# Synopsis (C0168T60)

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| **Name of Sponsor/Company:** Centocor, Inc | **Associated with Module 5.3 of the Dossier** | |
| **Name of Finished Product:** REMICADE® | | |
| **Name of Active Ingredient:** Infliximab | | |

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| **Protocol:** C0168T60 | **EudraCT No.:** 2004-000524-32 |

**Title of the study:** A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Anti-TNFα Monoclonal Antibody (Infliximab) to Treat Cancer-related Cachexia in Subjects with Pancreatic Cancer

**Principal/Coordinating Investigator(s):**

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| **United States**: | Daniel Von Hoff, MD, FACP, Arizona Cancer Center, 1515 N Campbell Ave., Tucson Arizona 85724 |
| **Germany**: | Prof. Stephan Rosewicz (until May 2004) and Prof. Bertram Wiedenmann (from May 2004) Campus Virchow Klinikum, Med. Klinik mit Schwerpunkt Hepathologie/Gastroenterologie, Berlin |
| **Belgium**: | Prof. Eric Van Cutsem, U. Z. Gasthuisberg Gastro-enterology, Leuven |
| **Italy**: | Prof. Giovanni Mantovani, Policlinico Universitario di Cagliari, Dip e Cattedra di Oncologia Medica, Monserrato |
| **The Netherlands**: | Prof. Dick Richel, Department of Internal Medicine, Academisch Medisch Centrum, Amsterdam |

**Study Center(s):** Overall 35 sites were initiated with 18 of these sites enrolling subjects: US (16 sites opened, with 6 sites enrolling subjects); Germany (7 sites opened, with 5 sites enrolling subjects), Belgium (3 sites opened, with all 3 enrolling subjects), Italy (4 sites opened, with 2 sites enrolling subjects), the Netherlands (3 sites opened, with 2 sites enrolling subjects); United Kingdom (2 sites opened, no subjects enrolled).

**Publication (reference)**: None

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| **Studied Period:** 07 May 2003/06 Feb 2006 | **Phase of Development:** 2 |

**Objectives:** The primary objective of the study was to evaluate the effect of treatment on subjects' loss of LBM, the critical hallmark of cancer-related cachexia. Secondary objectives included evaluation of the following:

- The safety of infliximab (including progression-free survival) when administered concomitantly with standard gemcitabine chemotherapy in this subject population
- The feasibility and utility of the 6MWT (ATS guideline) as an assessment of subjects' functional ability, and therefore an assessment of clinical benefit, during and following treatment of cancer-related cachexia
- The effect of study treatment on survival
- The effect of study treatment on subjects' quality of life
- The effect of study treatment on KPS
- The effect of study treatment on tumor response
- The 2 dose levels of infliximab in this subject population
- The pharmacokinetic and pharmacodynamic effect of infliximab in a subset of subjects
- The gemcitabine plasma concentration, if feasible, following the second infliximab infusion in the subset

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of subjects evaluated for pharmacokinetics/pharmacodynamics

**Methodology:** This was a Phase II, multicenter, randomized, double blind, placebo-controlled study, conducted to evaluate the efficacy and safety of REMICADE (infliximab) for the treatment of cancer-related cachexia. The study consisted of a Screening Period, a Study Treatment Period, an Extended Treatment Period for eligible subjects, a 6-Month Follow-up Period, and post study survival follow-up. After establishing eligibility during the Screening Period, subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment arms (placebo, 3 mg/kg infliximab, or 5 mg/kg infliximab, each of which was administered with gemcitabine) using an adaptive randomization method, with factors of documented weight loss over the 30 days immediately prior to randomization (≤ 5%, > 5%), tumor staging (II/III, IV), participation in the pharmacokinetic/ pharmacodynamic substudy (yes/no), and investigation site. Once randomized, subjects entered the Study Treatment Period during which they were to receive their randomized treatment for 5 cycles. The first cycle was 8 weeks in duration, and all subsequent cycles were 4 weeks in duration. At the end of the fifth cycle, subjects were to return for an End of Treatment Visit. If a subject had a response of stable disease or better at this time, they were eligible to receive extended treatment with their randomized treatment until disease progression. If a subject discontinued infliximab or placebo for any reason other than progressive disease, continued treatment with gemcitabine was permitted; however, in the event of progressive disease, all study treatments were to be stopped. Subjects were to return for follow-up visits at 2-month intervals for 6 months following their last treatment. Subjects were then to be contacted by telephone for survival every 2 months until death, until lost to follow-up, or until withdrawal of consent.

**Number of Subjects (Planned and Analyzed):**

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| Planned: | 90 subjects (30 per treatment arm) |
| Randomized: | 89 subjects (placebo: 30; 3 mg/kg infliximab: 30; 5 mg/kg infliximab: 29) |
| Treated: | 86 subjects (placebo: 30; 3 mg/kg infliximab: 28; 5 mg/kg infliximab: 28) |

**Diagnosis and Main Criteria for Inclusion:** Adult subjects were eligible for enrollment if they had newly diagnosed locally advanced or metastatic adenocarcinoma of the pancreas (Stages II to IV), were candidates for gemcitabine therapy, and reported unintended weight loss. The full list of entrance criteria are provided in the Protocol located in Appendix 1.

**Test Product, Dose and Mode of Administration, Batch Number:**

- 3 mg/kg infliximab + 1000 mg/m$^2$ gemcitabine
- 5 mg/kg infliximab + 1000 mg/m$^2$ gemcitabine

In the first cycle (8 weeks), subjects were to receive infliximab by IV infusion at Weeks 0, 2, and 4 and gemcitabine by IV infusion at Weeks 0, 1, 2, 3, 4, 5, and 6; no treatment was administered at Week 7. In all subsequent cycles (each 4 weeks), subjects were to receive infliximab by IV infusion at Week 0 and gemcitabine by IV infusion at Weeks 0, 1, and 2; no treatment was administered at Week 3. Lot numbers are provided in Attachments 1.2 and 1.3.

**Duration of Treatment:** The Study Treatment Period was 24 weeks in duration (Cycles 1 through 5); however, after the Study Treatment Period, subjects could continue to receive their randomized treatment until disease progression.

**Reference Therapy, Dose and Mode of Administration, Batch Number:**

- Placebo + 1000 mg/m$^2$ gemcitabine according to the same schedule as for the test products (see test product above). Lot numbers are provided in Attachments 1.2 and 1.3.

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**Criteria for Evaluation**

**Pharmacokinetics/Pharmacodynamics:** The primary pharmacokinetic parameters for infliximab evaluated in this study were the AUC, Cmax, CL, Vss, and terminal t1/2. Pharmacodynamic markers for evaluation included serum CRP, serum IL-6, sIL-2R, tumor necrosis factor alpha (TNF□), and CA19-9. Serum infliximab concentrations and pharmacodynamic markers were determined using individual ELISA methods. Subjects included in pharmacokinetic/pharmacodynamic analyses were those who had pre- and post treatment samples collected.

**Efficacy:** The primary efficacy endpoint was change in LBM from baseline to the end of the first cycle, as measured by BIA. Major secondary efficacy endpoints included change in 6MWT distance from baseline to the end of the first cycle, progression-free survival, overall survival, and KPS. Refer to Section **Error! Reference source not found.** for a list of efficacy endpoints. Efficacy was evaluated using an intent-to-treat approach, and therefore, all randomized subjects were included in these evaluations.

**Safety:** Safety was evaluated in this study through adverse events (AEs, all AEs regardless of toxicity, AEs of toxicity Grade 3 or higher [according to NCI CTC version 2.0], reasonably related AEs, serious AEs [SAEs], AEs resulting in discontinuation of study agent and/or gemcitabine, infusion reactions, delayed hypersensitivity reactions/anaphylactic reactions, and infections), laboratory tests, vital signs, and analysis of progression-free survival. All subjects who received any amount of study treatments were included in safety evaluations.

**Statistical Methods**: Continuous variables were summarized using descriptive statistics (mean, median, SD, and range) and comparisons among treatment arms were carried out using a rank test with van der Waerden scores. Quality of life scores were considered continuous variables. The detailed scoring algorithm can be found in the Statistical Analysis Plan (see Appendix 5). Categorical variables were summarized by frequency and percentage and were compared using the chi-square test or Fisher's exact test in case of rare events. Time to event variables were summarized by the survival rate at specific timepoints using the Kaplan-Meier method. The log-rank test was used to compare such variables among treatment arms. In addition, graphical display of survival was used to summarize the data. For a time variable potentially being interval censored, such as time to progression, the life table method was used to estimate the failure (success) rate for specific time intervals and the log-rank test for grouped survival data was used to test the difference among treatment arms.

**SUMMARY – CONCLUSIONS**

**Study Population Results:** Of the 89 subjects randomized, 48 (53.9%) were male and 41 (46.1%) were female, with a greater percentage of male subjects in the placebo group versus that observed in the active treatment groups (males - placebo: 20, 66.7%; 3 mg/kg infliximab: 13, 43.3%; and 5 mg/kg infliximab: 15, 51.7%). Most subjects were Caucasian (88, 98.9%). Median age was similar across groups (ranging from 61.5 to 66 years), as was median BMI (ranging from 22.62 to 23.46 kg/$m^2$), and median LBM (ranging from 42.76 to 53.92 kg). The majority of subjects had metastatic (from 82.8% to 90.0%) adenocarcinoma (from 96.6% to 100.0%), with more than half of all subjects in each treatment group having liver metastasis (from 60.0% to 65.5%). At baseline, each treatment group had a median pain score of 3. Across treatment groups, 36.7% to 37.9% of subjects were receiving a morphine equivalent of 0 to 49 mg/week; from 0 to 3.4% were receiving a morphine equivalent of 50 to 100 mg/week, and from 58.6% to 63.3% were receiving a morphine equivalent of more than 100 mg/week. Results of the baseline 6MWT indicated that the median walking distance was shorter among subjects in the 3 mg/kg infliximab group (330 meters) when compared with subjects in either the placebo or 5 mg/kg infliximab groups (360 and 380 meters, respectively).

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**Pharmacokinetic/Pharmacodynamic Results:** Of all subjects enrolled in the pharmacokinetic substudy, blood samples were collected from a total of 5 subjects (2 subjects in the placebo group, 2 subjects in the 3 mg/kg infliximab group, and 1 subject in the 5 mg/kg infliximab group); results of derived infliximab pharmacokinetic parameters are shown below:

| Infliximab Dose | Subject ID | Cmax g/mL | AUC g·day/mL | Vss mL/kg | CL mL/day/kg | t1/2 day |
|---|---|---|---|---|---|---|
| 3 mg/kg | 112-001 | 84.84 | 1008.25 | 35.10 | 2.98 | 4.81 |
| 3 mg/kg | 202-003 | 50.80 | 694.79 | 76.17 | 4.32 | 12.47 |
| | **Mean** | **67.82** | **851.52** | **55.63** | **3.65** | **8.64** |
| 5 mg/kg | 106-001 | 126.12 | 954.47 | 37.53 | 5.03 | 5.48 |

Pharmacodynamic evaluations indicated that some changes were observed following infliximab treatment; however, a clear treatment effect on serum CRP, serum IL-6, sIL-2R, TNFα, and CA19-9 could not be determined due to the small sample size in each dose cohort.

**Efficacy Results:** Subjects who received treatment with infliximab (3 mg/kg or 5 mg/kg) in combination with gemcitabine for the treatment of cancer-related cachexia showed no statistically significant evidence of treatment benefit versus placebo, as measured by analysis of the primary endpoint. The mean composite rank for change in LBM was 43.3 for placebo, 38.5 for 3 mg/kg infliximab, and 53.5 for 5 mg/kg infliximab.

Results generally were similar in subgroup analyses of the primary efficacy endpoint and analyses of major secondary efficacy endpoints. The median progression-free survival time was similar in the placebo and 5 mg/kg infliximab groups (3.5 and 3.9 months, respectively), but was lower in the 3 mg/kg infliximab group (2 months). The hazard ratio was 1.08 for the 3 mg/kg infliximab group vs. placebo group (95% confidence interval [CI]: 0.63 to 1.87). The hazard ratio was 0.99 for the infliximab 5 mg/kg group vs. placebo group (95% CI: 0.58 to 1.72). Median overall survival was similar in the placebo and the 5 mg/kg infliximab groups (7.4 and 7.3 months, respectively), but was lower in the 3 mg/kg infliximab group (5.3 months). The relative risk of dying was slightly lower in the 5 mg/kg infliximab group compared with the placebo group, with a hazard ratio of 0.89 (95% CI: 0.50 to 1.57), but was slightly higher in the 3 mg/kg infliximab group relative to the placebo group with a hazard ratio of 1.28 (95% CI: 0.74 to 2.22).

**Safety Results:**

***Exposure:*** Exposure to study agent (infliximab or placebo) and gemcitabine was similar in the placebo and 5 mg/kg infliximab groups, but was lower among subjects in the 3 mg/kg infliximab group.

| | Placebo | Infliximab | |
|---|---|---|---|
| | | 3 mg/kg | 5 mg/kg |
| Number of treated subjects | 30 | 28 | 28 |
| Study agent (placebo or infliximab) | | | |
| Median duration of exposure (weeks) | 13.0 | 4.21 | 12.14 |
| Median total infliximab dose (mg/kg) | 0 | 9.00 | 24.97 |
| Gemcitabine | | | |
| Median duration of exposure (weeks) | 14.14 | 6.07 | 15.57 |
| Median total gemcitabine dose ($mg/m^2$) | 11793.33 | 6363.30 | 12660.82 |

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***All Adverse Events Regardless of Toxicity or Relationship:*** During the Study Treatment Period, most subjects reported 1 or more AEs (placebo: 30, 100%; 3 mg/kg infliximab: 27, 96.4%; and 5 mg/kg infliximab: 28, 100%). No clinically meaningful trends were observed in the incidence or type of AEs reported with the possible exception of a greater frequency (difference between groups of ≥ 15.0%) of neutropenia, leucopenia, and fever among subjects in the 5 mg/kg infliximab group versus the placebo group. In addition, the difference between the 5 mg/kg infliximab and placebo groups in the percentage of subjects with thrombocytopenia was close to the cut-off of 15.0% (difference between groups 14.7%; values shown below). The greater frequency of neutropenia, fever, and leucopenia in the 5 mg/kg infliximab group did not appear to correspond to a greater frequency of infections, infections requiring treatment, infections of toxicity Grade 3 or higher, or serious infections. Further review of these events by toxicity grade (events of toxicity Grade 3 or higher), seriousness, and events resulting in an inability to continue treatment, ie, resulting in permanent discontinuation of study agent or gemcitabine, indicated no potential trends, with the possible exception of a greater frequency of Grade 3 neutropenia among subjects in the 5 mg/kg infliximab group.

| | **Number (%) of subjects** | | |
|---|---|---|---|
| | **Placebo** | **Infliximab** | |
| | | **3 mg/kg** | **5 mg/kg** |
| Number of treated subjects | 30 | 28 | 28 |
| Neutropenia | 16 (53.3) | 16 (57.1) | 21 (75.0) |
| Neutropenia of toxicity grade 3 or higher | 13 (43.3) | 13 (46.4) | 17 (60.7) |
| Serious neutropenia | 0 | 0 | 0 |
| Discontinuation of study agent due to neutropenia | 0 | 0 | 0 |
| Discontinuation of gemcitabine due to neutropenia | 0 | 0 | 1 (3.6) |
| Leucopenia | 15 (50.0) | 12 (42.9) | 19 (67.9) |
| Leucopenia of toxicity grade 3 or higher | 6 (20.0) | 6 (21.4) | 6 (21.4) |
| Serious leucopenia | 0 | 0 | 1 (3.6) |
| Discontinuation of study agent due to leucopenia | 0 | 0 | 0 |
| Discontinuation of gemcitabine due to leucopenia | 0 | 0 | 0 |
| Fever | 6 (20.0) | 5 (17.9) | 11 (39.3) |
| Fever of toxicity grade 3 or higher | 0 | 0 | 0 |
| Serious fever | 2 (6.7%) | 0 | 2 (7.1%) |
| Discontinuation of study agent due to fever | 0 | 0 | 0 |
| Discontinuation of gemcitabine due to fever | 0 | 0 | 0 |
| Thrombocytopenia | 17 (56.7) | 15 (53.6) | 20 (71.4) |
| Thrombocytopenia of toxicity grade 3 or higher | 0 | 2 (7.1) | 3 (10.7) |
| Serious thrombocytopenia | 0 | 0 | 0 |
| Discontinuation of study agent due to thrombocytopenia | 0 | 0 | 0 |
| Discontinuation of gemcitabine due to thrombocytopenia | 0 | 0 | 1 (3.6) |
| Infections | 15 (50.0) | 12 (42.9) | 12 (42.9) |
| Infections requiring oral or parenteral antimicrobial treatment | 15 (50.0) | 11 (39.3) | 12 (42.9) |
| Infections of toxicity grade 3 or higher | 5 (16.7) | 5 (17.9) | 5 (17.9) |

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| Serious infections | 7 (23.3) | 4 (14.3) | 5 (17.9) |

***Serious Adverse Events Including Deaths:*** SAEs were reported by generally similar percentages of subjects across treatment groups (placebo: 16, 53.3%; 3 mg/kg infliximab: 13, 46.4%; 5 mg/kg infliximab: 14, 50.0%). Overall, no trends were observed in the incidence or type of SAEs reported. Through the end of the second database lock (20 Mar 2006), 71 of the 86 treated subjects were reported to have died, including 27 subjects (90.0%) in the placebo group, 23 subjects (82.1%) in the 3 mg/kg infliximab group, and 21 subjects (75.0%) in the 5 mg/kg infliximab group. Most of these deaths were attributed to the underlying cancer and progression of disease. In addition, all deaths were assessed as unlikely to be related or not related to study treatments, with the exception of 1 subject in the 5 mg/kg infliximab group who died of interstitial pneumonitis after receiving 1 infusion of study agent. According to the investigator, this subject's death was possibly related to infliximab and gemcitabine.

***Other Significant Events:*** Additional AE analyses included a review of subjects who discontinued study agent and/or gemcitabine due to AEs, infusion reactions, delayed hypersensitivity/anaphylactic reactions, and infections during the Study Treatment Period. Overall, no clinically meaningful or unexpected trends were observed in these data.

| | **Number (%) of subjects** | | |
|---|---|---|---|
| | **Placebo** | **Infliximab** | |
| | | **3 mg/kg** | **5 mg/kg** |
| Number of subjects | 30 | 28 | 28 |
| Discontinuation of study agent due to AE | 6 (20.0) | 7 (25.0) | 5 (17.9) |
| Discontinuation of gemcitabine due to AE | 7 (23.3) | 7 (25.0) | 5 (17.9) |
| Infusion reaction | 0 | 1 (3.6) | 3 (10.7) |
| Delayed hypersensitivity/anaphylactic reaction | 0 | 0 | 0 |
| Infections | Refer to data shown above. | | |

***Adverse Events During Extended Administrations and the 2-Month Follow-up Period:*** For selected categories of AEs (AEs regardless of intensity or relationship, AEs of toxicity Grade 3 or higher, SAEs, and infections), data were examined also for events that occurred during extended administrations and/or during the 2-Month Follow-up Period. No clinically meaningful trends were apparent in the AEs reported during these time periods.

***Clinical Laboratory Test Results:*** Overall no trends were apparent in hematology data that suggested increased toxicity when gemcitabine was co-administered with infliximab, with the exception of a greater frequency of markedly abnormal decreases in neutrophil counts among subjects in the 5 mg/kg infliximab group (placebo: 12, 40.0%; 3 mg/kg infliximab: 12, 46.2%; 5 mg/kg infliximab: 17, 60.7%). When examined by maximum toxicity grade shift, results indicated that the number of subjects exhibiting a shift to Grade 4 similar among treatment groups (placebo: 3 subjects; 3 mg/kg infliximab: 4 subjects; 5 mg/kg infliximab: 4 subjects); whereas, a greater number of subjects in the 5 mg/kg infliximab group exhibited a shift to Grade 3 when compared with the placebo and 3 mg/kg infliximab groups (placebo: 9 subjects; 3 mg/kg infliximab: 8 subjects; 5 mg/kg infliximab: 13 subjects). Review of chemistry data suggested some trends toward a greater frequency of markedly abnormal elevations in alkaline phosphatase, ALT, and AST in 1 or both infliximab groups when compared with the placebo group; however, these results are not unexpected, as increased LFT have been observed in previous studies of infliximab. No trends were observed in the

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percentage of subjects with markedly abnormal total bilirubin values.

***Vital Signs:*** Overall, few subjects had markedly abnormal changes in vital signs (blood pressure, pulse, and temperature). No clinically meaningful trends were apparent in these data.

***Progression-free Survival:*** Results of this analysis indicated that subjects in the 3 mg/kg infliximab group had a shorter median duration of progression-free survival (1.91 months, 95% CI: 1.61, 5.06) than did subjects in the placebo (3.52 months, 95% CI: 2.76, 5.91) or 5 mg/kg infliximab (3.88 months, 95% CI: 3.45, 5.75) groups; however, no statistically significant differences were observed between the active treatment groups and placebo ($p \geq 0.850$).

**Conclusions:**

- Subjects who received treatment with 5 mg/kg infliximab in combination with gemcitabine for the treatment of cancer-related cachexia had a marginally greater increase in LBM when compared with placebo; in contrast, results among subjects who received 3 mg/kg infliximab appeared to be slightly worse than those who received placebo. The difference between the active treatment groups and placebo were not statistically significant.
- For the endpoints of progression-free survival and overall survival, results were similar between the 5 mg/kg infliximab group and the placebo group. In contrast, results among subjects in the 3 mg/kg infliximab group were slightly worse when compared with the placebo group. As observed for the primary endpoint, these differences were not statistically significant. Results generally were similar in analyses of other major secondary efficacy endpoints.
- Infliximab administered at 3 mg/kg or 5 mg/kg in combination with gemcitabine generally was well tolerated in adult subjects with pancreatic cancer and cancer-related cachexia defined by weight loss.
- Based on data from 3 subjects, pharmacokinetic evaluations indicated that the drug exposure (Cmax and AUC) increased with dose; drug accumulation was observed; there was no dramatic change for the t1/2 values; and due to the small sample size, it cannot be concluded whether CL and Vz were dose dependent.
- A clear treatment effect on pharmacodynamic markers including serum CRP, serum IL-6, sIL-2R, TNFα, and CA19-9 could not be determined due to the small sample size in each dose cohort.

**Date of Report:** 08 May 2007

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