# Synopsis (Protocol C0168T68)

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| **Name of Sponsor/Company:** Centocor, Inc | | |

**Protocol:** C0168T68

**Title of the Registry Review:** A Review of Reports of Lymphoma Occurring in Patients with Rheumatoid Arthritis or Crohn's Disease in Centocor-Sponsored and Centocor-Supported Disease Registries

**Registries Included:**
1. Therapy Resource Evaluation and Assessment Tool (TREAT™) Registry of Crohn's Disease,
2. Consortium of Rheumatology Researchers of North America, Inc. (CORRONA),
3. National Data Bank for Rheumatic Diseases (NDB)

**Publications (based on this report):** None

**Data Accrual Period:** 01 Jan 1976 - 31 Dec 2005
**Retrospective Lymphoma Data Collection Period:** 01 Jan 1999 - 31 Dec 2005
**Case Report Form Collection Period:** 29 Jun 2006 - 21 Aug 2006

**Objectives:**
- To estimate the occurrence of lymphoma in patients enrolled in TREAT, CORRONA, and NDB who were diagnosed with CD or RA;
- To estimate the risk of lymphoma in relevant registry patient populations, including patients not exposed to anti-TNFα therapies, patients exposed to infliximab, patients exposed to anti-TNFα therapies, and exposed to immunosuppressants including corticosteroids with or without exposure to anti-TNFα therapies; and
- To evaluate available data on tissue samples from individual lymphoma cases to evaluate the association of EBV with the development of lymphoma. While evaluating the association of EBV with the development of lymphoma was an original objective of this study, this information could not be obtained.

**Methodology:** A retrospective review of data from CD patients entered into a Centocor-sponsored registry, the TREAT Registry, and from RA patients from 2 Centocor-supported registries, the CORRONA Registry and NDB Registry, was conducted to determine the occurrence of lymphoma in patients treated with infliximab and/or other therapies for RA or CD.

**Number of Patients:** Data were available for 6,273 CD patients from the TREAT Registry, and for more than 33,620 RA patients from the CORRONA Registry and NDB Registry.

**Diagnosis and Main Criteria for Inclusion:** Data for patients with CD or RA who participated in the specified registries from 01 Jan 1999 through 31 Dec 2005 were included in the analyses. For the lymphoma analysis, patients reported as having had a lymphoma during their participation in 1 of these registries were included in the analysis with the exception of data for 5 patients whose CRFs were not received until after the database lock (21 Aug 2006).

**Criteria for Evaluation:** Data for patients with CD or RA who participated in the specified registries were included in the analysis. In the lymphoma analyses, patients must have had a report of lymphoma during their participation in 1 of these registries.

**Data Collection:** Demographics, clinical disease management including types of therapy, exposure to immunosuppressants, including biologics, baseline disease activity, and lymphoma characteristics, diagnosis date, type of lymphoma, stage of disease, treatments administered, and current status were collected.

**Statistical Methods:** Descriptive statistics and statistical comparisons were performed using data from patients in the lymphoma cohort for each registry. In the lymphoma cohort, the incidence calculations for the exposure groups exclude data for any patient whose report of lymphoma occurred prior to exposure.

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Descriptive statistics were used to summarize baseline demographic and disease characteristics, including age, gender, height, weight, race, smoking history, disease duration, and medication history among patients in the lymphoma cohort of each registry. Continuous variables were summarized by descriptive statistics (number, mean, standard deviation, minimum and maximum). Categorical variables were summarized by the frequency and percentage in each category.

The primary analyses evaluated the incidence of lymphoma in each registry with respect to each exposure category. The difference in the incidence rates in the exposure groups were compared with that of the non-exposed control group (ie, patients naive to anti-TNFα therapies) using either the chi-square test or Fisher's exact test as appropriate, and the 95% confidence intervals for the difference in incidence rates were determined. An asymptotic 95% confidence interval was determined when the chi square test was used, while an exact 95% confidence interval was determined whenever the Fisher's exact test was required. Additionally, for each registry, the standardized incidence ratio (SIR) comparing the observed registry lymphoma rate to the lymphoma rate derived from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Age, gender, and race adjustment was applied to each SIR value. The SIR values were determined by the investigators at each of the respective registries. All tests of hypotheses were 2-sided and were at the 5% level of significance.

**SUMMARY – CONCLUSIONS**

**Registry Review Population Results:** During the data collection period for this registry study, data for 39,893 patients were accrued from the 3 registries and comprised the overall registry population. A total of 23,167 and 10,453 patients with confirmed diagnosis of RA were enrolled in the NDB and CORRONA Registries, respectively. A total of 6,273 patients with confirmed diagnosis of CD were enrolled in the TREAT Registry.

**Analysis of Lymphoma Cases:**
In each registry, the number of patients with lymphoma who were exposed to anti-TNFα therapy (infliximab or other anti-TNFα therapy) was comparable to the number of patients who were in the non-exposed control group (ie, those naive to anti-TNFα therapy), each corresponding to approximately half of the populations in each registry. Specifically, of the 23,167 patients in the NDB Registry, 11,050 (47.7%) were naive, and 12,117 (52.3%) were exposed to anti-TNFα therapy. Likewise, among the 10,453 patients in the CORRONA Registry, 5,142 (49.2%) were naive, and 5,311 (50.8%) were exposed to anti-TNFα therapy. Similarly, of the 6,273 patients in the TREAT Registry, 2,999 (47.8%) were naive to TNFα therapy, and 3,274 (52.2%) were exposed to anti-TNFα therapy.

In the NDB Registry, there were 86 reports of lymphoma. The incidence of lymphoma among patients who were non-exposed, by virtue of being naive to anti-TNFα therapy (ie, the control group), was 0.38% compared with 0.36% among those who were exposed to anti-TNFα therapy and 0.40% among those who were exposed to infliximab. There was no significant difference in the incidence of lymphoma in either exposure group relative to the non-exposed group, $p = 0.8321$ and 0.8640 for the anti-TNFα therapy-exposed group and the infliximab-exposed group, respectively.

In the CORRONA Registry, there were 6 reports of lymphoma, corresponding to an incidence of 0.039% among patients who were non-exposed to anti-TNFα therapy compared with 0.075% among those who were exposed to anti-TNFα therapy and 0.081% among those who were exposed to infliximab. There was no significant difference in the incidence of lymphoma in either exposure group relative to the non-exposed group, $p = 0.6877$ and 0.5991 for the anti-TNFα therapy-exposed group and the infliximab-exposed group, respectively.

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| As with the TREAT Registry, there were few (7) reports of lymphoma, corresponding to an incidence of 0.067% among patients who were non-exposed to anti-TNFα therapy compared with 0.153% among those who were exposed to anti-TNFα therapy and 0.154% among those who were exposed to infliximab. Similarly, there was no significant difference in the incidence of lymphoma in either exposure group relative to the non-exposed group, p = 0.4560 and 0.4555 for the anti-TNFα therapy-exposed group and the infliximab-exposed group, respectively. | | |
| **Conclusions:** The incidence of lymphoma among the 39,893 patients with RA and CD in these registries was 0.25%. In each registry, there were no statistically significant differences in the incidence of lymphoma when comparing patients who were naive to anti-TNFα agents with patients exposed to anti-TNFα agents, patients exposed to infliximab, or patients exposed to immunosuppressants with or without anti-TNFα therapies. | | |
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