1. Title

Study Title	A Study of CNTO 148 (Golimumab) Given in Combination with MTX in Patients with Rheumatoid Arthritis
Investigational Product	CNTO 148 (non-proprietary name: golimumab)
Indication	Patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy
Study Design	A multicenter, randomized, double-blind, placebo-controlled study
Study Period	Screening period: from the time of informed consent until immediately before the first administration Treatment period: from the first administration until Week 156 (4 weeks after the final administration) or until the manufacturing/marketing approval of the study drug, whichever was shorter Follow-up period: from 4 weeks to 12 weeks after the last administration
Dose and Mode of Administration	Subjects were randomly assigned to one of three treatment groups (placebo + MTX group, CNTO 148 50 mg + MTX group or CNTO 148 100 mg + MTX group) at a ratio of 1:1:1, respectively. Placebo was administered to the placebo + MTX group, CNTO 148 50 mg was administered to the CNTO 148 50 mg + MTX group, and CNTO 148 100 mg was administered to the CNTO 148 100 mg + MTX group subcutaneously every 4 weeks, respectively. At the Week-14 assessment, subjects who could not attain ≥20% improvement from baseline in the number of tender joints and number of swollen joints were registered as Early Escapes (EE). From Week 16, CNTO 148 50 mg was administered to the placebo + MTX group instead of placebo, and for the CNTO 148 50 mg + MTX group, CNTO 148 100 mg was administered instead of 50 mg, and for the CNTO 148 100 mg + MTX group, the same treatment was continued without changing the dose. Subjects who were not registered as EE continued the initial dose up to Week 24. After Week 24, for the subjects registered as EE, the dose being given at Week 24 was continued. Of the subjects not registered as EE, for the placebo + MTX group, CNTO 148 50 mg was administered instead of placebo (the doses of CNTO 148 for the CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group were continued). From Week 52, for the subjects being treated with CNTO 148 100 mg (the subjects registered as EE in the CNTO 148 50 mg + MTX group, and all subjects in the CNTO 148 100 mg + MTX group), 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.
Name of the sponsors	Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation
Protocol number	JNS012-JPN-03 (CR015340)
Clinical phase	Phase II/III
Start date of study	May 30, 2008 (Date of informed consent in first subject)
End date of study	Dec 27, 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
Sponsors' contact information	Study Directors: Hidenori Honkawa, Director, Research and Development (R&D) Division, Janssen Pharmaceutical K.K. Masahiko Tanaka, Director, Clinical Planning 2, Mitsubishi Tanabe Pharma Corporation Responsible clinical research associates of the study: Janssen Pharmaceutical K.K. Takuya Oba, Clinical Leader, R&D 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.
Report 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 in Combination with MTX in Patients with Rheumatoid Arthritis</td></tr>
<tr><td colspan="3">Investigators: A total of 89 investigators including Fuminori Hirano (see Appendix 16.1.4)</td></tr>
<tr><td colspan="3">Investigator sites:
A total of 89 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. 2012 Jun;71(6):817-24. Epub 2011 Nov 25. (Week 24 cut-off report)</td></tr>
<tr><td colspan="2" rowspan="2">Study Period:
From May 30, 2008 (Date of informed consent obtained from the first subject) to Dec 27, 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 despite treatment with methotrexate (MTX), 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 investigational treatment (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 MTX. Treatment period was from the initial administration until Week 156 (4 weeks after the final administration) or until the manufacturing/marketing approval of the study drug, whichever was shorter. Subjects were randomly assigned to one of three treatment groups (placebo + MTX group, CNTO 148 50 mg + MTX group or CNTO 148 100 mg + MTX group) at a 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 + MTX 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 the Week-14 assessment, subjects who could not attain ≥20% improvement from baseline in the number of tender joints and number of swollen joints were registered as Early Escapes (EE). From Week 16, CNTO 148 50 mg was administered to the placebo + MTX group instead of placebo, and for the CNTO 148 50 mg + MTX group, CNTO 148 100 mg was administered instead of 50 mg, and for the CNTO 148 100 mg + MTX group, the same treatment was continued without changing the dose. Subjects who were not registered as EE continued the initial dose up to Week 24. After Week 24, for the subjects registered as EE, the dose being given at Week 24 was continued. Of the subjects not registered as EE, for the placebo + MTX group, CNTO 148 50 mg was administered instead of placebo (the doses of CNTO 148 for the CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group were continued). The blindness was maintained until database lock (DBL) in all subjects at Week 24, 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 (the subjects registered as EE in the CNTO 148 50 mg + MTX group, and all subjects in the CNTO 148 100 mg + MTX group), 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. For MTX used concomitantly, a certain amount of dose (6 mg/week to 8 mg/week) was to be administered orally from at least 4 weeks before the initial investigational treatment to the completion of assessment at Week 52. A dose reduction was allowed only if it was unavoidably required for the subject's safety. If the reduced dose was increased again, the dose used at the initial administration was considered the upper limit.</td></tr>
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Number of subjects (planned and analyzed):
Planned:
Target number of subjects enrolled (assigned): 255 (85 per group)
Number of subjects analyzed: 240 (80 per group)
Analyzed:
Number of subjects registered: 269
Analysis sets for efficacy:
Full analysis set (FAS): 261 subjects
(Placebo+MTX group: 88 subjects, CNTO 148 50 mg + MTX group: 86 subjects, CNTO 148 100 mg + MTX group: 87 subjects)
Safety population (SP): 261 subjects
(Placebo+MTX group: 88 subjects, CNTO 148 50 mg + MTX group: 86 subjects, CNTO 148 100 mg + MTX group: 87 subjects)
Analysis set for clinical pharmacology (pharmacokinetics, pharmacodynamic markers and immunogenicity): 261 subjects
(Placebo+MTX group: 88 subjects, CNTO 148 50 mg + MTX group: 86 subjects, CNTO 148 100 mg + MTX group: 87 subjects)

Diagnosis and Inclusion Criteria:

Patients who met all of the following items 1-6 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 who received a diagnosis of 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 are receiving MTX treatment (≥6 mg/week) from at least 3 months prior to initial treatment at the identical dose (6 mg/week to 8 mg/week) for at least 4 weeks prior to initial treatment.
5. Patients who have at least 4 swollen joints and 4 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.
6. Patients with active disease who meet at least two of the following four criteria:
   a. C-reactive protein (CRP) ≥ 2.0 mg/dL or ESR (Westergren method: 1-hour value) ≥ 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	Contains 50 mg of CNTO 148 per 0.5 mL	Contains 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	07HD, 10HH, 14HL, 18IB, 23IF, 25IG, 29IL	06HD, 11HH, 15HL, 19IB, 24IF, 26IG, 30IL, 33JC	07HD, 10HH, 14HL, 18IB, 23IF	06HD, 11HH, 15HL, 19IB, 24IF

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 24 according to the following table. From DBL at Week 24, after unblinding, CNTO 148 only was subcutaneously administered every 4 weeks. From Week 52, for the subjects being treated with CNTO 148 100 mg (the subjects registered as EE in the CNTO 148 50 mg + MTX group, and all subjects in the CNTO 148 100 mg + MTX group), 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.

<table>
<tr><th></th><th>Initial treatment to Wk 12</th><th>EE</th><th>Wk 16, Wk 20</th><th>Wk 24 to DBL at Wk 24</th><th>From DBL at Wk 24 to Wk 48</th><th>Wk 52 to Wk 152</th></tr>
<tr><td rowspan="2">Placebo +MTX group</td><td rowspan="2">0.5 mL (placebo)
1.0 mL (placebo)</td><td>Reg.</td><td colspan="2">0.5 mL (CNTO 148)
1.0 mL (Placebo)</td><td rowspan="2">0.5 mL (CNTO 148)</td><td rowspan="2">0.5 mL (CNTO 148)</td></tr>
<tr><td>Non-reg.</td><td>0.5 mL(Placebo)
1.0 mL (Placebo)</td><td>0.5 mL (CNTO 148)
1.0 mL (Placebo)</td></tr>
<tr><td rowspan="3">CNTO 148 50 mg +MTX group</td><td rowspan="3">0.5 mL (CNTO 148)
1.0 mL (placebo)</td><td rowspan="2">Reg.</td><td colspan="2" rowspan="2">0.5 mL (Placebo)
1.0 mL (CNTO 148)</td><td rowspan="2">1.0 mL (CNTO 148)</td><td>At dose reduction
0.5 mL (CNTO 148)</td></tr>
<tr><td>1.0 mL (CNTO 148)</td></tr>
<tr><td>Non-reg.</td><td colspan="2">0.5 mL (CNTO 148)
1.0 mL (Placebo)</td><td>0.5 mL (CNTO 148)</td><td>0.5 mL (CNTO 148)</td></tr>
<tr><td rowspan="2">CNTO 148 100 mg +MTX group</td><td rowspan="2">0.5 mL (placebo)
1.0 mL (CNTO 148)</td><td rowspan="2">Reg.</td><td colspan="2" rowspan="2">0.5 mL (Placebo)
1.0 mL (CNTO 148)</td><td rowspan="2">1.0 mL (CNTO 148)</td><td>At dose reduction
0.5 mL (CNTO 148)</td></tr>
<tr><td>Non-reg.</td><td>1.0 mL (CNTO 148)</td></tr>
</table>

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<tr><td colspan="3">Study period:
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Evaluation criteria:

Efficacy:

(1) Primary endpoint

ACR20% improvement at Week 14

(2) Secondary endpoints

a. At Week 14:

- Proportion of subjects who attained at least 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 Questionnaire; HAQ)

b. At Week 24, Week 52, Week 104 and Week 156:

- ACR20% improvement, ACR50% improvement, ACR70% improvement and ACR90% improvement
- DAS28
- Assessment of joint X-ray (change from baseline in van der Heijde-modified Sharp score)
- 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

d. ACR20% improvement, ACR50% improvement, ACR70% improvement and ACR90% improvement at Week 24 in subjects transferred to EE

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 a per protocol set (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 + MTX group, CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group were conducted using the chi-square test. Considering the multiplicity in the test, a comparison between a combined group (of the CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group) and the placebo + MTX group was conducted, and if a statistically significant difference was observed, a comparison between the CNTO 148 50 mg + MTX group and placebo + MTX group and a comparison between the CNTO 148 100 mg + MTX group and placebo + MTX group were conducted.

2) Secondary endpoints

The proportions of ACR20% improvement, ACR50% improvement, ACR70% improvement and ACR90% improvement at Week 24 were calculated. For details of the ACR improvement criteria, descriptive statistics were calculated. For HAQ, vdH-S, DAS28 and ACR-N at Weeks 14 and 24, the descriptive statistics (number of subjects, mean, standard deviation, minimum, median and 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.

Summary – Conclusion

Based on results of the combination treatment study of CNTO 148 and MTX in patients with active rheumatoid arthritis despite MTX treatment, the efficacy, safety and pharmacokinetics were assessed, and as a result, the following conclusions were obtained.

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 156 and at discontinuation up to Week 156 were interpreted as session 3. In this report, the analysis results based on session 3 are described.

In session 3, the median changes from baseline in TSS at Weeks 52, 104 and 156 in any of the treatment groups with or without missing data imputation were 0.00. This result indicated that joint destruction did not progress for 156 weeks. The median changes from baseline of erosion and joint space narrowing (JSN) were also zero. The improvement effect was maintained through 156 weeks. The proportions of the patients with no novel bone erosion and with no novel JSN were similar in any of the treatment groups and

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they were equal to or more than 70% at Week 104. The proportion of the patients whose TSS change from Week 52 to 156 exceeded SDC were 15.2% in combined CNTO 148 group, 13.4% in the CNTO 148 50 mg + MTX group and 16.9% in the CNTO 148 100 mg + MTX group and all these were higher than that of 1.4% in the placebo+MTX group. The proportion of the patients whose TSS change from Week 104 to 156 exceeded SDC were higher in combined CNTO 148 group, the CNTO 148 50 mg + MTX group and the CNTO 148 100 mg + MTX group than that of the placebo+MTX group. Any of the weighed kappa scores for the erosion score and the JSN score in each X-ray film reader at baseline, at Weeks 52, 104 and 156 were equal to or more than 0.7. Any of the inter class coefficiencies for the TSS and the TSS changes from baseline at baseline and at Weeks 52, 104 and 156 were equal to or more than 0.96. All these implied higher reliability of the results of both readers.

In the CNTO 148 50 mg+MTX group, the percentage of subjects who achieved ACR20%, ACR50%, ACR70% and ACR90% improvements were 94.0%, 73.1%, 49.3% and 19.4%, respectively, at Week 104 and 94.1%, 88.2%, 67.6% and 20.6%, respectively, at Week 156. ACR improvement was maintained from Week 104 to Week 156. The ACR20%, 50%, 70% and 90% improvements in the CNTO 148 100 mg + MTX group were 88.7%, 66.2%, 42.3% and 9.9% at Week 104 respectively and were 89.5%, 81.6%, 57.9% and 21.1% at Week 156, respectively. ACR improvement was maintained from Week 104 to Week 156. At after 12 weeks of the last treatment, the ACR20%, 50%, 70% and 90% improvements in the CNTO 148 50 mg + MTX group were 75.7%, 52.7%, 35.1% and 13.5%, respectively and those in the CNTO 148 100 mg + MTX group were 73.7%, 53.9%, 38.2% and 10.5%, respectively and those in the placebo+MTX group were 71.3%, 62.5%, 37.5% and 15.0%, respectively.

The improvements were also shown to be maintained through 156 weeks in any of the treatment groups from the results of the median numbers of tender or swelling joints, the pain VAS of the patients, the patient global assessment of disease, the physician global assessment of disease, CRP and HAQ improvement. However, all of the parameters showed declined tendency after 12 weeks of the last treatment in any of the treatment groups.

The median ACR-N in the CNTO 148 50 mg + MTX group were 68.42 at Week 104 and 78.36 at Week 156 and the improvement was maintained through Week 156. The median ACR-N in the CNTO 148 100 mg + MTX group were 60.00 at Week 104 and 73.21 at Week 156 and the improvement was maintained through Week 156. However, this parameter showed declined tendency after 12 weeks of the last treatment in any of the treatment groups.

The proportion of the patients whose DAS28 (ESR/CRP) showed good response and moderate response were maintained at 93% from Week 104 to Week 156 in any of the CNTO 148 50 mg + MTX group and the CNTO 148 100 mg + MTX group. The proportion of the patients whose DAS28 (ESR/CRP) showed good response were maintained more than 65% from Week 104 to Week 156. The improvement was maintained without any decline.

The proportion of the patients whose DAS28 (ESR) showed remission were 49.3% and 61.8% in the CNTO 148 50 mg + MTX group at Week 104 and Week 156, respectively. The proportion of the patients whose DAS28 (ESR) showed remission were 39.4% and 55.3% in the CNTO 148 100 mg + MTX group at Week 104 and Week 156, respectively. The proportion of the patients whose DAS28 (CRP) showed remission were 67.2% and 79.4% in the CNTO 148 50 mg + MTX group at Week 104 and Week 156, respectively. The proportion of the patients whose DAS28 (CRP) showed remission were 71.8% and 78.9% in the CNTO 148 100 mg + MTX group at Week 104 and Week 156, respectively. Both of the groups maintained the remission from Week 104 to Week 156.

DAS28 (ESR/CRP) and those changes from baseline at any of the evaluation did not show any decline and the improvement maintained through Week 156 in any of the CNTO 148 50 mg + MTX group and the CNTO 148 100 mg + MTX group.

HAQ and those changes from baseline at any of the evaluation did not show any decline and the improvement maintained through Week 156 in any of the CNTO 148 50 mg + MTX group and the CNTO 148 100 mg + MTX group.

The proportion of the patients whose HAQ showed remission did not show any decline and the improvement maintained through Week 156 in any of the CNTO 148 50 mg + MTX group and the CNTO 148 100 mg + MTX group.

The proportion of the patients who joined the study at Week 104 were 79.5% in the placebo+MTX treatment group, 77.9% in the CNTO 148 50 mg + MTX group and 81.6% in the CNTO 148 100 mg+ TX group. The proportion of the patients who joined the study at Week 156 were 38.6% in the placebo+MTX

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treatment group, 39.5% in the CNTO 148 50 mg + MTX group and 43.7% in the CNTO 148 100 mg + MTX group. These proportions at Week 156 showed no big difference among the treatment group.

Clinical pharmacology results:

When CNTO 148 was subcutaneously administered to RA patients by repeated dose administration in combination with MTX, the variability of serum concentration was large in the both CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group (CV%: 50.2% - 80.6%). The trough concentrations of serum CNTO 148 in the CNTO 148 50 mg + MTX group maintained the similar concentration through Week 156. However, the trough concentrations of serum CNTO 148 was 1.9 times difference between those at Week 104 (n=51) and at Week 156 (n=20) in the CNTO 148 100 mg + MTX group. The median serum concentrations in the patients who completed 156 weeks treatment in the CNTO 148 100 mg + MTX group were 1.83 µg/mL at Week 104 and 2.05 µg/mL at Week 156 (n=20).

When CNTO 148 was administered to subjects by repeated subcutaneous administration in combination with MTX, serum IL-6, haptoglobin, ICAM-1 and MMP-3 concentrations (median) at Weeks 104 and 156 generally showed low values compared with before the initiation of CNTO 148 treatment.

Anti-CNTO 148 antibody positive was found in 2 out of 257 patients (0.8%) who received CNTO 148 in combination with MTX, and the titers of those antibody were low (1:20).

Safety results:

Study treatment was initiated in 86 patients of the CNTO 148 50 mg+MTX group and in 87 patients of the CNTO 148 100 mg+MTX group. Of these, 59 and 66 patients completed the study treatment.

The incidence of adverse events was 97.7% (251/257 subjects, 2277 events) in All CNTO 148+MTX (total subjects treated with CNTO 148), and the incidences by treatment group were 76.1% to 99.0%. The incidence of adverse reactions was 94.6% (243/257 subjects, 1713 events) in All CNTO 148+MTX (total subjects treated with CNTO 148), and the incidences by treatment group were 636% to 97.9%. Among the adverse events and adverse reactions, the system organ class (SOC) that showed the highest incidence by treatment group except for subjects who changed treatment from CNTO 148 50 mg to CNTO 148 100 mg was “Infections and Infestations”.

The adverse event that occurred most frequently was nasopharyngitis in the All CNTO 148+MTX, which was followed by upper respiratory tract inflammation. Among the adverse events by treatment group, except for subjects who changed treatment from placebo to CNTO 148 50 mg from Week 24 and subjects registered as EE who changed treatment from CNTO 148 50 mg to CNTO 148 100 mg, the adverse events that occurred most frequently was nasopharyngitis, which was followed by upper respiratory tract inflammation. The incidence of mild adverse events observed was 64.6% (166/257 subjects) in the All CNTO 148+MTX, and the incidences by treatment group were 60.0% to 72.9%. In the adverse events by treatment group, moderate adverse event that occurred in 2 or more subjects were gastroenteritis, bronchitis, herpes zoster, pneumonia, urinary tract infection, upper respiratory tract infection, dental caries, liver disorder, spinal osteoarthritis and foot fracture. In the All CNTO 148+MTX, the moderate adverse events observed in 2 or more subjects were gastroenteritis, bronchitis, herpes zoster, pneumonia, urinary tract infection, sepsis, dizziness, upper respiratory tract infection, interstitial lung disease, dental caries, liver disorder, cholelithiasis, spinal osteoarthritis, rheumatoid arthritis and foot fracture. Sepsis was severe adverse event found each one of the subject the CNTO 148 50 mg + MTX group and CNTO 148 100 mg + MTX group. There was no severe adverse event observed in 2 or more subjects in any treatment group.

One death from pneumonia (community acquired pneumonia by reported term) and amiloidosis was found in the CNTO 148 100 mg + MTX group.

The incidence of serious adverse events was 21.0% (54/257 subjects) in the All CNTO 148+MTX, and the incidences by treatment group were 2.3% to 21.2%.

The incidence of adverse events resulting in discontinuation of investigational treatment was 16.7% (43/257 subjects) in the All CNTO 148+MTX, and the incidences by treatment group were 1.1% to 18.8%. In the adverse events by treatment group, adverse event that occurred in 2 or more subjects and resulted in discontinuation of investigational treatment was pneumonia in the CNTO 148 100 mg + MTX group. In the All CNTO 148+MTX, the adverse event that occurred in 2 or more subjects and resulted in discontinuation of investigational treatment was pneumonia, pneumonia pneumococcal, interstitial lung disease and liver function test abnormal.

In addition to adverse events resulting in discontinuation of investigational treatment, infection, injection site reaction, malignancy, anaphylactic reaction and serum sickness-like reaction were designated as

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Product name: To be determined		
Active ingredient name: golimumab		

important adverse events.

Incidences of the adverse events belong to SOC infection and infestations were 76.7% (197/257) in the All CNTO 148+MTX and the incidences by treatment group were 44.3% to 76.0%. No tuberculosis was reported.

Incidence of the injection site reaction was 21.0% (54/257) in the All CNTO 148+MTX and the incidences by treatment group were 8.0% to 25.0%. All the events occurred were mild intensity. No discontinuations of the study treatment because of the events were reported.

Malignancies reported during the study were from 6 patients; each one of the uterine cancer and extranodal marginal zone B-cell lymphoma (MALT type) in the patient who changed treatment from placebo to CNTO 148 50 mg from Week 24, each one of the testicular neoplasm, diffuse large B-cell lymphoma and colon cancer in the patient who received CNTO 148 50 mg+MTX, one of the breast cancer in the patient received CNTO 148 100 mg+MTX.

No anaphylactic reaction and serum sickness-like reaction were reported.

Incidences of the adverse events obtained by patient-year analysis were compared between the treatment group of CNTO 148 50 mg + MTX and CNTO 148 100 mg+MTX. The incidence of adverse events leading to discontinuation was slightly higher in CNTO 148 100 mg + MTX than CNTO 148 50 mg + MTX and death was reported only in CNTO 148 100 mg+MTX, however no big difference was reported in the incidences of the adverse events with severe intensity, serious adverse events and serious infection.

No clinically significant changes were found in the blood test, blood chemistry and other laboratory test and urine examination. Changes from baseline in vital sign showed no major differences between the treatment groups and no consistent trends due to the study treatment.

Report date: June 28, 2012

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