SYNOPSIS

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Name of Sponsor/Company	Centocor Research and Development, Inc.
Name of Finished Product	REMICADE
Name of Active Ingredient(s)	infliximab

Protocol No.: C0168T70

Title of Study: A Multicenter, Observational Study of the Long-term Safety of Infliximab (REMICADE®) in Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Name: RESULTS COPD: REMICADE Safety Under Long term Study in COPD

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Publication (Reference): None.

Study Period: The C0168T70 study initiated (first patient in) on 16 Apr 2006, and completed (last patient visit) on 15 Dec 2009. The database was locked on 27 Jan 2010.

Phase of Development: Observational long-term safety follow-up study.

Objectives: To evaluate long-term safety information on deaths and malignancies for subjects who have participated in clinical studies of infliximab in the treatment of COPD.

Methods: Information on deaths and malignancies was collected twice yearly for a period of 5 years from each subject's last safety visit in the primary study. The last safety visit in the primary study was defined as the last visit for each subject during which AEs were recorded in the primary study. A primary study is defined as a Centocor-sponsored study that evaluated infliximab on an investigational basis and that was identified, a priori, by the Sponsor or health authorities as requiring long term safety follow-up in the C0168T70 RESULTS COPD study (see below). The study was designed such that all subjects would begin participation in the C0168T70 as soon after the time of their last safety visit in the primary study and would be followed for a total duration of 5 years after each respective subject's last safety visit in the primary study. However, there was a gap period between the end of the C0168T54 study (the last subject completed the Week 44 visit on 03 Dec 2004) and the commencement of the C0168T70 study (16 Apr 2006), during which safety events (death and malignancy) were reported spontaneously to the Sponsor.

Number of Subjects (planned and analyzed): A total of 43 sites and 272 subjects participated in the 3 primary studies in COPD (C0168T54, EU0016 C0168X09, and EU0073 C0168X57). These 43 sites included 41 sites in the US that participated in the C0168T54 study (n = 234 subjects) and 2 sites in the Netherlands which conducted IISs (EU0016 C0168X09 [n = 22] and EU0073 C0168X57 [n = 16]). Of the 43 sites that participated in the 3 primary studies, 19 sites [17 in the US and the 2 in the Netherlands which conducted the IISs] opted not to participate in the C0168T70 study. Thus, the C0168T70 was only conducted in the US, and the "primary study" refers to only the C0168T54 study. Long-term safety follow-up data was available for 107 of the 234 subjects who participated in the primary study (C0168T54).

Diagnosis and Main Criteria for Inclusion: Subjects must have received at least 1 dose of study agent (ie, placebo or infliximab) in the primary studies (C0168T54, EU0016 C0168X09, and EU0073 C0168X57) to have been eligible for participation in this long-term follow-up study.

Test Product, Dose and Mode of Administration, Batch No.: No study agent was administered during the C0168T70 study. The primary study, C0168T54, was a randomized double blind-study in which subjects were assigned in a 1:1:1 ratio via an IVRS to 1 of 3 treatment groups (placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg).

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

Duration of Treatment: No study agent was administered during the C0168T70 RESULTS COPD study. Subjects received study agent through Week 24 in the primary study (C0168T54).

Criteria for Evaluation: Subjects must have received at least 1 dose of study agent (ie, placebo or infliximab) in the primary studies to have been eligible for participation in this long-term follow-up study.

Statistical Methods: C0168T70 RESULTS COPD is a long-term observational study for collecting additional safety data on subjects from studies of infliximab in COPD. No formal hypothesis was planned; however, comparative statistics such as hazard ratios and their confidence intervals were computed. Data analyses are provided for each treatment group (placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg) and for the combined infliximab treatment group. Statistical comparisons were made between the placebo and individual infliximab treatment groups, as well as between the placebo and combined infliximab treatment group. For categorical data, counts and percentages were used to describe the data. For continuous variables, descriptive statistics (mean, median, standard deviation and range) were provided.

Analyses were performed using 2 populations:

- all subjects who were treated in the primary study with long-term safety information (ie, subjects with data spontaneously reported to the sponsor during the gap in addition to subjects who consented to participate in the C0168T70 RESULTS COPD study)
- all treated subjects in the primary study (C0168T54)

Subjects were analyzed according the treatment received in the primary study. Data from the following time periods were pooled for the analyses:

- Primary study (C0168T54) through Week 44.
- Gap: The time period between the end of the primary study (C0168T54) and the beginning of the long-term safety follow-up C0168T70 RESULTS COPD study.
- Long-term safety follow-up study through the final visit in C0168T70.

Primary analysis:

The 2 co-primary endpoints of this study are:

- the number of subjects with a malignancy through all available follow-up, and
- the number of subjects who died through all available follow-up

The primary population for primary endpoint analysis is all subjects who were treated in the primary study.

Secondary analyses:

The number of subjects with a malignancy according to malignancy type was summarized by the treatment received during the primary study for all subjects who were treated in the primary study. The hazard ratios

for malignancies for the infliximab 3 mg/kg group versus placebo group, infliximab 5 mg/kg group versus placebo group, and combined infliximab group versus placebo group along with their 95% confidence intervals (CIs) were computed. The hazard ratio is based on the Cox proportional hazards model using treatment as the only covariate. The Kaplan-Meier estimates of the cumulative incidence of malignancies were also provided.

The hazard ratios for death for infliximab 3 mg/kg versus placebo, infliximab 5 mg/kg versus placebo, and combined infliximab versus placebo, along with their 95% confidence intervals (CIs) were computed for all subjects treated in the primary study. The hazard ratio is based on the Cox proportional hazards model using treatment as the only covariate. Data from subjects who did not die were censored at the subject's last follow-up visit date. The Kaplan-Meier estimates of the cumulative incidence of death are also provided.

Summaries of the following are provided:

- Subjects' baseline demographic and baseline characteristics by the actual treatment received in the primary study (C0168T54)
- Subject status in the C0168T70 RESULTS COPD study is provided by the treatment received in the primary study (C0168T54)
- Total subject-years of follow-up during the primary study and during the C0168T70 RESULTS COPD by treatment received during the primary study (C0168T54)
- Number of subjects who terminated study participation in the C0168T70 RESULTS COPD study for subjects with long-term safety follow-up information
- Exposure to study agent during the primary study (C0168T54) for all subjects with long-term safety follow-up information
- Subjects receiving commercial REMICADE® or anti-TNFα therapy other than REMICADE® at entry in the C0168T70 RESULTS COPD study by treatment received during the primary study (C0168T54).

RESULTS:

- A larger number of subjects in the infliximab 3 mg/kg group were reported to have developed malignancies compared with the infliximab 5 mg/kg and placebo groups.
- The incidence of malignancies per subject-year is greater in the infliximab 3 mg/kg group compared with the placebo group, and is similar between the infliximab 5 mg/kg and placebo groups.
- Malignancies commonly found in smokers (ie lung cancers and head and neck cancers) tended to occur more commonly in those treated with infliximab, whereas other malignancies tended to occur more commonly in the placebo group.
- A larger number of subjects in the infliximab group 5 mg/kg died compared with the infliximab 3 mg/kg and placebo groups, but this number was driven largely by a larger number of subjects that died in the infliximab 5 mg/kg group during the gap reporting period.
- The incidence of deaths per subject-year is greater in the infliximab 5 mg/kg group compared with the placebo group, and is similar between the infliximab 3 mg/kg and placebo groups. A total of 26 subjects died, 5 of whom died due to unknown causes. The remaining subjects died due to a variety of causes consistent with the demographics and disease comorbidities present in this population of subjects with COPD.

STUDY LIMITATIONS: This study is limited by its nature (observational study), spontaneous reporting during the study gap, and the fact that not all eligible sites and/or subjects participated. In some cases, due to the small number of events, results must be interpreted with caution.

CONCLUSIONS: In conclusion, the results of the C0168T70 RESULTS COPD study indicate that the disparity of excess malignancies observed during the 44 weeks of the C0168T54 study in both infliximab treated groups compared to the placebo group tended to diminish over the extended follow up period in the C0168T70 RESULTS COPD study. Of the malignancies observed during follow up, there tended to be more smoking related malignancies in the infliximab groups and fewer of the other types of malignancies in the infliximab groups. There also appeared to be a trend for more deaths in the 5 mg/kg infliximab group during follow up, with a similar incidence of death in the placebo and 3mg/kg infliximab groups. As a result of the limitations of the C0168T70 study (ie observational nature of the study, spontaneous reporting during the gap period, and the fact that less than half of the eligible subjects from the 3 primary studies of infliximab in COPD participated in the long term follow up), more definitive conclusions regarding the impact of infliximab on the development of malignancies and death in patients with COPD based solely on the results of this small study cannot be drawn.

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