SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: REGRANEX® Gel NAME OF ACTIVE INGREDIENT(S): Becaplermin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR003238 **Title of Study:** A Multicenter Clinical Evaluation of the Efficacy and Safety of REGRANEX® Gel in the Long-Term Treatment and Re-Treatment of Lower Extremity Diabetic Ulcers		
Coordinating Investigator: Ian Gordon, M.D. - VA Long Beach Healthcare System, Long Beach, CA USA		
Publication (Reference): None.		
Study Initiation/Completion Dates: 23 January 2001 — 27 February 2004		**Phase of development:** 3
Objectives: The primary objective of this study was to evaluate the efficacy and safety of REGRANEX Gel versus placebo when applied to recurring or nonhealing neuropathic diabetic lower extremity ulcers for up to 52 consecutive weeks including an initial treatment period of up to 20 weeks with REGRANEX Gel or for up to 2 re-treatment episodes.		
Methods: An individual subject's progress through the phases of the study was determined by the clinical course of his or her treatable ulcer(s). The study began with an **open-label phase**, during which all subjects received treatment with REGRANEX Gel for 20 weeks or until all treatable ulcers healed, whichever occurred first. The open-label phase was followed by the **double-blind phase** (extending treatment up to 52 weeks) for subjects with treatable ulcers and by the **observation phase** for subjects whose ulcers were healed. In the **double-blind phase**, subjects with treatable ulcers were randomized in a 2:1 ratio to REGRANEX Gel or placebo and continued to receive double-blind treatment until the end of the double-blind phase. A subject could enter up to 2 double-blind phases. The double-blind phase was followed by **study completion** for subjects who met the criteria for completion and by the **observation phase** for subjects whose ulcers healed and who had not completed the study. Subjects whose ulcers completely healed during the open-label phase or during the double-blind phase entered the **observation phase**. During the observation phase, subjects were not treated with study medication, but were observed regularly to determine whether ulcers were recurring or developing. A subject could enter up to 2 observation phases. The observation phase was followed by **study completion** for subjects who met the criteria for completion and by a 20-week **double-blind phase** for subjects who developed new or recurrent ulcers and who had not completed the study.		
Number of Subjects (planned and analyzed): Planned sample size was 200 evaluable subjects. The study was terminated early, resulting in a smaller number than planned. Actual sample size was 136 subjects.		
Diagnosis and Main Criteria for Inclusion: Subjects were men and women aged 18 through 80 years with diabetes mellitus Type I or Type II. Each subject had at least one Stage III or IV neuropathic diabetic ulcer measuring between 1 and 15 cm^2 (length x width) on the ankle or foot, with no exposed bone and no osteomyelitis.		
Test Product, Dose and Mode of Administration, Batch Numbers: REGRANEX Gel (Becaplermin topical gel). Active ingredient: becaplermin, 100 µg/g (0.01% concentration). Gel was applied once daily in a continuous thin layer to cover the entire surface of the treated ulcer(s). Batch numbers are shown in Section 3.4.1 of this report.		
Reference Therapy, Dose and Mode of Administration, Batch Numbers: Placebo gel containing the same ingredients as REGRANEX Gel except no active ingredient and having the same appearance as REGRANEX Gel. Mode of application was the same as for REGRANEX Gel. Batch numbers are shown in Section 3.4.1 of this report.		
Duration of Treatment: Subjects could be enrolled in the study for up to 137 weeks, which could include up to 52 uninterrupted weeks of treatment.		

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Criteria for Evaluation:

Efficacy: Functional assessment of each treated ulcer was based on the following scale:

1 = Complete healing; completely epithelialized with no drainage present.

2 = Less than complete healing; not completely epithelialized, or with drainage present.

The efficacy evaluation in this study was incidence of complete ulcer healing. A subject was defined as having complete ulcer healing if all treated ulcers had a functional assessment score of 1, "complete healing." Otherwise, the subject was defined as not having complete ulcer healing.

Safety: Treatment safety was evaluated based on the following parameters.

- Incidence of adverse events. Only serious adverse events were tabulated for the open-label and observation phases. All treatment-emergent adverse events, including serious adverse events, were tabulated for the double-blind phase.
- Clinical hematology, chemistry, and urinalysis results and changes from baseline.
- Vital signs and changes from baseline.

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Statistical Methods:

The analysis provided in this synopsis is different from that planned in the protocol. In the protocol, the primary efficacy variable is time to complete ulcer healing; the secondary analysis is the incidence of complete ulcer healing. The synopsis presents incidence of complete ulcer healing as the efficacy evaluation. The reason for the difference is that the study was closed early and the focus of the study report was safety. Early termination of the study meant that only limited information was available on the time to complete ulcer healing, and therefore only the incidence of complete ulcer healing was summarized and presented in the study report.

Study Populations: The populations for the analyses of efficacy and safety were:

All Enrolled Subjects: All subjects who received at least one dose of open-label study medication.

Open-Label Safety Population: All subjects who received at least one dose of open-label study medication and provided any safety information after the start of open-label study medication.

All Randomized Subjects: All randomized subjects who received at least one dose of post-randomization study medication.

Randomized Safety Population: All randomized subjects who received at least one dose of post-randomization study medication and provided any safety information after the start of randomized study medication.

Non-Randomized Safety Population: All subjects in the open-label safety population who did not get randomized into the double-blind #1 phase.

Intent-to-Treat (ITT) Population: All randomized subjects who received at least one dose of post-randomization study medication and provided any post-randomization efficacy data.

Long-Term Efficacy Ulcer Population: All subjects in the ITT population who had any ulcers that were present at the baseline visit and that did not heal during the 20 weeks of open-label treatment (thus, all subjects in this population received 20 weeks of treatment with REGRANEX Gel prior to randomization to double-blind therapy).

First Re-Treatment Triggering Ulcer Population: All subjects in the ITT population who entered an observation phase (i.e., had a gel-free break) before being randomized into the double-blind phase. (The observation and double-blind phases could be of any length allowed by the protocol.)

Efficacy Analyses: For each population, the numbers and percentages of subjects who achieved complete healing at the end of the double-blind #1 phase were tabulated by treatment group, by center and overall.

Safety Analyses: The following summaries of treatment-emergent adverse events were produced: adverse events reported by at least 5% of subjects; adverse events leading to discontinuation; wound infection-related adverse events; wound infection-related adverse events related to a treated ulcer; adverse events by severity; treatment-related adverse events; ulcer-related adverse events; and treatment application site reactions and neoplasms. Treatment-emergent serious adverse events (for all phases of the study), treatment-emergent serious adverse events leading to discontinuation from the study (for all phases of the study), and treatment-emergent wound infection-related serious adverse events related to a treated ulcer were also summarized.

Clinical laboratory values, changes from baseline, and numbers and percentages of subjects with markedly abnormal laboratory values were summarized. Vital signs and changes from baseline were summarized.

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Efficacy Results:
In the Intent-To-Treat (ITT) population, a greater proportion of subjects in the REGRANEX group (28 of 51 subjects, 55%) had complete healing of all new and recurrent treated ulcers at the end of the double-blind #1 phase than in the placebo group (10 of 25 subjects, 40%). Similarly, in the Long-Term Efficacy Ulcer population, a greater proportion of subjects in the REGRANEX group (26 of 46 subjects, 57%) had complete healing than in the placebo group (7 of 22 subjects, 32%). Results in the First Re-Treatment Triggering Ulcer population involved too few subjects to be of clinical relevance.

Safety Results:
Treatment-emergent adverse events that were reported by the highest percentage of subjects during the double-blind phase were infection, skin ulceration, bullous eruption, osteomyelitis, and cellulitis. Most of the cases of infection and osteomyelitis in each of the 2 treatment groups were considered wound infection-related adverse events related to a treated ulcer. With the exception of infection, reported adverse events were experienced by a similar proportion of subjects in each of the 2 treatment groups. Infection was reported by a higher proportion of subjects in the REGRANEX group (30%) than in the placebo group (16%), however, only 1 of the 15 subjects in the REGRANEX group reported an infection that was considered related to study treatment.

Serious adverse events were reported by 26% of subjects in the REGRANEX group and 28% of subjects in the placebo group during the double-blind phase of the study. The serious adverse events with the highest incidence during the open-label and double-blind phases were osteomyelitis, cellulitis, and infection, and most of these events were classified as treatment-emergent wound infection-related serious adverse events related to a treated ulcer. The frequent reporting of osteomyelitis and cellulitis are to be expected in this patient population. The most common event leading to discontinuation was osteomyelitis, an event likely to cause complications, including amputations, in this patient population. There were 3 deaths during the study, 1 in the open-label phase, and 2 during the double-blind phase, 1 in each treatment group. In the 2 cases where cause of death was known, death was considered not related to study medication.

A total of 16 subjects discontinued the study due to an adverse event: 11 subjects in the open-label phase, 4 subjects in the double-blind phase (2 subjects in each treatment group), and 1 subject who discontinued during the observation phase after completion of the double-blind phase. The most common events leading to discontinuation were osteomyelitis (5 subjects), condition aggravated (4 subjects); peripheral ischemia (3 subjects) and infection (2 subjects).

Mean changes from baseline in hematology, clinical chemistry and urinalysis values were not clinically significant and the incidence of markedly abnormal laboratory values during the open-label and double-blind phases was low. There was no evidence that any of the subjects produced antibodies to becaplermin. Overall, REGRANEX was safe and well tolerated in this study of extended treatment and safety results were similar to those observed in studies with a shorter treatment period (20 weeks).

Conclusions:

REGRANEX was safe and well tolerated in this study. Results from this study designed to evaluate long-term treatment with REGRANEX did not raise any new or unexpected safety concerns. While this study was not powered to demonstrate efficacy, a larger proportion of subjects had complete ulcer healing in the REGRANEX group than in the placebo group.

Date of the report: 15 DECEMBER 2004

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