1. Title

Study Title	A Study of CNTO 148 (Golimumab) Given Alone in Patients with Rheumatoid Arthritis
Investigational product	CNTO 148 (non-proprietary name: golimumab)
Indication	Patients with active rheumatoid arthritis (RA) despite DMARD therapy
Study Design	A multicenter, randomized, double-blind, placebo-controlled study
Study Period	Screening period: from the time of informed consent to immediately before the first administration Treatment period: from the initial administration to Week 120 (4 weeks after the final administration) or from the initial administration to approval for the manufacture and distribution of the drug, whichever is shorter Follow-up period: from 4 weeks to12 weeks after the last administration
Dose and Mode of Administration	The subjects were randomly assigned to one of three treatment groups (placebo group, CNTO 148 50 mg group or 100 mg group) at the ratio of 1:1:1, respectively. Employing the double dummy method to secure the blindness, subcutaneous administration was conducted every 4 weeks using two syringes of placebo for the placebo group, two syringes of placebo and CNTO 148 50 mg and two syringes of placebo and CNTO 148 100 mg for the CNTO 148 50-mg group and the CNTO 148 100-mg group, respectively. At Week 16 or later, for the placebo group, CNTO 148 50 mg was administered instead of placebo, and for the CNTO 148 50-mg group and the CNTO 148 100-mg group, the dose being used was continued, respectively. The blindness was maintained until database lock (DBL) in all subjects at Week 16, and after unblinding, administration with placebo that was used in the double-dummy method was discontinued, and administration with CNTO 148 only was conducted.
Sponsors	Janssen Pharmaceutical K.K. Mitsubishi Tanabe Pharma Corporation
Protocol Number	JNS012-JPN-04 (CR015343)
Clinical Phase	Phase II/III
Start Date of Study	May 28, 2008 (date of informed consent in the first subject)
End Date of Study	Oct 28, 2011 (Date of last observation of the last subject)
Medical Expert	Masayoshi Harigai, Professor, Pharmacovigilance, Department of Comprehensive Medical and Dental Research, Graduate School of Tokyo Medical and Dental University
Sponsor's Contact Information	Study Directors: Hidenori Honkawa, Director, Research and Development Division, Janssen Pharmaceutical K.K. Yoshihiro Kobayashi, Director, Clinical Planning 2, Mitsubishi Tanabe Pharma Corporation Persons in charge of the study Janssen Pharmaceutical K.K. Takuya Oba, Clinical Leader, Research and Development Division, Janssen Pharmaceutical K.K. 5-2, Nishi-kanda 3-chome, Chiyoda-ku, Tokyo 101-0065 TEL: 03-4411-5963 Mitsubishi Tanabe Pharma Corporation Toru Yoshinari, Group Manager, Clinical Planning 2, Research and Development Division 2-6, Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo 103-8405 TEL: 03-3241-4713 Hiromichi Yoshida, Group Manager, Clinical Development 2, Research and Development Division 2-6, Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo 103-8405 TEL: 03-3241-4740
Statement of compliance with GCP	This study was conducted in compliance with ethical principles of the Declaration of Helsinki and the Good Clinical Practice (GCP). All the study-related documents and materials are appropriately stored at each responsible department.
Reporting date	June 28, 2012

2. Synopsis

<table>
<tr><td>Sponsors:
Janssen Pharmaceutical K.K.
Mitsubishi Tanabe Pharma Corporation</td><td rowspan="3">Summary table of each study
Relevant place in application dossiers
Volume number:
Page:</td><td rowspan="3">(For official use)</td></tr>
<tr><td>Product name: To be determined</td></tr>
<tr><td>Active ingredient name: golimumab</td></tr>
<tr><td colspan="3">Study Title: A Study of CNTO 148 (Golimumab) Given Alone in Patients with Rheumatoid Arthritis</td></tr>
<tr><td colspan="3">Investigators: A total of 102 investigators including Fuminori Hirano (see Appendix 16.1.4)</td></tr>
<tr><td colspan="3">Investigator sites:
A total of 102 investigator sites including Internal Medicine II, Asahikawa Medical College Hospital (see Appendix 16.1.4)</td></tr>
<tr><td colspan="3">Published Papers: Ann Rheum Dis Published Online First: 14 September 2012 doi:10.1136/annrheumdis-2012-201796 (Week 24 cut-off report)</td></tr>
<tr><td colspan="2" rowspan="2">Study Period:
From May 28, 2008 (Date of informed consent obtained from the first subject) to Oct 28, 2011 (Date of last observation of the last subject)</td><td>Clinical phase:
II/III</td></tr>
<tr><td>Study type:
Dose finding study and confirmatory study to assess the efficacy</td></tr>
<tr><td colspan="3">Objectives:
In patients with active rheumatoid arthritis (RA) despite treatment with a disease-modifying antirheumatic drug (DMARD), CNTO 148 50 mg or 100 mg was subcutaneously administered every 4 weeks to assess the efficacy [primary endpoint: proportion of subjects who attained ≥ 20% improvement in ACR core set at Week 14 compared with immediately before initial treatment (hereinafter referred to as ACR20% improvement)] and safety using placebo as a control, and to assess the safety and efficacy in long-term administration. In addition, the pharmacokinetics (including determination of serum anti-CNTO 148 antibody) was assessed.</td></tr>
<tr><td colspan="3">Methodology:
The study was a multicenter, randomized, double-blind, placebo-controlled study in patients with active rheumatoid arthritis despite treatment with DMARD. Treatment period was from the initial administration to Week 120 (4 weeks after the final administration) or from the initial administration to manufacturing and marketing approval of the drug, whichever is shorter. The subjects were randomly assigned to one of three treatment groups (placebo group, CNTO 148 50 mg group or CNTO 148 100 mg group) at the ratio of 1:1:1, respectively. Employing the double dummy method to secure the blindness, subcutaneous administration was conducted every 4 weeks using two syringes of placebo for the placebo group, two syringes of placebo and CNTO 148 50 mg and two syringes of placebo and CNTO 148 100 mg for the CNTO 148 50-mg group and the CNTO 148 100-mg group, respectively. At Week 16 or later, for the placebo group, CNTO 148 50 mg was administered instead of placebo, and for the CNTO 148 50-mg group and the CNTO 148 100-mg group, the dose being used was continued, respectively. The blindness was maintained until database lock (DBL) in all subjects at Week 16, and after unblinding, administration with placebo that was used in the double-dummy method was discontinued, and administration with CNTO 148 only was conducted. From Week 52, for the subjects being treated with CNTO 148 100 mg, dose reduction of CNTO 148 to 50 mg was allowed after the physician in charge considered the subject's symptom and condition and confirmed the subject's will. However, no dose escalation was allowed after the dose reduction.</td></tr>
<tr><td colspan="3">Number of subjects (planned and analyzed):
Planned:
Target number of subjects enrolled (assigned): 300 (100 per group)
Number of subjects analyzed: 285 (95 per group)
Analyzed:
Number of subjects registered: 316
Analysis sets for efficacy:
Full analysis set (FAS): 308 subjects
(Placebo group: 105 subjects, CNTO 148 50-mg group: 101 subjects, CNTO 148 100-mg group: 102 subjects)
Per-protocol set (PPS): 296 subjects
(Placebo group: 99 subjects, CNTO 148 50-mg group: 96 subjects, CNTO 148 100-mg group: 101 subjects)
Safety population (SP): 308 subjects
(Placebo group: 105, CNTO 148 50-mg group: 101, CNTO 148 100-mg group: 102)
Analysis set for clinical pharmacology (pharmacokinetics, pharmacodynamic markers and immunogenicity):</td></tr>
</table>

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308 subjects
(Placebo group: 105 subjects, CNTO 148 50 mg group: 101 subjects, CNTO 148 100 mg group: 102 subjects)

Diagnosis and Inclusion Criteria:

Patients who met all of the following items 1-7 were enrolled as subjects for this study.

1. Prior to the conduct of the study, patients who were given a sufficient explanation about the investigational product and the study and have given consent in writing to participating in the study.
2. Male and female patients at least 20 years of age and younger than 75 years of age (at the time of informed consent).
3. Patients diagnosed with rheumatoid arthritis (RA) at least 3 months prior to registration, whose diagnosis was established according to the classification criteria published by the American College of Rheumatology (1987) at the time of informed consent.
4. Patients who showed no response to treatment with at least one DMARD in the past (prior to informed consent).
5. If the patients are receiving DMARD treatment, patients who can take a washout period of DMARD for at least 4 hours prior to initial treatment.
6. Patients who have at least 6 swollen joints and 6 tender joints at the time of registration and immediately prior to initial treatment.
   Note: Joints treated by artificial joint replacement or arthrodesis were to be excluded from the joints to be assessed.
7. Patients with active disease meeting at least two of the following four criteria:
   a. C-reactive protein (CRP) $\geq$ 2.0 mg/dL or ESR (Westergren method: 1-hour value) $\geq$ 28 mm at the time of registration.
   b. Morning stiffness persisting for at least 30 minutes at the time of registration.
   c. Evidence of bone erosion on X-ray film taken at the time of registration (or before registration)
   d. Positive test results for anti-CCP antibody or rheumatoid factors at the time of registration (if the test value exceeded the upper limit of reference range, it was considered positive.)

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Investigational Product, Dose and Mode of Administration, Lot Numbers:

	Investigational Product: CNTO 148		Control Drug: Placebo (indistinguishable from the investigational product in appearance)	
Dosage form	Injection solution in prefilled syringe		Injection solution in prefilled syringe	
Volume	0.5 mL	1.0 mL	0.5 mL	1.0 mL
Composition	50 mg of CNTO 148 per 0.5 mL	100 mg of CNTO 148 per 0.5 mL	Not containing CNTO 148.	
Additives	D-sorbitol, L-histidine, L-histidine hydrochloride, polysorbate 80		D-sorbitol, L-histidine, L-histidine hydrochloride, polysorbate 80	
Description	Colorless to yellow clear liquid, pH approx. 5.5		Colorless to yellow clear liquid, pH approx. 5.5	
Lot numbers	09HE, 12HH, 16HL, 20IB, 27IG, 31IL	08HE, 13HH, 17HL, 21IB, 28IG, 32IL, 34JC	09HE, 12HH, 16HL, 20IB	08HE, 13HH, 17HL, 21IB

In each treatment group, two types of the study drug at different doses were subcutaneously administered every 4 weeks under double-blind conditions from the initial treatment to DBL in all the subjects at Week 16 according to the following table. From DBL at Week 16, after unblinding, CNTO 148 only was subcutaneously administered every 4 weeks. From Week 52, for the subjects being treated with CNTO 148 100 mg, dose reduction of CNTO 148 to 50 mg was allowed after the physician in charge considered the subject's symptom and condition and confirmed the subject's will. However, no dose escalation was allowed after the dose reduction. The injection site was to be the abdomen, front thigh or upper arm (preference was given to the abdomen unless there was a special reason). After completion of the investigation, observation/examination (except for the physical examination and confirmation of the injection site reaction after investigational treatment) on that day, the study drug was subcutaneously administered slowly at the site different from the previous one.

	Initial treatment to Week 12	Week 16 to DBL at Week 16	From DBL at Week 16 to Week 116
Placebo group	0.5 mL (placebo) 1.0 mL (placebo)	0.5 mL (CNTO 148) 1.0 mL (placebo)	0.5 mL (CNTO 148)
CNTO 148 50 mg group	0.5 mL (CNTO 148) 1.0 mL (placebo)	0.5 mL (CNTO 148) 1.0 mL (placebo)	0.5 mL (CNTO 148)
CNTO 148 100 mg group	0.5 mL (placebo) 1.0 mL (CNTO 148)	0.5 mL (placebo) 1.0 mL (CNTO 148)	At dose reduction 0.5 mL (CNTO 148)
			1.0 mL (CNTO 148)

Study Period:
Screening period: From obtaining consent to immediately before initial treatment
Treatment period: from the initial administration to Week 120 (4 weeks after the final administration) or from the initial administration to the manufacturing and marketing approval of the drug, whichever is shorter
Follow-up period: From 4-12 weeks after the final treatment.

Evaluation Criteria:
Efficacy:
(1) Primary endpoint
ACR20% improvement at Week 14
(2) Secondary endpoints
a. At Week 14:
· Proportion of subjects who attained 50%, 70% or 90% improvement in ACR core set compared with immediately before initial treatment (hereinafter referred to as ACR50% improvement, ACR70% improvement and ACR90% improvement)
· Disease Activity Score (DAS) 28
· Change from baseline in physician's physical function assessment (Health assessment

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questionnaire; HAQ)

b. At Week 24, Week 52, Week 104 and Week 120:
- ACR20% improvement, ACR50% improvement, ACR70% improvement, ACR90% improvement
- DAS28
- Assessment of joint X-ray (change from baseline in van der Heijde-modified Sharp score; vdH-S)
- Change from baseline in HAQ
- Study continuation rate

c. ACR improvement index (ACR-N) at Week 14, Week 24, Week 52, Week 104, Week 120

Safety:
(1) Adverse events (Treatment-Emergent Signs and Symptoms; TESS)
(2) Subjective symptoms/ objective findings
(3) Assessment of injection site reaction
(4) Laboratory examinations (hematological examination, blood chemistry test, other blood tests, urinalysis)
(5) Vital signs and physical findings (blood pressure, pulse rate, body temperature, body weight)
(6) Chest X-ray

Clinical pharmacology:
(1) Serum CNTO 148 concentrations
(2) Pharmacodynamic markers (serum IL-6, MMP-3, ICAM-1, VEGF, TNFα and haptoglobin concentrations)
(3) Immunogenicity (anti-CNTO 148 antibody)

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Statistical methods:

1. Analysis sets

As populations for efficacy, FAS and PPS were employed, and FAS was considered the main analysis set. For assessment items for safety and clinical pharmacology, the safety population (SP) and analysis set for assessment items of clinical pharmacology were set, respectively.

2. Efficacy analyses

1) Primary endpoint

The ACR20% improvement at Week 14 was calculated by treatment group, and the group comparisons among the placebo group, CNTO 148 50 mg group and CNTO 148 100 mg were conducted using the chi-square test. Considering the multiplicity, the test was conducted using the closed testing procedure. First, a comparison between the CNTO 148 100 mg and placebo group was conducted, and only if a statistically significant difference was observed, a comparison between the CNTO 148 50 mg group and placebo group was conducted, and only if a statistically significant difference was observed in the pair comparison, respectively, the efficacy of CNTO 148 was considered to have been confirmed.

2) Secondary endpoints

The proportions of ACR20% improvement, ACR50% improvement, ACR70% improvement and ACR90% improvement at Week 24 and Week 52 were calculated. For details of the ACR improvement criteria, descriptive statistics were calculated. For HAQ, vdH-S, DAS28 and ACR-N at Week 24 and Week 52, the descriptive statistics (number of subjects, mean, standard deviation, minimum, median, maximum) were calculated, and the descriptive statistics for change from baseline were calculated as well.

3. Safety analyses

For adverse events and adverse reactions [adverse events of which the causal relationship could not be ruled out (“Doubtful”, “Possible”, “Probable”, “Very likely”)], the incidence was calculated for each event. The adverse events were calculated by severity, and serious adverse events were also calculated. In laboratory test values and vital signs, for quantitative items, descriptive statistics of test value at each examination time and the change from baseline were calculated by treatment group. For qualitative items, the frequency table was prepared by treatment group.

4. Analyses of clinical-pharmacology assessment items

In the pharmacokinetic analysis, descriptive statistics of serum CNTO 148 concentration at each blood sampling time [number of subjects, mean, standard deviation, coefficient of variance (CV% = standard deviation / mean ×100), median, interquartile range (first quartile [Q1] – third quartile [Q3]), and range (minimum – maximum)] were calculated by treatment group, and the profile of serum CNTO 148 concentration (median) was diagrammatically shown by treatment group.

In the analysis of pharmacodynamic markers, descriptive statistics of serum concentration at each blood sampling time [number of subjects, mean, standard deviation, coefficient of variance (CV% = standard deviation / mean ×100), median, interquartile range (first quartile [Q1] – third quartile [Q3]), and range (minimum – maximum)] were calculated by pharmacodynamic marker and treatment group, and the profile of serum concentration (median) was diagrammatically shown by treatment group.

For immunogenicity (anti-CNTO 148 antibody), the numbers of subjects who were antibody negative, antibody positive and unevaluable were calculated, and in the case of antibody positive, the antibody titer was calculated.

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Summary – Conclusion

Efficacy results:

In the previous reports of the study, the analysis results based on vdH-S of the X-ray films interpreted as session 1 and 2 has been described. Joint X-ray films at baseline, at Weeks 52, 104 and 120 and at discontinuation up to Week 120 were interpreted as session 3. In this report, the analysis results based on session 3 are described.

Changes from baseline in Total vdH-S Score (TSS) at Weeks 104 and 120 tended to be smaller in CNTO 148 100 mg group than in the CNTO 148 50 mg group and the placebo group. The proportion of the patients whose TSS change from baseline to Week 104 or to Week 120 was equal to or less than 0 was higher in CNTO 148 100 mg group than those in placebo and those in CNTO 148 50 mg group. The median changes from baseline of erosion score were 0.50 in any of the evaluation time point in CNTO 148 50 mg group, while they were 0.00 in the placebo and CNTO 148 100 mg group. The proportion of the patients whose JSN change from baseline to Week 104 or to Week 120 were smaller in CNTO 148 50 mg group and CNTO 148 100 mg group than those in placebo. The proportion of the patients with no novel bone erosion at Week 120 were 67.6% (48/71) in placebo, 58.8% (40/68) in CNTO 148 50 mg group and 60.5% (52/86) in CNTO 148 100 mg group, and there were no big difference among them. The proportion of the patients with no novel JNS at Week 120 were 70.4% (50/71) in placebo, 72.1% (49/68) in CNTO 148 50 mg group and 83.7% (72/86) in CNTO 148 100 mg group, and there were no big difference among them.

The changes in TSS were analyzed by sex, age, body weight, CRP and duration of the disease. As in the overall analysis, changes from baseline in TSS in the CNTO 148 100 mg group were equal to or smaller than in the CNTO 148 50 mg group in the in most of these subgroup analyses. Among subjects with body weight of <50 kg and subjects with a disease duration of <3 years, however, changes in TSS were larger in the CNTO 148 100 mg group than in CNTO 148 50 mg group.

The ACR20 improvements in the CNTO 148 50 mg group were 71.4% (60/84) at week 52, 85.1% (63/74) at week 104 and 87.0% (60/69) at Week 120, respectively. ACR improvement was maintained from Week 52 to Week 120. The ACR20 improvements in the CNTO 148 100 mg group were 81.9% (77/94) at week 52, 88.9% (80/90) at week 104 and 89.5% (77/86) at Week 120, respectively. ACR improvement was maintained from Week 52 to Week 120.

The percentage of subjects who achieved ACR20 improvements at the completion or premature discontinuation of treatment was 75.2% (76/101) in the CNTO 148 50 mg group and 85.3% (87/102) in the CNTO148 100 mg group. The ACR20 improvements at after 12 weeks of the last treatment showed 69.5% (66/95) in the CNTO 148 50 mg group and 74.0% (74/100) in the CNTO 148 100 mg group, and the value showed slight decrease from the last treatment however the ACR improvement was maintained with higher proportion.

The median numbers of tender or swelling joints, the median of pain VAS of the patients, patient global assessment of disease, physician global assessment of disease, CRP and HAQ improvement showed no big change from Week 52 to Week 120 and the improvement was maintained in both of the CNTO 148 50 mg group and CNTO 148 100 mg group.

The proportion of the patients whose DAS28 (CRP) or DAS (ESR) showed remission from week 52 to Week 120 in both of the CNTO 148 50 mg group and CNTO 148 100 mg group showed no decline and the improvement was maintained. The proportion of the patients whose HAQ showed remission from week 52 to Week 120 in both of the CNTO 148 50 mg group and CNTO 148 100 mg group showed no decline and the improvement was maintained.

The above results demonstrated that the effect of treatment with CNTO 148 50 or 100 mg every 4 weeks for improving RA symptoms was maintained during long-term treatment without any reduction. As reported in the literature, it was inferred that monotherapy of CNTO 148 was likely to inhibit the progression of joint destruction for 2 years.

Clinical pharmacology results:

When CNTO 148 alone was subcutaneously administered to RA patients by repeated dose administration, the variability of serum CNTO 148 concentration was large, however serum CNTO 148 concentration (median) increased almost dose-proportionally. Serum CNTO 148 concentrations at after 12 weeks of the last treatment decreased to below BQL in almost half of the patients. When CNTO 148 was administered to subjects by repeated subcutaneous dose administration, serum IL-6, haptoglobin, ICAM-1 and MMP-3

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concentrations (median) at Weeks 104 and 120 generally showed low values compared with before the initiation of CNTO 148 treatment. Those serum IL-6, haptoglobin, ICAM-1 and MMP-3 concentrations (median) slightly increased at after 12 weeks of the last treatment as compared with those in the repeated administration of CNTO 148. Serum VEGF concentrations at Weeks 104 and 120 increased as compared with before the initiation of CNTO 148 treatment.

Of the subjects treated with CNTO 148 by repeated subcutaneous dose administration, the number of subjects who showed anti-CNTO 148 antibody positive (positive rate) was 15/295 subjects (5.1%).

Safety results:

Study treatment was initiated in 101 patients of the CNTO 148 50 mg group and in 102 patients of the CNTO 148 100 mg group. Of these, 68 and 86 patients completed the study treatment. The incidence of adverse events was 94.9% (280/295 subjects, 2182 events) in total subjects treated with CNTO 148, it was 93.8% in the CNTO 148 50 mg group and it was 97.1% in the CNTO 148 100 mg group. The adverse events relevant to “Infections and Infestations” were the most frequent reported adverse events in any of the treatment group. Among the adverse events, the most frequent reported event was nasopharyngitis, however the incidence by treatment group showed the same result.

Most of the adverse events were mild in severity, and moderate adverse events observed in 2 or more subjects in each treatment group were herpes zoster, ovarian neoplasm, diabetes mellitus, dizziness, cataract, interstitial lung disease, colonic polyp, osteoporosis, rheumatoid arthritis and intervertebral disc protrusion in the CNTO 148 50 mg group, those were nasopharyngitis, cellulitis and dental caries in the CNTO 148 100 mg group.

Adverse events with severe intensity were each one subject of herpes zoster, cellulitis, pyelonephritis, intervertebral discitis, brain stem haemorrhage, cerebral infarction, lumber spinal stenosis, rheumatoid arthritis, arthritis, spondylolisthesis and hydrocele in the CNTO 148 50 mg group and those were each one subject of cellulitis, urocepsis, breast cancer, pancreatic carcinoma, cerebral haemorrhage, renal failure acute and epididymitis in the CNTO 148 100 mg group.

Two deaths were reported during the study. One patient in the CNTO 148 50 mg group died of brain stem haemorrhage on the day that the event occurred. The investigator ruled out the causal relationship to study treatment. One case of pancreatic carcinoma was reported in the CNTO 148 100 mg group, and the patient died 5 months after the report. The investigator assessed the causal relationship to study treatment as possible.

The incidence of serious adverse events was 16.9% (50/295 subjects) in the total subjects treated with CNTO 148, was 19.7% in the CNTO 148 50 mg group and was 11.8% in the CNTO 148 100 mg group.

The incidence of adverse events resulting in discontinuation of investigational treatment was 12.2% (36/295 subjects) in the total subjects treated with CNTO 148, 14.0% in the CNTO 148 50 mg group and 8.8% in the CNTO 148 100 mg group. The adverse events that occurred in 2 or more subjects and resulted in discontinuation of investigational treatment were herpes zoster, pyelonephritis and ovarian neoplasm (each 2 subjects), interstitial lung disease and rheumatoid arthritis (each 3 subjects), and 2 patients of cell marker increased (reported term: elevation of KL-6) in the CNTO 148 50 mg group. No tuberculosis was reported in any of the treatment group. Bronchopneumonia was reported in each one subject in the CNTO 148 50 mg group and CNTO 148 100 mg group. Organizing pneumonia which is not included in SOC infection and infestations but it belongs to SOC respiratory, thoracic and mediastinal disorders was one subject in the CNTO 148 100 mg group. Interstitial lung disease were reported in 4 subjects in the CNTO 148 50 mg group.

Ovarian neoplasm in 2 subjects and colon cancer of one subject were reported in the CNTO 148 50 mg group and each one of breast cancer and pancreatic carcinoma was reported in the CNTO 148 100 mg group. No anaphylactic reaction and serum sickness-like reaction was reported.

In all the subjects treated with CNTO 148 through whole treatment period (the mean observation period 106.9 weeks), the incidences of moderate adverse events, severe adverse events, serious adverse events and adverse events resulting in discontinuation of investigational treatment were 20.3% (60/295 subjects), 4.7% (14/295 subjects), 16.9% (50/295 subjects, 67 events) and 12.2% (36/295 subjects, 39 events), respectively. The incidences in all the subjects treated with CNTO 148 up to Week 52 (the mean treatment period 44.7 weeks) were 11.2% (33/295 subjects), 1.4% (4/295 subjects), 6.4% (19/295 subjects, 23 events) and 3.7% (11/295 subjects, 11 events), respectively. The incidences in all the subjects treated with CNTO 148 up to Week 16 (the mean treatment period 15.9 weeks) were 3.4% (7/203 subjects), 1.0% (2/203 subjects), 1.5%

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(3/203 subjects, 3 events) and 1.5% (3/203 subjects, 3 events), respectively (Interim CSRs of Week 52 and Week 16).

Incidences of the adverse events obtained by patient-year analysis were compared between the treatment groups of CNTO148 50 mg and CNTO148 100 mg. The incidence of any adverse events, the events with moderate intensity, the events with severe intensity, the events leading to discontinuation, the serious adverse events, the serious infections and the events of death were not apparently high in the CNTO148 100 mg group, while the incidence of the events with moderate intensity, the events leading to discontinuation and the serious adverse events were rather higher in CNTO148 50 mg group.

Report date: June 28, 2012

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