BRIEF SUMMARY OF REGRANEX-EPI-01

A Cohort Study of the Risk of Cancer in Users of REGRANEX® (becaplermin) and Matched Comparators

This brief summary was generated by the Medical Affairs department of Ethicon, Inc. and the Epidemiology department of Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

Study initiated Jan 2003, completed May 2005

Objectives:
To assess the incidence of cancer in REGRANEX® (becaplermin) users compared to similar patients who did not use REGRANEX®.

Methods:
A comparative, retrospective cohort study was performed utilizing the administrative, pharmacy and medical claims databases of United Healthcare, a large national healthcare insurance plan with representation across the United States with further follow-up using the National Death Index.

Selection of REGRANEX® user cohort
All subjects in the database with a pharmacy claim for REGRANEX® from January 1, 1998 through June 30, 2003 were identified. Subjects with fewer than 6 months in the database prior to the claim for REGRANEX® were excluded as were any subjects younger than 20 years of age at the time of the first REGRANEX® dispensing or any subject with a diagnosis of cancer during the 6-month baseline period. This initial REGRANEX® cohort was characterized in terms of their top 8 diagnoses using ICD-9 codes. The 8 diagnoses were ulcer of the skin (ICD-9 707), diabetes (ICD-9 250), open wound of the foot (ICD-9 892), soft tissue disorder (ICD-9 729), osteomyelitis (ICD-9 730), other peripheral vascular disorder (ICD-9 443), symptoms involving skin/other integument symptoms (ICD-9 782), and dermatophytosis (ICD-9 110).

Propensity score model for matching users to non-users
Propensity score models allow for matching populations in retrospective studies where randomization cannot be performed. In this case, a propensity score model was used to create 2 cohorts of subjects who were similar with regard to a wide range of characteristics associated with receiving REGRANEX® but differing specifically in whether REGRANEX® was actually received or not. The intent is to control for those characteristics that might distort the apparent association between exposure to REGRANEX® and risk of subsequent cancer.

The initial REGRANEX® cohort was analyzed to identify a wide variety of characteristics that may have been associated with prescribing REGRANEX® (predictors of therapy). There were over 100 identified characteristics that included patient demographics, pre-existing diagnoses, procedures, prior drug use, and baseline healthcare

utilization variables. Using logistic regression analyses, these characteristics were used to create a calendar-year-specific propensity score model that included all characteristics that were significantly different between REGRANEX® users and non-users. The propensity score was estimated for all subjects as the probability of being prescribed REGRANEX® regardless of the subject's actual exposure status.

Selection of the non-user cohort
Subjects with no pharmacy claim for REGRANEX® and with documentation for any 1 of the 8 diagnoses identified in the REGRANEX® cohort were selected for a starting pool of non-user comparators. Each REGRANEX® user was then matched with up to 2 non-users based on having the same propensity score (ie, the matched non-users had the same probability of receiving REGRANEX® based on their profile of identified characteristics, but did not actually receive it).

Final cohorts
Three thousand-five-hundred-seventy-five (3,575) subjects who initiated REGRANEX® between January 1, 1998 and June 30, 2003 were identified. This pool was reduced to 2,102 based on the aforementioned exclusion criteria, with the primary reason for exclusion being less than 6 months enrollment prior to the first dispensing of REGRANEX® One thousand-six-hundred-twenty-two (1,622) REGRANEX® users from this group were matched to subjects from the pool of potential non-user comparators. Not every REGRANEX® user could be matched to 2 non-user comparators, so the final number of non-users was 2,809. The remaining 480 REGRANEX® users could not be matched to a non-user. The index date was defined for the exposed cohort as the date of the start of the REGRANEX® prescription. For each non-exposed subject, an index date was chosen randomly from among the index dates of the included exposed subjects.

Study outcomes measured:
The 1,622 REGRANEX® users, 2,809 non-user comparators and 480 unmatched users were then followed for incidence of neoplasms of all kinds and for cancer mortality.

Exposed subjects entered the cohort on the date of filling their first prescription. The unexposed comparators entered the cohort on the same day as the exposed subject to whom they were matched. Subjects were followed for cancer incidence from the date of cohort entry to the earliest of: diagnosis of a study outcome, disenrollment from the health plan, or end of study, and for cancer mortality were followed until death or end of study. Average follow-up for cancer incidence was 20 months, and for cancer mortality was 36 months.

Incident neoplasms were identified by searching subjects' insurance claims for ICD-9 codes specific for neoplasms (140-239), as well as CPT procedure codes that might have been associated with a neoplasm. Candidate cases from this search were then subjected to further review and medical records abstraction. Medical records were reviewed by 1 of 3 clinical reviewers with expertise in internal medicine and oncology. These reviewers looked for evidence of a biopsy or pathology reports that were positive

for a malignant tumor, checked radiology reports, looked for documentation of chemotherapy or radiation therapy or surgical removal of a cancer. Neoplasms diagnosed more than 90 days apart in the same patient were considered separate cases.

Cancer mortality was identified by matching study subjects on social security numbers, names, birth dates, sex, marital status, residence and other characteristics with individuals included in the rosters of the National Death Index (NDI). The NDI provides cause of death codes for multiple underlying causes of death.

Cancer incidence rate ratios between user and non-users were estimated in 2 ways: "as matched" and separately, "as exposed". The "as matched" analysis is similar in spirit to an intent-to-treat analysis in a clinical trial. The "as-exposed" analysis was used to account for subjects who were initially identified as non-users but who became users during their follow-up period (ie, a REGRANEX® user remained a user throughout the follow-up period but a non-user could subsequently become a REGRANEX® user). The "as exposed" analysis estimated the relative risk of cancer according to cumulative exposure to REGRANEX®. The number of REGRANEX® dispensings identified from the pharmacy claims during the follow-up period was used to estimate cumulative exposure. Subjects with a similar number of dispensings of REGRANEX® were grouped into categories; their exposure time was pooled together as person-years and cancer incidence outcomes were assigned to categories of exposure. This analysis accounts for changes in REGRANEX® exposure over time, however, unlike the subjects in the as-matched analyses, subjects in the as-exposed analyses may not be well matched for the characteristics that contributed to the propensity score. Because exposed and non-exposed subjects were not matched on wound size or other features that may have been associated with the number of tubes dispensed, it is possible that subjects exposed to 3 or more tubes may differ in important ways from their matched unexposed subjects.

Results:

Cancer incidence

Four hundred-twenty-six (426) insurance claims that were possibly compatible with incidence of neoplasms were identified (163 in REGRANEX® users and 263 in non-users) and subjected to medical record abstraction and expert clinical review. Clinical reviewers classified 133 (31.2%) of these possible cases as confirmed cancers. All cancers were remote from the site of application in the REGRANEX® user cohort. Of these 133 confirmed cancer cases, 47 occurred in the REGRANEX® users (2.9% of total cohort) and 86 in the non-users comparators (3% of total cohort). Incidence rates between the 2 cohorts were computed as events per 1,000 person-years.

In the "as matched" analysis, the cancer incidence rate ratio between REGRANEX® users and non-users was 1.2 (95% CI = 0.7-1.9). The rate ratio indicated a minimal increase in cancer incidence, however the confidence interval contained the null value and indicated an unreliable or non-significant finding.

The "as exposed" analysis also indicated no significantly elevated risk for cancer incidence. The rate ratio for incidence of all malignant neoplasms between subjects with a single REGRANEX® dispensing versus non-users was 1.3 (95% CI= 0.7-2.2); for subjects with 2 dispensings the rate ratio was 0.8 (95% CI= 0.3-2.4) and for subjects with 3 or more dispensings the rate ratio was 1.1 (85% CI= 0.4-2.8).

Overall, these findings were consistent with chance and with residual confounding due to factors that could not be captured in the propensity score such as wound size, race, obesity, and smoking (none of these factors were available in the healthcare claims database).

Cancer mortality
The NDI search identified 158 deceased study subjects; in 16 of whom death was documented as due to a malignant neoplasm. Eight of these deaths were among REGRANEX® users and 8 were among non-users. Of these 16 cancer deaths, 9 of the cases had been identified through the claims identification and medical records abstraction process.

When exposure time was accounted for among the 16 cancer deaths, the rate ratio for risk of death from cancer between all REGRANEX® users and non-users was 1.9 (95% CI= 0.7 – 5.0).

When cumulative exposure to REGRANEX® was considered, 4 of the 8 deaths were in users with a single dispensing, none in users with 2 dispensings and 4 in users with 3 or more dispensings. Compared to non-users, the rate ratio for cancer death in users with a single dispensing was 1.5 (95% CI= 0.4 – 4.9), for those with 2 dispensings the rate ratio was indeterminate (no observed deaths in the either the exposed or non-exposed group), and for users with 3 or more dispensings the rate ratio was 5.2 (95% CI = 1.6 – 17.6). The latter finding of elevated risk in the highest exposure group of users was statistically significant, however the confidence interval was wide and the estimate was based on few observations (4 deaths), so it might reflect either a chance finding or bias due to residual confounding.

Conclusions:
In general, the results of this study were consistent with no increased incidence of cancer among REGRANEX® users relative to non-user comparators. Cumulative exposures to REGRANEX® did not appear to be associated with an increased risk of cancer incidence as there was no significant increase in the relative risk comparing subjects with 1, 2, or 3 or more dispensings.

The rate of cancer mortality showed a statistically significant increase in the highest exposure group (users with 3 more dispensings), but this observation was based on a small number of exposed cases.

Adverse events:

Not applicable in this study

Additional Follow-up

An additional analysis was done to assess the potential for confounding in the original analysis of outcome according to cumulative REGRANEX® exposure and to estimate the relative rates with increased precision. Patients who received no REGRANEX® were compared to those who received progressively more dispensings of REGRANEX® (1, 2, and 3 or more) in a cumulative dose analysis. REGRANEX® initiators and matched comparators were enrolled into annual matched cohorts and all patients were followed until diagnosis of cancer, death, disenrollment from the health plan, or the end of the study period (December 31, 2003). Among REGRANEX® initiators with no matches, 28.3% had 3 or more becaplermin dispensings compared to 25.6% of becaplermin initiators with 1 match and 19.9% with 2 matches. This gradient in the number of matches across cumulative REGRANEX® exposure categories such that higher exposure categories (2 or 3+ dispensings) had fewer matches than the lowest exposure category, and the lowest exposure category (1dispensing) had more matches than the higher categories. This suggests that analyses across these categories would need to account for potential confounding, and the magnitude of the difference in the proportion of matches across the categories provides insight into the magnitude of difference in rates that might be attributable to confounding.

An extension of the study cohort's follow-up for cancer mortality, not planned as part of the original study, examined NDI data to identify all cancer deaths through 2006. Person-years were accumulated from date of entry into the cohort until the earlier of death or the end of the NDI period (December 31, 2006). Patients were not censored upon the end of their enrollment in the health plan. Cumulative exposures to REGRANEX® did not appear to be associated with cancer mortality, as there was no increase in the relative risk comparing different cumulative dose levels (relative risk (RR) = 0.7, 95% confidence interval (CI) = 0.3-2.2 for subjects with 1 REGRANEX® (becaplermin) dispensing compared to those with none, RR = 0.6, 95% CI = 0.1 4.2 for subjects with 2 REGRANEX® dispensings compared to those with none, and RR =2.4, 95% CI = 0.8-7.4 for subjects with 3 or more REGRANEX® dispensings compared to those with none). When REGRANEX® dispensings are collapsed, there was no increase in the relative risk between comparators and REGRANEX ® initiators (unadjusted RR=1.0, 95% CI=0.4-2.2 and adjusted RR 1.0, 95% CI=0.5-2.3). These results indicated that the earlier finding of an elevated risk of cancer mortality among REGRANEX® users in the highest cumulative dose category is attenuated by additional follow-up data. The narrower confidence intervals around the estimates based on analyses incorporating these additional data reflect the greater statistical power of this study extension and indicate the range of plausible alternative conclusions.

In addition to the above extension of the cohort's follow-up for cancer mortality, there was an extension of the exposure follow-up for the cancer deaths. Like the extension of the mortality follow-up, this exposure follow-up was not planned as part of the original study. It was intended to ascertain whether any of the cancer deaths classified as having a less than maximal exposure as of the end of the initial study might have acquired

additional exposure afterward. It examined the all exposure data available through 2006 for each of the 21 subjects who died of cancer and, as of the end of the initial study, were classified as unexposed or exposed to 1 or 2 tubes of REGRANEX®, ie, the subjects for whom additional exposure information might change their classification. It found no record in the database for 2004-2006 of any additional exposure to becaplermin among these 21 subjects. It also estimated extent to which these 21 subjects were enrolled in plans covered by the database during this additional follow-up period. It found for these 21 subjects that "The mean fraction of follow-up person-time with complete exposure information across all subjects was 0.95. The subset of deaths occurring among subjects who did not have complete exposure information (3 unexposed and 2 exposed subjects) had a mean fraction of follow-up person-time with exposure information of 0.81."

Study Limitations:

The healthcare claims database did not include factors such as race, wound size, obesity, smoker status that could represent residual confounding in the comparative results.

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