## SYNOPSIS

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| Name of Sponsor/Company | Janssen Research & Development |
| Name of Finished Product | NA |
| Name of Active Ingredient(s) | CNTO 888 (carlumab) |
| Date: | 15 January 2013 |

**Protocol No.:** CNTO888PUL2001

**Title of Study:** A Phase 2, Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study Evaluating the Efficacy and Safety of CNTO 888 Administered Intravenously in Subjects With Idiopathic Pulmonary Fibrosis

**EudraCT Number:** 2008-001281-86

**NCT No.:** NCT00786201

**Clinical Registry No.:** CR015235

**Coordinating Investigator(s):** Ganesh Raghu, MD, University of Washington, [redacted] USA

**Study Center(s):** 23 sites in 5 countries (Belgium, Canada, Germany, the Netherlands, and United States).

**Publication (Reference):** None

**Study Period:** The date the first subject consented was 24 October 2008 and the date of the last subject last visit was 18 January 2012. The final database lock occurred on 11 August 2012.

**Phase of Development:** 2

**Objectives:** The primary objective was to determine the efficacy (as measured by pulmonary function) and safety of carlumab in subjects with idiopathic pulmonary fibrosis (IPF). The secondary objectives were to assess the effect of carlumab on measures of disease progression, to assess the effect of carlumab on patient reported outcomes, functional capacity measurements, and health-related quality of life in subjects with IPF, and to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of carlumab in subjects with IPF.

**Methodology:** CNTO888PUL2001 was a Phase 2, multicenter, multinational, randomized, double-blind placebo-controlled, parallel-group, dose-ranging study to determine the efficacy and safety of carlumab administered intravenously in subjects with IPF and to assess the PK and PD after treatment with carlumab. Subjects were randomized in a 1:1:1:1 ratio using permuted block randomization scheme to 1 of 4 treatment groups (placebo, carlumab 1 mg/kg, carlumab 5 mg/kg, carlumab 15 mg/kg). Randomization was stratified by 2 factors: high risk category (yes/no) and baseline oral corticosteroid use (OCS; yes/no). High risk was defined as having one or more of the following risk factors: significant honeycombing on high-resolution computed tomography

(HRCT), desaturation of oxygen during the 6-minute walk test (6MWT) at screening, and forced vital capacity (FVC) <60% predicted at screening.

The study enrolled and treated the first 20 subjects (with 1 of the 3 doses of study agent or placebo) as part of the safety run-in phase, in a subset of sites. These subjects were randomized in a 1:1:1:1 ratio to placebo, 1 mg/kg, 5 mg/kg, or 15 mg/kg carlumab. A formal planned Data Monitoring Committee (DMC) review, where only the DMC was unblinded occured after this safety run-in and further enrollment in the trial continued as per the DMC recommendation.

The study began with a screening phase (1 to 4 weeks) followed by a 48-week treatment period. The primary endpoint was measured at Week 52, and subjects were followed for an additional 20 weeks, out to Week 72, for assessment of safety, measurement of PK/PD parameters, and the maintenance of any clinical effects after the discontinuation of therapy.

Dosing in all treatment groups was stopped in the study prematurely. Investigators were notified of this decision via written communication on 05 August 2011. Subjects were encouraged to return for all follow-up visits through the planned Week 72 visit, or until 18 January 2012, whichever came first. This provided for all subjects to be followed for 24 weeks after their last dose, as per the original safety follow-up period in the protocol.

**Number of Subjects (planned and analyzed):** A target of approximately 120 subjects was planned to be randomly assigned to 1 of 4 treatment groups (placebo, 1 mg/kg, 5 mg/kg, or 15 mg/kg carlumab).

A total of 126 subjects were randomly assigned across treatment groups with 29 subjects in the placebo group, 33 subjects in the 1 mg/kg group, 32 subjects in the 5 mg/kg group, and 32 subjects in the 15 mg/kg group.

**Diagnosis and Main Criteria for Inclusion:** The study population consisted of men and women, 40 to 80 years of age, inclusive, with a diagnosis of IPF within 4 years of screening (according to a modified version of the American Thoracic Society [ATS]/European Respiratory Society [ERS] criteria; ATS, 2000), and who had progressive IPF despite treatment. Subjects were permitted, but not required to be on 1 or more of the medications from 3 classes of conventional treatments for IPF (in the absence of any approved therapies). These classes included corticosteroids, immunosuppressive/cytotoxic agents (eg azathioprine or cyclophosphamide), and/or antifibrotic agents (eg, D-penicillamine and colchicines), alone or in combination. Other treatments described in the ATS/ERS guidelines as “potential alternative treatments” (eg, N-acetylcysteine) were permitted at the discretion of the investigator. The baseline IPF medications were to have been prescribed at stable doses for at least 30 days prior to the study and kept stable during the treatment phase unless a significant medical complication required adjustment or cessation of therapy.

**Test Product, Dose and Mode of Administration, Batch No.:** Carlumab was supplied as a sterile, preservative-free, lyophilized white solid cake either in a 50 mg/vial or the 100 mg/vial for intravenous (IV) administration. Each reconstituted vial contained 50 mg/mL carlumab (or 100 mg/mL carlumab), L-histidine, L-histidine monohydrochloride, sucrose, and polysorbate 80 at a pH of approximately 5.5. Twelve lots of carlumab (Batch No.: 360325, 360911, 362411, 362412, 362457, 362607, 362936,363126, 363127, 363148, D08PA7653, and D08PH7674) were used in this study.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Each investigational site sourced 100 mL infusion bags containing 5% Dextrose in water, United States Pharmacopeia

utilized as placebo for IV infusion. No separate placebo batches were manufactured by the Sponsor for this study.

**Duration of Treatment:** Randomized subjects received treatment for 48 weeks. All subjects were to be followed through Week 72, even if the study agent treatment was prematurely discontinued for any reason.

**Criteria for Evaluation:**

Pharmacology: Serum samples were collected for PK and immune response analyses. Pharmacodynamic assessments included the evaluation of relevant markers in serum, urine, peripheral blood mononuclear cells (PBMCs), exhaled breath condensates (EBC), and induced sputum (IS).

Efficacy: All analyses were conducted in accordance with the statistical analysis plan. However, for the purposes of this abbreviated clinical study report, only the primary and major secondary endpoints results are included. The efficacy evaluations for the primary and secondary endpoints included pulmonary function tests (PFTs; spirometry), diffusing capacity of the lung for carbon monoxide (DLCO), disease progression by HRCT, St. George's Respiratory Questionnaire (SGRQ) score, and dyspnea scores (ie, Medical Research Council [MRC] dyspnea score, University of California San Diego Shortness of Breath Questionnaire [UCSD SOBQ], and Borg's CR10 dyspnea score).

Safety: All subjects were monitored for safety; safety evaluations included a physical examination, and an electrocardiogram (ECG) measurement at the baseline visit. Safety evaluations were performed at every scheduled visit and included vital signs, adverse event (AE) review, concomitant medication review, and medical evaluation for tuberculosis. Blood and urine samples for routine and other laboratory tests were collected.

**Statistical Methods:**

Efficacy endpoints were analyzed using the modified intent to treat (ITT) population (unless otherwise specified) and were based on assigned treatment. Safety analyses were based on treatment received.

In general, descriptive statistics such as mean, median, standard deviation (SD), interquartile range, minimum, and maximum were used to summarize continuous variables; counts and percentages were used to summarize categorical variables. Time–to-event data were summarized using the Kaplan-Meier survival curves, hazard ratios, and confidence intervals (CI).

For continuous endpoint parameters, analyses were based on the analysis of covariance (ANCOVA) models or the van Elteren test to compare treatment groups. Time-to-event variables were analyzed using the Kaplan-Meier product-limit method and Cox proportional hazards models. Proportions were analyzed by logistic regression models, Fisher's exact test or the Cochran-Mantel-Haensze l test.

**RESULTS:**

STUDY POPULATION:

Of the 205 subjects who were screened, 126 subjects were randomized. Of these 126 subjects, 29 subjects were assigned to the placebo group, 33 subjects were assigned to the 1 mg/kg group, and 32 subjects each were assigned to the 5 mg/kg group and 15 mg/kg groups, respectively. All

randomized subjects received their assigned treatment at Week 0 with the exception of 1 subject in the placebo group who withdrew consent and was never treated. Overall, the discontinuation rate was higher in each active treatment group compared with the placebo group. The most common reason for discontinuation of study agent was discontinuation due to the sponsor's decision to stop dosing (20 [15.9%] subjects). The second most common reason for discontinuation was due to an AE (14 [11.1%] subjects); all but 1 of these 14 subjects received carlumab.

Demographic characteristics were similar across all treatment groups. The majority of subjects were male (101 [80.2%]); most subjects were Caucasian (124 [98.4%]); the mean (SD) age was 64.98 (8.030) years; and the mean (SD) weight was 90.94 (19.521) kg.

A total of 48 subjects had at least 1 major protocol deviation. Thirty eight of these subjects were in the combined carlumab group (18 subjects in the 1 mg/kg, 11 subjects in the 5 mg/kg, and 9 subjects in the 15 mg/kg groups), while 10 subjects were in placebo group. The 6 subjects reported to have deviations to study selection criteria were generally detected during monitoring, and based upon the safety evaluation a decision was made whether to continue study agent. Subjects with deviations related to safety and who were under treatment when the deviation was identified were discontinued. The deviations identified did not have an impact on the overall conclusions of the study.

The mean duration of exposure from first to final administration was similar across all treatment groups.

PHARMACOKINETIC and IMMUNOGENICITY RESULTS:

The mean serum concentration of carlumab after Week 0, Week 4 and Week 48 IV infusions peaked at the end of the infusion for all treatment groups. After the last IV infusion at Week 48, the mean serum concentration of carlumab peaked at the end of the infusion and then declined exponentially until carlumab was undetectable in most subjects at Week 72 for all treatment groups. Steady state appears to be achieved after the second dose of carlumab across all dose levels. Accumulation of carlumab concentrations in serum did not occur in any of the treatment groups after repeated IV infusion of carlumab every 4 weeks.

After the first IV infusion of carlumab, the mean values for maximum observed serum concentration ($C_{max}$) and the area under serum concentration versus time curve during a dosing interval (tau) at steady state ($AUC_{tau}$) appear to increase with increasing dose in a dose-proportional manner. The mean half-life ($t_{1/2}$) ranged from 6.29 to 9.01 days, the mean values for total systemic clearance of carlumab after intravenous administration (CL) ranged from 5.50 mL/day/kg to 9.94 mL/day/kg, and the mean volume of distribution at the terminal phase (Vz) ranged from 70.80 mL/kg to 88.13 mL/kg following the first IV infusion of carlumab across all treatment groups.

A summary of antibodies to carlumab results showed that out of the 32 treated subjects with appropriate samples in the 1 mg/kg treatment group, 5 subjects (15.6%) tested positive for antibodies to carlumab through Week 72. Of the 30 treated subjects with appropriate samples in the 5 mg/kg treatment group, 1 subject (3.3%) tested positive for antibodies to carlumab through Week 72. Of the 30 treated subjects with appropriate samples in the 15 mg/kg treatment group, 1 subject (3.3%) tested positive for antibodies to carlumab through Week 72. The combined incidence of antibodies to carlumab in all subjects given repeated IV infusions of carlumab was

7.6%. There were no AEs or clinical sequelae noted in subjects who developed a positive antibody response.

EFFICACY RESULTS:

The primary endpoint was the rate of percent change (relative to baseline per 4-week interval) in FVC through Week 52. Based upon the modified ITT analysis of the rate of percent change per 4-week interval from baseline (SE) in FVC through Week 52, there was no difference among the treatment groups: -0.58 [0.1584] in the placebo group, -0.53 [0.1433] in the 1 mg/kg group, -0.80 [0.1544] in the 5 mg/kg group, and -0.47 [0.1620] in the 15 mg/kg group. The overall test was not significant (p=0.261); therefore, the study was not positive.

The results of the major secondary endpoints were consistent with the primary endpoint. None of the 3 active treatment groups demonstrated improvement when compared with the placebo group for any of the major secondary endpoints. The results of the major secondary endpoints are presented below:

- Time to disease progression through Week 52: the hazard ratio (95% CI) for the time to disease progression with respect to the placebo group was 1.078 (0.24, 4.86) in the 1 mg/kg group, 1.977 (0.51, 7.72) in the 5 mg/kg group, and 0.852 (0.17, 4.26) in the 15 mg/kg group.
- Absolute change from baseline in FVC at Week 52: the model based mean changes (SE) from baseline in FVC were similar in all treatment groups. In addition, there was an absolute decline (worsening) that tended to be larger in the active treatment groups (-0.29 [0.085] in the 1 mg/kg group, -0.37 [0.085] in the 5 mg/kg group, and -0.32 [0.086]) in the 15 mg/kg group) compared with the placebo group (-0.13 [0.092]),
- Relative change from baseline in DLCO at Week 52: the model based mean changes (SE) from baseline in DLCO were similar in all treatment groups with -0.10 (0.056) in the placebo group, -0.08 (0.052) in the 1 mg/kg group, -0.22 (0.052) in the 5 mg/kg group, and -0.07 (0.053) in the 15 mg/kg group.
- Change from baseline in SGRQ total score at Week 52: there was a trend for worsening in the active treatment groups. The model based mean changes (SE) from baseline in SGRQ were: -0.41 (2.315) in the placebo group, 2.73 (2.173) in the 1 mg/kg group, 4.74 (2.098) in the 5 mg/kg group, and 4.31 (2.155) in the 15 mg/kg group.

SAFETY RESULTS:

Carlumab administered intravenously in subjects with IPF was generally well tolerated. No new safety signals were observed. Overall, there was no appreciable difference between the treatment groups.

**Adverse Events**: Most of the subjects had at least 1 AE. The proportion of subjects with 1 or more AEs was 99% in the combined carlumab group (97.0%, 100.0% and 100.0% of subjects in the 1 mg/kg, 5 mg/kg and 15 mg/kg groups, respectively) and 100% in the placebo group. The 3 system organ classes (SOCs) with the highest incidence of AEs in the combined carlumab group were infections and infestations; respiratory, thoracic and mediastinal disorders; and general disorders and administration site conditions. The 3 SOCs with the highest incidence of AEs in the placebo group were infections and infestations; respiratory, thoracic and mediastinal disorders; and musculoskeletal and connective tissue disorders.

**Deaths:** A total of 19 subjects died (12 subjects in the combined carlumab group [1, 7, and 4 subjects in the 1 mg/kg, 5 mg/kg and 15 mg/kg groups, respectively] and 7 subjects in the placebo group). Fourteen subjects died while participating in the study. Five additional deaths were reported by the site investigators after the subjects had completed/withdrawn from participation in the study. Overall, 6 subjects died due to IPF exacerbation and 5 subjects died due to respiratory failure.

**Serious Adverse Events (SAEs):** The proportion of subjects with 1 or more SAEs was higher in the 5 mg/kg group (53.1%) compared with other treatment groups: 15.2% in the 1 mg/kg group, 21.9% in the 15 mg/kg group, and 46.4% in the placebo group. The greatest proportion of SAEs were reported within the respiratory, thoracic and mediastinal disorders SOC. Among the treatment groups, the highest proportion of subjects with SAEs in this SOC was observed in the carlumab 5 mg/kg group (28.1%) compared with the other treatment groups (17.9%, 6.1%, and 15.6% in the placebo, 1 mg/kg, and 15 mg/kg groups, respectively). Idiopathic pulmonary fibrosis was the most commonly reported SAE in the respiratory, thoracic and mediastinal disorders SOC for both the carlumab combined and placebo groups. The percentage was higher in the 5 mg/kg group (18.8%) compared with the 1 mg/kg (6.1%), 15 mg/kg (9.4%), and placebo (14.3%) groups.

**Study Agent Discontinuation Due to AEs:** The proportion of subjects who discontinued study agent because of 1 or more AEs was higher in the combined carlumab group than in the placebo group. A total of 19.6% of subjects in the combined carlumab group (15.2%, 28.1%, and 15.6% in the 1 mg/kg, 5 mg/kg, and 15 mg/kg, respectively) and 14.3% in the placebo group discontinued study agent because of 1 or more AEs. The greatest proportion of AEs leading to discontinuation was observed in the respiratory, thoracic and mediastinal disorders SOC. Idiopathic pulmonary fibrosis was the most commonly reported AE leading to treatment discontinuation not only in this SOC, but also in the study.

**Infections:** The proportion of subjects with 1 or more treatment-emergent infections was higher in the combined CNTO 888 group than in the placebo group, with 69.1% in the combined carlumab group (66.7%, 71.9% and 68.8% in the 1 mg/kg, 5 mg/kg and 15 mg/kg, respectively) and 60.7% in the placebo group. The most frequently reported infections were upper respiratory tract infection, bronchitis and nasopharyngitis, which occurred in 28.9%, 12.4%, and 9.3%, of subjects, respectively, in the combined carlumab group. The most frequently reported infections in the placebo group were upper respiratory tract infection and urinary tract infection (17.9% of subjects each).

**Serious Infections:** A larger proportion of subjects in the placebo group experienced at least 1 serious infection compared with the combined carlumab group. Overall, 9.3% of subjects in the combined carlumab group (3.0%, 18.8% and 6.3% of subjects in the 1 mg/kg, 5 mg/kg and 15 mg/kg groups, respectively) and 17.9% of subjects in the placebo group had at least 1 serious infection. Serious infections reported in more than 1 subject in the combined carlumab group included pneumonia and respiratory syncytial virus infection. In the placebo group, urinary tract infection was reported in 2 subjects.

**Malignancies:** There were 6 malignancies that occurred throughout the study that included 3 non melanoma skin cancers (NMSC) and 3 malignancies other than NMSC. The 3 subjects with the NMSC included 1 subject in the 5 mg/kg group with a squamous cell carcinoma of the forehead and 1 subject each in 1 mg/kg and 15 mg/kg groups with basal cell carcinoma. Three subjects were reported to have malignancies other than NMSC: 1 subject in the 15 mg/kg group had an adenocarcinoma of the lung; 1 subject in the 5 mg/kg group had a suspected neuroendocrine

tumor; and 1 subject in the 1 mg/kg group had a lung neoplasm. There were no malignancies reported in the placebo group.

**Infusion and administration-site Reactions:** A larger proportion of subjects in the placebo group experienced infusion reactions compared to the combined carlumab group. Overall, 15.5% of subjects in the combined carlumab group and 25.0% of subjects in the placebo group had at least 1 infusion reaction. Infusion reactions reported in more than 1 subject in the combined carlumab group were flushing, nausea, hypotension, infusion site extravasation and infusion-related reaction. Hypotension was the only infusion reaction reported by more than 1 subject in the placebo group. Overall, 9.3% of subjects in the combined carlumab group had at least 1 administration site reaction. No subjects in the placebo group had any administration-site reaction.

**Laboratory Assessments:** Laboratory assessments did not identify any safety issues.

STUDY LIMITATIONS:

Dosing in all treatment groups was stopped in the study prematurely. On 21 July 2011, in accordance with the protocol, an external DMC for the study met to perform a preplanned benefit-risk analysis on the Week 24 data. The DMC recommended the discontinuation of further study agent administration for subjects who had been randomized to the 2 highest dose groups (carlumab 5 mg/kg or 15 mg/kg) based on the observed benefit-risk profile of carlumab in these treatment groups. On 03 August 2011, after reviewing these recommendations, an internal Sponsor Executive Committee (SEC) advised stopping administration of study agent in all groups, but continuing the safety follow-up for all subjects in the study. Investigators were notified of this decision via written communication on 05 August 2011. Subjects were encouraged to return for all follow-up visits through the planned Week 72 visit, or until 18 January 2012, whichever came first.

There are no plans to administer carlumab in future studies. For purposes of this abbreviated clinical study report, the key PK and efficacy analyses are presented with full disclosure of all safety data results that were planned and analyzed following the decision to terminate study agent administration.

CONCLUSION:

The study demonstrated that treatment of IPF with carlumab did not improve lung function or reduce associated symptoms. Carlumab was well tolerated by subjects with IPF with no unexpected safety concerns and no dose response in terms of adverse events or changes in laboratory parameters.

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