB or AA dimers.[5] In addition, treatment of chronic or acute ulcers with the BB dimer has been shown to enhance ulcer healing.[6]

Published results from a number of relatively small clinical studies generally suggested that topically applied platelet-derived factors promote healing in subjects with chronic nonhealing ulcers.[7-12] Most of those studies used heterogeneous mixtures of autologous platelet-derived factors. However, several studies used rhPDGF-BB in an aquaeous formulation to treat pressure ulcers and were able to demonstrate a greater decrease in ulcer size compared with placebo-treated subjects [13-16]

Based on the results from both preclinical and early clinical studies, becaplermin was chosen for study as a potential wound healing agent. For this purpose, becaplermin was formulated into a hydrogel composed of sodium carboxymethlcellulose (NaCMC) with preservatives (methyl and propyl parabens, m-cresol) added. During the clinical development of becaplermin gel, L-lysine was added to the formulation as a stabilizing agent. The resulting commercial preparation is a low bioburden NaCMC gel containing 100 µg/g becaplermin (0.01%).

Prior to Food and Drug Administration (FDA) approval, four 20-week efficacy studies were performed. These were all randomized, multicenter, blinded, parallel group studies designed to evaluate the effect of once daily topical treatment with becaplermin gel on the healing of chronic, full-thickness lower extremity, primarily neuropathic, diabetic ulcers.[17,18] Study medication was administered in conjunc-

tion with good wound care which included twice daily dressing changes and ulcer debridement, as needed, to remove necrotic and/or infected tissue. The good wound care procedures used in the 4 studies were consistent with "standard care" and were closely standardized among the investigators. Subjects for the 4 studies were diabetic males and females of at least 19 years of age who had at least one chronic Stage III or IV diabetic ulcer.

In each of the 4 studies, after a screening visit, subjects enrolled into the study started receiving study medication within the following two weeks. Subjects were to have a target limb transcutaneous partial pressure of oxygen ($TcPo_2$) greater than or equal to 30 mmHg at screening. The four 20-week studies also were similar with respect to subject selection criteria, study endpoint (after 20 weeks of study drug therapy or after complete healing of the target ulcer without drainage or need for a dressing), and the primary efficacy measure of complete healing. Secondary efficacy measures included time to complete healing and relative ulcer area at endpoint.

The 4 studies enrolled a total of 925 subjects, 922 of whom were considered intent-to-treat. The results from those studies revealed that when used as an adjunct to, and not a substitute for, good wound care practices including sharp debridement, infection control, and pressure relief, becaplermin gel 100 µg/g increased the incidence of complete healing of diabetic ulcers.[17,18] Based on the results of the 4 studies, the commercially available becaplermin gel product, Regranex Gel 0.01%, was approved by the FDA on December 16, 1997.

Following approval and marketing of Regranex Gel 0.01%, a Phase IV postmarketing trial was performed. This report describes the Phase IV trial and integrates its results with those of the previously reported 4 trials.

## MATERIALS AND METHODS

The primary objective of the Phase IV study was to demonstrate that Regranex Gel 0.01% treatment, with once daily dressing changes, in combination with standardized good care, resulted in a greater incidence of complete healing in comparison to standardized good care alone when used for full-thickness diabetic neuropathic foot ulcers having an adequate blood supply. In contrast to previous clinical trials in this patient population where twice daily saline-moistened gauze dressings were used with the study medication, this study utilized once daily dressing of Adaptic nonadhering dressing covering the study medication with a gauze topping and overwrap.

The study was an investigator-blinded, randomized, parallel group, multicenter trial of up to 25 center sites and a maximum of 340 subjects. Subjects' participation for the efficacy component of the study was limited to 20 weeks or until complete healing was achieved, whichever occurred first. A subject whose ulcer was not healed after 20 weeks was eligible to receive 20 weeks of open-label treatment with Regranex Gel 0.01%.

### Protocol Design

All participants provided informed consent prior to the start of the protocol. Each institution's Human Investigation Committee (ie, IRB) gave approval to the protocol before any subjects were enrolled. There was a screening period of up to two weeks. At the first visit, the expected target ulcer was debrided of all necrotic tissue and surrounding callous to reveal a clean ulcer bed. The ulcer was photographed, traced for planimetry, and a tissue biopsy obtained for quantitative and qualitative bacteriology.[19] Following the biopsy, the ulcer was dressed with Adaptic gauze and a dry gauze outer covering. If the biopsy was

**Table 1.** Inclusion Criteria

To be eligible for entry into this study, a subject must have met the following criteria:

- Be 18 years of age or older.
- If female, must be practicing birth control.
- Have documented wound etiology resulting from complications of diabetes mellitus.
- Have at least one chronic nonhealing cutaneous full thickness diabetic neuropathic foot ulcer between 1.7-12 $cm^2$ area, 4-52 weeks duration, on the plantar aspect of the forefoot (midarch forward) and free of necrotic and infected tissue postdebridement.
- Have a supine TcPO2 > 30 mmHg on the dorsum of the target ulcer foot.
- Have an ulcer tissue biopsy with < 1 x $10^6$ organisms/g of tissue and no beta hemolytic streptococci.
- Be willing and able to comply with the protocol.

not supportive of an active wound infection (colony count of < 1 □ $10^6$ CFU/g of tissue and no beta-hemolytic streptococci), screening could continue to randomization. However, if the biopsy was supportive of an active wound infection (bacterial count ≥ 1 □ $10^6$ CFU/g of tissue or any beta-hemolytic streptococci), the infection was treated with a full course of antibiotics and a repeat biopsy done to confirm the ulcer was in bacterial balance.[20] Other screening procedures included a complete medical history and physical examination, laboratory assessments, edema evaluation, $TcPo_2$ determination on the dorsum of the foot with the subject in the supine position, ankle-brachial index measurement, and neuropathic assessment with a 10 g (5.07 Semmes-Weinstein) monofilament. These assessments were all performed to assure the potential subjects met the inclusion and exclusion eligibility criteria. Inclusion criteria for the study are enumerated in Table 1. Exclusion criteria are listed in Table 2.

**Dosage and Application of Growth Factor**

Following screening, satisfactory subjects for enrollment were randomized by the sponsor to receive Regranex Gel 0.01% plus the Adaptic dressing or the Adaptic dressing alone. The dosage of Regranex Gel 0.01% was determined by study personnel on a weekly basis by multiplying the greatest length of the target ulcer by the greatest width. The resultant area in square centimeters ($cm^2$) was then divided by 4 and the number was used as the number of centimeters of expressed Regranex Gel to be applied to the ulcer by the subject or caregiver each day. In addition to the once daily dressing changes, standardized good wound care procedures (maintenance of a clean moist environment, infection control, non-weightbearing regimen, and debridement) were followed.

**Measurement of Treatment Efficacy and Statistics**

On each subject visit, an acetate tracing of the target ulcer was made with a fine-tip, permanent ink-marking pen. Planimetric analysis of the acetate tracings was performed by the sponsor's designee to determine the percentage of the target ulcer covered with epithelial cells. The primary efficacy parameter was the incidence of complete healing (ie, closure) for each treatment group. A secondary parameter was the time to complete healing. A logistic regression analysis, stratified by center, was used to assess the statistical significance of any differences between treatment groups in the proportion of subjects who healed.

**Table 2.** Exclusion Criteria

To be eligible for entry into this study, the subject must not:

- Have the target ulcer other than on the plantar surface forward of the midarch.
- Be a pregnant female or a nursing mother.
- Have a known hypersensitivity to any of the study drug components.
- Have a malignant disease at the ulcer site.
- Have a target ulcer < 1.7 or > 12 $cm^2$ postdebridement (L □ W).
- Have more than one diabetic ulcer on the same foot as the target ulcer.
- Have more than three chronic wounds on the same extremity as the target ulcer.
- Have thermal, electrical, chemical, or radiation wounds at the site of the target ulcer.
- Have wounds resulting from large vessel arterial insufficiency, venous insufficiency, or necrobiosis lipoidica.
- Have significant metabolic, rheumatic, collagen vascular disease, chronic renal insufficiency, or chronic severe liver disease.
- Have osteomyelitis confirmed by bone biopsy.
- Have received any investigational drug, Procuren solution, or prior Regranex Gel 0.01% usage within the past 30 days.
- Have a preexisting disease or condition that could interfere with evaluation of the effectiveness of Regranex Gel 0.01% or be adversely affected by Regranex Gel 0.01%.
- Be receiving any systemic corticosteroids, immunosuppressive agents, radiation, or chemotherapy.
- Have had revascularization surgery in the past 6 weeks.
- Have exposed bone or tendon, or presence of Charcot foot.
- Have severe pitting limb edema.

The statistical significance of any difference between the treatment groups in time to complete healing was assessed by Log-Rank test stratified by center. Relative ulcer area was defined as the area at the end of the study divided by the baseline ulcer area. When a subject withdrew early, the ulcer area from the last evaluation was carried forward for the remaining visits. The statistical significance of any difference between treatments in the relative ulcer area was determined by an analysis of covariance with treatment and center effects and baseline area as a covariate.

**Integrated Analyses of Four Previous Studies and the Phase IV Postmarketing Study**

To update the previous pooled analysis of the 4 preapproval studies[17,18] to include all current data from controlled trials, analyses of the incidence of complete healing, time to complete healing, and relative ulcer area at endpoint were performed that included the 4 studies from the previous analysis plus the study described in this paper. For the type of formal analyses needed for the combined results of the 5 efficacy studies meta-analysis is a commonly used method for obtaining combined estimates of treatment effect contrasts. Gleser and Olkin showed how to combine contrasts for published studies that are unbalanced with regard to treatment design.[21] Their technique is applicable to continuous response variables and a common control treatment in every study.[21] The data from the 5 efficacy studies were pooled in a straightforward manner to analyze the primary and sec-

ondary variables. A logistic regression model adjusting for baseline ulcer area was used to analyze the incidence of complete healing. In addition, formal combined statistical analyses were conducted for the population of subjects with baseline ulcer areas less than or equal to 10 $cm^2$, a criterion common to the 5 studies.

## RESULTS

### Phase IV Postmarketing Clinical Trial

The study was not totally enrolled. The sponsor terminated enrollment because of slow patient accrual. Of the planned 340 maximum possible subjects, 146 were enrolled at 21 centers. This included 74 subjects treated with Regranex Gel 0.01% and 72 treated with standardized therapy alone. Of the 146 subjects, 146 were evaluable for safety and 143 subjects were evaluable for efficacy.

Baseline characteristics were generally comparable between groups. The mean duration of diabetes mellitus in the Regranex Gel 0.01% group (17.9 years) was slightly longer than that in the standardized therapy group (14.7 years). The median ulcer at baseline was similar in the two treatment groups (1.5 and 1.6 $cm^2$).

Forty-two percent of the once daily Regranex Gel 0.01% treatment group achieved complete (100%) healing, compared to 35% of the standardized therapy group. This 20% increase in the likelihood of complete healing was not statistically significant ($P = 0.316$, two-sided 0.05-level test). Of the subjects who achieved complete healing, there was evidence for preferential healing of target ulcers with baseline areas less than 1.46 $cm^2$ in favor of subjects treated with Regranex Gel 0.01% ($P = 0.0286$).

Analysis of the time to healing using Kaplan-Meier estimates revealed no statistically significant difference between the Regranex Gel 0.01% and standardized therapy groups ($P = 0.283$). The median weekly wound healing rate was 0.05 for both treatment groups, indicating there was no difference between treatment groups in the weekly wound healing rate. The relative ulcer area at endpoint for all subjects in the Regranex Gel 0.01% group (mean 0.57) was similar to that in all subjects in the standardized therapy group (mean 0.31) ($P = 0.390$).

### Integrated Results of Analyses of All Efficacy Trials

The 5 total efficacy trials enrolled 1,071 subjects, 1,065 of whom were considered intent-to-treat. Subjects were enrolled into one of 4 treatment groups (standardized therapy, vehicle gel, becaplermin gel 30 µg/g, or becaplermin gel 100 µg/g (Regranex Gel 0.01%). Not all groups were present in each study.

The percent of ulcers healed for the intent-to-treat population of all 5 studies were combined and are presented in Figure 1. Based on this pooling, a dose-response relationship is suggested, with 100 µg/g gel formulation of becaplermin having the greatest proportion healed. The Fisher's exact $P$ values (two-sided) for the comparison of becaplermin gel 100 µg/g versus standardized therapy was $P = 0.002$, and versus the vehicle gel $P = 0.015$.

Due to the sparsity of data for subjects with baseline ulcer areas of greater than 10 $cm^2$ and statistical interactions among the studies when data for these subjects are included, an analysis as presented above can be problematic. A more reasonable approach is to do the combined logistic regression analysis using subjects with baseline ulcers less than or equal to 10 $cm^2$. This size range represents 95% of the subjects in the 5 trials and their analysis does not involve significant treatment interactions. Of the 1,065 intent-to-treat in the 5 studies, 1,016 (95%) had baseline ulcer areas less than or equal to 10 $cm^2$.

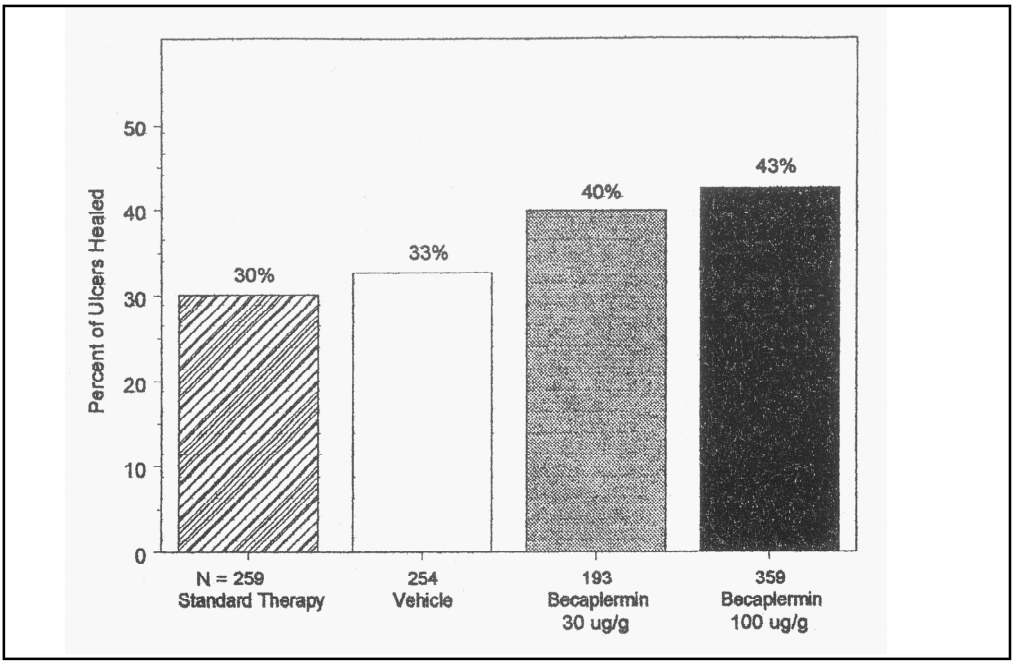


**Figure 1**. Incidence of complete healing in intent-to-treat subjects from five 20-week diabetic ulcer studies combined.

The plot of estimated probability of complete healing for the 4 treatment groups across the 5 trials is shown in Figure 2. Based on the model of the ulcers less than 10 $cm^2$, the estimated probability of complete healing was significantly higher in the becaplermin gel 100 µg/g group than in the standardized therapy ($P = 0.006$) and the vehicle gel group ($P = 0.011$). In contrast, the estimated probability of complete healing was not significantly higher in the becaplermin gel 30 µg/g group than in the vehicle gel group ($P = 0.327$).

Figure 3 shows the actual incidence of ulcers less than or equal to 10 $cm^2$ that achieved complete healing. The integrated results showed that a significantly greater incidence of complete healing occurred in the becaplermin gel 100 µg/g group compared with the vehicle gel group ($P = 0.011$) in these smaller ulcers. At a median baseline ulcer of 1.5 $cm^2$, the becaplermin gel 100 µg/g demonstrated a 36% increase in complete healing when compared to the vehicle gel (49% vs 36%). The difference was similar when comparing becaplermin gel 100 µg/g group to the standardized therapy group (49% vs 37%). In contrast, both the estimated probability of complete healing and the incidence of ulcers healed was not statistically different when comparing the becaplermin 30 µg/g group and the vehicle gel group ($P = 0.327$).

The results for the time to healing for the pooled intent-to-treat population also suggested a dose response with a shorter time to healing associated with increasing concentrations of becaplermin gel. The Kaplan-Meier estimates of the number of days to healing (35th percentile) were 113 days for becaplermin gel 30 µg/g, 100 days for becaplermin gel 100 µg/g, 141 days for vehicle gel, and 141 days for standardized therapy. An analysis of time to complete healing for subjects with baseline ulcer areas up to 10 $cm^2$ demonstrated that ulcers treated with becaplermin gel 100 µg/g healed in a significantly shorter time ($P = .010$)

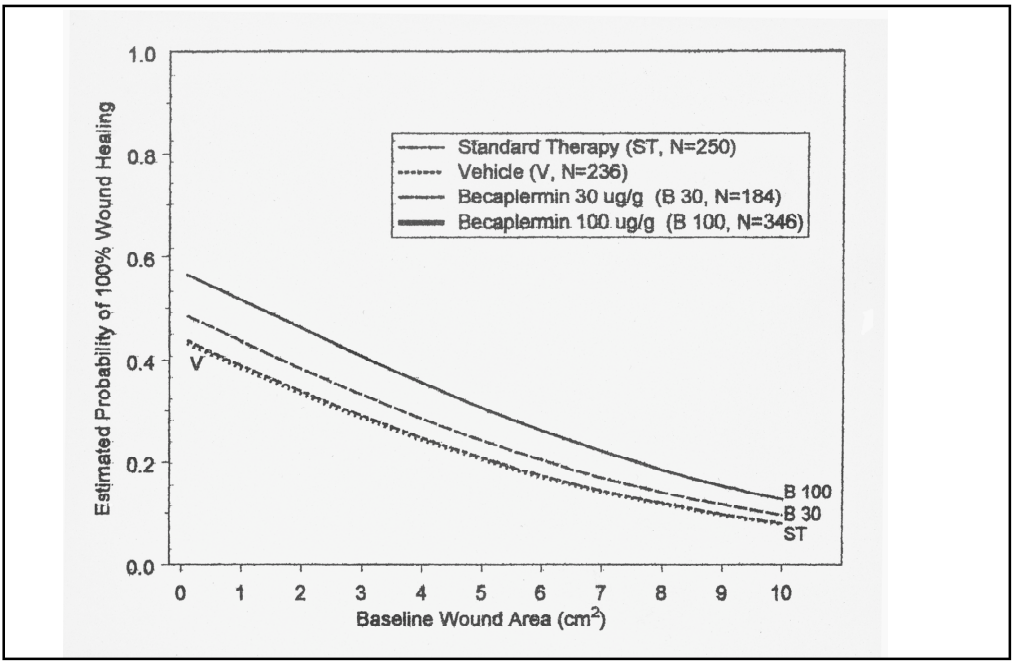


**Figure 2.** Estimated probability of complete healing at endpoint for subjects with baseline ulcer area ≤ 10 $cm^2$ (five 20-week diabetic ulcer studies combined).

than those treated with the vehicle gel (99 days vs 141 days).

Median relative ulcer areas at endpoint for all the intent-to-treat subjects were 0.12 for standardized therapy, 0.13 for the vehicle gel group, 0.13 for becaplermin 30 µg/g treatment, and 0.07 for the 100 µg/g becaplermin gel group. When comparing the median ulcer areas at endpoint for the subgroup of subjects with baseline ulcer areas less than or equal to 10 $cm^2$, similar results were achieved (0.11, 0.13, 0.13, and 0.06 respectively). The differences between the becaplermin gel 100 µg/g treatment and the vehicle gel treatment were not statistically significant ($P = 0.112$).

## DISCUSSION

The accrual rate into the Phase IV postmarketing trial was so slow that the sponsor terminated the trial after enrolling 146 subjects. There were several possibilities for the slow accrual rate. As can be seen in Tables 1 and 2, the ulcer site in this trial was limited to the forefoot (midarch forward). This eliminated many diabetic foot ulcers. More importantly, since this was a postmarketing study, many potential subjects with an eligible ulcer were already being treated with Regranex Gel 0.01% in the wound care centers. As seen in Table 2, this was an exclusion criterion. In the 143 subjects evaluated for efficacy in the trial, 20% more achieved complete healing in those treated with Regranex Gel 0.01% than with standardized therapy (42% vs 35%). The 35% healing rate in the standardized therapy group was the highest for standardized therapy of all the becaplermin clinical trials.[17,18] The steadily increasing complete closure rate in standardized therapy arms is due to a better understanding of good ulcer care and wound bed preparation including having the wound in bacterial balance.[20,22] As standardized care arm results improve, it is more difficult to show statistically different improve-

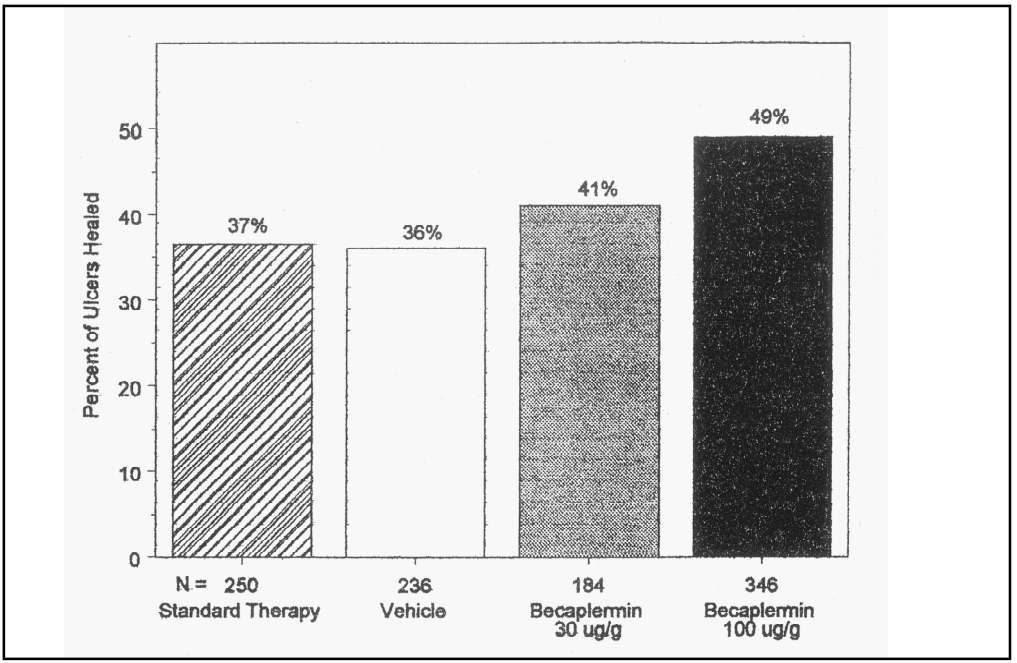


**Figure 3.** Estimated incidence of complete healing in subjects with a baseline ulcer area of ≤10 $cm^2$ (median 1.5 $cm^2$) from five 20-week diabetic ulcer studies combined.

ments with the addition of growth factors.[23,24] Despite these caveats, there was evidence for preferential healing of target ulcers with baseline areas of less than 1.46 $cm^2$ in subjects treated with Regranex Gel 0.01% ($P = 0.0286$).

Olkin and Sampson demonstrated that in situations such as that presented by the 5 becaplermin trials, where all subject level data are available, meta-analysis on summary data is equivalent to a two-way analysis of variance with study and treatment as factors.[25] However, when subject level covariates are available, they noted that the meta-analytic approach must use subject level data. Using an approach based upon the meta-analytic concepts mentioned, we first performed a formal analysis to estimate treatment contrasts for subjects with target ulcer baseline areas less than or equal to 10 $cm^2$ taking into account the lack of treatment balance across the 5 studies, and accounting for possible effects of baseline ulcer area. We then performed the analysis in a model without the baseline ulcer area-by-treatment interaction. The results of these two analyses were similar and showed that becaplermin gel 100 µg/g is statistically superior to vehicle gel and to standardized therapy regardless of baseline ulcer area up to 10 $cm^2$.

As seen in Figure 3, for a median ulcer area of 1.5 $cm^2$, the estimated incidence of complete healing was 49% for becaplermin gel 100 µg/g and 36% for vehicle gel. This is consistent with the observed healing rates in the major pivotal efficacy trial (50% for becaplermin gel 100 µg/g and 35% for vehicle gel).[17,18,26] While the estimated probability of complete healing in the becaplermin gel 30 µg/g (41%) was not statistically different from that in the vehicle gel group (36%, $P = 0.327$), it was numerically greater. This suggests that once daily becaplermin gel treatment increases the probability of complete healing in a dose-related fashion.

As expected for a complex disease state such as diabetes mellitus complicated by a neuropathic foot ulcer, there were differences in outcome for all treatment groups across the 5 clinical trials. Scarcity of data in a minor subset (approximately 15% of the total study population) of subjects with ulcers greater than 5 $cm^2$ contributed appreciably to the variability across studies in the intent-to-treat populations. Despite this, the results from the five 20-week controlled studies have demonstrated that becaplermin gel 100 µg/g significantly increases the incidence of complete healing of diabetic neuropathic ulcers.

In conclusion, the results of the pooled integrated analyses are consistent with those reported from the 4 preapproval studies demonstrating that Regranex Gel 0.01% significantly increases the incidence of complete healing and reduces the time to complete healing of diabetic neuropathic ulcers. These results reinforce the position that Regranex Gel 0.01% is a useful adjunct for the treatment of diabetic foot ulcers.

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