2.0 Synopsis

Abbott Japan Co., Ltd. **EISAI Co., LtD.**	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Humira		
Name of Active Ingredient: adalimumab (JAN)		

Title of Study:

A Multi-Center, Randomized, Double-Blind, Placebo-controlled study of Adalimumab for the Induction of Clinical Remission in Japanese Subjects with Crohn's Disease

Investigator:

Satoshi Motoya, M.D. and others, total 31 personnel

Study Sites:

Division of Gastroenterology, Sapporo Kosei General Hospital and others, Total 31 sites in Japan

Publications:

(N/A)

Studied Period (Years): Jan 2007 to Dec 2007 First Subject First Visit: 30 Jan 2007 Last Subject Last Visit: 25 Dec 2007	**Phase of Development:** 2/3

Objectives:

The objective of this study was to demonstrate the efficacy and safety of two doses of adalimumab, 160 mg at Week 0 and 80 mg at Week 2 and 80 mg at Week 0 and 40 mg at Week 2 for the induction of clinical remission in Japanese subjects with moderate to severe Crohn's disease. The pharmacokinetics of adalimumab following subcutaneous (sc) injection including anti-adalimumab antibody (AAA) was also assessed.

Methodology:

This was a Phase 2/3, multi-center, randomized, double-blind, placebo-controlled, efficacy, safety and pharmacokinetic study designed to demonstrate the effectiveness of adalimumab in Japanese subjects with moderate to severe Crohn's disease. At Week 0, subjects who met all of the inclusion criteria and none of the exclusion criteria were randomized 3:3:2 to one of the following treatment arms: 1) adalimumab 160 mg at Week 0 and 80 mg at Week 2 (160/80 mg group) or, 2) adalimumab 80 mg at Week 0 and 40 mg at Week 2 (80/40 mg group) or, 3) placebo at Weeks 0 and Week 2 (placebo group) under the double blinded condition. Stratified randomization was performed by baseline CDAI ≥300 or < 300), history of infliximab treatment and clinical site. At Week 4, subjects were evaluated for efficacy. Subjects that were responders (CDAI decrease of ≥ 70 points compared to Baseline) were rolled-over into a maintenance study M06-837.

Methodology (Continued):

Subjects that were non-responders (did not attain a CDAI decrease of ≥ 70 points compared to Baseline) continued in the induction study and received the following treatments: 1) adalimumab 40 mg at Week 4 and Week 6 (160/80 mg + 40/40 mg group) or, 2) adalimumab 40 mg at Week 4 and Week 6 (80/40 mg + 40/40 mg group) or, 3) adalimumab 160 mg at Week 4 and adalimumab 80 mg at Week 6 (placebo + 160/80 mg group) under the double blinded conditions. At Week 8, non-responders subjects from Week 4 were offered to enroll in the Maintenance study M06-837 whether they were responders or non-responders at Week 8. Efficacy and Safety assessments were performed at Week 0, 1, 2, 4, 5, 6 and 8 (or the time of discontinuation).

Number of Subjects (Planned and Analyzed):

Planned: 80 subjects (30 subjects per each adalimumab group and 20 in the placebo group), informed consent 108 subjects, randomized 90 subjects, completed 84 subjects. All 90 subjects randomized (Placebo: 23 subjects; adalimumab 80/40 mg: 34 subjects, adalimumab 160/80 mg: 33subjects) were included in the efficacy and safety analysis.

Diagnosis and Main Criteria for Inclusion:

Subjects were screened to determine if they met all of the inclusion criteria and had none of the exclusion criteria specified below.

Inclusion criteria

1. Diagnosis of Crohn's disease for greater than 4 months and a diagnosis of ileal, colonic or ileocolonic Crohn's disease confirmed by endoscopy or radiologic evaluation based on "The guideline for the diagnostic criteria of Crohn's disease" (January 2002, Dr. Simoyama Study Group of the Health and Welfare Ministry) within 3 years of Baseline.
2. For subjects that had had operations in the ileocolonic region of the intestine after documented diagnosis of ileocolonic disease, postoperative recurrence of the disease must be documented according to the inclusion criteria 1.
3. CDAI score of ≥ 220 and ≤ 450 at Baseline.
4. If subjects had previously been administered infliximab, subjects who discontinued use due to a loss of response or intolerance to infliximab therapy.
5. Males and females ≥ 15 and ≤ 75 years of age at the time of informed consent.
6. Adequate cardiac, renal and hepatic function as determined by the investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results.
7. If female, subject was either not of child bearing potential, defined as post menopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and practicing one of the following methods of birth control during the study and for 150 days after the last dose:
   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device
   - Oral contraceptives for three months prior to study drug administration
   - A vasectomized partner
8. If female of child bearing potential, the result of a urine pregnancy test performed at the screening and week 0 visit are negative.
9. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol. If the subject was < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Diagnosis and Main Criteria for Inclusion (Continued):

Exclusion criteria

1. Subject had a history of cancer, lymphoma, leukemia or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix for 5 years.
2. Subject had a history of listeriosis, Histoplasmosis, active TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous anti-infectives within 28 days or oral anti-infectives within 14 days prior to the screening evaluation for non-Crohn's related infections.
3. Subject was known to have immune deficiency or a history of HIV, was immunocompromised or immunosuppressed or cannot discontinue alkylating agents, e.g. cyclophosphamide or, anti-cancer alkaloids, e.g. vindesine sulfate for at least 6 months prior to the baseline visit and during the study.
4. Subject had a history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease.
5. Subjects with abscess or suspicion of abscess.
6. Subject with a history of clinically significant drug or alcohol abuse.
7. Subject had a poorly controlled medical condition such as follows and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study;
   - Uncontrolled diabetes
   - Unstable ischemic heart disease, congestive heart failure
   - Recent cerebrovascular accidents, recent stroke (within 1 year prior to the screening evaluation)
8. Subject who was diagnosed with dysplasia of the gastrointestinal tract.
9. Subjects with clinically significant abnormalities found during the electrocardiogram (ECG) evaluation at the screening visit.
10. Subject had had positive serology for anti-human immunodeficiency virus (HIV) antibody (HIV Ab), Hepatitis B surface antigen (HBs Ag), anti-hepatitis C antibody (HCV Ab), in screening laboratory analysis.
11. Subjects with positive C. difficile stool assay at Screening.
12. At Screening, subject's body weight was below 30 kg.
13. Screening laboratory analysis showed any of the following abnormal results:
    - Hemoglobin < 9.0 g/dL for male, or < 8.5 g/dL for female;
    - Total white blood cell (WBC) count < 3,000/mm^3;
    - Platelet count < 100,000/mm^3;
    - Aspartate transaminase (AST) or alanine transaminase (ALT) > 2 x the upper limit of the reference range;
    - Total bilirubin ≥ 3 mg/dL;
    - Serum creatinine > 1.5 mg/dL
14. Subjects who revealed any findings, which showed a history of tuberculosis (TB) infection (calcified nodules or granulomas and/or fibrotic scar, apical or basilar thickening) by chest X-ray (CXR) examination at the screening evaluation.

Diagnosis and Main Criteria for Inclusion (Continued):

Exclusion criteria (Continued)

15. Subjects judged as "strongly positive" in a purified protein derivative (PPD) skin test for the detection of latent TB infection at the screening evaluation.
    - "Strongly positive" was defined as induration and erythema (≥ 10 mm of diameter) with either bulla, necrosis or double redness.
    - Subjects who demonstrated evidence of latent TB infection (either PPD ≥ 5 mm of induration, irrespective of Bacillus Calmette-Guérin (BCG) vaccination status, and negative CXR findings for active TB) but not be evaluated as "strongly positive" were included to participate in the study under the condition that the prophylactic treatment (isoniazide 300 mg/day for 9 months) for latent TB must be initiated 21 days prior to administration of study drug, however the course of prophylaxis needed not be completed prior to the onset of study drug (screening period was extended to ≤ 4 weeks in subjects who received a TB prophylaxis). Subject had documented and completed prophylactic treatment for TB and so needed not repeat this treatment. If the subject withdrawed from the study they needed to complete the TB prophylactic treatment.
16. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis as determined by the investigator.
17. Subject with symptomatic known obstructive strictures.
18. Subject who had had surgical bowel resections within the past 6 months or was planning any resection at any time point while enrolled in the study.
19. Subject with an ostomy or ileoanal pouch. (Subjects with a previous ileo-rectal anastomosis were not excluded).
20. Subject who had short bowel syndrome as determined by the investigator.
21. Subject who received total parenteral nutrition (TPN) within 14 days before baseline.
22. Subjects on enteral nutrition > 1200 kcal/day and subjects on enteral nutrition who had not been on stable amount for at least 28 days prior to Baseline.
23. Subject who had previously used infliximab or any biological agents within 8 weeks of Baseline.
24. Subject who had previously used infliximab or any anti-TNF agent and had not clinically responded.
25. Previous treatment with adalimumab, previous participation in an adalimumab clinical study, or a history of an allergic reaction or significant sensitivity to constituents of study drug.
26. Subjects with any prior exposure to natalizumab.
27. Subject who had received any investigational chemical agent in the past 28 days or 5 half-lives prior to Baseline (whichever is longer).
28. Subject who had received any investigational biological agents in the past 6 months or 5 half-lives prior to Baseline (whichever is longer).
29. Subject was administered a live vaccine within 12 weeks prior to screening or plans to use during the study.
30. Subjects on Imuran® (azathioprine), 6 MP, or methotrexate (MTX) who had not been on stable doses of these medications for at least 28 days prior to Baseline. For subjects on those medications, doses were to remain stable during the entire course of the study. Additionally, for subjects on those medications, subjects must have been on azathioprine, 6 MP, or MTX for at least 12 weeks prior to Baseline. Moreover, subjects who had been on azathioprine, 6 MP, or MTX who had discontinued these medications within 12 weeks of Baseline are excluded.

Diagnosis and Main Criteria for Inclusion (Continued):

Exclusion criteria (Continued)

31. Subjects on aminosalicylates, sulfasalazine, or Crohn's related antibiotics who had not been on stable doses of these medications for at least 28 days prior to Baseline. In addition, subjects on aminosalicylates, sulfasalazine or Crohn's related antibiotics who had discontinued these medications within 28 days of Baseline were excluded.
32. Subjects on prednisolone > 40 mg/day (or equivalent) and subjects who were not on stable doses for 14 days prior to Baseline. In addition, subjects who discontinued prednisolone (or equivalent) within 14 days of Baseline were excluded.
33. Subjects who had undergone therapeutic enemas within 14 days prior to Baseline were excluded.
34. Subjects who had been on cyclosporine (intravenous, oral), tacrolimus (any form) or Mycophenolate mofetil within 8 weeks of Baseline were excluded.
35. Subjects who had been on Leukocytapheresis (LCAP) or Granulocytapheresis (GCAP) within 8 weeks of Baseline were excluded.
36. Females who were pregnant or breast-feeding or considering becoming pregnant during the study. There should be at least a 150-day period between the last dose of study drug and either conception or initiation of breast-feeding in women of childbearing potential.
37. Subject considered by the investigator, for any reason, to be an unsuitable candidate for the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Test Product: Aqueous injection containing 50 mg/mL adalimumab (pre-filled syringe) and Placebo syringe undistinguishable with active drug in appearance.

Dose/Strength/concentration: Placebo, 40 mg, 80 mg, 160 mg

Mode of administration: subcutaneous administration

Investigational Product	Lot number / Product number	Manufacturing number	Strength	Manufacturing date	Expiration date
Adalimumab (D2E7) 40 mg/0.8 mL	06-006532 / 17102472	RTZA	50 mg/mL	May 2006	Nov 2008
Placebo 0.8 mL	06-006520 / D0600193	RTZA	50 mg/mL	May 2006	

Duration of Treatment:

8 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Reference Therapy: Placebo

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects with a clinical remission (CDAI <150) at Week 4.

Secondary efficacy variables were listed below:

1. Proportion of subjects in each treatment group in clinical remission (CDAI < 150) at Week 2, Week 6 and Week 8.
2. Proportion of subjects in each treatment group with a clinical response (CDAI decrease of ≥ 70 compared to Baseline, CR-70) at Week 2, Week 4, Week 6, and Week 8.

Criteria for Evaluation (Continued)

Efficacy (Continued):

3. Proportion of subjects in each treatment group with a clinical response (CDAI decrease of ≥ 100 compared to Baseline, CR-100) at Week 2, Week 4, Week 6 and Week 8.
4. Changes from Baseline in CDAI scores in each treatment group at Week 2, Week 4, Week 6, and Week 8.
5. Changes from Baseline in IOIBD scores in each treatment group at Week 2, Week 4, Week 6, and Week 8.
6. Changes from Baseline in IBDQ scores in each treatment group at Week 4 and Week 8.
7. Changes from Baseline in outcomes variables in the SF-36 Health Survey in each treatment group at Week 4, and Week 8.

Pharmacokinetic:

Evaluation of serum adalimumab concentration and anti-bodies against Adalimumab (AAA) at Week 0, Week 1, Week 2, Week 4, and Week 8.

Safety:

Adverse events (AEs), laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

Randomized subjects who received at least one dose of study drug were referred to as the "full analysis set (FAS)". In order to evaluate the impact of major protocol violations on the results of the trial, additional analyses were performed on the "per-protocol set (PPS)" after excluding from the FAS population all subjects with major protocol deviations. This will be the additional analysis population for primary efficacy variable. The safety population consists of all subjects who received at least one dose of the study medication.

Demographics and Baseline Characteristics: Demographic and baseline characteristics among the three treatment groups were summarized.

Efficacy:

Primary Efficacy Analysis

The primary analysis was demonstrated using descriptive statistics of the proportion of subjects with a clinical remission (CDAI < 150) in 160/80mg and 80/40mg groups and placebo group at Week 4. The subject who did not have an evaluation of the CDAI score was analyzed as a subject with not achieving clinical remission (NRI). The above efficacy analysis was also carried out for the per-protocol analysis set as supportive evidence.

Secondary Efficacy Analysis

The secondary efficacy analysis was demonstrated using descriptive statistics in the three treatment groups.

For Week 6 and Week 8 the analysis was demonstrated only for the subjects who did not attain the CDAI reduction ≥ 70 points at Week 4.

Pharmacokinetic:

Adalimumab concentration was summarized by treatment group at each time point using descriptive statistics. Individual subject concentration vs time plots and mean concentration vs time plots by treatment group were provided. Serum AAA concentration was summarized by treatment group at each time point using descriptive statistics.

Statistical Methods (Continued)

Safety:

Pre-treatment SAEs were summarized as well. A treatment emergent AE was defined as an event with onset or worsening after the first study drug injection and within 70 days after the last study drug injection. However, for the subject entering the extension study, the AE was collected until the completion of this study. The number and percentages of subjects experiencing treatment emergent AE were tabulated by Medical Dictionary for Drug Regulatory Affairs (MedDRA version 9.1) system organ class and MedDRA preferred term. In addition, a summary of AEs by severity and relationship to study drug was presented. Treatment-emergent AEs that were judged by the investigator to be probably or possibly related and probably, possibly or probably not related to study drug were also tabulated. For the subjects who didn't enter the extension study or discontinue this study, AEs in the duration of 28 days after completion or discontinuation and 70 days after the last administration of study drug were also included. A summary of serious and severe AEs, deaths, and AEs leading to discontinuation were also provided.

Statistical Analyses of Laboratory Data and Vital Signs

Mean change in laboratories variable and vital signs variables at each visit were summarized for all treated subjects. The last evaluation prior to the first dose of study drug was used as baseline for all analyses.

Summary/Conclusions

The period from the first dose of study drug to the evaluation at Week 4 is designated as Period A, and the period from the study drug injection on Week 4 to the evaluation at Week 8 is designated as Period B in this summary.

Efficacy Results:

- The clinical remission rate at Week 4 (a primary endpoint) was 13.0% (3/23 subjects) in the placebo group, 17.6% (6/34 subjects) in the 80/40 mg group and 33.3% (11/33 subjects) in the 160/80 mg group. Treatment with adalimumab increased the number of subjects in whom Crohn's disease showed clinical remission. Such improvement was particularly marked in the 160/80 mg group.
- During Period A, the clinical remission rate and the percentages of CR-70 and CR-100 subjects were higher in the adalimumab dose groups than in the placebo group (clinical remission at Week 2: 4.3% in placebo group, 14.7% in 80/40 mg group, 18.2% in 160/80 mg group, CR-70 at Week 2 and 4: 17.4% and 30.4% in placebo group, 50.0% and 58.8% in 80/40 mg group, 45.5% and 69.7% in 160/80 mg group, CR-100 at Week 2 and 4: 8.7% and 17.4% in placebo group, 32.4% and 50.0% in 80/40 mg group, 30.3% and 45.5% in 160/80 mg group). The mean change in CDAI and IOIBD scores from the baseline to Week 2 decreased (improved) in the two adalimumab dose groups compared to the placebo group. The proportion of subjects achieving remission and CR-70 at Week 4 was higher in the 160/80 dose group than in the 80/40 dose group. The proportion of subjects with CR-100 at Week 4 was similar compared to the 160/80 mg group than in the 80/40 mg group. It should be pointed out that the number of subjects who had a deterioration of CDAI score at Week 4 compared to Baseline was more than twice as high in the 80/40 dose group compared with the 160/80 dose group.
- Analysis of the change in IBDQ and SF-36 scores during Period A revealed improvement in the two adalimumab dose groups as compared to the placebo group. In addition, compared with the 80/40mg group, the 160/80mg group had a greater improvement in IBDQ and SF-36.
- The results of efficacy collected during Period B demonstrated that continued adalimumab treatment was effective in some cases, even in subjects showing no response to the study drug during the first 4 weeks of treatment (clinical remission, CR-70 and CR-100 response was 8.3%, 41.7%, and 16.7% in 80/40 mg + 40/40 mg group, and 0%, 33.3%, and 0% in 160/40 mg + 40/40 mg group, respectively).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- Treatment with adalimumab was effective for clinical remission, CR-70, and CR-100 irrespective of the baseline activity level of Crohn's disease, presence/absence of previous infliximab therapy and responses or tolerability to previous infliximab therapy. Moreover, adalimumab showed higher inprovement in mean change in CDAI, IBDQ score, and SF-36 socres than in placebo group. Within adalimumab treatment groups, the clinical response in these stratified populations showed the same trend as in the main population.

Taken together, these results suggest that biweekly adalimumab therapy is useful as a therapy for inducing remission of Crohn's disease since it alleviated the disease activity and improved the QOL in subjects with Crohn's disease. Adalimumab was particularly effective at a dose level of 160/80 mg. These results were similar to those in western studies (M02-403 and M04-691) indicating that the similar efficacy seen in USA and EU could be provided in Japanese Crohn's disease patients.

Pharmacokinetic Results:

- The serum adalimumab concentrations were approximately dose proportional during Week 1 to Week 4 for the 160/80 mg and 80/40 mg treatment groups.
- Serum adalimumab concentrations were comparable for the Japanese population in this study and the Western population at the 160/80 mg and 80/40 mg dose levels.
- No subjects developed antibodies to adalimumab in this study.

Safety Results:

- In Period A, the incidence of AEs differed little between the placebo group (52.2%) and the total adalimumab dose group (55.2%). the incidence of AEs in 80/40 mg group and 160/80 mg group were similar (58.8% in 80/40 mg group and 51.5% in 160/80 mg group). In Period B, the incidence of AEs was 59.5% in the total adalimumab dose group.
- Among the 95 AEs seen in Period A in the two adalimumab dose groups, the causal relation to the study drug was rated as at least "possibly related" for 34 events (35.8%) and at least "probably not related" for 67 events (70.5%). Of the 34 AEs whose causal relation to the study drug was rated as at least "possibly related", 85.3% (29 events) were mild, 5.9% (2 events) were moderate and 8.8% (3 events, pyrexia, C-reactive protein increased, and lymphocyte count decreased) were severe. Thus, most of these events were mild. Even 3 severe events recovered during the study.
- No death occurred in this study.
- SAE occurred in 2 subjects (2 events, 8.7%) from the placebo group and 4 subjects (6 events, 6.0%) from the total adalimumab dose group in Period A. In analysis of the causal relation of the 6 SAE seen in the total adalimumab dose group, only one (C-reactive protein increased) was rated as "probably related" and the other events were rated as "probably not related" or "not related". Of these 6 events, 4 (2 subjects of Crohn's disease and one subject each of C-reactive protein increased, abdominal abscess) were severe and 2 were moderate. 2 subjects in the total adalimumab dose group discontinued because of SAEs (C-reactive protein increased and Crohn's disease in one subject and Crohn's disease in another subject). Except for one SAE (epididymitis), all SAEs seen in the total adalimumab dose group recovered after the discontinuation. In Period B, SAEs were seen in 2 subjects (2 events, each aggravation of Crohn's disease).

Summary/Conclusions (Continued)

Safety Results (Continued):

- AE leading to discontinuation is observed in one subject (one event, Crohn's disease) from the placebo group and 3 subjects (5 events, 2 events in 2 subject: Crohn's disease, 1 event in 1 subject: C-reactive protein increased, chest discomfort, and mood altered) from the total adalimumab dose group in Period A. In Period B, AE leading to discontinuation is observed in 2 subjects (2 events, intestinal obstruction and Crohn's disease) from the total adalimumab dose group. All of these events recovered after discontinuation.
- Infections developed in 2 subjects (2 events, 8.7%) from the placebo group and 9 subjects (10 events, 13.4%) from the total adalimumab dose group in Period A. Of the 10 infections seen in the total adalimumab dose group, abdominal abscess was severe but the other infections were mild and could be controlled satisfactorily with drug therapy or without any particular treatment. In Period B, infections developed in 9 subjects (9 events, 24.3%) from the total adalimumab dose group. Except for one subject of infection (upper respiratory tract infection) where the study drug was interrupted, all infections could be controlled satisfactorily with medication or without any particular treatment.
- Injection site reactions developed in 2 subjects (2 events, 8.7%) from the placebo group and 9 subjects (10 events, 13.4%) from the total adalimumab dose group in Period A. All the 10 events seen in the total adalimumab dose group were mild and could be controlled satisfactorily without any particular treatment. In Period B, one injection site reaction was seen in one subject from the total adalimumab dose group.
- Hepatic event developed in one subject (1 subject, 4.3%) from the placebo group and 5 subjects (9 subjects, 7.5%) from the total adalimumab dose group in Period A. Hepatic event seen in the total adalimumab dose group was mild in all subjects. In analysis of causal relationship to the study drug, no subject of hepatic event was rated as at least "possibly related". In Period B, no subject developed hepatic event.
- Ovarian neoplasm (benign), cytomegalovirus and hypersensitivity were seen in one subject (one event) from the total adalimumab dose group.
- No subject developed tuberculosis, demyelinating disease, lupus-like syndrome, congestive heart failure or hematologic event.
- There was no marked difference in laboratory values, vital signs or physical findings between the placebo group and the total adalimumab dose group.
- There was no difference in the incidence of any treatment-emergent AE, laboratory values, vital signs or physical findings depending on the dose level of adalimumab.

Taken together, these results suggest that treatment with adalimumab is safe and well tolerant for Japanese patients with moderate or severe Crohn’s disease. These results were similar to those in western studies [redacted]

Conclusions:

In this study, treatment with adalimumab with dosing regimens (160 mg in Week 0 + 80 mg in Week 2 or 80 mg in Week 0 + 40 mg in Week 2) improved the disease activity and QOL of Japanese subjects with moderate or severe Crohn's disease. Adalimumab treatment was shown to be useful as a means of inducing clinical remission of Crohn's disease. Efficacy of adalimumab was exerted irrespective of loss of responses to infliximab and/or intolerable to previous infliximab therapy. Adalimumab treatment was shown to be highly safe and well tolerable for the two dose regimens evaluated. Efficacy of adalimumab tended to be higher with the regimen of 160 mg (Week 0) + 80 mg (Week 2) than with the regimen of 80 mg (Week 0) + 40 mg (Week 2). By the result that no safety problem was noted with adalimumab treatment, it is concluded that 160 mg in Week 0 + 80 mg in Week 2 is recommended clinically as a means of inducing clinical remission of Crohn's disease.