Clinical Study Report

Issue Date: 11 September 2002

Prepared by: The R.W. Johnson Pharmaceutical Research Institute

Document No.: EDMS-USRA-6570212:2.0

Name of Sponsor/Company	The R.W. Johnson Pharmaceutical Research Institute.
Name of Finished Product	REGRANEX®
Name of Active Ingredient(s)	Becaplermin

Protocol No.: PRI/PDG-INT-5 (PDGF-DBFT-010) CR004156

Title of Study: A multicenter clinical evaluation of the safety follow-up of becaplermin or placebo gel following treatment of chronic, full thickness diabetic ulcers.

Coordinating Investigator: None

Publication (Reference): None.

Study Period: 27 July 1999 to 11 April 2001.

Phase of Development: 3

OBJECTIVES:

The primary objective of this study was to retrospectively evaluate the safety of sterile becaplermin gel versus sterile placebo gel treatment 12 months or more after the last dose was administered in one of 2 double-blind trials PDGF-DBFT-003 or PDGF-DBFT-005. The secondary objective of the trial was to evaluate recurrence of the Target Ulcer if it had healed in the previous trial.

METHODS:

This single-visit, retrospective study was designed to evaluate the long-term safety of becaplermin gel 100 µg/g versus placebo gel. Subjects previously enrolled in protocol PDGF-DBFT-003 or PDGF-DBFT-005 were evaluated during a single-study visit in which retrospective safety data were collected. Recurrence data on the Target Ulcer were also obtained. The maximum possible number of subjects in this study was 651, the sum of subjects from the 2 previous trials, PDGF-DBFT-003 and PDGF-DBFT-005. A combined total of approximately 500 subjects were expected to be enrolled overall, allowing for failure to trace some subjects from the previous studies. The investigators made every effort to contact all subjects enrolled in the previous double-blind trials in order to get follow-up information on as many subjects as possible. If the subject was deceased, the cause of death, if known, was collected by the investigator (where permitted by the local authorities). Subjects or legally authorized representatives signed an Informed Consent Form prior to any study-related procedures.

After evaluation of the entrance criteria, demographic data, significant new intercurrent illnesses, a current medication profile, therapies received for the treatment of any diabetic neuropathic foot ulcer in the past 12 or more months and surgeries in the last 12 or more months were collected and recorded. A questionnaire was used by the investigational staff to elicit subject information. At the visit, a complete physical examination was done (special attention was given to assess the presence of any malignancies), the feet were carefully examined and the footwear was assessed. The site of the Target Ulcer treated in the previous double-blind trial was assessed and photographs of the plantar, dorsal, medial and lateral surfaces of the foot, as well as a distance shot of the foot, were taken.

Number of Subjects (planned and analyzed):

In total 632 out of a possible 651 subjects were enrolled in this study following completion of PDGF-DBFT-003 and PDGF-DBFT-005. Of the 632 subjects, 491 (77.7%) had data available and were included in the evaluable population for this study (200 [76.6%] placebo subjects; 291 [78.4%] becaplermin subjects).

Diagnosis and Main Criteria for Inclusion:

Subjects eligible to enter into PDGF DBFT-010 were defined as those who were enrolled in PDGF-DBFT-003 or PDGF-DBFT-005 and had any postbaseline data in the previous study.

Inclusion Criteria

Subjects were required to satisfy the following criteria before entering the study: had given written informed consent prior to the performance of any study-related procedures. If the subject was deceased, the cause of death, if known, was collected by the investigator (where permitted by the local authorities); had received at least 1 dose of study medication in one of the double-blind trials PDGF-DBFT-003 or PDGF-DBFT-005 and had any post-baseline data; a minimum of 12 months had elapsed since last study drug dosing in one of the double-blind trials PDGF-DBFT-003 or PDGF-DBFT-005.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from participating in the study: subjects who were unwilling to participate; subjects who, despite multiple and documented efforts, could not be contacted. The investigator was asked to try at least 3 times to contact the subject or subject's representative or parents by mail and phone.

Test Product, Dose and Mode of Administration, Batch No.: Not applicable.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable**.**

Duration of Treatment: Not applicable.

CRITERIA FOR EVALUATION:

The following safety evaluations were performed to measure the long-term safety and tolerability of becaplermin 100 µg/g or placebo gel: physical examination; assessment of ulcer recurrences; significant new intercurrent illnesses; major surgeries; incidence and severity of tumorigenic events. Safety data were summarized for all subjects enrolled who received at least 1 dose of study medication in 1 of the double-blind trials (PDGF-DBFT-003 or PDGF-DBFT-005) and had any postbaseline data. Adverse event reporting was not relevant in this study, since more than 1 year had elapsed since the last treatment with study medication

STATISTICAL METHODS:

It was planned to prepare both interim and final analyses. The interim analysis was carried out with data from subjects who entered PDGF-DBFT-010 and had previously participated in study PDGF-DBFT-003. This interim analysis was required for regulatory submission purposes. Subjects who previously participated in either study PDGF-DBFT-003 or PDGF-DBFT-005 were included in the final analysis. Any subject who was eligible for entry into this study and had information recorded in the case report form (CRF) beyond page 2 (Demographics, study history, and methods of data collection) was included in the evaluation of safety. Subjects who entered the study more than 1 month (30 days) early were to be listed separately. These subjects were not to be excluded from the safety evaluation.

1. ANALYSES PLANNED

The treatment groups for all summaries were becaplermin 100 µg/g and placebo, as determined by the treatment assignment in the previous trial. The incidence (frequency and percent) of tumors (specifically cutaneous), skin changes in the areas surrounding the previously treated Target Ulcer, and cardiovascular events were summarized by event and by treatment group in the previous double-blind trial. No inferential statistical analyses were planned. Summaries of the occurrences were stratified by 6-month intervals based on the time between onset and the last dose of study drug: 1 to 6, 7 to 12, 13 to 18, 19 to 24, 25 to 30, 31 to 36 and 36 months or more after the last dose of study drug. The incidence (frequency and percent) of recurrence of the Target Ulcer was summarized by treatment group and compared descriptively. It was planned that the summary of recurrences of the Target Ulcer would be stratified based on recurrence within 1 year or less after the last treatment and greater than 1 year after last treatment. No inferential statistical analyses were planned.

2. ANALYSES PERFORMED

Information on recurrence of the Target Ulcer was summarized under safety evaluation, instead of efficacy evaluation as specified in the protocol. The incidence (frequency and percent) of recurrence of the Target Ulcer was summarized as planned, except the summary was stratified based on recurrence within 1 year or less *of the date of first healing of the Target Ulcer*, and greater than 1 year *since the date of first healing of the Target Ulcer* rather than stratifying on time since cessation of study medication. The stratification categories were further split to display the time to recurrence in 6-month intervals up to >36 months from time of healing.

Two codes additional to those detailed on the CRF were used for recording the type of significant cardiovascular events experienced on the database. The 'other' category on the CRF was subdivided into 'hypertension,' 'arrhythmia (nos)' and 'other' events in the database. Two locations additional to those detailed on the CRF, were used for recording the location of rashes and lesions on the database. The 'other' location on the CRF was subdivided into 'left leg/ankle,' 'right leg/ankle' and 'other' locations in the database.

All evaluable subjects were included in the denominator for the calculation of percentages (including missing data) for summary tables.

3. RETROSPECTIVE EVALUATIONS

A retrospective evaluation of the Target Ulcer location, and skin lesion(s) and rash(es) was performed by an independent dermatologist. These evaluations were not detailed in the original protocol. These additional evaluations were listed and summarized.

SAFETY RESULTS:

1. ADVERSE EVENTS

1.1. Deaths

Approximately one seventh of subjects (92) had died since the previous study completion although data was available for 11 of these and they were therefore included in the study. Mortality rates were similar between the two treatment groups (35 [13.4%] placebo group; 57 [15.4%] becaplermin group).

1.2. Neoplasms

The incidence of new or recurrent systemic and local neoplasms during the follow-up period was low in both treatment groups (8 [2.7%] in the becaplermin group compared with 2 [1.0%] in the placebo group).

1.3. Skin Rashes and Lesions

A comparable proportion of subjects in each treatment group had rashes at the time of the study visit (28 [9.6%] in the becaplermin group compared with 21 [10.5%] in the placebo group) but very few subjects had a rash near the Target Ulcer location.

Skin lesions were defined as any detectable pathological or traumatic deviations from the normal skin structure due to injury or disease. Overall a comparable proportion of subjects in each treatment group reported lesions since the cessation of study treatment (63 [21.6%] in the becaplermin group, 50 [25.0%] in the placebo group).

More than 80% of the subjects in each treatment group presenting with a rash or a lesion at the study visit had a retrospective evaluation performed by the independent dermatologist. Of these retrospective evaluations, only 1 subject (in the becaplermin group) had a presumptive diagnosis of pre-cancerous and there were no diagnoses of cancer.

1.4. Significant Cardiovascular Events

The incidence of significant cardiovascular events during the follow-up period was comparable between treatment groups (69 [34.5%] in the placebo group compared with 80 [27.5%] in the becaplermin group) with peripheral ischemia/ischemic necrosis being the most common event in both treatment groups. This is to be expected in subjects suffering from diabetic neuropathy. Most subjects reported one new event each.

Nearly a quarter (47 [23.5%] placebo group; 64 [22.0%] becaplermin group) of subjects in each treatment group had a lower extremity amputation. For most subjects the highest level of amputation was the toe, and similar results were seen in both treatment groups.

2. RECURRENCE OF THE TARGET ULCER

The recurrence rates in the placebo group were slightly higher than those in the becaplermin group (66 [28.7%] in the becaplermin group compared with 52 [33.1%] in the placebo group). The time to recurrence in both groups was in general within 6 months of healing. It should be remembered, however, that Target Ulcer recurrence is often the result of inadequate wound care, and cannot be solely attributed to compromised drug efficacy. The most common cause given for recurrence was trauma in PDGF-DBFT-003 and non-compliance with non-weight-bearing device in PDGF-DBFT-005. Retrospective evaluations of the Target Ulcer location were performed by the independent dermatologist. No subjects in the placebo group had a presumptive diagnosis of either cancerous or pre-cancerous. Three subjects (1.0%) in the becaplermin group had a presumptive diagnosis of cancer (subjects 537, 856 and 457), but no subjects were diagnosed as pre-cancerous.

STUDY LIMITATIONS:

More than 20% of each of the original treatment groups was unavailable for data collection at this safety follow-up visit. In addition, no formal comparisons have been made between the two treatment groups and so the results presented here should therefore be treated appropriately. Moreover, the interpretation of the cancer data is complex since the PDGF-DBFT-010 was conducted only in western and southern Europe. It is well recognized that the incidences of certain cancers may vary among countries and geographic areas for many reasons.

CONCLUSION:

The descriptive comparisons on evaluable subjects appear to show only small differences between subjects previously treated with becaplermin or placebo with regards to cardiovascular events, deaths, neoplasms and skin rashes and lesions. As no formal methods have been used this difference cannot be quantified. The incidence of new neoplasms was low in both groups and the incidence of cardiovascular events was similar in both groups. Overall the data suggest that the use of becaplermin gel for treatment of chronic, full thickness diabetic ulcers is safe, and there are no long-term (up to 3 years) safety problems. The rates for recurrence of target ulcer were also similar in subjects previously treated with becaplermin or placebo.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.