Synopsis (C0328T01 Part 1)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		
Protocol: C0328T01	**EudraCT No.:** 2004-000546-20	
Title of the study: A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma		
Principal/Coordinating Investigator(s): The 2 participating investigators involved in the conduct of Part 1 of the study were Prof. Jean-Francois Rossi and Prof. Frans M.J. DeBruyne.		
Study Center(s): Prof. Rossi - CHU de Montpellier, Hôpital Lapeyronie, Montpellier, France. Prof. Frans M.J. DeBruyne - UMC St. Radboud, University Medical Center Nijmegen, The Netherlands.		
Publication (reference): Prabhakar U, Jang H, Jiao Q, Ford J, Miller B, Graham M, Davis H. Correlation of serum CNTO 328 anti-IL-6 monoclonal antibody concentrations and biomarker expression in renal cell carcinoma patients. *ASCO*. 2004. Abstract 2560.		
Studied Period: The first and last subjects treated in the 4 cohorts discussed in this report were enrolled (signed informed consent) between 23 Jun 2003 and 08 Nov 2004.		**Phase of Development:** Phase 1/2
Objectives: **Primary**: The primary objectives of Part 1 of the study were to assess the safety, toxicity, pharmacokinetics, and pharmacodynamics of CNTO 328 in subjects with metastatic renal cell carcinoma (RCC), so that 2 possible dose levels could be evaluated in Part 2. **Secondary**: The secondary objectives of Part 1 of the study were to assess the immunogenicity, clinical benefit, and quality of life benefit of CNTO 328 in subjects with metastatic RCC.		
Methodology: Part 1 of this 3-part study was an open-label, dose escalation study of CNTO 328 administered at 4 dose levels (1, 3, 6, and 12 mg/kg) to confirm a regimen for Part 2 and for extended dosing. The study consisted of 3 periods: Screening, Treatment, and Follow-up. During the Treatment Period, the 4 dose levels were evaluated to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of CNTO 328. The SMC evaluated the study for DLTs through an assessment of the data collected 48 hours postadministration following the first infusion. Dose escalation or de-escalation at each dose level was based on the number of subjects with DLT attributable to CNTO 328. Dose escalation proceeded only after a dose level was determined to be safe and tolerable. Determination of the MTD of CNTO 328 was based on the number of subjects experiencing any DLT attributable to CNTO 328. Subjects returned to the site for physical examinations, adverse event (AE) evaluation, pharmacokinetic, pharmacodynamic, and laboratory assessments at protocol specified times between scheduled administrations. A full pharmacokinetic profile was required for all subjects after the first and fourth administration, with peak and trough concentration assessments performed on samples from all other administrations. Any subject who received any part of an infusion was considered evaluable for safety, pharmacokinetics, pharmacodynamics, and response to treatment. An additional 4 doses could be administered if a subject was responding to treatment with at least stable disease. After the last dose of study agent, subjects entered a 6-week follow-up period for pharmacokinetics, pharmacodynamics, and immune response evaluations. Immune response was also measured at 12, 18, and 24 weeks after the last dose of study agent. Subjects were to be followed for up to 1 year after the last dose for survival.		

Synopsis (C0328T01 Part 1)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

Number of Subjects (Planned and Analyzed): Three to 21 subjects were planned for Part 1, allowing for cohort expansion in the event of a DLT. In total, 11 subjects were enrolled in the 4 cohorts: 1 mg/kg (1 subject), 3 mg/kg (3 subjects), 6 mg/kg (3 subjects), and 12 mg/kg (4 subjects).

Diagnosis and Main Criteria for Inclusion: The study population consisted of men and women at least 18 years of age. For Part 1, subjects in the study were required to have clinically diagnosed measurable or evaluable metastatic RCC; detectable serum C-reactive protein (CRP) ≥ 4 mg/L for the 1, 3, and 6 mg/kg dose cohorts and ≥ 50 mg/L for the 12 mg/kg dose cohort; a life expectancy of ≥ 6 months; Karnofsky performance status of ≥ 60; adequate bone marrow, liver and renal function; and a time period of at least 4 weeks since prior cancer therapy or surgery.

Test Product, Dose and Mode of Administration, Batch Number: CNTO 328 was administered intravenously at 4 dose levels (1, 3, 6, and 12 mg/kg). Subjects received study agent from batch numbers D03PB7227 and D03PB7231.

Duration of Treatment: CNTO 328 was administered as 4 doses (Days 1, 29, 43, and 57), unless unacceptable toxicity or disease progression occurred. Subjects responding to treatment with at least disease stabilization were eligible to receive up to 4 additional administrations. Study agent was to be administered over a period of not less than 2 hours.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics: The pharmacokinetic parameters used to evaluate the serum concentration of CNTO 328 were AUC, Cmax, terminal t1/2, CL, and volume of distribution (Vz). The pharmacokinetic evaluation was conducted following the first and fourth infusions, but was not evaluated for the extended administrations. Peak and trough assessments were performed on samples from all other administrations. Serum concentration of CNTO 328 for each subject was determined and is summarized and plotted over time.

The primary pharmacodynamic endpoints for Part 1 of the study were percent change from baseline in CRP and IL-6 (total and free) levels at each timepoint. Individual CRP and IL-6 values were summarized by dose level for each timepoint. Mean CRP and IL-6 were plotted by dose level over time. Secondary pharmacodynamic markers (serum amyloid A [SAA], GP80, soluble GP130, serum C-telopeptide [CTx], and serum N-telopeptide [NTx]) were analyzed for each timepoint specified in the protocol.

Efficacy: Radiological assessments were performed 9 weeks after initiating treatment. Subjects responding to treatment with stable disease or better were required to have a repeat scan 4 to 6 weeks later to confirm the response. These subjects were also eligible to receive up to 4 additional administrations.

Safety: The primary safety endpoint was the incidence of DLT defined as any Grade 3 or 4 toxicity identified by the SMC as dose-limiting. Safety assessments were performed on 48-hour postinfusion data. The following data were provided to the SMC for assessment of safety: Confirmation of eligibility, renal cancer history and clinical staging, prior cancer-related therapy, Karnofsky performance status, vital signs (systolic and diastolic blood pressure (BP), pulse, temperature, and respiration rate), ECG, medical history and physical exam findings, existing signs and symptoms related to cancer, laboratory data, radiological data, study agent administration, concomitant medications, and AEs. The SMC determined if a subject experienced a DLT based upon these data, investigator reports, and any other relevant information. All toxicities were graded according to the National Cancer Institute (NCI) CTC Version 2.0. The overall safety of CNTO 328 treatment

Synopsis (C0328T01 Part 1)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

was assessed by an evaluation of all AEs, serial measurements of laboratory parameters and vital signs, ECG and ophthalmic exams, and the pharmacokinetics of CNTO 328. Serum samples were collected for detection of immune response to CNTO 328.

Statistical Methods: No formal hypothesis testing was performed for any endpoint. Descriptive statistics, such as mean, median, and range for continuous variables, and percentage for categorical variables were used to summarize most data.

SUMMARY – CONCLUSIONS

Study Population Results: Eleven subjects with measurable or evaluable metastatic RCC were enrolled in the 4 dose cohorts in Part 1 of this study. One subject received 1 mg/kg, 3 subjects each received 3 or 6 mg/kg , and 4 subjects received 12 mg/kg. There were 9 male and 2 female subjects ranging in age from 56 to 73 years. Eight of the 11 treated subjects received the planned 4 infusions; 5 of these subjects continued in the study and received extended treatment.

Pharmacokinetic/Pharmacodynamic Results: Drug exposure increased with dose between the 1 to 12 mg/kg dose range. The increase in Cmax and AUC appeared to be near dose-proportional from the 1 to 6 mg/kg range, but was less than dose-proportional between the 2 higher doses, 6 and 12 mg/kg. Steady-state conditions were not reached by Day 57. The CL and Vz values estimated following the first dose might not be highly precise, and there were no significant differences with respect to t1/2 across the four dose cohorts.

Serum CRP levels that were greater than 30 mg/L were not adequately suppressed (below LOQ) in the current study. Total IL-6 levels increased in a time dependent manner following CNTO 328 administration. The increase in total IL-6 concentrations most likely reflects total IL-6 complexed with CNTO 328. The increase in free IL-6 concentrations cannot be fully explained. Other serum markers, which exhibited sustained inhibition following CNTO 328 administration, include GP80 and SAA in all dose cohorts, NTx in the 12 mg/kg dose cohort only, and sIL-6R in the 1, 3, and 6 mg/kg dose cohorts.

Efficacy Results: Conclusions about the overall efficacy or the efficacy of a dose cohort cannot be drawn because of the small number of subjects included in Part 1 of the study. Five out of 10 evaluable subjects had stable disease during the study. Five subjects, 3 subjects, and 2 subjects were clinical benefit responders at Weeks 4, 6, and 8, respectively. Clinical benefit responders at Weeks 6 and 8 were in the 6 and 12 mg/kg dose cohorts.

Safety Results: CNTO 328 was generally well tolerated by the 11 subjects treated at the 4 dose levels tested in Part 1 of this study and during extended dosing. All treated subjects had 1 or more AE, however the majority of AEs were reported only in 1 subject. No DLT or dose-related toxicities were observed. All AEs of toxicity Grade 3 or higher and SAEs were considered unlikely or not related to CNTO 328. One subject experienced Grade 3 pneumonia and was subsequently discontinued from the study as a result of this continuing AE. One subject was withdrawn from the study because of a SAE that was considered not related to treatment with CNTO 328. One subject reported a mild infusion reaction after the first infusion but continued in the study without further incident. No subjects were diagnosed with possible anaphylactic or possible delayed hypersensitivity reactions. No dose-response relationship was noted across any specific AEs or for any system organ class. No changes in vital signs, ECG, urinalysis, clinical hematology or clinical chemistry parameters identified by laboratory investigations appeared to have a correlation with exposure to study agent. Two subjects died as a result of disease progression: 1 subject died during study participation and 1 subject died during extended administration. Immune response results will be reported in the Part 3 CSR.

Synopsis (C0328T01 Part 1)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		
Date of Revised Report: 07 Mar 2008		

Synopsis (C0328T01 Part 2)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

Protocol: C0328T01	**EudraCT No.:** 2004-000546-20
Title of the study: A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma	
Principal/Coordinating Investigator(s): Prof. Jean-François Rossi, CHU de Montpellier, Hôpital Lapeyronie, Montpellier, France	
Study Center(s): 14 initiated study centers (5 in France, 4 in the United Kingdom [UK], 3 in the Czech Republic, and 2 in the Netherlands)	
Publication (reference): None	
Studied Period: 04-Dec-2003 / 14-Dec-2004	**Phase of Development:** 1/2

Objectives: The primary objectives of Part 2 were to assess the safety, pharmacokinetics, and efficacy (measured by tumor response) of CNTO 328 in subjects with metastatic renal cell carcinoma (RCC); the secondary objectives included the assessment of immunogenicity, pharmacodynamics, clinical benefit, and quality of life benefit of CNTO 328 in subjects with metastatic RCC.

Methodology: Part 2 was designed to further evaluate the 2 dose levels from Part 1 that were well tolerated and were determined to offer clinical benefit (3 mg/kg and 6 mg/kg). This was a randomized, 2-treatment, Simon 2-stage design study to evaluate potential tumor response for the selected dose strengths, and to determine an appropriate regimen for further studies of CNTO 328. In Stage 1, subjects were scheduled to receive a total of 4 IV infusions of CNTO 328 (1 infusion every 3 weeks on study Days 1, 22, 43, and 64). Subjects were followed for an additional 6 weeks, for collection of data, including but not limited to pharmacokinetics, pharmacodynamics, and immune responses.

An interim analysis was conducted at the end of Stage 1. The planned Stage 2 efficacy success criterion for the primary endpoint was for at least 8 of 43 subjects (ie, 18 in Stage 1 plus 25 in Stage 2) in either dose cohort to have complete response (CR), partial response (PR), or stable disease (SD). Both dose cohorts met this criterion in Stage 1. Based on that review and in consultation with the chairman of the Safety and Efficacy Monitoring Committee (SEMC), the following was determined: first, further evaluation would be required to determine which subjects were more likely to benefit from treatment; second, further evaluation was required to assess which doses would best achieve complete neutralization of circulating interleukin 6 (IL-6) (as indicated by C reactive protein [CRP] suppression). Therefore, Centocor decided not to proceed with Stage 2 of Part 2, but to amend the study and add Part 3.

Number of Subjects (Planned and Analyzed): Planned: 36 subjects in Stage 1 and 50 subjects in Stage 2, for up to a total of 86 subjects. In Stage 1, 38 subjects were randomized, and 37 subjects were analyzed for both efficacy and safety. Stage 2 was not conducted (refer to Protocol Amendment 3, Appendix 1).

Diagnosis and Main Criteria for Inclusion: Subjects who had metastatic RCC with detectable CRP levels (ie, $\geq$ 4 mg/L). All subjects must also have had documented disease progression (PD).

Test Product, Dose and Mode of Administration, Batch Number: CNTO 328 was supplied as 100 mg vials containing 5 mL of liquid at a concentration of 20 mg/mL. During Part 2, the study agent was administered by infusion intravenously at the 2 dose strengths determined to be well tolerated and to offer clinical benefit from Part 1 (3 mg/kg and 6 mg/kg). Subjects received study agent from batch numbers

Synopsis (C0328T01 Part 2)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		
D03PB7231 and D03PB7227.		

Duration of Treatment: Subjects received 4 administrations of CNTO 328 on study Days 1, 22, 43, and 64. Study agent was to be administered over a period of not less than 2 hours. Subjects were discontinued from treatment with CNTO 328 for lack of tolerance, for AEs, or for PD. The total participation was expected to be approximately 19 weeks (including screening and 6-week follow-up). However, subjects who responded to therapy with at least SD were allowed to receive additional infusions of CNTO 328 in extended administration.

Reference Therapy, Dose and Mode of Administration, Batch Number: None.

Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics: The pharmacokinetic parameters used to assess the serum concentration of CNTO 328 were: area under the serum concentration time curve (AUC), maximum observed concentration (Cmax), terminal half-life (t1/2), clearance (CL), and volume of distribution (Vz).

The primary pharmacodynamic parameters for Part 2 were CRP and IL-6 (total and free). Individual CRP values were summarized by dose cohort for each timepoint. Mean CRP and IL-6 levels were plotted by dose cohort over time. Secondary pharmacodynamic markers (serum amyloid A [SAA], GP80, soluble GP130, serum CTx, and serum NTx) were analyzed for each timepoint specified in the protocol. Blood samples were collected for detection of immune response to CNTO 328.

Efficacy: The primary efficacy endpoint was the proportion of subjects who had an overall tumor response including disease stabilization within 11 weeks after the first administration of CNTO 328. Subjects responding to treatment with SD or better were required to have further radiologic and clinical assessment performed 4 to 6 weeks later to determine if an objective response was confirmed. The major secondary efficacy endpoints were: the proportion of subjects with clinical benefit, time to PD, duration of tumor response (CR + PR), and the proportion of subjects with an overall tumor response (CR + PR).

Safety: The overall safety of CNTO 328 treatment was assessed by an evaluation of treatment related toxicities (Grade 3 or 4), all adverse events (AEs) (including hypersensitivity and Grade 3 or 4 infusion reactions), serial measurements of laboratory parameters (hematology, chemistry, and urinalysis), vital signs, abnormal ECGs, and ophthalmologic exams.

Statistical Methods: Subjects were randomized (1:1) to the 2 dose cohorts that were determined to be well tolerated and to offer clinical benefit from Part 1. Randomization was stratified by pretreatment CRP levels (detectable to < 50 mg/L; 50 to < 100 mg/L; and ≥ 100 mg/L) and by previous RCC treatment (yes/no; excluding surgery). Subjects and investigators were blinded to study treatments. The sample size was based on the optimal Simon 2-stage design. Stage 1 data was evaluated after 18 subjects per cohort (36 total) had been recruited and the safety and efficacy data were available for those subjects. The planned sample size for Stage 2 was up to 50 evaluable subjects depending on the decision in Stage 1; however, per Amendment 3, Stage 2 was not conducted.

Synopsis (C0328T01 Part 2)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

SUMMARY – CONCLUSIONS

Study Population Results: A total of 38 subjects were randomized: 18 in the 3 mg/kg dose cohort and 20 in the 6 mg/kg dose cohort. One subject in the 3 mg/kg dose cohort terminated study participation prior to receiving treatment with CNTO 328, reducing the total to 37 treated subjects. Seventeen subjects received infusions of CNTO 328 in extended administration.

Of all 38 randomized subjects, 68.4% (26) were male, and all subjects were Caucasian. The median age across dose cohorts was 56.5 years (3 mg/kg dose cohort range: 39 to 72 years; 6 mg/kg dose cohort range: 26 to 82 years). The median weight was 82.0 kg. The majority of subjects had at least 1 prior cancer-related systemic therapy. A total of 9 subjects (8 in the 6 mg/kg dose cohort; 1 in the 3 mg/kg dose cohort) received treatment with radiotherapy prior to randomization.

Of all randomized subjects, 22 (57.9%) subjects did not meet the study entry criteria. The most common reason for not meeting the study entry criteria was baseline disease characteristics (which includes subjects whose baseline radiologic scans were outside of the protocol-specified window and subjects who lacked documentation of PD within 6 months of study entry). During the study, the most common reason for deviations in treatment was administration of study agent outside of the protocol-specified window (5 subjects in the 3 mg/kg dose cohort; 5 subjects in the 6 mg/kg dose cohort).

Of the 37 treated subjects, 15 (40.5%) subjects discontinued treatment with study agent through Week 9 prior to receiving 4 scheduled study agent infusions, and the most common reason was PD (13 subjects, 35.1%).

Pharmacokinetic/Pharmacodynamic Results: Drug exposure increased with an increase in CNTO 328 dose strength from 3 mg/kg to 6 mg/kg. Increases in both Cmax and AUC appeared to be approximately dose-proportional. A steady-state condition did not appear to have been attained by the fourth dose on Day 64. The estimated CL and Vz values following the first dose were dose-independent. No significant difference was identified in terminal t1/2 between the 2 dose cohorts.

In this study, CNTO 328 treatment in both the 3 mg/kg and 6 mg/kg dose cohorts resulted in a sustained suppression of circulating levels of both CRP and SAA. In all but 1 subject, a complete suppression of CRP (below LOQ) was not achieved in individual subjects in either dose cohort when the baseline serum CRP levels were greater than 30 mg/L. Overall, a decrease in serum CRP levels from baseline was evident in both the 3 mg/kg and 6 mg/kg dose cohorts.

There was a gradual increase in both total and free IL-6 levels following CNTO 328 administration in both dose cohorts. While the increase in total IL-6 concentrations could be attributed to the formation of immune complexes, the increase in free IL-6 concentrations could not be fully explained. Due to the fact that certain caveats were identified (post sample analysis) in the free IL-6 assay methodology, it was not possible to make reasonable conclusions from these results.

In general, levels of soluble IL-6R (GP80) and soluble GP130 both increased from baseline for the 3 mg/kg and 6 mg/kg dose cohorts following CNTO 328 administration. The increase for soluble IL-6R was greater in the 6 mg/kg dose cohort than in the 3 mg/kg dose cohort. Subjects in the 6 mg/kg dose cohort generally had higher levels of serum NTx and CTx than those in the 3 mg/kg dose cohort. Data from serum NTx and CTx levels showed considerable variability in both dose cohorts and did not follow any specific trend.

Synopsis (C0328T01 Part 2)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

Efficacy Results: The primary efficacy endpoint for Part 2 was overall tumor response including disease stabilization through the Week 11 radiologic assessment. Of the 37 treated subjects in Part 2, 17 were in the 3 mg/kg dose cohort and 20 were in the 6 mg/kg dose cohort. Of the 17 subjects treated with 3 mg/kg CNTO 328, 1 subject had a PR, 10 subjects had SD, and 6 subjects had PD. Of the 20 subjects treated with 6 mg/kg CNTO 328, 10 subjects had SD, and 10 subjects had PD.

Response to treatment with CNTO 328 (defined as SD or better) was similar between the 2 dose cohorts. A higher proportion of subjects who responded to treatment with CNTO 328 was seen among those who had received previous treatment for RCC and among those with a low level of CRP at baseline.

One subject in the 3 mg/kg dose cohort had PR to treatment and was assessed for duration of response. The subject received a total of 10 administrations of CNTO 328. The PR was observed at the first radiologic assessment at Week 7 (study Day 55) and was sustained for a total of 228 days. Radiologic examination at study Day 283 showed PD and treatment was discontinued. Overall, the median time to PD for all treated subjects was 102.0 days (95% CI, 52.0 to 169.0 days). The median time to PD was shorter for the 6 mg/kg dose cohort (66.0 days; 95% CI, 50.0 to 189.0 days) than for the 3 mg/kg dose cohort (104.0 days; 95% CI, 60.0 to 210.0 days).

Quality of life and clinical benefit could not be adequately assessed for this study as a result of 2 factors: lack of a control group and lack of concomitant drug use data at treatment intervals. Additionally, the results of pain and fatigue questionnaires after Week 6 were unreliable as a result of the sizable cohort attrition that occurred after that point. Overall, there was no meaningful variation across treatment cohorts or over time in temperature, Karnofsky performance status scores, or body weight.

Safety Results: CNTO 328 was generally well-tolerated. The safety profiles of subjects in the 3 mg/kg dose cohort and the 6 mg/kg dose cohort were similar to each other. All 17 treated subjects in the 3 mg/kg dose cohort had 1 or more AEs. Nineteen (95.0%) of the 20 treated subjects in the 6 mg/kg dose cohort had 1 or more AEs. Certain AEs (including constipation, headache, lethargy, cough, and hot flush) were more prominent in the 3 mg/kg dose cohort than in the 6 mg/kg dose cohort; other AEs (bone pain, haemoptysis, and anorexia) were reported by more subjects in the 6 mg/kg dose cohort than in the 3 mg/kg dose cohort. Overall, the most commonly reported AEs of any grade were fatigue and nausea (27.0% each); dyspnoea (21.6%); cough and back pain (18.9% each); headache and arthralgia (16.2% each); constipation, vomiting, asthenia, dizziness, and lethargy (13.5% each); abdominal pain, diarrhea, chest pain, nasopharyngitis, and hyperhidrosis (10.8% each).

Seven (41.2%) subjects in the 3 mg/kg dose cohort had 1 or more Grade 3 or higher AEs. Ten (50.0%) subjects in the 6 mg/kg dose cohort had 1 or more Grade 3 or higher AEs. The most common Grade 3 or higher AEs were fatigue, chest pain, back pain, dyspnoea, and hypertension (5.4% each). Two subjects in the 6 mg/kg dose cohort permanently discontinued study agent as a result of SAEs (cardiac failure and ARDS). Two subjects in the 6 mg/kg dose cohort died as a result of PD. A total of 33 subjects received no prophylactic medications during the study. The most commonly markedly abnormal postbaseline vital sign was increased BP (both diastolic and systolic).

Among the hematology parameters, trends toward decrease from baseline with prolonged administration of CNTO 328 were observed for platelets, as well as WBCs and neutrophils. For all 3 parameters, the trend was toward recovery upon discontinuation of treatment with study agent. No major changes from baseline were identified in vital signs, ECGs, urinalysis, or clinical chemistry parameters.

Synopsis (C0328T01 Part 2)

Name of Sponsor/Company: Centocor, Inc. and Centocor, B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		
Date of Revised Report: 07 Mar 2008		

Synopsis (C0328T01 Part 3)

Name of Sponsor/Company: Centocor, Inc and Centocor, B.V	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

Protocol: C0328T01	**EudraCT No.:** 2004-000546-20
Title of the study: A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma	
Principal/Coordinating Investigator(s): Prof. Jean-François Rossi, CHU de Montpellier, Hôpital Lapeyronie, Montpellier, France	
Study Center(s): 10 study centers were initiated: 4 in France, 3 in the Netherlands, and 3 in the UK.	
Publication (reference): None	
Studied Period: 29 Mar 2005 to 24 May 2006	**Phase of Development:** 1/2
Objectives: The primary objectives of Part 3 were to assess the safety, pharmacokinetics, and efficacy (measured by tumor response) of CNTO 328 in subjects with metastatic renal cell carcinoma (RCC). The secondary objectives were to assess the immunogenicity, pharmacodynamics, clinical benefit, and quality of life benefit of CNTO 328 in subjects with metastatic RCC.	
Methodology: Part 3 was an open-label design with a single dose level of CNTO 328 (6 mg/kg). The study consisted of 3 periods: screening, treatment, and follow-up. During the treatment period, subjects were scheduled to receive a total of 6 IV infusions of 6 mg/kg CNTO 328 (1 infusion every 2 weeks on study Days 1, 15, 29, 43, 57, and 71). The 6 mg/kg dose level was selected to further evaluate the safety, pharmacokinetics, and efficacy of CNTO 328 in the treatment of subjects with metastatic RCC. Any subject who received at least 1 infusion of CNTO 328 was considered evaluable for analyses of efficacy and safety. Subjects received radiologic evaluation of disease at Screening, Week 7, Week 11, and at the 6-week follow-up. For subjects who went on to receive extended administrations of CNTO 328, radiologic evaluations were performed after the third and sixth extended administrations of CNTO 328 and earlier if clinically indicated. Subjects returned to the site at protocol-specified times between scheduled administrations for physical examinations, AE evaluation, pharmacokinetic, pharmacodynamic, and laboratory assessments. A full pharmacokinetic profile was required for all subjects after the first and last administration of CNTO 328, with peak and trough concentration assessments performed on samples from all other administrations. After the last dose of study agent, subjects entered a 6-week follow-up period for data collection for pharmacokinetics, pharmacodynamics, and immune response evaluations. Subjects were followed for up to 1 year after the last dose of study agent for clinical response (survival) and immunogenicity.	
Number of Subjects (Planned and Analyzed): Twenty subjects were planned, enrolled, and analyzed for safety and efficacy in Part 3.	
Diagnosis and Main Criteria for Inclusion: Subjects must have had measurable metastatic RCC, documented disease progression (PD), and serum C-reactive protein (CRP) levels detectable to ≤ 30 mg/L. Additionally, subjects were required to have a life expectancy of ≥ 6 months, a Karnofsky performance status of ≥ 60, a Motzer score of ≤ 1, adequate bone marrow, liver and renal function, and ≥ 4 weeks since prior cancer therapy or surgery.	

Synopsis (C0328T01 Part 3)

Name of Sponsor/Company: Centocor, Inc and Centocor, B.V	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

Test Product, Dose and Mode of Administration, Batch Number: CNTO 328 was supplied as 100 mg vials containing 5 mL of liquid at a concentration of 20 mg/mL. The study agent was administered intravenously at a single dose level of 6 mg/kg CNTO 328 every 2 weeks. All subjects received study agent from cell line C175H (lot number D04PJ7380).

Duration of Treatment: Subjects received 6 administrations of CNTO 328 at a dose level of 6 mg/kg on study Days 1, 15, 29, 43, 57, and 71. Study agent was to be administered over a period of not less than 2 hours. Subjects were discontinued for unacceptable toxicity or PD. The duration of study participation was expected to be 21 weeks (including screening and 6-week follow-up). However, subjects who received all 6 infusions of CNTO 328 in extended administration participated for approximately 22 additional weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: None.

Criteria for Evaluation: Two analysis populations were defined in this study: treated subjects and subjects evaluable for tumor response. The treated subject population included subjects who received at least 1 administration of CNTO 328. All planned analyses were based on this population. The population of subjects evaluable for tumor response was defined as subjects who received at least 1 administration of CNTO 328 and had either progressed or had their Week 11 radiologic assessment.

Pharmacokinetics/Pharmacodynamics: The pharmacokinetic parameters used to evaluate the serum concentration of CNTO 328 were AUC, Cmax, terminal t1/2, CL and volume of distribution (Vz). A complete pharmacokinetic profile was performed after the first and last infusion during the treatment period. Peak and trough assessments were performed on samples from all other administrations. Serum concentration of CNTO 328 for each subject was determined and is summarized and plotted over time. The primary pharmacodynamic endpoint for Part 3 was percent change from baseline in CRP levels at each timepoint. Individual CRP values were analyzed for each timepoint and plotted over time. IL-6 [total and free] was not assessed in this study because of interference of the drug with the performance of the assay. The following secondary pharmacodynamic markers were analyzed for each timepoint and plotted over time: soluble IL-6 receptor, soluble GP130, serum NTx, serum CTx, and serum amyloid A (SAA).

Efficacy: The primary efficacy endpoint for Part 3 was the proportion of subjects who had a confirmed overall response of complete response (CR) or partial response (PR). The major secondary efficacy endpoints summarized were: proportion of subjects with clinical benefit, time to PD, duration of tumor response (CR + PR), and proportion of subjects with tumor response (CR + PR + SD). Other secondary efficacy endpoints included: change from baseline in quality of life (FACIT-Fatigue), change from baseline in temperature, change from baseline in Karnofsky performance status, change from baseline in weight, change from baseline in pain intensity (Brief Pain Inventory [BPI] Question 3), and survival.

Safety: The safety endpoints summarized include the incidence of the each of the following: all AEs; Grade 3 or higher AEs; SAEs; hypersensitivity and Grade 3 or above infusion reactions; clinically significant changes in vital signs; clinically significant changes in safety-related laboratory parameters; and abnormal ECGs.

Statistical Methods: In general, descriptive statistics (eg, number of observations, means, standard deviations, medians, and ranges) were used to summarize data in Part 3. Formal hypothesis testing was performed for the primary efficacy endpoint (proportion of subjects who had a confirmed overall response of CR or PR). The analysis included and was summarized by all subjects who received at least 1 administration of CNTO 328. CNTO 328 was considered not effective if less than 3 of the 20 treated subjects had a confirmed overall response of CR or PR. This criterion was based on exact binomial calculations with a Type I error rate of 0.10.

Synopsis (C0328T01 Part 3)

Name of Sponsor/Company: Centocor, Inc and Centocor, B.V	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: Anti-IL-6 immunoglobulin G monoclonal antibody		

SUMMARY – CONCLUSIONS

Study Population Results: The 19 males and 1 female in the study ranged in age from 50 to 77 years with a median age of 62 years. Nineteen subjects were Caucasian and 1 subject was Asian. The overall median body weight was 85.5 kg. Clear cell carcinoma was the predominate tumor histology (18 subjects). Histopathologic grade was available for 19 subjects, of which 13 had a high-grade classification of poorly differentiated tumor cells. All subjects were confirmed to have metastatic disease (M1), 11 subjects had disease extending beyond the kidney (T3 and T4), and 5 subjects had evidence of nodal involvement (N1 to N2). At baseline, the median level of fatigue was similar to that found in the general US population and little anemia treatment was observed. In general, subjects had mild to no pain and were using very few analgesics, most of which were non-opioids.

Of the 20 subjects enrolled and treated, 7 subjects discontinued treatment with study agent during the first 6 IV administrations of CNTO 328. Reasons for study agent discontinuation included PD, withdrawal of consent, AE, and renal failure and elevated hypertension. Three subjects terminated study participation, and the reasons included death and withdrawal of consent. Two treated subjects did not meet the study selection criteria at baseline, and the reasons included unmeasurable RCC and not having appropriate medical history and laboratory results. The most common reason for deviating from per-protocol treatment was administration of study agent after progressive disease (7 subjects). Additionally, 1 subject had a 1-week delay in treatment prior to Infusion 5.

Pharmacokinetic/Pharmacodynamic Results: In Part 3, systemic exposure to CNTO 328 (Cmax and AUC) indicated moderate drug accumulation with a dose regimen of 6 mg/kg every 2 weeks. A steady-state condition had not been attained by the sixth dose on study Day 71.

Across all 3 parts of the study, a total of 44 subjects were evaluated for antibodies to CNTO 328. No subject in any part of the study demonstrated a positive antibody response to CNTO 328. Eight subjects tested negative for antibodies to CNTO 328 after the last treatment, and 36 subjects could not be classified as being negative for antibodies due to potential interference from circulating drug so they were described as having an undetectable status after last treatment.

In Part 3, treatment with CNTO 328 resulted in a sustained suppression of circulating levels of both CRP and SAA. Even though complete suppression of CRP levels (below LOQ) was not achieved when serum levels were greater than 30 mg/L (Parts 1 and 2), overall, a decrease in serum CRP levels from baseline was evident in all 3 studies (Parts 1, 2 and 3). Levels of free and total IL-6 were not evaluated in Part 3 due to interference of the drug with the performance of the assay. Levels of soluble IL-6R (GP80) and serum soluble GP130 showed an increase above baseline following CNTO 328 administrations. These results were consistent with the increase in GP80 and GP130 levels observed in Part 2. In Part 3, an increase in levels of both serum NTx and CTx was evident following the initial CNTO 328 administrations, then levels of both decreased to below baseline levels by the end of the study. In Part 2, there was considerable variability in the levels of NTx and CTx observed in both dose cohorts, and they did not follow any specific trend. Data for NTx and CTx did not follow any specific trend across any of the 3 studies (Parts 1, 2, or 3).

Efficacy Results: Of the 20 treated subjects, 13 (65.0%) subjects had SD and 7 (35.0%) subjects had PD. Of the 18 subjects evaluable for tumor response, 11 (61.1%) subjects had SD and 7 (38.9%) subjects had PD. No subjects had CR or PR. There was no meaningful variation over time in fatigue, temperature, performance status, weight, or pain. Additionally, pain and fatigue questionnaire results after Week 6 were unreliable as a result of the sizable cohort attrition that occurred after that point.

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Safety Results: A total of 20 subjects received treatment with CNTO 328. The median time from the first to the final administration was 71.0 days, with a range of 1 to 239 days. The average duration of follow-up was 20.1 weeks. Thirteen subjects completed all 6 per-protocol infusions, 9 of whom went on to receive study agent in extended administrations. Nineteen (95.0%) subjects experienced 1 or more treatment-emergent AEs, the majority of which were reported for only 1 subject. The most commonly reported treatment emergent AE was dizziness, which was reported for 6 (30.0%) subjects, 5 of which were Grade 1 and 1 of which was Grade 2. Other frequently reported treatment emergent AEs were diarrhea, reported for 5 (25.0%) subjects, and fatigue, reported for 4 (20.0%) subjects. Three subjects had AEs of rash that occurred within 14 days of infusions. All of these events were Grade 1, and no subject discontinued treatment with study agent as a result of these events.

One death occurred during the study as a result of a Grade 4 SAE of massive cerebral hemorrhage. Three subjects had 4 SAEs, none of which were considered to be reasonably related to treatment with CNTO 328. Temporal AEs were recorded for 15 (75.0%) subjects, 2 of which were severe (ie, Grade 3 or 4): pain and musculoskeletal pain. Three subjects had possible infusion reactions of hot flush, hypotension, and dysgeusia. No subjects had possible delayed hypersensitivity or anaphylactic reactions. One subject discontinued treatment with study agent as a result of a treatment-emergent AE of Grade 2 proteinuria. No subject had an abnormal ECG finding after the first infusion of study agent.

Among the hematology parameters, trends toward decreases from baseline with prolonged administration of CNTO 328 were observed for platelets, WBCs, and neutrophils. For all 3 parameters, the trend was toward recovery upon discontinuation of treatment with study agent. No major changes from baseline were identified in vital signs, ECGs, urinalysis, or clinical chemistry parameters.

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