CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125057 / S-0089

Trade Name: Humira

Generic Name: Adalimumab

Sponsor: Abbott laboratories

Approval Date: February 27, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125057/89

Abbot Laboratories
Attention: Meg Drew, MPH
Associate Director
Global Pharmaceuticals Regulatory Affairs
200 Abbott Park Road
Dept. RA72, AP34-3
Abbot Park, IL 60064

Dear Ms. Drew:

Your request to supplement your biologics license application (BLA) for Humira (adalimumab) to include a new indication for "reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab," has been approved.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and the text for the patient package insert) and the submitted labeling (carton label submitted February 26, 2007). Marketing product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Within 21 days of the date of this letter, submit content of labeling in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, which is identical in content to the enclosed Package Insert and Patient Package Insert labeling text. Upon receipt and verification, we will transmit that version to the national Library of Medicine for public dissemination.

We reference your request dated August 25, 2006, for a waiver (21 CFR 201.58) to allow the Highlights section of the PLR-formatted package insert to extend beyond the one-half-page requirement. We hereby grant this waiver.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to less than 6 years and deferring pediatric studies for ages greater than or equal to 6 to less than or equal to 17 years for this application

We acknowledge your written commitments to conduct postmarketing studies as described in your letter of February 26, 2007, as outlined below:

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

1. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this post-marketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.

   To complete and submit data from study protocol M06-806, a one-year, multi-center, randomized, double-blind study designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in the induction and maintenance of clinical remission in pediatric subjects 6 to 17 years of age with moderate to severe Crohn's disease. The study will include collection of baseline data on prior loss of response to or intolerance to infliximab, using definitions similar to those used in protocol M04-691. The final study protocol was submitted to Abbott's IND on January 24, 2007. Enrollment of 186 patients will begin by March 31, 2007, and will be complete by March 31, 2008. The study will be complete by March 31, 2009, and the final clinical study report will be submitted by December 31, 2009.

   Final Report Submission: December 31, 2009

   Submit final study reports to this BLA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitments".

2. To conduct study protocol P06-134, a 5-year, 5000 patient, multi-center, uncontrolled, observational study of adult patients with Crohn's disease treated in a routine clinical setting with adalimumab. The final protocol will be submitted by April 30, 2007, for concurrence, the study will be initiated by August 31, 2007, and enrollment will be complete by August 31, 2009. The study will be complete by August 31, 2014. Abbott will submit interim safety analyses of the study by February 28, 2009, February 28, 2011, and February 28, 2013, and will submit a final clinical study report by May 31, 2015.

   Final Report Submission: May 31, 2015

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL 125057. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

Brian E. Harvey MD PhD 2/27/07

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HUMIRA® safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) solution for subcutaneous injection
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
Tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred. Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)

----------RECENT MAJOR CHANGES----------

Indications and Usage, Psoriatic Arthritis (1.2)	11/2006
Indications and Usage, Ankylosing Spondylitis (1.3)	7/2006
Indications and Usage, Crohn's Disease (1.4)	2/2007
Dosage and Administration, Ankylosing Spondylitis (2.1)	7/2006
Dosage and Administration, Crohn's Disease (2.2)	2/2007
Warnings and Precautions, Serious Infections (5.1)	2/2007
Warnings and Precautions, Malignancies (5.2)	2/2007
Warnings and Precautions, Hepatitis B Virus Reactivation (5.4)	6/2006
Warnings and Precautions, Immunizations (5.10)	2/2007

----------INDICATIONS AND USAGE----------
HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
Rheumatoid Arthritis (RA) (1.1)
- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Psoriatic Arthritis (1.2)
- Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Ankylosing Spondylitis (1.3)
- Reducing signs and symptoms in patients with active disease.

Crohn's Disease (1.4)
- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

----------DOSAGE AND ADMINISTRATION----------
Humira is administered by subcutaneous injection.
Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1)
- 40 mg every other week. Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Crohn's Disease (2.2)
- 160 mg initially at Week 0, 80 mg at Week 2, followed by a maintenance dose of 40 mg every other week beginning at Week 4. Initial dose may be given as 4 injections on 1 day, or divided over 2 days.

----------DOSAGE FORMS AND STRENGTHS----------
- 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- 40 mg/0.8 mL in a single-use prefilled glass syringe (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious infections – do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- Malignancies – are seen more often than in controls, and lymphoma is seen more often than in the general population (5.2)
- Anaphylaxis or serious allergic reactions may occur (5.3)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- Demyelinating disease, exacerbation or new onset, may occur (5.5)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- Heart failure, worsening or new onset, may occur (5.8)
- Lupus-like syndrome – stop HUMIRA if syndrome develops (5.9)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Anakinra – increased risk of serious infection (5.7, 7.1)
- Live vaccines – should not be given with HUMIRA (5.10, 7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Physicians are encouraged to enroll pregnant patients in the HUMIRA pregnancy registry by calling 1-877-311-8972 (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2007

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving HUMIRA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with HUMIRA. However, active tuberculosis has developed in patients receiving HUMIRA whose screening for latent tuberculosis infection was negative.

Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating HUMIRA and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection. ***[See Warnings and Precautions (5.1) and Adverse Reactions (6.1)]***

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

1.3 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.4 Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

2 DOSAGE AND ADMINISTRATION

HUMIRA is admininstered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 40 mg administered every other week.

Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA. In rheumatoid arthritis, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease is 160 mg initially at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2, followed by a maintenance dose of 40 mg every other week beginning at Week 4. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with HUMIRA. The use of HUMIRA in Crohn's disease beyond one year has not been evaluated in controlled clinical studies.

2.3 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

The solution in the HUMIRA Pen or prefilled syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the HUMIRA Pen or prefilled syringe should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Patient Information Leaflet *[see Patient Counseling Information (17.3)]*.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard.

3 DOSAGE FORMS AND STRENGTHS

- **Pen**

A single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

- **Prefilled Syringe**

A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious infections, sepsis, tuberculosis and cases of opportunistic infections, including fatalities, have been reported with the use of TNF blocking agents including HUMIRA. Many of the serious infections have occurred in patients on concomitant

immunosuppressive therapy that, in addition to their rheumatoid arthritis could predispose them to infections. In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Treatment with HUMIRA should not be initiated in patients with active infections including chronic or localized infections. Patients who develop a new infection while undergoing treatment with HUMIRA should be monitored closely. Administration of HUMIRA should be discontinued if a patient develops a serious infection. Physicians should exercise caution when considering the use of HUMIRA in patients with a history of recurrent infection or underlying conditions which may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. The benefits and risks of HUMIRA treatment should be carefully considered before initiation of HUMIRA therapy.

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported. While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose.

Before initiation of therapy with HUMIRA, patients should be evaluated for tuberculosis risk factors and should be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with HUMIRA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG). If latent infection is diagnosed, appropriate prophylaxis should be instituted in accordance with the current guidelines from the Centers for Disease Control and Prevention.

The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with HUMIRA should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blocking agents. Anti-tuberculosis therapy should be considered prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating HUMIRA should also be considered in patients who have several, or highly significant, risk factors for tuberculosis infection and have a negative test for latent tuberculosis, but the decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Patients receiving HUMIRA should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. Patients should be instructed to seek medical advice if signs or symptoms (e.g., persistent cough, wasting, weight loss, low grade fever) suggestive of a tuberculosis infection occur.

5.2 Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.3, 1.0)/100 patient-years among 2887 HUMIRA-treated patients versus a rate of 0.4 (0.2, 1.1)/100 patient-years among 1570 control patients (median duration of treatment of 5.7 months for HUMIRA-treated patients and 5.5 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population.[1] During the controlled portions of HUMIRA rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease trials, the rate (95% confidence interval) of non-melanoma skin cancers was 0.8 (0.47, 1.24)/100 patient-years among HUMIRA-treated patients and 0.2 (0.05, 0.82)/100 patient-years among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease, 2 lymphomas were observed among 2887 HUMIRA-treated patients versus 1 among-1570 control patients. In combining the controlled and uncontrolled open-label portions of these clinical trials-with a median duration of approximately 2 years, including 4843 patients and over 13,000 patient-years of therapy, the observed rate of lymphomas is approximately 0.12/100 patient-years. This is approximately 3.5-fold higher than expected in the general population.[1] Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

5.3 Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other

medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA *[see Adverse Reactions (6)]*. The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.1)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

5.11 Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood *[see Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*. The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The most serious adverse reactions were *[see Warnings and Precautions (5)]*:

- Serious Infections
- Neurologic Reactions
- Malignancies

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of Studies RA-I, RA-II, RA-III and RA-IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In completed and ongoing global clinical studies that include over 13,000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of miliary, lymphatic, peritoneal, as well as pulmonary. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal *[see Warnings and Precautions (5.1)]*.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials *[see Warnings and Precautions (5.2)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those

receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with ankylosing spondylitis, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. In patients with Crohn's disease, the rate of antibody development was 2.6%.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse reaction rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1: Adverse Reactions Reported by ≥ 5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

Adverse Reaction (Preferred Term)	HUMIRA 40 mg subcutaneous Every Other Week (N=705) Percentage	Placebo (N=690) Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6

Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Reactions

Other infrequent serious adverse reactions occurring at an incidence of less than 5% in rheumatoid arthritis patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia *[see Warnings and Precautions (5.6)]*

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma.

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis in two placebo-controlled studies. The safety profile for patients with psoriatic arthritis and ankylosing spondylitis treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, HUMIRA Studies RA-I through IV. In the clinical trials of patients with psoriatic arthritis and ankylosing spondylitis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving HUMIRA than in controls, both when HUMIRA was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most elevations of ALT and AST observed were in the range of 1.5 to 3 times the upper limit of normal. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of HUMIRA, or modification of concomitant medications.

Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 patients with Crohn's disease in four placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis.

6.2 Postmarketing Experience

Adverse reactions have been reported during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Hematologic Reactions: Thrombocytopenia *[see Warnings and Precautions (5.6)]*

Hypersensitivity reactions: Anaphylaxis, angioneurotic edema *[see Warnings and Precautions (5.3)]*

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis.

Skin reactions: cutaneous vasculitis.

7 DRUG INTERACTIONS

7.1 Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities *[see Warnings and Precautions (5.7)]*.

7.2 Live Vaccines

Live vaccines should not be given concurrently with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.3 Methotrexate

Humira has been studied in rheumatoid arthritis patients taking concomitant methotrexate. Although methotrexate reduced the apparent adalimumab clearance *[see Clinical Pharmacology (12.3)]*, the data do not suggest the need for dose adjustment of either HUMIRA or methotrexate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

8.5 Geriatric Use

A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher

incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:κ constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-use, 1 mL prefilled glass syringe. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue

remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

12.3 Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 μg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab in rheumatoid arthritis (RA) patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 μg/mL and 8 to 9 μg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 μg/mL and 8.5 to 12 μg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with ankylosing spondylitis were similar to those in patients with RA.

In patients with Crohn's disease, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 μg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 μg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg HUMIRA every other week.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

HUMIRA has not been studied in children.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 104 weeks.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active rheumatoid arthritis of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 2.

Table 2: ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			Study RA-III Methotrexate Combination (24 and 52 weeks)	
Response	Placebo N=110	HUMIRA 40 mg every other week N=113	HUMIRA 40 mg weekly N=103	Placebo/MTX N=200	HUMIRA/MTX 40 mg every other week N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*

* $p<0.01$, HUMIRA vs. placebo

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (every other week) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

Table 3: Components of ACR Response in Studies RA-II and RA-III

	Study RA-II				Study RA-III			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week

[b] Visual analogue scale; 0 = best, 10 = worst

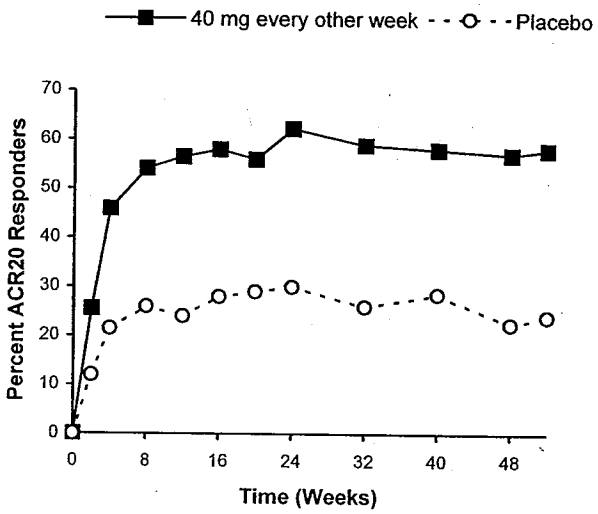
[c] Disability Index of the Health Assessment Questionnaire[5]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* $p<0.001$, HUMIRA vs. placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

Figure 1: Study RA-III ACR 20 Responses over 52 Weeks



In Study RA-IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA (adalimumab) and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset rheumatoid arthritis, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 4).

Table 4: ACR Response in Study RA-V (Percent of Patients)

Response	MTX[b] N=257	HUMIRA[c] N=274	HUMIRA/MTX N=268
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%

ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period

[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20
$p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response

[c] $p<0.001$, HUMIRA/MTX *vs.* HUMIRA

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 5. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 5: Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6: Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	HUMIRA[a,b] N=274	HUMIRA/MTX N=268
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)

	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)

* mean (95% confidence interval)

[a] $p<0.001$, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks

[b] $p<0.01$, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

In studies RA-I through IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX ($p<0.001$) patients. Eighty-two percent of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study maintained that improvement through week 104 of open-label treatment. Improvement in SF-36 was also maintained through week 104.

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement ($p<0.001$) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic

arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 7: ACR Response in Study PsA-I (Percent of Patients)

Response	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%

* $p<0.001$ for all comparisons between HUMIRA and placebo

Table 8: Components of Disease Activity in Study PsA-I

	Placebo N=162		HUMIRA* N=151	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints[a]	23.0	17.0	20.0	5.0
Number of swollen joints[b]	11.0	9.0	11.0	3.0
Physician global assessment[c]	53.0	49.0	55.0	16.0
Patient global assessment[c]	49.5	49.0	48.0	20.0
Pain[c]	49.0	49.0	54.0	20.0
Disability index (HAQ)[d]	1.0	0.9	1.0	0.4
CRP (mg/dL)[e]	0.8	0.7	0.8	0.2

* $p<0.001$ for HUMIRA *vs.* placebo comparisons based on median changes

a Scale 0-78

b Scale 0-76

c Visual analog scale; 0=best, 100=worst

d Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

e Normal range: 0-0.287 mg/dL

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by ≥3 tender joints and ≥3 swollen joints at enrollment.

Radiographic Response

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on HUMIRA or placebo and at Week 48 when all patients were on open-label HUMIRA. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 9).

Table 9: Change in Modified Total Sharp Score in Psoriatic Arthritis

	Placebo N=141	HUMIRA N=133	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change ± SD	0.9 ± 3.1	-0.1 ± 1.7	-0.2 ± 4.9*

* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of HUMIRA every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with HUMIRA showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function based on the HAQ-DI was maintained for up to 84 weeks through the open-label portion of the study.

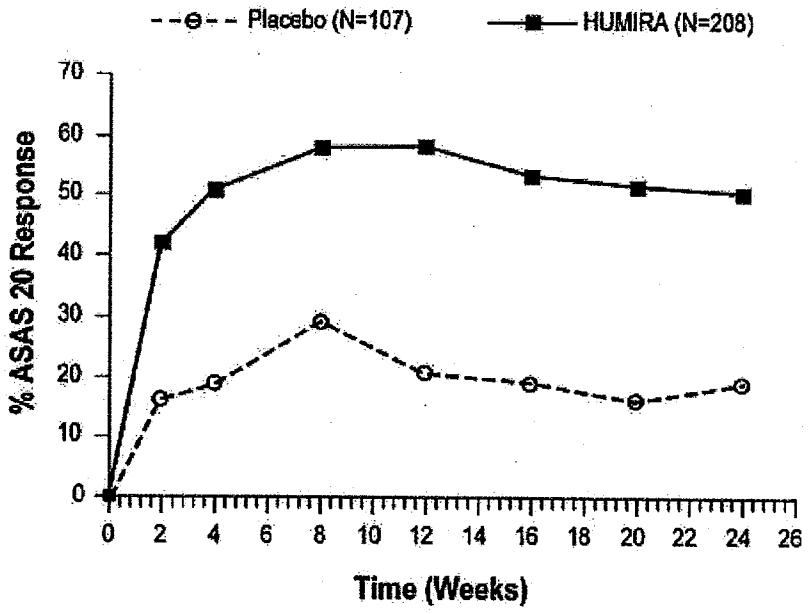
14.3 Ankylosing Spondylitis

The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour. The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 28 weeks.

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 10.

Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

Figure 2: ASAS 20 Response By Visit, Study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p < 0.001$). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table 10: Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		HUMIRA N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a]*	65	60	63	38
Total back pain*	67	58	65	37
Inflammation[b]*	6.7	5.6	6.7	3.6
BASFI[c]*	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8

CRP[f]*	2.2	2.0	1.8	0.6

[a] Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"

[b] mean of questions 5 and 6 of BASDAI (defined in 'd')

[c] Bath Ankylosing Spondylitis Functional Index

[d] Bath Ankylosing Spondylitis Disease Activity Index

[e] Bath Ankylosing Spondylitis Metrology Index

[f] C-Reactive Protein (mg/dL)

* statistically significant for comparisons between HUMIRA and placebo at Week 24

A second randomized, multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 vs. -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 vs. 1.9) compared to placebo-treated patients at Week 24.

14.4 Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI ≥70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg HUMIRA achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II) (see Table 11).

Table 11: Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		CD-II	
	Placebo N=74	HUMIRA 160/80 mg N=76	Placebo N=166	HUMIRA 160/80 mg N=159
Week 4				
Clinical remission	12%	36%**	7%	21%**
Clinical response	34%	58%*	34%	52%*

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.

* p<0.001 for HUMIRA *vs.* placebo pairwise comparison of proportions

** p<0.01 for HUMIRA *vs.* placebo pairwise comparison of proportions

Maintenance of Clinical Remission

In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 12). The group that received HUMIRA therapy every week did not demonstrate significantly higher remission rates compared to the group that received HUMIRA every other week.

Table 12: Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo N=170	40 mg HUMIRA every other week N=172
Week 26		
Clinical remission	17%	40%*
Clinical response	28%	54%*
Week 56		
Clinical remission	12%	36%*
Clinical response	18%	43%*

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.

* p<0.001 for HUMIRA *vs.* placebo pairwise comparisons of proportions

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA every other week group maintained remission for a longer time than patients in the placebo maintenance group. Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 11 Registries, 1993-2001.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied in prefilled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

- **HUMIRA Pen Carton**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-02.

- **HUMIRA Pen – Crohn's Disease Starter Package**

HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Crohn's Disease Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-06.

- **Prefilled Syringe Carton – 40 mg**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-3799-02.

- **Storage and Stability**

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 2 to 8° C (36 to 46° F). DO NOT FREEZE. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.3)

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Patient Package Insert before starting HUMIRA therapy and to reread each time the prescription is renewed.

- **Immunosuppression**

Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Patients should be counseled about the risk of lymphoma and other malignancies while receiving HUMIRA.

- **Allergic Reactions**

Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

- **Other Medical Conditions**

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

17.2 Instruction on Injection Technique

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA *[see Patient Counseling Information (17.3)]*.

A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

17.3 FDA–Approved Patient Labeling

HUMIRA® (HU-MARE-AH)

(adalimumab)

Patient Information

Read the Patient Information that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment with HUMIRA.

What is the most important information I should know about HUMIRA?

HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. **Serious infections, including tuberculosis (TB) have happened in patients receiving HUMIRA. Some patients have died from these infections.**

Before starting HUMIRA, tell your doctor if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as a fever, cough, or flu-like symptoms
- have any open cuts or sores on your body
- get a lot of infections or have infections that keep coming back
- have or had hepatitis B infection
- have TB, or have been in close contact with someone who has TB. Your doctor should test you for TB before starting HUMIRA. If your doctor prescribes any medicine for the treatment of TB, you should start taking it before starting HUMIRA and take the full course of TB medicine prescribed.
- take the medicine Kineret (anakinra)

After starting HUMIRA, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open cuts or sores on your body, **call your doctor right away.**
HUMIRA can make you more likely to get infections or make any infection that you may have worse.

What is HUMIRA?

HUMIRA is a medicine called a Tumor Necrosis Factor (TNF) blocker. HUMIRA is used in adults to reduce the signs and symptoms of:

- **moderate to severe rheumatoid arthritis (RA)** in adults. HUMIRA can be used alone or with methotrexate or with certain other medicines. HUMIRA may prevent further damage to your bones and joints and may help your ability to perform daily activities.

- **psoriatic arthritis (PsA).** HUMIRA can be used alone or with certain other medicines. HUMIRA may prevent further damage to your bones and joints and may help your ability to perform daily activities.
- **ankylosing spondylitis (AS)**
- **moderate to severe Crohn's disease (CD)** in adults who have not responded well to other treatments.

People with these diseases have too much protein called tumor necrosis factor (TNF), which is made by the body's immune system. HUMIRA can reduce the amount of TNF in the body and block the damage that too much TNF can cause, but it can also lower the ability of the immune system to fight infections. See "**What is the most important information I should know about HUMIRA?**" and "**What are the possible side effects of HUMIRA?**"

HUMIRA has not been studied in children.

Who should not take HUMIRA?

Do not take HUMIRA if you have an allergy to HUMIRA or to any of its ingredients (including sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80). **The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.**

What should I tell my doctor before starting HUMIRA?

To help your doctor decide if HUMIRA is right for you, before starting HUMIRA tell your doctor about all of your health conditions, including if you:

- **have an infection.** (See "**What is the most important information I should know about HUMIRA?**")
- **have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis**
- **have heart failure**
- **are scheduled to have major surgery**
- **are scheduled for any vaccines.** Patients receiving HUMIRA should not receive live vaccines.

Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding. HUMIRA should only be used during a pregnancy if needed. Women who are breastfeeding should talk to their doctor about whether or not to use HUMIRA.

Pregnancy Registry: Abbott Laboratories has a registry for pregnant women exposed to HUMIRA. The purpose of this registry is to check the health of the pregnant mother and her child. Talk to your doctor to contact the registry for you at 1-877-311-8972.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Your doctor will tell you if it is okay to take your other medicines while taking HUMIRA. Especially, tell your doctor if you take:

- **Kineret (anakinra).** You may have a higher chance for serious infections and a low white blood cell count when taking HUMIRA with Kineret.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take HUMIRA?

See the section, **"How do I prepare and give an injection of HUMIRA?"** at the end of this leaflet for complete instructions for use.

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than prescribed.**
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection.
- If you take more HUMIRA than you were told to take, call your doctor.
- Do not miss any doses of HUMIRA. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the patient information booklet.

What are the possible side effects with HUMIRA?

Serious side effects have happened in people taking HUMIRA, including:

- **Serious infections.** See **"What is the most important information I should know about HUMIRA?"**
- **Certain types of Cancer.** There have been cases of certain kinds of cancer in patients taking HUMIRA or other TNF blockers. Patients with more serious RA that have had the disease for a long time may have a higher chance for getting a kind of cancer called lymphoma.
- **Allergic reactions.** Signs of a serious allergic reaction include a skin rash, a swollen face, or trouble breathing.
- **Hepatitis B virus reactivation in patients who carry the virus in their blood.** Your doctor should monitor you carefully during treatment with HUMIRA if you carry the hepatitis B virus in your blood.

- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your legs, and dizziness.
- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have.** Symptoms include shortness of breath or swelling of your ankles or feet.
- **Immune reactions including a lupus-like syndrome.** Symptoms include shortness of breath, joint pain, or a rash on your cheeks or arms that is sensitive to the sun. Symptoms may go away when you stop HUMIRA.

Call your doctor or get medical care right away if you develop any of the above symptoms. Your treatment with HUMIRA may be stopped.

Common side effects with HUMIRA include:

- **Injection site reactions** such as redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. If you have pain, redness or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away.
- **Upper respiratory infections** (sinus infections)
- **Headaches**
- **Rash**
- **Nausea**

These are not all the side effects with HUMIRA. Ask your doctor or pharmacist for more information.

How do I store HUMIRA?

- Store HUMIRA in a refrigerator at 36 to 46°F (2°C to 8°C) in the original container until it is used. Protect from light. **Do not freeze HUMIRA**. Refrigerated HUMIRA remains okay to use until the expiration date printed on the prefilled syringe or Pen. If you need to take HUMIRA with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light. If your HUMIRA has been frozen, do not use it, even after it has thawed. Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it. For additional information or questions, you can call 1-800-4HUMIRA (488-6472).
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

General information about HUMIRA

Medicines are sometimes prescribed for purposes not mentioned in a Patient Information Leaflet. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that was written for healthcare professionals.

For other information and ideas you can enroll in a patient support program by calling 1-800-4HUMIRA (448-6472).

What do I need to do to prepare and give an injection of HUMIRA?

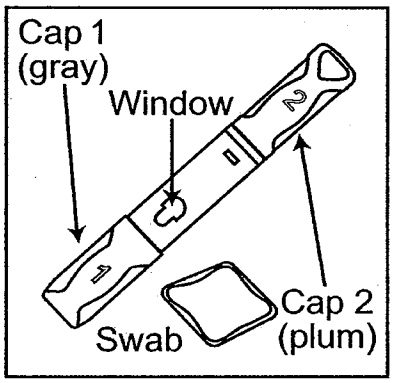
HUMIRA comes as:

1. a single-use pen (HUMIRA PEN) containing a prefilled syringe
2. a single-use prefilled syringe (HUMIRA)

Follow the directions below for your dose form.

IF YOU ARE USING THE HUMIRA PEN

1) Setting up for an injection



- Find a clean flat surface.
- Do not use if the seals on top and bottom of carton are broken or missing. Contact your pharmacist if the seals are broken.
- Take one dose tray containing a Pen of HUMIRA from the refrigerator. Do not use a Pen that has been frozen or if it has been left in direct sunlight.

  You will need the following items for each dose:

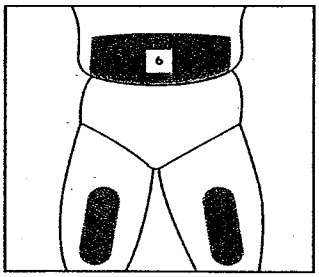
  - 1 HUMIRA Pen
  - 1 alcohol prep (swab)
  - 1 cotton ball or gauze pad (not included in your HUMIRA box)

If you do not have all of the items you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and Pen label.
- Check the expiration date on the dose tray label and the Pen label to make sure the date has not passed. Do not use a Pen if the date has passed.
- Have a special sharps (puncture proof) container nearby for disposing of the used Pen.

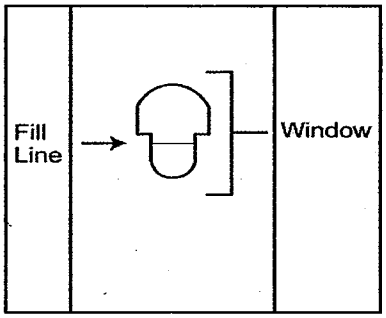
For your protection, it is important that you follow these instructions.

2) Choosing and preparing an injection site



- Wash your hands well
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
  - Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. **Never** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
  - You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where HUMIRA is to be injected with an alcohol prep (swab), using a circular motion. Do **not** touch this area again until you are ready to inject.

3) How to prepare your HUMIRA dose for injection with a HUMIRA Pen



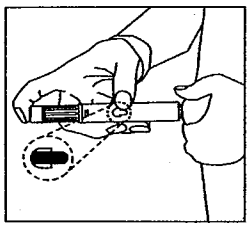
- Hold the Pen with the gray cap pointing up. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. Do not use a Pen if the liquid is cloudy or discolored or has flakes or particles in it. Do not use if frozen.
- Turn the Pen over and hold the Pen with the gray cap pointed down. Check to make sure that the amount of liquid in the Pen is the same or close to the fill line seen through the window. The fill line represents a full dose of the product. The top of the liquid may be curved. If the Pen does not have the full amount of liquid, **do not use that pen**. Call your pharmacist.

4) Injecting HUMIRA

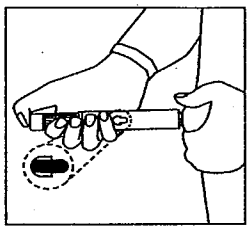
- Hold the Pen with one hand. With your other hand, remove the gray cap (1) and discard cap. Pull the cap straight off. Do not twist the cap. Check that the small gray needle cover of the syringe has come off with the cap. After removal, the needle cover is held in the cap. Do not touch the needle. The white needle sleeve, which covers the needle, can now be seen. **Do not put the gray cap (1) back on** or you may damage the needle. Do not drop or crush the product as it contains a glass syringe that may break.
- Remove the plum colored safety cap (2) to expose the plum colored push button at the top. Pull the cap straight off. Do not twist the cap. The Pen is now ready to use. Please note that the Pen is activated after removing the plum colored safety cap 2 and that pressing the button under the plum colored safety cap 2 will release the medicine from the syringe. Do not press the button until you are

ready to inject HUMIRA. **Do not put the plum colored cap (2) back on the pen as this could cause medicine to come out of the syringe.**

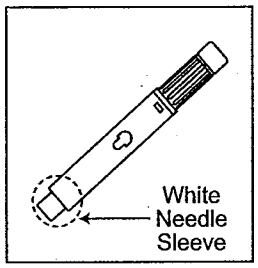
- Hold the Pen so that the window can be seen.
- With your free hand, gently squeeze an area of the cleaned skin at the injection site. You will inject into this raised area of skin.



- Place the white end of the Pen straight (a 90° angle) and flat against the raised area of skin. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin.



- With your first (index) finger, press the plum colored button to begin the injection. You may also use your thumb to press the plum colored button to begin the injection. Try not to cover the window. You will hear a 'click' when you press the button, which means the start of the injection. Keep pressing the button and continue to hold the Pen against the raised skin until all of the medicine is injected. This can take up to 10 seconds. It is important to keep holding the pen against the raised skin of your injection site for the whole time.

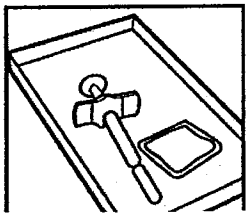


- You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.
- When the injection is finished, pull the Pen from the skin. The white needle sleeve will move to cover the needle tip.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the Pen right away into your special sharps container.
- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle. (See "**How Do I Dispose of Syringes and Needles?**")

IF YOU ARE USING THE PREFILLED SYRINGE

1) Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on top and bottom of carton are broken or missing. Contact your pharmacist if the seals are broken.
- Take one dose tray containing a prefilled syringe of HUMIRA from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.



You will need the following items for each dose:

- A dose tray containing a prefilled syringe of HUMIRA with a fixed needle
- 1 alcohol prep (swab)
- 1 cotton ball or gauze pad (not included in your HUMIRA box)

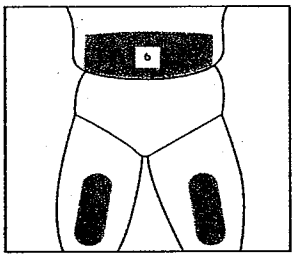
If you do not have all of the items you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and prefilled syringe label.
- Check the expiration date on the dose tray label and prefilled syringe to make sure the date has not passed. Do not use a prefilled syringe if the date has passed.
- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2) Choosing and preparing an injection site

- Wash your hands well
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
  - Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. **Never** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
  - You may find it helpful to keep notes on the location of your injection sites.



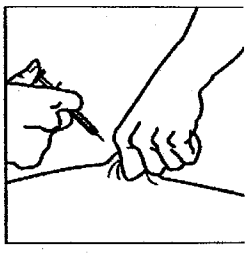
- Wipe the site where HUMIRA is to be injected with an alcohol prep (swab), using a circular motion. Do **not** touch this area again until you are ready to inject.

3) How to prepare your HUMIRA dose for injection with a Prefilled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line shown on the prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay. Do not shake the syringe.

4) Injecting HUMIRA



- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly. You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. **Do not** use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the HUMIRA is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container. (See "**How Do I Dispose of Syringes and Needles?**")

How Do I Dispose of Syringes and Needles?

You should always check with your doctor's office for instructions on how to dispose of used needles and syringes. You should follow any special state or local laws regarding the disposal of needles and syringes. **Do not throw the needle or syringe in the household trash or recycle trash**.

- Place the used needles and syringes in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled "Used Syringes". Do not use glass or clear plastic containers.
- **Always keep the container out of the reach of children.**
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. **Do not throw the container in the household trash or recycle trash.**

- Used alcohol pads may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be placed in your recycle trash.

Rev. February, 2007

U.S. Govt. Lic. No. 0043

Abbott Laboratories
North Chicago, IL 60064, U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

SUMMARY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

Date: **February 28, 2007**

From: **John Hyde, Ph.D., M.D., Clinical Team Leader, DGP**

Through: **Brian Harvey, M.D., Ph.D., Division Director, DGP**

Subject: **Supervisory Summary Review of sBLA/STN 125057/89 Humira for Crohn's Disease**

To: **sBLA 125057/89 File**

John E Hyde 2-27-07
I concur with this review and with the approval of this product for the proposed indications.
Brian E. Harvey
2/27/07

Identifying information

BLA/STN#:	125057/89
Applicant:	Abbott Labs
Biologic name:	Adalimumab
Trade name:	Humira
Submission date:	August 25, 2006
Stamp date:	August 28, 2006
PDUFA goal date:	February 27, 2007
Formulation:	40 mg/0.8 mL in pre-filled glass syringe and pre-filled pen
Proposed indication:	Treatment of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy. Treatment of adult patients with moderately to severely active Crohn's disease who have lost response to or are intolerant to infliximab.
Proposed regimen:	160 mg SC initially, 80 mg after two weeks, followed by 40 mg every other week.

Recommended regulatory action: Approval under 21 CFR 601.

Introduction and Regulatory Background

This supplemental BLA is to expand the induction for Humira to include the treatment of Crohn's disease. This would be the first non-rheumatologic indication for Humira.

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Humira is a formulation of adalimumab, a chimeric IgG monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors, which in turn inhibits TNFα-induced pro-inflammatory effects.

Humira was originally approved for rheumatoid arthritis in 2002. Since then it has also been found to be effective in treating several other diseases, and it is currently approved for the following conditions:

- rheumatoid arthritis
- psoriatic arthritis
- ankylosing spondylitis

The safety and efficacy have not been established for pediatric patients for any of these approved indications.

Humira has no specific contraindications. The approved labeling has a boxed warning for the risk of TB and other opportunistic infections. There are also warnings and precautions for other serious infections, malignancies, hypersensitivity, HBV reactivation, demyelinating disease, cytopenias, use with anakinra, heart failure, autoimmunity, use with live vaccines, and immunosuppression. The pregnancy category is B. The most common adverse reactions are infections, injection site reactions, headache, and rash. The labeling includes a patient insert.

The recommended dosing for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis is 40 mg every other week. The labeling states that patients with rheumatoid arthritis who are not receiving methotrexate may benefit from dosing of 40 mg every week.

Abbott has received an Orphan Designation for use of Humira in treating pediatric patients with moderately to severely active Crohn's disease (granted 10/19/06) and for JRA (granted 3/21/05). Fast Track status for treating patients who are no longer responsive to or are intolerant to infliximab was granted on 9/16/04. The Applicant has several outstanding postmarketing commitments from the prior approvals. These include long-term studies in RA, a study in JRA, a pregnancy registry, and a study of the impact of adalimumab on pneumococcal vaccine and influenza vaccine in RA patients.

Clinical studies of Humira in inflammatory bowel disease were conducted under Abbott's IND 10,425. An End-of-Phase-2 meeting was held on June 22, 2004, at which FDA indicated that a submission for induction alone would not be sufficient. FDA agreed it was appropriate to conduct investigations targeting patients who had an inadequate response to or were intolerant to infliximab, but that it would be important to clearly document the criteria for treatment failure. In discussion of maintenance Study 433 (described below), FDA had concerns that it might not be adequate to robustly address the benefit of chronic therapy. FDA agreed that a primary endpoint of clinical remission defined by CDAI < 150 was acceptable and that Week 4 would be an acceptable time to assess efficacy for induction. FDA stated that the proposed safety data base, of 600 with any exposure, 406 exposed for six months, and 227 exposed for a year, appeared acceptable to support a submission. FDA said the proposal to target infliximab failures might be eligible for Fast Track status, but that a formal application for that status would need to be submitted. There was discussion of a secondary endpoint of fistula response, but the minutes do not reflect any discussion concerning steroid sparing or patient-reported outcomes.

A pre-sBLA meeting was held on 5/11/06. At the meeting FDA indicated that the general submission plan appeared reasonable and that a priority review for infliximab failures could be entertained. Abbott proposed recommending giving the initial dose as divided dosing over two days, although that dosing had not been used in the clinical studies. FDA recommended that it be studied in a bioequivalence study, but data from modeling could be submitted for consideration. In response to questions about use of patient-reported outcomes, such as IBDQ and SF-36, in the labeling, FDA noted that those topics had not been discussed at the End-of-Phase-2 meeting, and would they would be considered in accordance with the recently published draft guidance.

The sBLA submission was received on August 28, 2006. The application was granted Priority review status because the submission appeared to be able to support labeling stating that Humira could be effective for treating patients who had lost response to or were intolerant to infliximab, and that was viewed as representing, if approved, a significant improvement over currently available therapies for patients with Crohn's disease.

No Advisory Committee meeting was convened to discuss this application.

The relevant primary review disciplines have all written review documents, which should be consulted for more specific details of the application. This memorandum summarizes selected information from these documents. The primary review documents relied upon are the following:

Clinical Efficacy and Safety Review, by L. Liang, draft of 2/26/07.
Statistical Review and Evolution, by M. Fan, dated 2/27/07.
Clinical Pharmacology and Biopharmaceutics Review, by T. Chen & C. Tornoe, dated 1/22/07.
Carton Label Review, by K. Brorson, dated 2/25/07.
DSI Clinical Inspection Summary, by D. Tesch, dated 2/13/07.
SEALD Study Endpoint Review, by A. Trentacosti & L. Burke, dated 2/6/07.
SEALD Proposed Labeling Format Review, by J. Delasko, dated 10/20/06.
SEALD Review of Product Labeling in PLR Format, by J. Delasko & I. Masucci, dated 2/16/07.
DSRCS Review of Patient Labeling for Humira, by J. Best, dated 1/4/07.
DDRE T-cell lymphoma Memo, by A. Mackey & A. Brinker, dated 4/26/06
OSE Drug Utilization Patterns for TNF alpha biologic agents, by L. Governale, dated 4/27/06.
DDRE Postmarketing Safety Review, by J. Weaver, dated 5/9/06.
DDRE AERS Crude Counts and Data Mining Review, by A. Raval & A. Brinker, dated 6/21/06.

(Some of these documents, namely those dealing with postmarketing safety, were actually completed in the months before the current supplement was received. This was due to recent applications, by other Applicants, that had generated an interest in examining postmarketing safety issues for biologic anti-TNF agents as a group, and Humira was included in that evaluation.)

Clinical Background

Crohn's disease, also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. The disease is manifest as discontinuous transmural inflammatory changes that can occur anywhere in the GI tract but it primarily involves small bowel or colon. Involved areas classically show noncaseating granulomas and fissuring. Complications include strictures, obstruction, malabsorption, malnutrition, and fistula formation. Growth retardation is a complication of concern in pediatric patients. There is an increased risk of malignancy with longstanding disease. Crohn's disease is more common in whites vs. non-whites and in Jews vs. non-Jews. Peak ages of diagnosis are the teens to twenties, but it can occur at any age. Presentation much before the age of five or six years is uncommon. Pediatric Crohn's disease is infrequent enough to be eligible for an Orphan Drug Designation.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used, but unapproved, therapies are aminosalicylates, azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX). Use of any of the preceding has come to be considered part of "conventional therapy" for the disease. For the proposed indication of moderately to severely active Crohn's disease with inadequate response to conventional therapy, the only approved treatment in adults or children is Remicade. There is no approved therapy for patients who have had an inadequate response to conventional therapy and who have also lost response to infliximab or are intolerant to infliximab.

Chemistry, manufacturing, and controls issues

This is a currently market product, and there were no substantial new CMC issues in this application. Humira is currently supplied in pre-filled glass syringes and pre-filled pens. Both these presentations deliver a dose of 40 mg. The Applicant is proposing to supply the product in a new Crohn's Disease Starter Package carton containing six pens, in order to facilitate the administration of the multiple doses needed for the first two weeks of treatment for Crohn's disease. The new carton label was found to be acceptable by the Product Reviewer. These product presentations are adequate for providing the recommended dosing for adults with Crohn's disease.

Pre-clinical pharmacology and toxicology issues

This is a currently marketed product. No new preclinical studies were presented in the application.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology Review by T. Chen and C. Tornoe.

Pharmacokinetics and pharmacodynamics of the induction regimens were evaluated in Study 403 (see study descriptions below), and trough levels appeared dose-proportional, with a trend for

increased response with increased trough level. For the recommended dosing regimen of 160 mg on Week 0 and 80 mg at Week 2, the mean trough concentration at Week 4 was about 13 μg/mL. The concentrations were similar in the infliximab failure population. In Crohn's disease patients the fraction that developed anti-adalimumab antibodies was 1.6% overall, and did not appear related to the dose that was administered. With chronic dosing, mean steady state adalimumab trough levels were 7 μg/mL for Humira 40 mg biweekly, and 12 μg/mL with Humira 40 mg weekly.

Concomitant medications seemingly had only a minor effect on clearance in Crohn's disease patients. In Study 691 (infliximab failures) use of immunosuppressants (6-MP, AZA, MTX) increased adalimumab concentration by 18%, but that was not expected to be clinically significant.

Based on PK modeling, the proposal to administer the initial 160 mg dose as a divided dose, of 80 mg on the first day and 80 mg on the second day, was deemed to produce nearly superimposable concentration curves compared to a single administration. The proposed dosing alternative was therefore considered to be acceptable.

The samples for two of the three pharmacokinetic studies were analyzed at an [redacted]. Recently, the quality of the work done at the [redacted] has come into question. The Office of Clinical Pharmacology (OCP) requested a DSI inspection of the [redacted] but the inspection request was declined by DSI due to budgetary constraints. Because the Switzerland site is not the [redacted], that was the subject of concern, OCP elected to treat the pharmacokinetic data as reliable. b(4)

Conclusions and Recommendations

The Clinical Pharmacology reviewer recommended that the supplement was approvable from the Clinical Pharmacology standpoint, provided certain clarifying changes and minor corrections were made to the labeling as described in the Clinical Pharmacology and Biopharmaceutics Review. No Phase 4 commitment was recommended.

Clinical/Statistical Issues

The reader is referred to the Clinical Review by L. Liang and to the Statistical Review and Evaluation by M. Fan.

This supplement included reports of four controlled studies, two for induction therapy and two for maintenance therapy. Study 403 was a four-week induction study using three different doses of Humira. The highest dose in that study was also used in Study 692, a four-week induction study that only included "infliximab failures," i.e., patients who had lost response to or who were intolerant to infliximab. Study 404 was a large maintenance study in which patients were first given open-label induction therapy with Humira, and then randomized to a year of maintenance therapy comparing two doses of Humira with placebo. Study 433 was a small follow-on study to Study 403, in which clinical responders were also randomized to a year of maintenance therapy comparing the same two doses of Humira with placebo. The supplement also included an

uncontrolled extension study (Study 690) in which patients exiting the other studies were offered open-label Humira and were followed to collect safety data.

In the study descriptions below, clinical remission, which was the primary endpoint in all four studies, is defined as obtaining a Crohn's Disease Activity Index (CDAI) score of < 150. The secondary clinical response endpoints included CR-70 (reduction in CDAI of at least 70 compared to baseline) and CR-100 (reduction of at least 100 points compared to baseline). Moderately to severely active disease was defined as CDAI $\geq$ 220 and $\leq$ 450.

Phase 2/3 Induction Study 403 (M02-403, "Classic I")

This was a randomized, double-blind, placebo-controlled, dose-exploration induction study in 299 adult Crohn's disease patients at 55 sites. The object was to obtain efficacy, safety, and pharmacokinetic information for Humira induction therapy and to provide a basis for selecting a dose for subsequent study.

To be eligible, patients had to be age 18 through 75 years of age and have moderately to severely active Crohn's disease for at least four months. Reasons for exclusion included history of TB or HIV, history of cancer, prior anti-TNF therapy, complicating GI disease, and unstable concomitant medications. See Clinical Review for complete eligibility criteria.

Patients were randomly assigned with equal probability to one of four treatment groups in which doses were administered at Weeks 0 and 2: the placebo group received placebo at both weeks, the 40/20 group received Humira 40 mg at Week 0 and 20 mg at Week 2, the 80/40 group received Humira 80 mg at Week 0 and 40 mg at Week 2, and the 160/80 group received Humira 160 mg at Week 0 and 80 mg at Week 2. Because the dose unit is 40 mg, patients assigned to doses above 40 mg required multiple injections. Concomitant medications were allowed but were to remain stable during the study. Patients who completed the study could enroll in a controlled extension study (Study 433, described below).

Patients were evaluated at Weeks 1, 2, and 4 following the initial injection. The primary endpoint was clinical remission at Week 4, and the primary analysis was a comparison of the two highest doses (pooled) vs. placebo, to be followed by pairwise comparisons if the pooled analysis was statistically significant. Patients with missing data were considered not in remission. Secondary endpoints included CR-70, CR-100, changes in inflammatory bowel disease questionnaire (IBDQ), improvement in fistulas, and fistula remission. PK samples were also taken.

The study succeeded in the primary analysis, with p=0.004 for the comparison of remission rates at Week 4 of the two highest dose groups pooled vs. placebo. In pairwise testing, only the 160/80 group showed a statistically significant difference from placebo. The primary endpoint results for the different treatment groups over time are shown in the following table taken from the Clinical Review by Dr. Liang:

Pairwise Comparisons in Induction of Clinical Remission in Study 403

Full Analysis Set (N=299)				
Adalimumab Dose/ Time Point in Study	Adalimumab n (%)	Placebo (N=74) n (%)	Difference[a] (95% CI)	Treatment Effect p-value
40 mg/20 mg (N=74)				
Week 1	12 (16)	5 (7)	9.5 (-0.7, 19.6)	0.071
Week 2	10 (14)	10 (14)	0.0 (-11.0, 11.0)	1.000
Week 4	13 (18)	9 (12)	5.4 (-6.0, 16.8)	0.355
Week 4 (LOCF)	13 (18)	9 (13)	5.3 (-6.3, 16.9)	0.373
80 mg/40 mg (N=75)				
Week 1	10 (13)	5 (7)	6.6 (-3.0, 16.2)	0.182
Week 2	15 (20)	10 (14)	6.5 (-5.5, 18.4)	0.289
Week 4	18 (24)	9 (12)	11.8 (-0.4, 24.0)	0.061
Week 4 (LOCF)	18 (25)	9 (13)	12.2 (-0.3, 24.7)	0.060
160 mg/80 mg (N=76)				
Week 1	12 (16)	5 (7)	9.0 (-1.0, 19.0)	0.081
Week 2	18 (24)	10 (14)	10.2 (-2.2, 22.5)	0.110
Week 4	27 (36)	9 (12)	23.4 (10.3, 36.4)	0.001
Week 4 (LOCF)	27 (36)	9 (13)	23.0 (9.8, 36.2)	0.001
All adalimumab (N=225)				
Week 1	34 (15)	5 (7)	8.4 (1.0, 15.7)	0.064
Week 2	43 (19)	10 (14)	5.6 (-3.7, 14.9)	0.274
Week 4	58 (26)	9 (12)	13.6 (4.2, 23.0)	0.015
Week 4 (LOCF)	58 (26)	9 (13)	13.6 (4.0, 23.2)	0.017

a. Difference refers to the difference between the proportion (%) of adalimumab-treated subjects achieving clinical remission compared with the placebo-treated subjects.

The Clinical and Statistical Reviewers concluded that the study showed evidence of superiority of Humira over placebo in inducing remission. The Statistical Reviewer observed that the effect on remission was consistent across subgroups of country, gender, age, body weight, alcohol use, concomitant medication use, and baseline CDAI, but not for tobacco use. In the Applicant's analysis the two highest doses showed greater CR-70 rates compared to placebo, and the highest dose had a statistically significantly greater CR-100 rate compared to placebo. However, the Statistical Reviewer noted the lack of pre-specified adjustment for analysis of the multiple secondary endpoints, and he considered any findings for those endpoints to be exploratory.

Phase 3 Induction Study 691 (M04-691, "GAIN")

This was a randomized, double-blind, placebo-controlled, induction study at 52 sites in 325 adult Crohn's disease patients who were infliximab failures. The object was to evaluate the efficacy and safety of Humira for induction.

To be eligible, patients had to be 18 through 75 years of age, and have moderately to severely active Crohn's disease. Patients were required to have either initially responded to infliximab but lost response, or to be intolerant to infliximab, according to specific criteria described in the protocol. Reasons for exclusion included history of TB or HIV, history of cancer, complicating GI disease, and unstable concomitant medications. See Clinical Review for complete eligibility criteria.

Patients were randomly assigned with equal probability to one of two treatment groups in which doses were administered at Weeks 0 and 2: the placebo group received placebo at both weeks, and the treatment group received Humira 160 mg at Week 0 and 80 mg at Week 2. Concomitant medications were allowed but were to remain stable during the study. Patients who completed the study could enroll in the open-label extension, Study 690.

Patients were evaluated at Weeks 1, 2, and 4 following the initial injection. The primary analysis was comparison of clinical remission rates at Week 4. Patients with missing data were considered not in remission. Secondary endpoints included CR-70, CR-100, changes in inflammatory bowel disease questionnaire (IBDQ), SF-36, improvement in fistulas, and fistula remission, VAS joint pain score, and CRP.

The study succeeded on the primary analysis. The primary efficacy results are shown in the following table taken from the Clinical Review by Dr. Liang:

Clinical Remission at Week 4 in Study 691

	Treatment Group n (%)			
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Difference in Proportions (95% CI)	p-value[a]
Week 4 Visit	12 (7)	34 (21)	14.2 (6.7, 21.6)	<0.001

The Statistical reviewer noted that the remission rate results were consistent across subgroups for gender, age, body weight, tobacco use, immunosuppressant use, baseline CRP, intolerance or loss of response to infliximab, but not for country, alcohol use, other concomitant medication use, and baseline CDAI. The Applicant's secondary analysis showed differences between groups at Week 4 for CR-70, CR-100, IBDQ, SF-36, CRP, as well as differences in CR-70 and remission at Week 2. There were no statistically significant differences in VAS joint pain score or proportion of patients with no draining fistulas. However, the Statistical Reviewer concluded that no adjustments were prospectively defined for the secondary analyses, and he considered the secondary endpoint analyses exploratory.

Phase 3 Maintenance Study 404 (M02-404, "CHARM")

This was a randomized, double-blind, placebo-controlled study of 854 Crohn's disease patients at 92 sites treated for 56 weeks. The object was to evaluate the efficacy and safety of Humira in maintenance of clinical remission.

To be eligible, patients had to be age 18 through 75 years of age, and have moderately to severely active Crohn's disease for at least four months. Patients could be included if they had had prior anti-TNF therapy and responded or did not tolerate it; but there was no requirement that the response had to have been lost. Reasons for exclusion included history of TB or HIV, history of cancer, complicating GI disease, and unstable concomitant medications. See Clinical Review for complete eligibility criteria.

All patients were treated initially with 80 mg at Week 0 and 40 mg at Week 2. Patients were evaluated for clinical response at Week 4. Those who met the criterion of CR-70 (CDAI score decrease of at least 70) were allocated to the primary analysis stratum, but all patients were randomized with equal probability to placebo, Humira 40 mg biweekly, or Humira 40 mg weekly, with randomization stratified by response status at Week 4. Treatment continued through Week 56. Concomitant medications could be continued, but were to be kept stable. Corticosteroids were to be kept stable through Week 8 and then could be tapered as specified in the protocol. After Week 12, patients who experience flair or who were consistent non-responders could be considered failures and treated with open label Humira 40 mg biweekly. If they then had flair or were non-responders, the dose could be escalated to Humira to 40 mg weekly.

Assessments were done at Weeks 2 and 4, and then every four weeks through Week 20, then every six weeks through Week 32, and then every eight weeks through Week 56. Samples for PK analysis were taken at selected visits.

The primary endpoint was clinical remission. Patients with missing data were considered not to be in remission. The primary analysis was declared to be the comparison of the remission rates at Week 26 for the Humira arms vs. placebo in the subgroup of patients who had a clinical response at Week 4, although the protocol acknowledged that finding a difference in this subgroup using the comparison at Week 56 was important for supporting a regulatory submission. The analysis used a hierarchical Hochberg method to control for multiplicity. Protocol-specified secondary analyses included CR-70, CR-100, fistula response, time in remission, steroid-free remission, IBDQ, and SF-36.

At Week 4, 499 patients (58%) had a clinical response and were therefore part of the primary analysis stratum. The primary analysis for the remission rates at both Week 26 and Week 56 demonstrated highly statistically significant differences between Humira and placebo, but not between the two Humira arms. The results in this stratum for the remission rates at Weeks 26 and 56 are shown in the table below (taken from Statistical Review):

Clinical Remission at Week 26 and Week 56 in Study 404

	Placebo	Adalimumab eow	Adalimumab ew
	N=170	N=172	N=157
Visit		n (%)	
Week 26	29 (17.1)	68 (39.5)	73 (46.5)
Week 56	20 (11.8)	62 (36.0)	65 (41.4)

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 26	Adalimumab 40 mg eow vs. placebo	22.5	(13.2, 31.7)	< 0.001
Week 26	Adalimumab 40 mg ew vs. placebo	29.4	(19.8, 39.1)	< 0.001
Week 26	Adalimumab 40 mg ew vs. adalimumab 40 mg eow	7.0	(-3.7, 17.7)	0.220
Week 56	Adalimumab 40 mg eow vs. placebo	24.3	(15.6, 32.9)	< 0.001
Week 56	Adalimumab 40 mg ew vs. placebo	29.6	(20.5, 38.7)	< 0.001
Week 56	Adalimumab 40 mg ew vs. adalimumab 40 mg eow	5.4	(-5.2, 15.9)	0.344

eow = every other week; ew = weekly; CI = confidence interval

a. The p-value is from CMH test stratified by previous anti-TNF use.

Note: Subjects without CDAI assessments at Weeks 26 or 56 were to be classified as remission "failures."

Cross Reference: Section 14, Table 14.2__1.1.2.

The Clinical and Statistical reviewers considered the study to demonstrate superiority of Humira over placebo for maintenance of clinical remission. The Statistical Reviewer found the effect on clinical remission to be consistent across subgroups of gender, age, body weight, tobacco use, alcohol use, concomitant medication use, baseline CRP, and baseline CDAI.

The Statistical Reviewer raised concerns about the analysis of the secondary endpoints of steroid-free remission and time in remission (see Statistical Review for details). He noted that the specific steroid-free remission endpoint required 90 days of steroid-free remission in the SAP but the endpoint was not clearly identified in that way in the original protocol. He also was concerned about imbalance in the numbers of steroid-free patients at baseline, and about apparent inconsistencies in the steroid-free remission rates in the different analysis populations. The Statistical Reviewer noted that time in remission was not specified in the original protocol, only in the SAP. He observed that the finding of any nominal statistical significance appeared to be highly dependent on the analysis subgroup and type of statistical test used.

Phase 3 Maintenance Study 433 (M02-433)

This was a randomized, placebo-controlled, dose-comparison maintenance study that was a follow-on to the dose-response induction study (Study 403). In this study 55 patients who entered this study from Study 403 were initially treated with Humira 40 mg at Week 0 and Week 2 (weeks numbered subsequent to completion of Study 403). Patients were then randomized with equal probability to receive placebo, Humira 40 mg biweekly, or Humira 40 mg weekly. Treatment was continued through Week 56. Concomitant therapy could be continued but was to remain stable, although steroid taper was to begin at Week 8 according to protocol specifications.

The primary endpoint was clinical remission at Week 56. The primary analysis was an overall comparison of the three groups, to be followed by pairwise testing if the overall comparison was significant. Secondary endpoints included clinical remission at Week 24, and the following evaluated at Weeks 24 and 56: CR-70, CR-100, changes in IBDQ, steroid discontinuation, time to flair, number of fistulas, and CRP levels.

Primary results are given in the table below taken from the Statistical Review. Although there was a trend favoring an effect of Humira, the study was small and the results did not achieve statistical significance.

Clinical Remission at Week 56 in Study 433

	Randomized Analysis Set (Up to Week 56)			
	Placebo N = 18	Adalimumab 40 mg eow N = 19	Adalimumab 40 mg ew N = 18	
	n (%)			p-value[a]
Week 56	6 (33.3)	9 (47.4)	12 (66.7)	0.142

eow = every other week; ew = every week

a. The p-value is from Fisher's Exact test for the comparison across the three treatment groups.

Cross Reference: Section 14, Table 14.2__3.1.1

The Statistical Reviewer noted that as a follow-on to Study 403, this study was underpowered for a pivotal study, and he considered it to be exploratory.

Clinical Site Inspections

The clinical sites in Vancouver, BC, Calgary, AB, Chicago IL, and Germantown, TN, were inspected. All four participated in both Study 691 and Study 404. At the sites in Chicago and Germantown the inspections found some discrepancies between the CDAI totals on the source documents and the CRF's. In one of the 12 patients at Chicago the response status was considered questionable. The DSI Reviewer concluded that the problems were not of such a magnitude as to indicate that official action be taken, and that the data from all the sites could be considered reliable with the one exception noted.

Safety

The reader is referred to the Clinical Review for full details of the safety analysis. A total of 1478 patients with Crohn's disease were enrolled in the four clinical studies, and 1459 of these were exposed to at least one dose of Humira. In the clinical studies or the open-label extension, 883 patients were exposed for at least six months, 661 were exposed for at least one year, and 240 were exposed for two years or more.

Clinical Study Safety Findings

Two deaths were reported, both were in Study 404, the larger maintenance study. One death was due to a pulmonary embolism in a patient with a prior history of arrhythmia and pulmonary embolism; it was reported as probably not related to Humira. The other death was due to leukemia. In addition, there were two non-fatal malignancies with Humira in the maintenance

studies: squamous cell carcinoma diagnosed 15 days after beginning Humira and labial neoplasm 254 days after beginning treatment. There was also a case of breast cancer in a patient receiving placebo in Study 404. A total of 97 serous adverse events were reported in Humira treatment groups in the clinical trials; most of these were observed in Study 404, and the large plurality of these was referable to the GI system. In the maintenance studies, the SAE rates were lower in the Humira treatment groups than in the placebo, mainly reflecting a reduction in serious Crohn's disease symptoms. There were two cases of tuberculosis in Study 404. The common AE's were nausea, headache and injection site pain or irritation. The Clinical Reviewer considered the spectrum of AE's and SAE's to be similar to that already presented in the Humira labeling for the current indications.

Postmarketing Safety Findings

Postmarketing safety experience of the three approved biologic TNF-blocking agents (infliximab, etanercept, and adalimumab) was recently examined by the Division of Drug Risk Evaluation, Office of Drug Safety, due to interest in the group generated by several recent efficacy supplements. Most of the events identified were events that were consistent with the current labelings. However, the search did uncover six cases of hepatosplenic T-cell lymphoma (HSTCL), a rare and aggressive lymphoma, in association with long-term infliximab use in children and young adults with Crohn's disease. The finding led to an additional boxed warning in the Remicade labeling when it was approved for pediatric Crohn's disease in October 2006. Additional cases have been identified subsequently in patients using Remicade, but there have been no reports to date of HSTCL with Humira.

Conclusions and Recommendations

The Clinical and Statistical reviewers concluded that Studies 403 and 691 showed superiority over placebo of Humira at the recommended induction dose for efficacy in inducing clinical remission. The reviewers also concluded that Study 404 showed superiority of Humira 40 mg biweekly over placebo for maintenance of clinical remission. The Statistical reviewer concluded there was no evidence of greater efficacy of the higher dose.

The Statistical reviewer was concerned by the possible discrepancies between the initial protocol description of the secondary analysis plan for Study 404 and the plan in the SAP submitted just prior to unblinding. Due to that, and the observation of imbalance in baseline corticosteroid use, he was not convinced that the submission provided substantial evidence of an effect of Humira on producing steroid-free remission. He also was not convinced by the analysis of duration of remission, because of lack of clear pre-specification of the analysis for that endpoint.

The Clinical reviewer felt that the safety findings from the clinical studies were reasonably consistent with the safety information currently in the Humira labeling. He recommended as Phase 4 commitments that the Applicant be required to conduct the proposed pediatric study and registry study.

Advisory Activities

This supplemental application was not presented to an Advisory Committee.

Consults

The Division received consults from DSRCS regarding the Patient Labeling, and from SEALD regarding the PLR reformatting and the patient-reported outcome of IBDQ. The recommendations regarding the labeling were generally adopted by the Division, with some exceptions (see Labeling under Regulatory Conclusions, below). The SEALD team identified several deficiencies with the use of the IBDQ, and recommended that IBDQ results not be presented in the labeling (see Study Endpoint Review by A. Trentacosti and L. Burke).

Pediatrics

This supplemental application did not contain any pediatric studies. The Applicant has already submitted to its IND a protocol for a pediatric study in 186 patients aged 6 to 17 years and plans to begin the study in March 2007. The Applicant is requesting a waiver for children under 6 years and a deferral for children aged 6 to 17 years. Given the very low incidence of Crohn's disease in children five and under, a waiver for that age range is reasonable. The Applicant should be granted the requested waiver and deferral. The proposed pediatric study should be included as a postmarketing commitment.

Regulatory Conclusions

The data in this supplemental application support approval of Humira under 21 CFR 601 for Crohn's disease in adult patients at a dosage regimen of 160 mg initially (which can be administered as divided doses on two consecutive days), followed by 80 mg at Week 2, then 40 mg every other week starting at Week 4, and with the indication as stated in the labeling negotiated with the Applicant.

Evidence of Efficacy

The two induction studies, Study 403 and Study 691, are two adequate and well-controlled studies that provide substantial evidence of the efficacy of Humira in inducting clinical remission in patients with moderately to severely active Crohn's disease at a dose of 160 mg followed by 80 mg after two weeks. Because one of these studies (Study 691) evaluated the effect in a potentially more challenging population, those who had lost response to infliximab or were intolerant to infliximab, the finding of efficacy in that population deserves specific recognition in the labeling. Given the substantial evidence of efficacy for induction of remission, and given the clinically significant and statistically persuasive findings from the relatively large multicenter maintenance study (Study 404), there is also substantial evidence that Humira has efficacy as therapy for maintaining remission in Crohn's disease. The smaller maintenance study, Study 433, can be viewed as supportive of the findings in Study 404, but did not provide substantial evidence by itself. There was not substantial evidence that the dose of 40 mg every week provided greater efficacy than 40 mg every other week. The open-label dose escalation experience, which suggested some benefit of a higher dose, was uncontrolled, whereas the parallel controlled experience in the large maintenance study (Study 404) did not demonstrate a difference between the doses.

Indication

The statement of the indication as originally proposed by the Applicant, viz., [redacted] is too vague. This reviewer recommends the that the wording of the indication reflect the specific effects demonstrated, similar in spirit to that of the previous approved TNF blocker for Crohn's, Remicade. In particular, Humira should be indicated for reducing signs and symptoms and inducting and maintaining clinical remission is adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. b(4)

While recognizing that the official Division approved labeling will be otherwise, this reviewer recommends that the indication not include statements about the effect in patients who have lost response to or are intolerant to infliximab. Such a statement does not change the description of the nature of the effect produced by the product nor does it expand or restrict the indicated population otherwise described in the indication, but it does encumber the statement of the indication. The observation of efficacy for induction in "infliximab failures" is most appropriately presented in the clinical trials section, where it still offers the Applicant a promotable claim. In this reviewer's view, efficacy in infliximab failures is more reasonably considered a supplemental claim about the Crohn's disease indication rather than an additional indication. If a statement about infliximab failures is to be included in the indication, it should be worded to clearly reflect that the substantial evidence for efficacy has only been provided for induction; although the maintenance study recorded whether patients had prior infliximab use, it did not adequately document reasons for infliximab discontinuation. Any broadening of the claim to include maintenance for infliximab failures should be based on clinical studies of patients who have well documented loss of response or intolerance.

Dosing

The approved Humira labeling already cites increased risk of tuberculosis reactivation with increased doses. The controlled maintenance studies did not demonstrate better efficacy at higher doses. Although the primary endpoint of remission rates was numerically (but definitely not statistically significantly) higher with weekly vs. biweekly dosing, some outcomes, such a steroid-free remission, were numerically lower with weekly dosing. The Applicant pointed to the experience with escalating the dose in patients who were failures in Study 404.

However, this reviewer finds those data unconvincing for recommending higher chronic dosing. For one, the experience was uncontrolled. A patient who is temporarily doing worse may be more likely to show a subsequent improvement (a clinical regression to the mean). Without a control group it is hard to know the magnitude of that effect or to say that the dose escalation significantly improved it. Patients with exacerbation might only need a temporary dose elevation for re-induction to restore control with the recommended dose. It would be unfortunate to subject patients to the risks from exposure to a chronically higher dose if only a temporarily higher dose would suffice.

In the absence of controlled data showing a sustained benefit of a sustained higher dose, and without investigation of whether a temporary dose elevation strategy might afford the same benefit with less risk than permanent dose elevation, the recommended dosing should only be 40 mg every other week. In that spirit, the labeling should limit discussion of results to the

outcomes obtained with the recommended dosing, otherwise the labeling could be construed as recommending other dosing (cf. *Guidance for Industry: Clinical Studies Section of Labeling …*, Section 3 E.)

This reviewer accepts the recommendation of the Biopharmaceutics reviewers, that based on the PK modeling the initial dosing can be recommended as 80 mg per day on two consecutive days as an alternative to 160 mg on one day, even though that is not how the treatment was administered in any of the clinical studies.

Labeling Recommendations

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Changes should be made to the CLINICAL PHARMACOLOGY-Pharmacokinetics section as recommended by the Clinical Pharmacology reviewer.

New Phase 4 Commitments

The applicant has offered to conduct a controlled study of 186 pediatric patients with Crohn's disease ages 6 to 17. A pediatric protocol has already been submitted and appears reasonable. The Applicant is also proposing to conduct a registry study to obtain five years of follow up in 5000 adult patients with Crohn's disease. These studies should be formalized as Phase 4 commitments.

Other Issues

With the recent approval of Remicade (infliximab) for pediatric Crohn's disease, an unexpected number of cases of the rare hepatosplenic T-cell lymphoma (HSTCL) were found in adolescents and young adults with Crohn's disease who had used Remicade, and a boxed warning regarding the risk of HSTCL was added to the Remicade labeling. To date, the cases have only been seen with Remicade (infliximab), although, because Remicade was approved for Crohn's disease over eight years ago, there has been much more off-label use of Remicade in the pediatric Crohn's disease population than there has been for Humira. Too little is known at this point to include a boxed warning for the risk of HSTCL in the Humira labeling in the face of no reported cases with the product. Humira labeling already contains a general warning about malignancies. If the Applicant is granted a pediatric indication it will be appropriate to consider requesting a pediatric registry similar to that being conducted for Remicade, taking into consideration what else might be known about the issue by then. The postmarking reviewers are attuned to the concern about HSTCL, and if FDA begins to receive any reports of HSTCL with Humira, the situation will need to be quickly re-evaluated, and, at a minimum, a warning will undoubtedly be appropriate for Humira too. Given the current state of knowledge, the sponsor's proposal to conduct a

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

OFFICE DIRECTOR MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: February 27, 2007

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

Brian E. Harvey M.D., Ph.D.
2/27/07

SUBJECT: Division Director Concurrence Memo
sBLA/STN 125057/89
Humira for Crohn's Disease

APPLICANT: Abbott Labs

PRODUCT: Humira (Adalimumab)

DATE SUBMITTED: August 28, 2006

DIVISION RECOMMENDATION:

The primary Medical Officer and Medical Team Leader have both recommended that sBLA/STN 125057/89, Humira (Adalimumab) subcutaneous injection be approved for the following indications: "HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab." I concur with these recommendations.

I. BACKGROUND:

Humira (Adalimumab) is a genetically-engineered monoclonal antibody against human tumor necrosis factor (TNF). As described in the product label, "Adalimumab is

produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons." In addition, "Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses."

Humira is currently approved for the following indications:

> *HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs).*
>
> *HUMIRA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.*
>
> *HUMIRA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. PRODUCT AND MANUFACTURING:

This submission is a sBLA for a new indication of a previously approved product. The review team did not report any unresolved nonclinical safety issues based upon their review of this data. In addition, the Product Review Team has reviewed the product carton, as well as the subsequent revisions and has recommended approval of this product.

B. PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:

The sponsor's submission is a sBLA for a new indication of a previously approved product. The review team did not report any unresolved nonclinical safety issues based upon their review of this data.

C. BIOPHARMACEUTICS:

As outlined by the Clinical Pharmacology Team memo, there were "five clinical trials, i.e., two double-blind randomized studies and two long-term randomized studies for the maintenance of clinical remission plus an extension study for a long-term safety and efficacy study. For all these studies, the currently marketed Humira SC formulation was used. Pharmacokinetic (PK) data was obtained from 3 clinical studies. A population PK (PPK) approach was also employed for PK analyses and PK/PD (pharmacodynamic) assessments." The team also found that "Immunogenicity of adalimumab in patients with CD showed that the % of CD patients who developed anti-adalimumab antibody (AAA) is considered low and seemingly the incidence is not proportional to the dose administered. Overall, the immunogenicity of adalimumab in subjects with CD who developed AAA was 1.6%."

Of note, the team described the following: "The analytical methodology and validation of the assays used for this submission are found acceptable. Due to recent in-house report on problematic [redacted] Office of Clinical pharmacology (OCP) made a request for an audit at the [redacted] site in [redacted] for the two (out of three) PK studies. However, the above audit request was unable to be executed due to DSI being in short of budget. OCP would presume that the analytical work done at the [redacted] is acceptable. Nevertheless, if further information on [redacted] indicates problematic, the Agency should audit the [redacted] subsequently." Given the large amount of clinical data in this submission, all of the review teams concluded that if PK data issues were discovered at some future date, the approval of this product still would be adequately supported by the clinical data alone.

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The Clinical Pharmacology Team has recommended approval of this product and supports the final product label as attached to the approval letter dated February 27, 2007.

E. CLINICAL AND STATISTICAL:

Both the primary Medical Officer and the Medical Team Leader provided a detailed review and analysis of the clinical data submitted in support of this sBLA. As described in the finalized product label, the "safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 79% of patients continued to receive at least one of these medications. Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were

randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4. In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4. Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI $\geq$70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4."

The clinical team did not report any unresolved issues based upon their review of this data. They concluded that benefits outweighed the risks in these proposed populations and have recommended approval of this product. The statistical team has completed their review and has not raised any issues that would prevent the approval of this product. Both the clinical and statistical teams support the information in the final product label as attached to the sBLA approval letter.

III. RECOMMENDATIONS FOR REGULATORY ACTIONS

The primary Medical Officer and Medical Team Leader have both recommended that sBLA/STN 125057/89, Humira (Adalimumab) subcutaneous (SC) injection at a dose of 160 mg SC initially, 80 mg after two weeks, followed by 40 mg every other week, be approved for the following indications: "HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab." I concur with these recommendations.

I concur with the granting of a deferral for pediatric studies required under PREA and with the proposed plan as summarized in the approval letter:

> *Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this post-marketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.*

To complete and submit data from study protocol M06-806, a one-year, multi-center, randomized, double-blind study designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in the induction and maintenance of clinical remission in pediatric subjects 6 to 17 years of age with moderate to severe Crohn's disease. The study will include collection of baseline data on prior loss of response to or intolerance to infliximab, using definitions similar to those used in protocol M04-691. The final study protocol was submitted to Abbott's IND on 24 January 2007. Enrollment of 186 patients will begin by 31 March 2007 and will be complete by 31 March 2008. The study will be complete by 31 March 2009, and the final clinical study report will be submitted by 31 December 2009.

Final Report Submission: December 31, 2009

Submit final study reports to this BLA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "Required Pediatric Study Commitments".

I concur with the proposed study as a post-marketing commitment (PMC) as summarized in the approval letter:

To conduct study protocol P06-134, a 5-year, 5000 patient, multi-center, uncontrolled, observational study of adult patients with Crohn's disease treated in a routine clinical setting with adalimumab. The final protocol will be submitted by 30 April 2007 for concurrence, the study will be initiated by 31 August 2007, and enrollment will be complete by 31 August 2009. The study will be complete by 31 August 2014. Abbott will submit interim safety analyses of the study by 28 February 2009, 28 February 2011, and 28 February 2013, and will submit a final clinical study report by 31 May 2015.

Final Report Submission: May 31, 2015

IV. LABELING RECOMMENDATIONS

After discussions with the sponsor and the review team, I concur with the final negotiated label as attached to the approval letter dated February 27, 2007 for this sBLA.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

MEDICAL REVIEW(S)

March 13, 2007

Team Leader's Preface to the Clinical Review

Humira (adalimumab) Supplemental BLA for Crohn's Disease

STN 125057.89

After Dr. Liang reviewed the supplemental BLA for Humira in the treatment of Crohn's disease, circumstances prevented him from completing the write-up of his findings in the CLINCAL REVIEW document. With Dr. Liang's consent, this Team Leader has undertaken to edit Dr. Liang's last draft of the CLINICAL REVIEW so that it could be entered into the administrative record in as final a form as possible. The draft has been edited for typographic corrections, clarity, consistency of style and formatting, and any needed rectification in the presentation of objective facts. The text has otherwise been essentially unmodified, with the exceptions of updating information about the Applicant's Phase 4 commitments, and copying forward a statement of the safety conclusions from the Integrated Review of Safety into the Executive Summary. In particular, no change was made to Section 1.1 (Recommendation on Regulatory Action). While this version of the CLINICAL REVIEW document may not completely reflect Dr. Liang's full intent for it, his willingness to let this be done for the record is appreciated.

John E. Hyde 3-13-07

John Hyde, Ph.D., M.D.
Clinical Team Leader

CLINICAL REVIEW

Application Type	Supplemental BLA
Submission Number	STN 125057.89
Submission Date	August 24, 2006
PDUFA Goal Date	February 27, 2007
Reviewer Name	Li-ching Liang, M.D. CDER/ODE III/DGP
Through	John Hyde, Ph.D., M.D. CDER/ODE III/DGP and Brian Harvey, M.D., Ph.D. CDER/ODE III/DGP
Review Completion Date	XXXXX
Established Name	Humira®
Therapeutic Class	TNF Antagonist
Applicant	Abbott Labs
Priority Designation	Priority
Formulation	40 mg/0.8 mL in prefilled syringe or pen
Dosing Regimen	160 mg SC at Week 0, 80 mg SC at Week 2, followed by 40 mg eow
Indication	Crohn's disease
Intended Population	Moderately to severely active Crohn's disease patients who have had an inadequate response to conventional therapy and/or who were intolerant to or lost response to infliximab therapy

1 EXECUTIVE SUMMARY **4**
1.1 RECOMMENDATION ON REGULATORY ACTION 4
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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving the efficacy supplement with revisions to the proposed label. The information in this supplement provides substantial evidence to support the proposed changes to the indication, and there are data to provide adequate directions for use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

1.2.2 Required Phase 4 Commitments

[ ]

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

HUMIRA® (adalimumab) is currently approved in the U.S. for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. For rheumatoid arthritis, adalimumab is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease. It is indicated in psoriatic arthritis for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function. Lastly, HUMIRA® is also currently indicated in ankylosing spondylitis for reducing signs and symptoms in patients with active disease.

In June 2004, Abbott met with the Agency at an End of Phase 2 meeting after promising results from an investigator-initiated study prompted the Sponsor to develop the use of adalimumab in Crohn's disease patients who previously received and responded to infliximab, but who no longer had a sustained response and/or tolerance to infliximab.[1]

The current submission addresses the benefit of HUMIRA® therapy both in inducing and maintaining clinical remission in moderately to severely active Crohn's disease in adult patients

[1] Sandborn et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastro. 2004 Oct;99(10):1984-9.

who have had an inadequate response to conventional therapy, and who have lost response to or are intolerant to infliximab (REMICADE®) therapy. In support of this goal, Abbott conducted two induction of clinical remission studies and two long-term maintenance studies, enrolling a total of 1478 subjects.

The primary objective of the Phase 2/3 Study M02-403 (CLASSIC I trial) was to determine the efficacy and safety of three doses of adalimumab (160 mg at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, or 40 mg at Week 0 and 20 mg at Week 2) vs. placebo at Week 0 and 2, to induce clinical remission in moderately to severely active adult Crohn's disease (CD) subjects who had an inadequate response to conventional therapy. This study was designed to determine which dose provided the greatest clinical benefit, measured by a primary endpoint of clinical remission at Week 4.

Study M04-691 (GAIN trial) was a Phase 3 study conducted in adult CD subjects who previously had a response and subsequently lost response to infliximab, or, were intolerant to infliximab. Subjects were randomized to receive either adalimumab sc 160 mg at Week 0 and 80 mg at Week 2, or placebo sc doses at Weeks 0 and 2. In similar fashion to Study M02-403, the primary endpoint was clinical remission at Week 4. Subjects who completed Study M04-691 were eligible to enroll in a currently ongoing Study M04-690 addressing the long-term safety and tolerability of repeated adalimumab administration.

Study M02-433 (CLASSIC II trial) was a Phase 2/3 study designed as a follow-on study where subjects who achieved clinical remission from Study M02-403 were randomized to either adalimumab 40 mg weekly, adalimumab 40 mg every other week, or placebo therapy in order to evaluate the benefit of maintenance adalimumab therapy. The primary endpoint in this study was clinical remission at Week 56 for subjects in clinical remission at Week 4 from lead-in Study M02-403.

The fourth submitted study was Study M02-404 (CHARM trial) which was designed as a Phase 3 induction and maintenance trial evaluating weekly or every other week adalimumab therapy vs. placebo therapy for subjects who achieved a clinical response at Week 4 after open-label induction therapy.

1.3.2 Efficacy

Adalimumab was found to have efficacy in the induction and maintenance of clinical remission in adult subjects with moderately to severely active CD who were unresponsive to conventional therapies. Adalimumab was also efficacious in the treatment of adult subjects with active CD who previously received infliximab and subsequently lost response to or were intolerant to infliximab therapy. Study reports from two large and well-controlled trials support the proposed induction claim. Both induction studies had the same primary endpoint of clinical remission (defined as a CDAI score < 150) at Week 4. Study M02-403 was a randomized, dose-ranging study of adalimumab vs. placebo in anti-TNF naïve subjects. In contrast, Study M04-691 evaluated one adalimumab dose group (160 mg at Week 0, and 80 mg at Week 2) vs. a placebo group in subjects who were anti-TNF (infliximab) experienced.

Study M02-403 showed a dose-response relationship with adalimumab for clinical remission. The 160 mg/80 mg dosing regimen was the most effective adalimumab dose to induce clinical remission with 36% of subjects achieving the primary endpoint, in comparison to 12% of subjects in the placebo group. Study M04-691 used the optimal adalimumab dose from Study M02-403 (160 mg/80 mg) and compared this dose to placebo injections in active CD subjects who failed previous infliximab therapy. In this anti-TNF experienced subpopulation, 21% of adalimumab-treated subjects achieved clinical remission at Week 4 compared to 7% in the placebo group.

The two large studies submitted to support the proposed maintenance claim (Studies M02-433 and M02-404) both examined the efficacy of two long-term adalimumab dosing regimens (40 mg every other week [eow] sc or 40 mg every week [ew] sc) vs. placebo in double-blind phases of the trials. The primary analysis populations in both maintenance studies were subjects that had either achieved remission at Week 4 from a lead-in study (for Study M02-433, the lead-in study was Study M02-403), or, had achieved a clinical response (decrease in CDAI of $\geq$ 70 points) after open-label induction (in Study M02-404). Thus, both maintenance studies employed a randomized withdrawal type of study design to demonstrate the benefit of one or both adalimumab treatment regimens over placebo. Both studies also had a primary endpoint of clinical remission at Week 56 (this was a co-primary endpoint for Study M02-404). Using this strategy, the Sponsor demonstrated that adalimumab maintenance treatment was superior to placebo therapy out to 56 weeks for subjects that either achieved clinical remission (Study M02-433) or clinical response (Study M02-404) at Week 4. Week 26 response and remission rates also supported the use of adalimumab maintenance treatment for subjects who achieved a clinical benefit after induction therapy.

1.3.3 Safety

Based on extensive prior experience, the use of adalimumab is associated with a number of adverse events that appear drug related which are fully described in the current package insert. In this submission, there were no specific adverse events identified that are not already appropriately reflected in the package insert.

1.3.4 Dosing Regimen and Administration

The recommended adalimumab induction regimen in adult subjects with moderately to severely active Crohn's disease is 160 mg sc given at Week 0, followed by 80 mg sc given at Week 2. Beginning at Week 4, adalimumab should be given at 40 mg sc every other week. Subjects who do not have a clinical response may benefit from having their adalimumab dose increased to 40 mg every week.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were explored in this supplement.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adalimumab is the first human-derived monoclonal antibody to tumor necrosis factor-alpha (TNF-α) engineered by gene technology and does not contain non-human sequences. It binds only to TNF and has a half-life of approximately two weeks. This is in contrast to soluble TNF receptors (which bind both TNF and lymphotoxin with moderate to high affinity), and chimeric monoclonal antibodies (which bind only TNF but contain foreign protein sequences that are immunogenic).

2.2 Currently Available Treatment for Indications

Currently approved products for the treatment of Crohn's disease include budesonide (Entocort EC®) and infliximab (Remicade® for IV injection). Budesonide is indicated for the treatment of mild to moderate Crohn's disease involving the ileum and/or the ascending colon and the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to three months. Infliximab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

2.3 Availability of Proposed Active Ingredient in the United States

This product is currently licensed and marketed in the United States. There are no known availability issues with the proposed ingredient.

2.4 Important Issues with Pharmacologically Related Products

An increased risk of serious infections and lymphoma is associated with currently approved TNF-antagonists. A higher rate of lymphoma has been observed in RA and Crohn's disease patients receiving TNF-blockers compared to the general U.S. population.

2.5 Presubmission Regulatory Activity

Adalimumab (HUMIRA®) was originally approved in the United States in December 2002 for the treatment of moderately to severely active rheumatoid arthritis (RA) and has subsequently been approved for psoriatic arthritis and ankylosing spondylitis. The application outlining the CD development plan received Fast Track designation by the Agency in September 2004 for the treatment of adult CD in patients who were unresponsive to or intolerant of infliximab therapy for: 1) the reduction of signs and symptoms of moderate to severe adult Crohn's disease patients,

and 2) induction of clinical remission. The sBLA supplement and request for priority review was received on August 28, 2006. At the October 12, 2006, filing meeting, the efficacy supplement was given a six-month review clock, with a PDUFA goal date of February 27, 2007.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of the clinical data for this review consisted of study reports and datasets from four Abbott-sponsored, randomized, controlled clinical trials in multiple international sites, M02-403 (CLASSIC I Study), M04-691 (GAIN Study), M02-433 (CLASSIC II Study), and M02-404 (CHARM Study).

4.2 Tables of Clinical Studies

The four clinical studies reviewed in support of this efficacy supplement for adalimumab induction and maintenance in CD are listed below:

Study	Description
M02-403	CLASSIC I: A Phase 2/3, 4-week randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and PK of three adalimumab doses compared to placebo in moderately to severely active CD subjects: 299 subjects with active CD randomized 1:1:1:1 to placebo, adalimumab 160 mg/80 mg, 80 mg/40 mg, or 40 mg/20 mg at Weeks 0 and 2, respectively.
M04-691	GAIN: A Phase 3, 4-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and PK of adalimumab 160 mg at Week 0 and 80 mg at Week 2 compared to placebo at both Week 0 and Week 2 in moderately to severely active CD subjects who were previously unresponsive to or intolerant to infliximab therapy: 325 subjects with active CD randomized 1:1 to either adalimumab 160 mg at Week 0 and 80 mg at Week 2 compared to placebo at both Weeks 0 and 2.
M02-433	CLASSIC II: A Phase 2/3 randomized, double-blind, placebo-controlled follow-on study of the efficacy, safety, and PK of adalimumab for the maintenance of clinical remission in subjects who participated in lead-in study M02-403. Subjects in clinical remission from Week 4 of Study M02-403 were assigned to one of three blinded treatment groups or open label (OL) treatment: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo treatment every week. The primary endpoint was the proportion of subjects in clinical remission at Week 45 who were also in remission at Study M02-433 Baseline.
M02-404	CHARM: A Phase 3 randomized, double-blind, placebo-controlled induction and maintenance of clinical remission study where subjects with active CD were given OL adalimumab 80 mg at Week 0 and 40 mg at Week 2. Week 4 responders were then randomized to adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo. The two co-primary endpoints were the proportion of subjects 1) in clinical remission at Week 26 with at least a CR-70 response at Week 4, and 2) in clinical remission at Week 56 who had at least a CR-70 response at Week 4.

4.3 Review Strategy

Studies M02-403 and M02-433 were considered Phase 2/3 trials that 1) explored three doses of adalimumab as induction therapy at Weeks 0 and 2, and 2) explored the role of adalimumab in maintenance therapy, respectively.

Study M04-691 was a pivotal Phase 3, four-week induction trial to compare adalimumab therapy (160 mg at Week 0 and 80 mg at Week 2) against placebo at Weeks 0 and 2 in active CD subjects who were previously unresponsive to or intolerant to infliximab therapy.

The pivotal Phase 3 maintenance trial was Study M02-404 which randomized subjects to one of three possible maintenance regimens after open-label induction therapy. All four studies were randomized, double-blind, and placebo-controlled trials.

These four studies were designed to substantiate the use of adalimumab in the treatment of adults with moderately to severely active CD who have had an inadequate response to conventional therapy or who lost response to or were intolerant to previous infliximab therapy.

4.4 Data Quality and Integrity

4.5 Compliance with Good Clinical Practices

4.6 Financial Disclosures

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

For the Crohn's disease indication, the Sponsor proposed adding the underlined wording to the HUMIRA® in the new PLR format:

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:

Crohn's Disease
Treatment of moderately to severely active disease in adult patients:
- **who have had an inadequate response to conventional therapy**
- **who have lost response to or are intolerant to infliximab**

6.1.1 Methods

The clinical data from all four randomized, double-blind, placebo-controlled studies were analyzed to determine whether a clinical benefit was seen for subjects with active CD who received adalimumab therapy versus placebo. The FDA statistical reviewer confirmed the major efficacy analyses and performed sensitivity analyses to corroborate the findings of the Sponsor.

6.1.2 General Discussion of Endpoints

In the CLASSIC I (M02-403) and the GAIN (M04-691) Studies, the primary endpoint was clinical remission at Week 4 based upon the use of the Crohn's Disease Activity Index (CDAI). The CDAI score was agreed upon by the Agency in the Sponsor's End of Phase 2 meeting and is a universally accepted and validated measure of disease activity in CD patients. In current literature and current CD submissions to the Agency, the standard definition of "remission" is considered an absolute CDAI score of < 150. The Sponsor also evaluated the proportions of subjects who were able to achieve clinical "response" (defined as a reduction in the CDAI score of ≥ 70 points [CR-70] or ≥ 100 points [CR-100]) as secondary endpoints. The maintenance trials evaluated the proportion of subjects in either remission or response at Weeks 26 and/or 56 using a randomized withdrawal design. The timepoints of Week 4 and Week 56 have generally been accepted by the Agency as supportive of an induction and maintenance claim for CD, respectively.

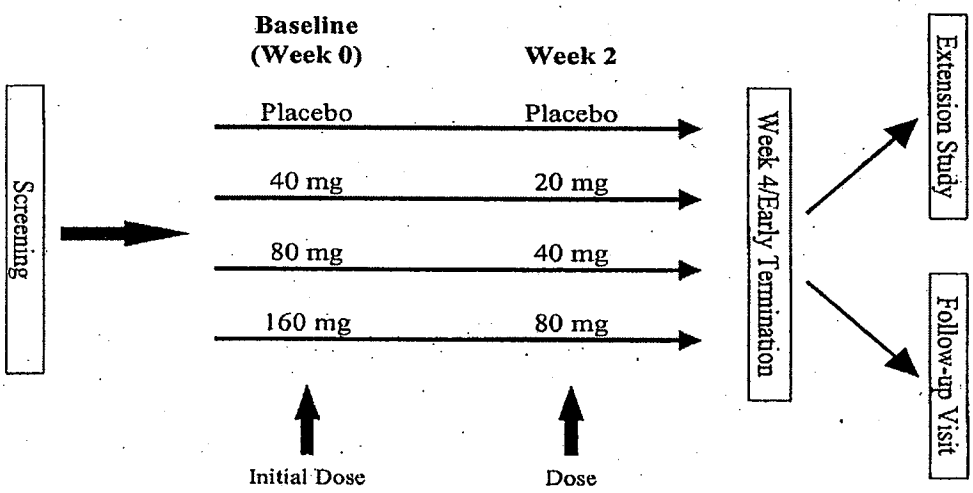
6.1.3 Study Design

6.1.3.1 General Study Designs and Treatment Schemas

Study M02-403:

The CLASSIC I Study (M02-403) was a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the role of adalimumab in the induction of clinical remission in active CD subjects who were TNF-blocker naïve. The study was conducted from July 2002 to December 2003 and involved 55 international sites (U.S., Canada, Poland, Belgium, the Netherlands, and the Czech Republic). The objective of the study was to determine the most effective induction dose combination to be given at Weeks 0 and 2. Subjects were required to have moderately to severely active CD (defined as a CDAI $\geq$ 220 and $\leq$ 450 points) for at least four months. A total of 299 outpatient subjects were randomized to one of four treatment groups as depicted in the study design diagram below:

Figure 1: Study Schema – M02-403:



Doses for this induction study were chosen from PK data accumulated from the HUMIRA® rheumatoid arthritis (RA) development program. The study duration was up to 10 weeks (with a 4-week blinded portion). Subjects who completed the study were given the opportunity to roll over into Study M02-433 (the CLASSIC II Study). Adalimumab therapy was injected subcutaneously by study staff to outpatients.

The primary endpoint for the CLASSIC I Study was clinical remission (CDAI < 150 points) at Week 4. The pre-specified primary analysis was to compare the rate of clinical remission of the adalimumab 160 mg/80 mg and the 80 mg/40 mg dose groups to the placebo group rate at Week

4 using Pearson's Chi-square test. If significant, pairwise comparisons of each adalimumab dose group vs. placebo were performed. Subjects with missing primary endpoint data at Week 4 were classified as nonresponders. Adjustment for multiple testing was done following the closed testing procedure.

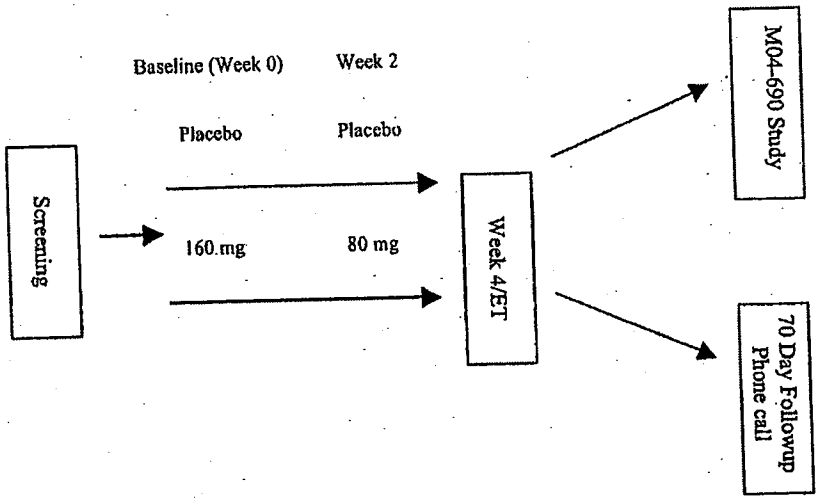
The major secondary endpoints of the study were:

- Clinical response (decrease in Baseline CDAI score > 70 points) at Week 4;
- Clinical response (decrease in Baseline CDAI score > 100 points) at Week 4;
- CDAI scores;
- IBDQ scores;
- Improvement in number of draining cutaneous fistulas at Week 4, where improvement was defined as a decrease of > 50% in the number of draining cutaneous fistulas at Baseline for at least 2 consecutive visits;
- Fistula remission at Week 4 (closure of all fistulas that were draining at Baseline) for at least 2 consecutive visits;
- Fistula counts;
- Achievement of clinical remission in the 40 mg/20 mg adalimumab dose group at Week 4;
- Achievement of clinical response (CDAI score decrease of > 70 points) in the 40 mg/20 mg adalimumab dose group at Week 4; and
- CRP (mg/dL) values.

Study M04-691

Study M04-691 (the GAIN Study) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled two-arm induction study of moderately to severely active CD subjects who either previously lost response to (defined as having previously been administered infliximab and discontinued use due to a loss of response) or were intolerant to infliximab therapy. In order to satisfy enrollment criteria, the subject must have received at least two doses of $\geq$ 5 mg/kg infliximab every eight weeks and experienced a lack of improvement or worsening in at least one of the following Crohn's-related signs/symptoms at least two weeks after the last dose of infliximab: stool frequency, daily abdominal pain, fever, recurring drainage from a previously non-draining fistula or development of a new draining fistula, rectal bleeding, and/or change in usage or new introduction of use of anti-diarrheal medication. Subjects were considered intolerant to infliximab therapy if infliximab therapy was discontinued by a physician due to a significant acute (< 24 hours) or delayed (> 24 hours and $\leq$ 14 days) adverse reaction after infliximab administration. This study lasted up to six weeks and was conducted from November 2004 to January 2006 in approximately 300 subjects randomized at 50 sites worldwide. Subjects were randomized to either adalimumab 160 mg/80 mg or placebo sc at Weeks 0 and 2. Subjects who successfully completed Week 4 of the study were given the opportunity to roll over into Study M04-690 which is an ongoing long-term safety and tolerability study of repeated adalimumab administration. The study schema for Study M04-691 is shown below:

Figure 2: Study Schema – M04-691



ET = early termination

The primary endpoint for the GAIN Study was identical to the CLASSIC I Study, namely, clinical remission at Week 4. The primary analysis was to compare the rates of induction of clinical remission of the adalimumab 160 mg/80 mg treatment arm vs. the placebo group at Week 4 using Pearson's Chi-square test. Those subjects with missing primary endpoint data at Week 4 were imputed as nonresponders. All statistical tests were to be 2-sided and conducted at the 0.05 significance level. The secondary endpoints for Study M04-691 were similar to the CLASSIC I Study:

- Clinical response (decrease in Baseline CDAI score $\geq$ 70 points) or CR-70 at Week 4;
- Clinical response (decrease in Baseline CDAI score $\geq$ 100 points) or CR-100 at Week 4;
- Changes in IBDQ scores at Week 4;
- Proportion of subjects with CR-70 at Week 2;
- Proportion of subjects with CR-70 at Week 1;
- Change from Baseline in SF-36 Physical Component Summary (PCS) score at Week 4;
- Change from Baseline in VAS score for joint pain at Week 4;
- Proportion of subjects with no draining fistulas at the last two evaluations;
- Change from Baseline in CRP at Week 4;
- Change from Baseline in SF-36 Mental Component Summary (MCS) score at Week 4; and
- Proportion of subjects with remission at Week 2.

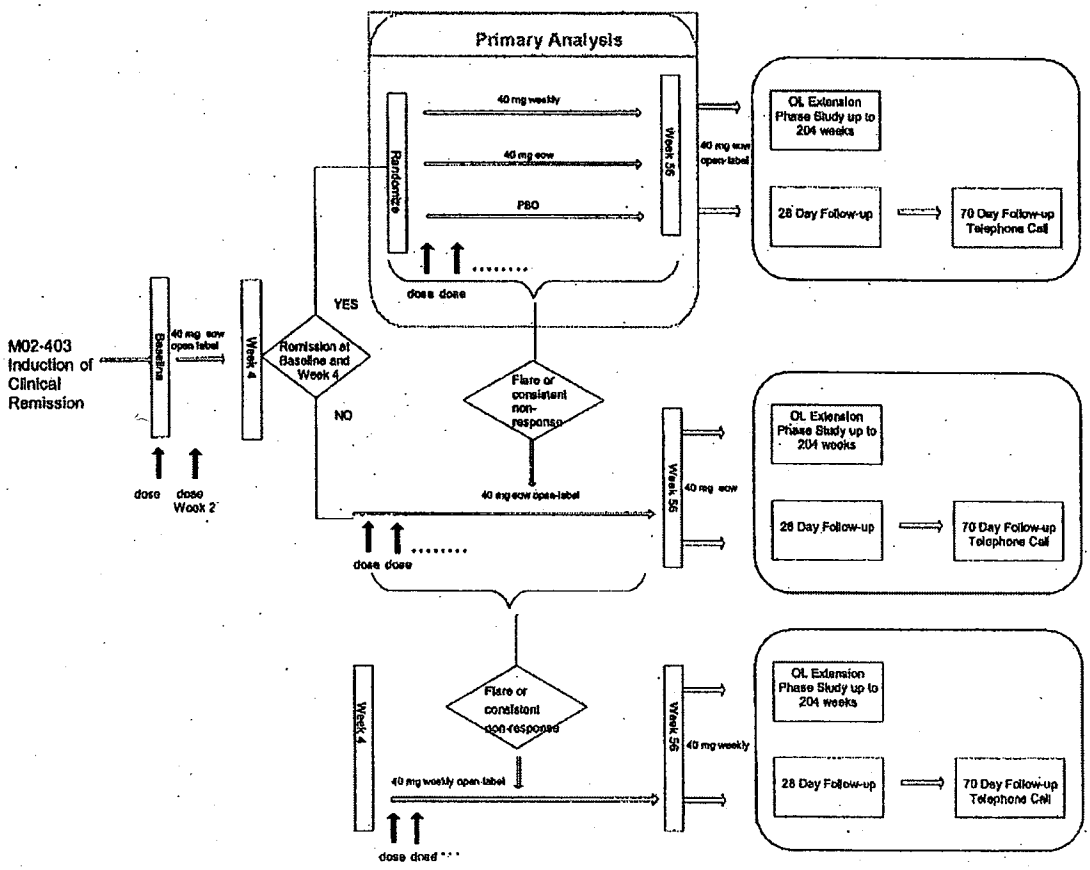
Study M02-433

Study M02-433 (the CLASSIC II Study) was a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled follow-on study for subjects who participated in lead-in Study M02-403 to evaluate the efficacy, safety, and PK of adalimumab for the maintenance of clinical remission. Subjects from the lead-in study were given the opportunity to participate in the CLASSIC II Study whether or not they were in clinical remission at Week 4. Of the 284 subjects who completed lead-in Study M02-403, 276 subjects continued in Study M02-433.

Subjects in clinical remission at Week 4 from the lead-in study were assigned to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo ew. This group was called the "randomized analysis set." Subjects not in clinical remission after the end of Week 4 from the lead-in study were given open-label adalimumab 40 mg eow and followed out to Week 56. This group of subjects was called the "open-label analysis set."

Subjects in the randomized analysis group who had disease flares or were consistent nonresponders received adalimumab 40 mg eow in open-label fashion until Week 56. Subjects in the open-label group who were initially given 40 mg eow were given open-label adalimumab 40 mg weekly (see schema). After the Week 56 response/remission rates were assessed subjects in the randomized group continued an adalimumab open-label extension study up to 204 weeks. Subjects in the initial open-label group continued on 40 mg eow unless they had a flare between Weeks 4 and 56. If their adalimumab dose was increased to 40 mg ew due to a flare, these subjects were then continued on adalimumab 40 mg ew in the open-label extension study until 204 weeks. This open-label extension study is currently ongoing at the time of this review.

Figure 3: Study Schema for Study M02-433



The primary endpoint for Study M02-433 was the proportion of subjects in clinical remission at Week 56 who were also in remission at Study M02-433 Baseline. The primary analysis was to initially compare the three treatment groups overall. If a significant difference was observed across the three treatment groups, a pairwise comparison of each adalimumab dose group vs. placebo then performed.

The following secondary endpoints in this study were evaluated for both the **randomized analysis set** and the **open-label analysis set**.

- Clinical remission at Week 24.
- Clinical remission at Week 56 for subjects who were not in remission at Baseline (Week 0) or Week 4.
- Clinical response (decrease in M02-403 Baseline (Week 0) CDAI score $\geq$ 70 points at Week 24 and at Week 56.
- Clinical response (decrease in M02-403 Baseline (Week 0) CDAI score $\geq$ 100 points at Week 24 and at Week 56.
- Changes in Baseline (Week 0) IBDQ scores at Week 24 and Week 56.

- Corticosteroid discontinuation at week 24 and Week 56, defined as complete withdrawal of corticosteroid therapy without development of relapse (re-initiation of corticosteroid therapy).
- Time to flare (first increase in the CDAI score compared to the M02-433 Week 4 values of $\geq$ 70 points and a CDAI score above 220 points).
- CDAI Total Score at Week 24 and Week 56
- Number of Draining Fistulas at Week 24 and Week 56
- IBDQ Total Score at Week 24 and Week 56
- CRP levels at Week 24 and Week 56

Study M02-404

Study M02-404, also known as the CHARM trial, was a Phase 3, multicenter, randomized, double-blind, placebo-controlled induction and maintenance trial lasting 62 weeks conducted between July 2003 and September 2005 at 92 international (EU, U.S., Canada, Australia, and South Africa). In this study, all subjects with moderately to severely active CD were given open-label adalimumab 80 mg at Week 0 and 40 mg at Week 2. Subjects with previous TNF-therapy were allowed in the study if they became intolerant to or lost response to an anti-TNF agent. At Week 4, subjects were stratified by responder status and previous anti-TNF use and then randomized 1:1:1 to adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo. Subjects who had a disease flare at or after Week 12 of the study could be switched to the open-label phase of the study to receive adalimumab 40 mg eow. Subjects who were consistent nonresponders (defined as those subjects who did not meet the definition of a flare but also did not attain a CDAI decrease of $\geq$ 70 points compared to Baseline) could also be switched to the open-label phase of the study after Week 12. Subjects were required to maintain the dose of Crohn's-related concomitant medications but could taper steroids (prednisone or budesonide) or decrease the dose of other concomitant medications due to Grade 3 or higher toxicities. No increase in Crohn's-specific concomitant medications was allowed.

The analyzable populations for this study were defined as follows:

"All treated" population: these were subjects who received at least one dose of study drug.

"Modified ITT" population: these were all treated subjects who achieved clinical response (CR-70) at Week 4 and were randomized to receive one of three blinded treatments. This was the population for the primary and secondary efficacy analyses.

"Per protocol" population: this was an additional an alysis population for primary efficacy variables and excluded all subjects with major protocol deviations in the mITT population.

Important pre-specified subset populations included the following:

1) The Week 4 nonresponder subset of the all treated population.
2) Subjects with previous and/or concomitant use of other Crohn's medications subset of the mITT population.

3) Subset of all treated population with endoscopic evaluation, and
4) Subjects with a Baseline CRP of $\geq$ 1.0 mg/dL.

There were two co-primary endpoints in this study. These were the proportion of subjects in clinical remission (CDAI < 150) at Week 26 with at least a clinical response (CR-70) at Week 4, and, the proportion of subjects in clinical remission at Week 56 who had at least a CR-70 at Week 4.

The primary analysis was to test for an adalimumab treatment effect at Weeks 26 and 56 in the modified intent-to-treat (mITT) population (defined as all treated subjects who achieved CR-70 at Week 4 and were randomized to receive one of three blinded treatments). This involved comparisons of the proportion of responders at Week 4 and in clinical remission at Week 26 or Week 56, with comparison between each adalimumab arm and the placebo treatment group using the Chi-square test and adjusting for previous anti-TNF use. Hypothesis testing for the co-primary endpoints was to be carried out in a hierarchical order. The Week 26 remission rate was to be tested first. If the hypothesis test for Week 26 remission rates was rejected, then the Week 56 remission rates were to be tested. Otherwise, testing was to stop.

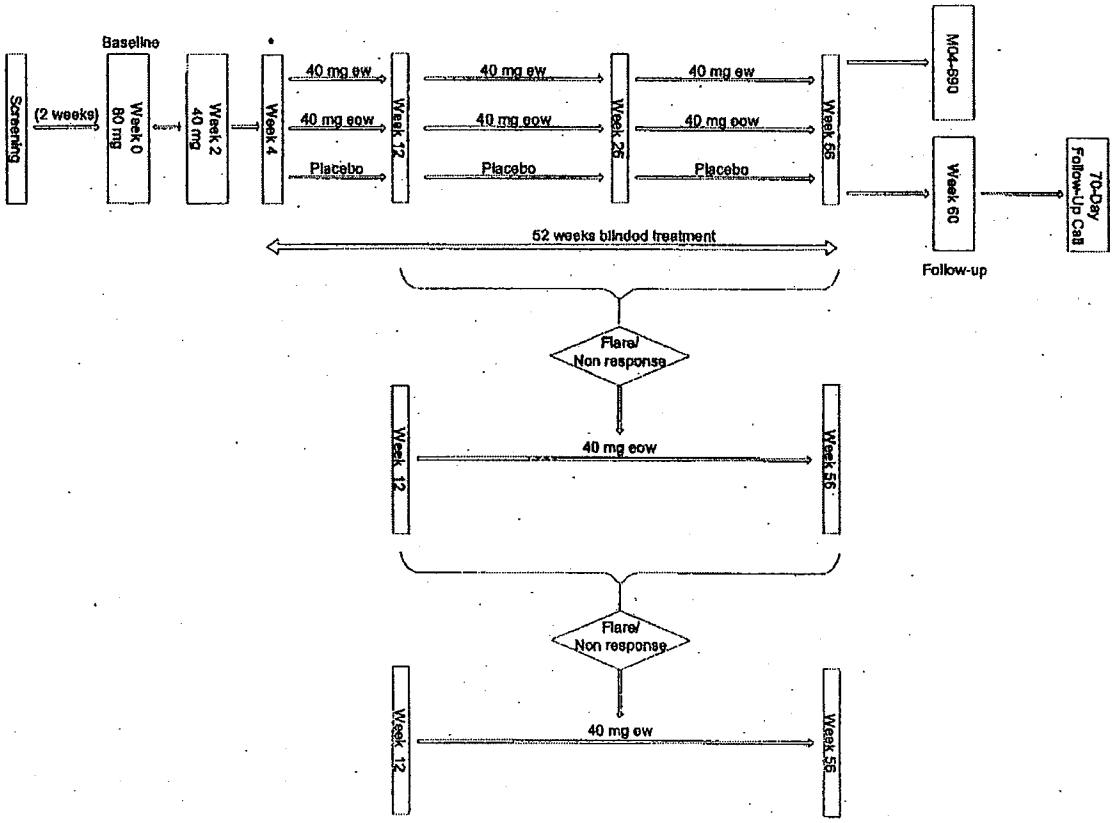
To be considered a positive trial, adalimumab needed to demonstrate efficacy at both the Week 26 and 56 endpoints. The Hochberg procedure was to be applied to control for multiplicity. If one hypothesis test derived a non-significant p-value ($p \geq 0.05$), then the other hypothesis would be tested against an adjusted 0.025 alpha level. A positive conclusion would still be made if the p-value was significant at the 0.025 alpha level.

Subjects who were consistent non-responders or switched to open-label treatment after a flare were to be considered "failures" for all visits post-flare.

The secondary endpoints of Study M02-404 were to be assessed in all of the analyzable populations as follows:

- Proportion of subjects with a clinical response (CR-70) at Weeks 26 and 56.
- Proportion of subjects with a clinical response (CR-100) at weeks 26 and 56.
- Changes from Baseline in IBDQ scores at Weeks 26 and 56.
- Proportion of subjects with improvement in the number of draining fistulas (defined as a decrease from Baseline in the number of draining fistulas of $\geq$ 50% for at least two consecutive visits).
- Proportion of subjects with fistula remission (complete closure of all fistulas draining at Baseline for at least two consecutive visits).
- Steroid sparing at Week 26 and 56 (the proportion of subjects at Weeks 26 and 56 in clinical remission [CDAI < 150] able to discontinue steroid use); and
- Of those with a clinical response (CR-70) at Week 4, time to flares, up to and including Week 56 (recurrence of active disease, with an increase in the CDAI score of $\geq$ 70 points and a CDAI score > 220).

Figure 4: Study Schema – Study M02-404



This protocol was also designed to evaluate approximately 100 subjects in a separate endoscopic substudy. Colonoscopy results based on the Crohn's Disease Endoscopic Index of Severity (CDEIS) were to be reviewed and scored by an on-site endoscopist for the following additional secondary endpoints:

1) Mean change in CDEIS score from Week 0 to Week 12 and Week 0 to Week 56
2) Mean change in SES-CD from Week 0 to Week 12 and Week 0 to Week 56, and
3) Proportions of subjects with ulcers on colonoscopy at Week 0 with complete healing of ulcers at Week 12 and at Week 56.

6.1.3.2 Study Inclusion/Exclusion Criteria

Across the four studies included in this efficacy supplement, the inclusion criteria for enrolled subjects were similar. Subjects were required to be adults between 18 and 75 years of age, inclusively, and have moderately to severely active Crohn's disease (defined by a CDAI score between 220 and 450, inclusively) diagnosed by endoscopy or radiologic evaluation, for at least four months. Females were required to use a highly-effective method of birth control or not be of childbearing potential. All subjects in the studies were required to have adequate cardiac, renal, and hepatic function, and physical examination results within normal limits.

Some inclusion criteria differed among the studies: 1) subjects in Study M04-691 were required to have been previously administered infliximab and discontinued use due to a loss of response or intolerance to infliximab therapy; 2) subjects in Study M02-404 could have been enrolled if he/she used infliximab or any anti-TNF agent and had responded and then stopped the agent, responded and lost response, responded and became intolerant, or did not tolerate the anti-TNF agent; 3) subjects in Study M02-433 were required to have successfully enrolled in and completed the lead-in study, Study M02-403. Concomitant treatment with stable doses of immunosuppressives (azathioprine, 6-MP, or MTX), aminosalicylates, and either prednisone (or equivalent) or budesonide, but not both, were allowed in all studies.

Key exclusion criteria, common to all four studies, included subjects with: a history of cancer; active TB; *Listeria*, *C. difficile*, or HIV infection; ulcerative colitis; symptomatic obstructive strictures; recent or planned surgical resections; extensive small bowel resection or short bowel syndrome; ostomies; receipt of TPN; significant lab abnormalities; abnormal Screening laboratory results; and a history of a poorly controlled medical condition.

The complete inclusion/exclusion criteria for all four studies can be found in **Appendix 1.**

6.1.3.3 Prior and Concomitant Therapy

Across all four studies, subjects were allowed to continue receiving most Crohn's-related medications if they had been receiving stable doses of these medications for a specific period of time prior to Screening. Doses of these medications were to remain stable during the study. The simultaneous use of budesonide and prednisone (or equivalent) was not permitted.

Permitted therapies and the period of time that these medication doses had to be stable are listed in the table below:

Table 1: Permitted Prior and Concomitant Therapy

Permitted Therapy	Receipt of Stable Doses for:
5-ASA	≥ 4 weeks prior to Screening
6-MP	≥ 12 weeks prior to Screening
Azathioprine	≥12 weeks prior to Screening
Budesonide ≤ 9 mg/day	≥ 2 weeks prior to Screening
Crohn's-related antibiotics	≥ 4 weeks prior to Screening
Mesalamine	≥ 4 weeks prior to Screening
Methotrexate	≥ 12 weeks prior to Screening
Prednisone ≤ 20 mg/day (or equivalent)	≥ 2 weeks prior to Screening
Sulfasalazine	≥ 4 weeks prior to Screening

Exceptions to permitted therapies for each study are further outlined below:

Study M02-403

Cyclosporine, tacrolimus, enemas, and live vaccines were prohibited during the study. Subjects receiving cyclosporine and tacrolimus were required to discontinue use within eight weeks prior to enrollment.

Study M04-691

In this study, corticosteroids (≤ 40 mg/day of prednisone, or equivalent) were permitted provided subjects were on stable doses for at least two weeks prior to Screening. Doses were to remain stable during the entire course of the (four-week) study.

Study M02-433

In this long-term follow-on study (from lead-in Study M02-403), vaccines administered during Study M02-433 were recorded as concomitant medications. Subjects were permitted to continue receiving the medications listed in **Table 1** provided they had been receiving stable doses of these medications for a specific time period prior to Screening for Study M02-403 according to the schedule in **Table 1**. At Week 8 of Study M02-433, subjects in the blinded portion of the study who were receiving prednisone or budesonide were required to begin a mandatory discontinuation of these medications according to the table below:

Table 2: Prednisone and Budesonide Discontinuation

Medication	Dose	Rate
Prednisone	30 mg to 10 mg 10 mg to 0 mg	5 mg/week 2.5 mg/week
Budesonide	9 mg to 0 mg	3 mg/week

The selected schedule for corticosteroid reduction was at the Investigator's discretion. Beginning at or after the Week 8 visit, subjects in the open-label portion of the study who were on prednisone or budesonide and met the CR-70 responder criteria (compared to the Study M02-403 Baseline) were allowed to discontinue corticosteroid use according to the rates suggested in **Table 2** or at a pace as per the discretion of the Investigator. Steroid tapering was to stop for subjects who were nonresponders.

Study M02-404

In this long-term study, subjects were permitted to be on a maximum of ≤ 30 mg/day of prednisone (or equivalent), provided they were on stable doses for at least two weeks prior to Screening. No escalations of Crohn's-related concomitant medications were allowed and no reductions in concomitant therapies were allowed, except for corticosteroids and for Crohn's treatment-related toxicities that were Grade 3 or higher as per Common Toxicity Criteria (CTC).

Setons were authorized as concomitant therapy for subjects with perianal fistulas and were documented in case report forms as such.

6.1.3.4 Planned Methods of Analysis

Study M02-403

The primary analysis in this study was an overall comparison of the clinical remission rates of the adalimumab 80 mg/40 mg, 160 mg/80 mg, and placebo groups at Week 4, using Pearson's Chi-square test. If significant, then pairwise comparisons of each adalimumab dose group vs. placebo were carried out. Subjects with missing primary endpoint data at Week 4 were imputed as nonresponders. Adjustment for multiple testing was done following the closed testing procedure.

Study M04-691

The primary efficacy analysis was to compare the rates of clinical remission of the adalimumab 160 mg/80 mg group vs. the placebo group at Week 4 using Pearson's Chi-square test. Subjects with missing primary endpoint data were imputed as nonresponders.

Study M02-433

The primary analysis was to be the comparison of the proportion of subjects maintaining clinical remission at Week 56 between treatment groups using Pearson's Chi-square test, or Fisher's Exact test if more than 20% expected cell count < 5. Adjustment for multiple testing was done following the closed testing procedure. An initial overall comparison of the three treatment groups (adalimumab 40 mg ew, adalimumab 40 mg eow, and placebo) was to be tested. If significant, pairwise comparison of each adalimumab dose group vs. placebo was performed.

Study M02-404

The primary analysis for Study M02-404 was to be hypothesis tests for adalimumab treatment effect at Weeks 26 and 56 in the mITT population. The proportion of responders at Week 4 and in clinical remission at Week 26 or Week 56 were co-primary endpoints to be compared between each adalimumab arm and the placebo treatment group using the CMH Chi-square test, adjusting for previous anti-TNF use. Subjects with missing data at Week 26 or Week 56 were classified as remission failures.

Hypothesis testing (the individual null hypothesis was no treatment difference between the adalimumab dose group vs. the placebo group) for the co-primary endpoints was to be carried out in a hierarchical order. The Week 26 remission rate was tested first. If the hypothesis test for Week 26 remission rate was rejected, then the Week 56 remission rate was tested; otherwise, testing was to stop. Achieving significant at the Week 26 endpoint alone qualified the trial as a positive study. However, based on End of Phase 2 agreements with the Agency, the study drug

needed to demonstrate efficacy at both Week 26 and 56 endpoints to support a claim of maintenance of clinical remission.

The Hochberg procedure was applied to control for multiplicity while hypothesis testing was done for the two dose arms at the Week 26 endpoint. Each adalimumab dose group was compared to the placebo group in the proportion of subjects in clinical remission at Week 26. If both p-values were less than 0.05, the individual null hypotheses were to be rejected and the hypothesis test for Week 56 was continued. If one p-value did not show significance at the 0.05 alpha level, then the hypothesis test for this dose at Week 56 was to stop and the hypothesis test for the other dose was to be evaluated at an adjusted alpha level of 0.025.

If the null hypothesis was rejected at Week 26, then the Week 56 clinical remission rates would be tested using the same testing procedure as for the Week 26 clinical remission rates. If both dose arms showed significance, this would support the labeling claim of maintenance of clinical remission.

6.1.3.5 Discontinuation of Individual Subject Rules

In all four of the studies, subjects could be withdrawn from the study at any time at their own request. Subjects were immediately withdrawn from their respective studies if any of the following occurred:

- The subject's response to therapy was unsatisfactory, as determined by the Investigator.
- There were clinically significant abnormal laboratory results, as determined by the Investigator and the Abbott Medical Monitor.
- There was a clinically significant deterioration of the medical status of the subject.
- The Investigator believed it was in the best interest of the subject.
- The subject or subject's legally authorized representative requested withdrawal from the study.
- A selection criterion violation was noted after the subject started study drug.
- The subject became pregnant.

6.1.3.6 Schedule of Study Events

The schedule of study events for each of the four studies discussed in this review are displayed as per the individual protocols and can be found in **Appendix 2**.

6.1.4 Efficacy Findings

6.1.4.1 Demographics

Baseline Demographics

The baseline demographics across all four studies were comparable and typical of Crohn's disease trials studying patients with moderately to severely active disease. The demographic charts of each of the four studies are displayed below.

Study M02-403

In this four-week induction of clinical remission study (**Table 3**), subjects randomized to one of three adalimumab dose groups had a median age of 38. Subjects randomized to placebo had a comparable median age of 36 years. Among those subjects randomized to any adalimumab dose group, 56% were females compared to 50% of subjects who received placebo. The majority of subjects were under 40 years of age (69%), with 93% less than 64 years of age. The racial/ethnic demographics in this study were representative of the prevalence of Crohn's disease. The subjects were predominantly White (92%), with few Black, Hispanic, and "Other" subjects (3% each). No Asians were enrolled in this study.

Table 3: Baseline Demographics – Study M02-403

Demographic Parameter	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160 mg/80 mg (N=76)	All Adalimumab (N=225)	Placebo (N=74)
Age (yrs)					
Median	38	38	38	38	36
(Range)	(18-73)	(20-74)	(20-63)	(18-74)	(19-74)
Age n (%)					
< 40 years	39 (53)	40 (53)	43 (57)	122 (54)	51 (69)
40-64 years	32 (43)	34 (45)	33 (43)	99 (44)	18 (24)
65-74 years	3 (4)	1 (1)	0	4 (2)	5 (7)
Sex n (%)					
Female	35 (47)	50 (67)	40 (53)	125 (56)	37 (50)
Race/Ethnicity n (%)					
Black	2 (3)	7 (9)	3 (4)	12 (5)	2 (3)
White	67 (91)	64 (85)	67 (88)	198 (88)	68 (92)
Hispanic	0	4 (5)	3 (4)	7 (3)	2 (3)
Asian	2 (3)	0	1 (1)	3 (1)	0
Other	3 (4)	0	2 (3)	5 (2)	2 (3)
Body weight (kg)					
Median	73	70	74	73	72
(Range)	(48-125)	(41-126)	(50-125)	(41-126)	(41-134)
Body weight n (%)					
≤ 60 kg	13 (18)	20 (27)	15 (20)	48 (21)	18 (24)
> 60-70 kg	19 (26)	18 (24)	16 (21)	53 (24)	15 (20)
> 70-85 kg	26 (35)	17 (23)	21 (28)	64 (28)	21 (28)
> 85-100 kg	11 (15)	11 (15)	16 (21)	38 (17)	13 (18)
> 100 kg	5 (7)	9 (12)	8 (11)	22 (10)	7 (10)
Height (cm)					
Median	173	168	172	170	172
(Range)	(145-191)	(150-193)	(150-191)	(145-193)	(150-193)

Study M04-691

In this induction study which enrolled subjects who previously received infliximab therapy and then lost a response to or were intolerant to infliximab, no significant differences were seen in the demographics of subjects randomized to adalimumab or to placebo (**Table 4**). The demographics were comparable overall to those seen in Study M02-403.

The median age for all enrolled subjects was 37 years, nearly all (98%) subjects were under 64 years of age, slightly more females than males were enrolled, and subjects were predominantly White.

Table 4: Baseline Demographics – Study M04-691

Demographic Parameter	Treatment Group n (%) Placebo (N=166)	Adalimumab 160/80 mg (N=159)	p-value[a]
Age (years)			0.149
Mean ± SD	37.4 ± 11.94	39.4 ± 11.87	
Median (range)	37.0 (18075)	37.0 (19-75)	
Age group (n, %)			0.265
< 40 years	102 (61)	88 (55)	
40-64 years	60 (36)	68 (43)	
65-74 years	3 (2)	2 (1)	
>74 years	1 (<1)	1 (<1)	
Gender (n, %)			0.146
Female	101 (61)	109 (69)	
Male	65 (39)	50 (31)	
Race (n, %)			0.121
White	160 (96)	147 (93)	
Black	3 (2)	6 (4)	
Hispanic	2 (1)	2 (1)	
Asian	1 (<1)	2 (1)	
Other	0	2 (1)	
Weight (kg)			0.934
Mean ± SD	71.91 ± 19.183	71.74 ± 19.021	
Median (range)	68.0 (41-141.5)	68.0 (35.4-140.1)	
Height (cm)			0.043
Mean ± SD	169.5 ± 9.98	167.8 ± 9.95	
Median (range)	170.0 (121.0 – 193.0)	167.6 (147.0 – 200.0)	

Study M02-433

Subjects who entered into Study M02-433 could do so only if they completed lead-in study M02-403. Each subject was assigned to either the "randomized analysis set" or the "open-label analysis set" based upon their remission status at Week 4 from the lead-in study which was the Week 0 or Baseline for Study M02-433 (**Table 5**). Demographics for subjects in the randomized analysis set and the open-label analysis set were comparable across all dosing groups and did not change significantly compared to the demographic parameters seen in the lead-in study.

Table 5: Baseline Demographics – Study M02-433

	Randomized Analysis Set					Open-Label Analysis Set		
Demographic Parameter	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55	p-value	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=18	Total N=204
Sex, n (%)					0.615			
Female	12 (67)	12 (63)	9 (50)	33 (60)		57 (50)	47 (53)	104 (51)
Male	6 (33)	7 (37)	9 (50)	22 (40)		58 (50)	42 (47)	100 (49)
Race, n (%)					0.429			
White	17 (94)	17 (90)	15 (83)	49 (89)		105 (91)	77 (87)	182 (90)
Black	1 (6)	0	1 (6)	2 (4)		5 (4)	3 (3)	8 (4)
Hispanic	0	0	1 (6)	1 (2)		3 (3)	5 (6)	8 (4)
Asian	0	2 (11)	0	2 (4)		1 (<1)	0	1 (<1)
Other	0	0	1 (6)	1 (2)		1 (<1)	4 (5)	5 (3)
Age, years					0.434			
Mean ± SD	35.7±12.9	34.2±11.5	38.1±9.8	36.0±11.4		40.4±13.1	38.9±11.7	39.8±12.5
Median	32.0	31.0	37.5	34.0		38.0	38.0	38.0
Age, n (%)					1.000			
< 40 yrs	12 (67)	13 (68)	12 (67)	37 (67)		60 (52)	47 (53)	107 (53)
40-64 yrs	5 (28)	6 (31)	6 (33)	17 (31)		49 (43)	40 (45)	89 (44)
65-74 yrs	1 (6)	0	0	1 (2)		6 (5)	2 (2)	8 (4)
Weight, kg					0.868			
Mean ± SD	69.6±12.5	69.1±18.8	72.1±19.9	70.2±17.1		77.7±18.8	75.2±17.6	76.7±18.3
Median	68.8	68.0	67.0	68.0		76.0	71.0	74.0

Study M02-404

In this long-term maintenance study, all subjects were initially given an induction dose regimen of adalimumab and then randomized to receive either placebo or one of two adalimumab maintenance regimens. Baseline demographics across all maintenance regimens were comparable (**Table 6**), with a median age of 36 years for all subjects. Nearly all (98%) were under 64 years of age, with 62% of subjects being female. As in the three other studies included in this submission, 93% of subjects were White.

Table 6: Baseline Demographics – Study M02-404

Demographic Parameter	Treatment Group			Not randomized Subjects	Total
	Placebo	Adalimumab eow	Adalimumab ew		
	N=261	N=260	N=257	N=76	N=854
Age (years)					
Mean ± SD	36.9±11.43	36.8±11.48	37.8±12.09	36.1±13.63	37.1±11.85
Median (range)	37.0 (18-75)	35.0 (17-73)	36.0 (18-75)	35.5 (19-75)	36.0 (17-75)
Age group (n, %)					
< 40 years	155 (59)	162 (62)	149 (58)	48 (63)	514 (60)
40-64 years	102 (39)	96 (37)	101 (39.3)	24 (32)	323 (38)
65-74 years	3 (1)	2 (<1)	6 (2)	3 (4)	14 (2)
≥ 75 years	1 (<1)	0	1 (<1)	1 (1)	3 (<1)
Gender (n, %)					
Female	162 (62)	163 (63)	157 (61)	46 (61)	528 (62)
Race (n, %)					
White	246 (94)	245 (94)	231 (90)	74 (97)	796 (93)
Black	8 (3)	7 (3)	12 (5)	0	27 (3)
Hispanic	0	1 (<1)	3 (1)	1 (<1)	5 (<1)
Asian	3 (1)	4 (2)	7 (3)	0	14 (2)
Other	4 (2)	3 (1)	4 (2)	1 (1)	12 (1)
Weight (kg)					
Mean ± SD	71.1 ± 18.38	70.5 ± 16.89	71.0 ± 18.48	67.1 ± 15.95	70.5 ± 17.76
Median	67.0	68.5	67.0	65.0	67.0

6.1.4.2 Baseline Disease Characteristics

The baseline disease characteristics for all subjects across the four studies in this supplement were consistent with subjects with moderately to severely active Crohn's disease despite conventional therapy.

Study M02-403

Study M02-403 enrolled subjects who had predominantly ileal Crohn's disease, and comparable proportions of subjects with ileocolonic and colonic disease only (**Table 7**). The median CDAI score for subjects who were randomized to one of three adalimumab dose groups was 288 and was 276 for subjects randomized to receive placebo injections. The median fistula count was 0 for all dose groups, but was not unexpected because this study was not intended to study the effect of adalimumab for fistula response. All subjects had either been treated previously with corticosteroids, 5-ASA products, or immunosuppressive agents. At the time of enrollment into Study M02-403, 42% of subjects randomized to any adalimumab dose group were receiving mesalazine, 16% were receiving prednisone, and between 12-14% of subjects were on either azathioprine or 6-MP. These proportions were comparable in the group receiving placebo.

Table 7: Disease Characteristics – Study M02-403

Disease Characteristic	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160 mg/80 mg (N=76)	All Adalimumab (N=225)	Placebo (N=74)
Crohn's disease location					
Colonic n (%)	23 (31)	17 (23)	22 (29)	62 (28)	14 (19)
Ileal n (%)	45 (61)	48 (64)	41 (54)	134 (60)	50 (68)
Ileocolonic n (%)	5 (7)	9 (12)	9 (12)	23 (10)	10 (14)
Perianal n (%)	0	1 (1)	1 (1)	2 (<1)	0
Small bowel n (%)	1 (1)	0	2 (3)	3 (1)	0
Unclassifiable n (%)	0	0	1 (1)	1 (<1)	0
CDAI score					
Median	284	287	291	288	276
(Range)	(220-450)	(191-448)	(201-424)	(191-450)	(216-437)
IBDQ score					
Median	129	128	127	128	131
(Range)	(81-218)	(63-200)	(37-192)	(37-218)	(52-200)
Number of draining enterocutaneous fistulas					
Median	0	0	0	0	0
(Range)	(0-2)	(0-4)	(0-3)	(0-4)	(0-7)
Previous Crohn's disease medication, PT, n (%)					
Prednisone	36 (49)	31 (41)	34 (45)	101 (45)	33 (45)
Mesalazine	24 (32)	22 (29)	21 (27)	67 (30)	33 (45)
Azathioprine	15 (20)	11 (15)	13 (17)	39 (17)	16 (22)
Budesonide	11 (15)	5 (7)	14 (18)	30 (13)	12 (16)
Sulfasalazine	12 (16)	10 (13)	4 (5)	26 (12)	10 (14)
6-Mercaptopurine	7 (10)	8 (11)	9 (12)	24 (11)	8 (11)
Concomitant Crohn's disease medication, PT, n (%)					
Mesalazine	29 (39)	31 (41)	35 (46)	95 (42)	32 (43)
Prednisone	10 (14)	15 (20)	11 (15)	36 (16)	16 (22)
Azathioprine	13 (18)	9 (12)	10 (13)	32 (14)	12 (16)
Budesonide	6 (8)	11 (15)	12 (16)	29 (13)	8 (11)
6-Mercaptopurine	6 (8)	10 (13)	10 (13)	26 (12)	8 (11)
Loperamide	1 (1)	10 (13)	4 (5)	15 (7)	2 (3)
Sulfasalazine	5 (7)	6 (8)	3 (4)	14 (6)	1 (1)

Study M04-691

Baseline disease characteristics for subjects in Study M04-691 (**Table 8**) were comparable between the two study arms. A total of 73% of subjects had ileal CD involvement and 67% had colonic involvement. Rectal CD involvement was reported in 23% of subjects and 18% had anal or peri-anal involvement. A total of 10% of subjects reported proximal small bowel (gastroduodenal or jejunal) involvement of CD.

Table 8: Disease Characteristics – Study M04-691

Crohn's Disease Location	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)	Total (N=325) n (%)
Ileum	124 (75)	112 (70)	236 (73)
Colon	113 (68)	105 (66)	218 (67)
Rectum	37 (22)	36 (23)	73 (23)
Anal/Peri-anal	31 (19)	27 (17)	58 (18)
Gastroduodenum	16 (10)	5 (3)	21 (7)
Jejunum	4 (2)	6 (4)	10 (3)
Other	6 (4)	5 (3)	11 (3)

The median CDAI score for all subjects was 304 (**Table 9**), consistent with moderately to severely active CD. Concomitant aminosalicylate use was seen in 32% of subjects, 39% were also on concomitant corticosteroids, and nearly 50% of subjects were taking concomitant immunosuppressants. The proportion of subjects on concomitant immunosuppressants in this study was likely higher than in the previously discussed induction study, Study M02-403, due to the practice of treating this patient population with immunosuppressants and infliximab, concurrently.

Table 9: Baseline Disease Severity – Study M04-691

	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Total (N=325)
Baseline CDAI Score			
Mean ± SD	313.2 ± 65.5	312.5 ± 57.5	312.9 ± 61.6
Median (range)	303.0 (156.0-454.0)	304.0 (220.0 – 444.0)	304.0 (156.0 – 454.0)
	n (%)		
Concomitant aminosalicylate use	60 (36)	45 (28)	105 (32)
Concomitant corticosteroid use	73 (44)	55 (35)	128 (39)
Concomitant immunosuppressant use	85 (51)	73 (46)	158 (49)

A summary of subjects who were intolerant to infliximab treatment and/or lost response to infliximab therapy is displayed in **Table 10**. Subjects who were intolerant to infliximab therapy (had either an acute or delayed adverse reaction to infliximab infusion) accounted for 59% of treated subjects, and 51% of subjects lost response to infliximab. 40 of 325 (12%) subjects were both intolerant to and lost response to infliximab treatment, whereas 11 of 325 (3%) subjects did not meet the definition of being intolerant to or lost response to infliximab, due to protocol violations.

Table 10: Summary of Intolerance and/or Loss of Response to Infliximab by Treatment Group – Study M04-691

	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)	Total (N=325) n (%)
Intolerant	95 (58)	95 (60)	190 (59)
Lost response	87 (52)	77 (48)	164 (51)
Intolerant and lost response	21 (13)	19 (12)	40 (12)
Did not meet criteria	5 (3)	6 (4)	11 (3)

Study M04-691 was not intended to study the role of adalimumab in fistula response, but 11% and 2% of subjects had one and two draining cutaneous fistula(s), respectively. There were few subjects with abdominal fistulas and 9% had one perianal fistula. Fistula counts were comparable between the two treatment groups.

Table 11: Fistula Counts at Study Baseline – Study M04-691

Fistula Type	Number of Fistulas	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)	Total (N=325) n (%)	p-value
Draining Cutaneous Fistulas					0.724
	0	141 (85)	139 (87)	280 (86)	
	1	20 (12)	14 (9)	34 (11)	
	2	4 (2)	3 (2)	7 (2)	
	3	0	1 (<1)	1 (<1)	
	≥4	1 (<1)	2 (1)	3 (<1)	
Abdominal Fistulas					
	0	164 (99)	156 (98)	320 (99)	
	1	2 (1)	2 (1)	4 (1)	
	2	0	0	0	
	3	0	1 (<1)	1 (<1)	
	≥4	0	0	0	
Perianal Fistulas					
	0	143 (86)	142 (89)	285 (88)	
	1	18 (11)	12 (8)	30 (9)	
	2	4 (2)	3 (2)	7 (2)	
	3	0	0	0	
	≥4	1 (<1)	2 (1)	3 (<1)	

Study M02-433

Study M02-433 enrolled subjects who completed lead-in Study M02-403. These subjects were assigned to either the "randomized analysis set" or the "open-label analysis set" depending on clinical remission status at Week 4 of the lead-in study. Consistent with the median fistula counts from the lead-in study (**Table 7**), subjects in both analysis sets in Study M02-433 had median fistula counts of 0. Subjects in the randomized analysis set had a median CDAI score of

102, reflecting their clinical remission status at the Week 4 timepoint of the lead-in study. Whereas in the open-label analysis set, subjects had a median CDAI score of 238, consistent with their lack of clinical remission at the Week 4 timepoint of Study M02-403. Baseline use of corticosteroids, immunosuppressants, and aminosalicylates were generally comparable across the three possible maintenance regimens, although it should be noted that the total number of subjects in the randomized analysis set was small, resulting in either 18 or 19 subjects randomized to receive either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew.

Table 12: Baseline Disease Characteristics – Study M02-433

	Randomized Analysis Set					Open-Label Analysis Set[a]		
Baseline Disease Characteristic	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55	p-value[b]	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
# Draining Fistulas					0.041			
Mean ± SD	0.17±0.38	0	0	0.05±0.23		0.13±0.45	0.12±0.39	0.13±0.43
Median	0	0	0	0		0	0	0
CDAI Score					0.589			
Mean ± SD	107.2±62.4	106.1±33.2	87.6±50.3	100.4±49.7		237.3±59.3	255.4±86.8	245.2±73.0
Median	95	110	94.5	102		224.0	267	237.5
IBDQ Score					0.412			
Mean ± SD	187.2±22.1	180.6±27.7	191.5±22.2	186.4±24.2		151.4±31.9	139.9±34.7	146.3±33.6
Median	191	188	200	193.5		155	143	149
Baseline Corticosteroid Use								
n (%)	10 (56)	9 (47)	9 (50)	28 (51)	NA	NA	NA	74 (36)
Baseline Immunosuppressant Use								
n (%)	3 (17)	4 (21)	5 (28)	12 (22)	NA	NA	NA	67 (33)
Baseline Aminosalicylate Use,								
n (%)	8 (44)	14 (74)	12 (67)	34 (62)	NA	NA	NA	110 (54)

a. Subjects who had dosing at or after Week 4.
b. P-value is from Fisher's Exact test for comparison across the three treatment groups.

Study M02-404

In Study M02-404, all subjects received an induction course of adalimumab and were then randomized to receive either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew. Subjects with a history of previous anti-TNF use were also allowed into the study. Mean CDAI scores were consistent with CD subjects with moderately to severely active disease. The proportion of subjects with prior anti-TNF use, concomitant corticosteroid use, and concomitant immunosuppressant use were comparable across all randomized arms of the study (**Table 13**). Subjects with previous anti-TNF use accounted for 50% of the study population, and 44% and 47% of subjects were on concomitant corticosteroids and immunosuppressants, respectively.

Table 13: Baseline Disease Severity (All Subjects) – Study M02-404

Baseline	Treatment Group, n (%)			Not Randomized Subjects	Total
	Placebo N=261	Adalimumab eow N=260	Adalimumab ew N=257	N=76	N=854
Mean CDAI Scores ± SD	315.8 ± 65.7	309.6 ± 60.70	308.2 ± 55.3	333.3 ± 70.8	313.1 ± 61.9
	n (%)				
Previous Anti-TNF Use	130 (50)	133 (51)	127 (49)	34 (45)	424 (50)
Concomitant Corticosteroid Use	114 (44)	109 (42)	116 (45)	37 (49)	376 (44)
Concomitant Immunosuppressant Use	133 (51)	112 (43)	121 (47)	33 (43)	399 (47)

The modified intent-to-treat (mITT) population was the population for the primary and secondary efficacy analyses. As seen in **Table 14**, in the modified ITT population for Study M02-404 (all treated subjects who achieved clinical response [CR-70] at Week 4 and were randomized to receive one of three blinded treatments), the mean CDAI score, proportion of subjects with previous anti-TNF use (48%), proportion of subjects on concomitant corticosteroid use (42%), and the proportion on concomitant immunosuppressants (48%) were comparable to the disease severity characteristics seen in the "all subjects" group (**Table 13**).

Table 14: Baseline Disease Severity by Treatment Group (mITT Dataset) – Study M02-404

Baseline	Treatment Group			Total
	Placebo N=170	Adalimumab eow N=172	Adalimumab ew N=157	N=499
Mean CDAI Scores ± SD	321.1 ± 67.1	309.6 ± 60.70	308.2 ± 55.3	333.3 ± 70.8
	n (%)			
Previous Anti-TNF Use	81 (48)	86 (50)	71 (45)	238 (48)
Concomitant Corticosteroid Use	69 (41)	65 (38)	76 (48)	210 (42)
Concomitant Immunosuppressant Use	83 (49)	78 (45)	79 (50)	240 (48)

The numbers of subjects with draining cutaneous fistulas at study Baseline for Study M02-404 are shown in **Table 15**. The majority of subjects (85%) had no draining cutaneous fistulas, but 10% of subjects in Study M02-404 had one draining cutaneous fistula. Similarly, 10% of subjects had one draining perianal fistula. Few subjects in the study had greater than one fistula and less than 1% of subjects had abdominal fistulas. The proportions of subjects with these fistulas were comparable across randomized treatment groups, although it should be noted that this study was also not designed to evaluate the efficacy of adalimumab for fistula response.

Table 15: Number of Draining Cutaneous Fistulas at Study Baseline (All Subjects) – Study M02-404

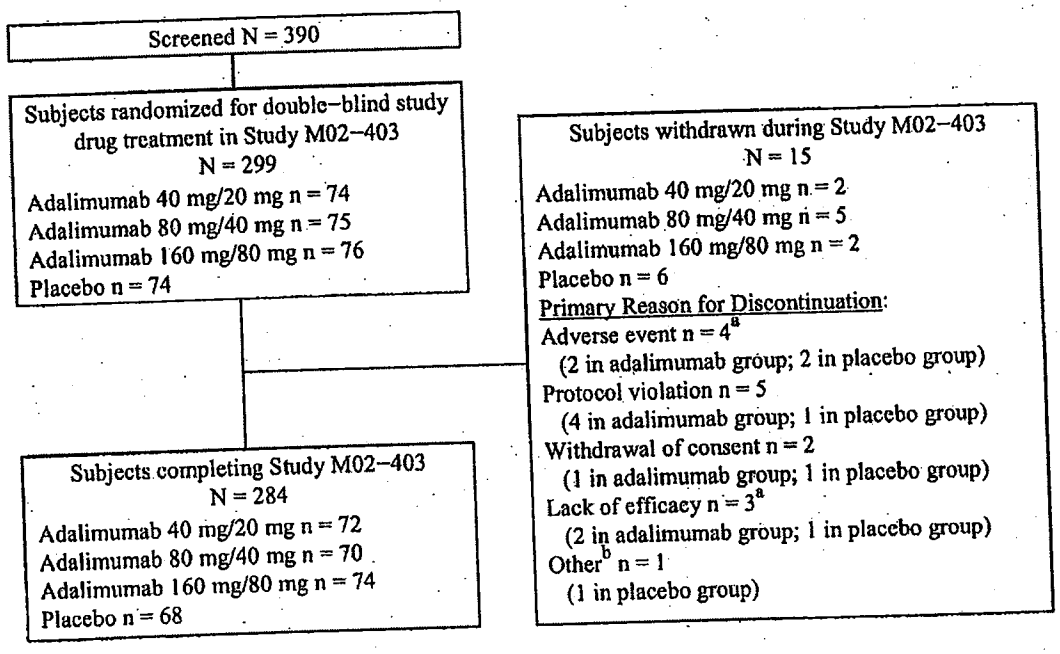
	Randomized Subjects				Not Randomized	
Number of Fistulas	Placebo N=261 n (%)	40 mg eow N=260 n (%)	40 mg ew N=257 n (%)	Total N=778 n (%)	Subjects N=76 n (%)	Total N=854 n (%)
Draining Cutaneous Fistulas						
0	214 (82)	230 (89)	217 (84)	661 (85)	63 (83)	724 (85)
1	30 (12)	19 (7)	23 (9)	72 (9)	13 (17)	85 (10)
2	7 (3)	6 (2)	7 (3)	20 (3)	0	20 (2)
3	6 (2)	1 (<1)	5 (2)	12 (2)	0	12 (1)
>4	4 (2)	4 (2)	5 (2)	13 (2)	0	13 (2)
Abdominal Fistulas						
0	259 (99)	260 (100)	255 (99)	774 (100)	75 (99)	849 (99)
1	1 (<1)	0	2 (<1)	3 (<1)	1 (1)	4 (<1)
2	0	0	0	0	0	0
3	0	0	0	0	0	0
>4	1 (<1)	0	0	1 (<1)	0	1 (<1)
Perianal Fistulas						
0	216 (83)	230 (89)	219 (85)	665 (86)	64 (84)	729 (85)
1	29 (11)	19 (7)	21 (8)	69 (9)	12 (16)	81 (10)
2	7 (3)	6 (2)	7 (3)	20 (3)	0	20 (2)
3	6 (2)	1 (<1)	5 (2)	12 (2)	0	12 (1)
>4	3 (1)	4 (2)	5 (2)	12 (2)	0	12 (1)

6.1.4.3 Subject Disposition

Study M02-403

The subject disposition schema for the dose-ranging induction study, Study M02-403, is shown in **Figure 5**. Out of 390 subjects screened for the study, 299 were enrolled and randomized to either one of three adalimumab dosing groups (40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg at Weeks 0 and 2, respectively) or placebo at Weeks 0 and 2. A tabular representation of the subject disposition is shown in **Table 16**. Of the 299 subjects randomized and treated with two doses of any adalimumab dosing regimen vs. placebo (at Weeks 0 and 2), a total of 15 (5%) subjects were withdrawn during Study M02-403. Of all the adalimumab dosing groups combined, 4% withdrew from the study early, compared with 8% of those subjects treated with placebo.

Figure 5: Subject Disposition Schema – Study M02-403



a. One subject was not counted as an AE withdrawal. Although the occurrence of an AE was noted as a reason for discontinuation for this subject in some of the statistical tables, it was not the primary reason for discontinuation for this subject in some of the statistical tables, it was not the primary reason for discontinuation. The primary reason for premature discontinuation for this subject was lack of efficacy (indicated in this figure).

b. This subject did not receive study drug at Week 2 due to an inability to come in for the clinic visit; therefore, study participation was prematurely terminated for this subject.

Of the 74 subjects randomized to receive placebo injections, 2 subjects (3%) withdrew from the study due to an adverse event compared to 2 out of 225 (<1%) adalimumab-treated subjects who withdrew from the study due to an AE. One subject each from the adalimumab 80 mg/40 mg group, the adalimumab 160 mg/80 mg group, and the placebo group, withdrew due to lack of efficacy. No subjects withdrew from the study due to being lost to follow-up, and no deaths occurred. Of all subjects who received any adalimumab dosing regimen, 96% completed the study compared to 92% of the placebo group.

Table 16: Disposition of Subjects by Randomized Treatment Group – Study M02-403

Result	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Completed Screening visit	74 (100)	75 (100)	76 (100)	225 (100)	74 (100)
Completed Baseline (Week 0) visit	74 (100)	75 (100)	76 (100)	225 (100)	74 (100)
Completed Week 1 visit	73 (99)	73 (97)	76 (100)	222 (99)	72 (97)
Completed Week 2 visit	73 (99)	73 (97)	76 (100)	222 (99)	69 (93)
Completed Week 4 visit	72 (97)	70 (93)	74 (97)	216 (96)	68 (92)
Completed Early Termination visit	2 (3)	5 (7)	2 (3)	9 (4)	6 (8)
Completed Follow-up visit	1 (1)	6 (8)	1 (1)	8 (4)	5 (7)
Primary reason for discontinuation:					
Adverse event[a]	1 (1)	1 (1)	0	2 (<1)	2 (3)
Lost to follow-up	0	0	0	0	0
Protocol violation	1 (1)	3 (4)	0	4 (2)	1 (1)
Death	0	0	0	0	0
Withdrawal of consent	0	0	1 (1)	1 (<1)	1 (1)
Lack of efficacy	0	1 (1)	1 (1)	2 (<1)	1 (1)
Administrative reasons	0	0	0	0	0
Other[b]	0	0	0	0	1 (1)

Study M04-691

Study M04-691 was a two-arm study comparing the efficacy and safety of an adalimumab induction regimen of 160 mg/80 mg vs. placebo injections at Weeks 0 and 2, respectively (**Figure 6**). In this study of subjects who either lost response to or were intolerant to previous infliximab therapy, 325 active CD subjects were randomized to receive an induction regimen of either adalimumab 160 mg/80 mg or placebo at Weeks 0 and 2. In the adalimumab-treated group, 4 of 159 subjects (3%) discontinued from the study compared to 10 of 166 (6%) placebo-treated subjects (**Table 17**). Adverse events during the study accounted for 1% of adalimumab-treated subjects discontinuing from the study vs. 2% of the placebo-treated subjects. Overall, 96% of all subjects completed this short induction study with 6 of 325 subjects (2%) discontinuing the study due to an AE.

Figure 6: Study Disposition Schema – Study M04-691

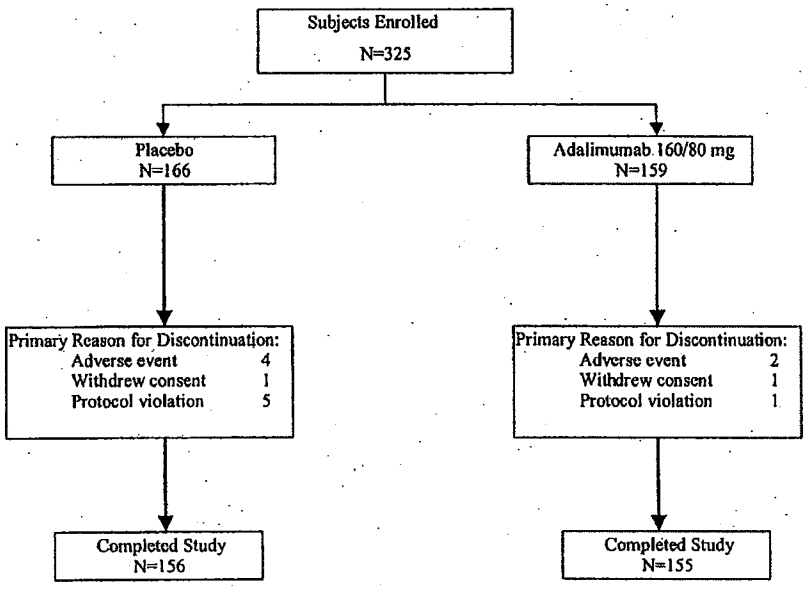


Table 17: Disposition of Subjects - Study M04-691

	Treatment Group n (%)	
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)
Completed study	156 (94)	155 (98)
Number of discontinued subjects	10 (6)	4 (3)
Primary reason for discontinuation		
Adverse event	4 (2)	2 (1)
Withdrew consent	1 (<1)	1 (<1)
Protocol violation	5 (3)	1 (<1)

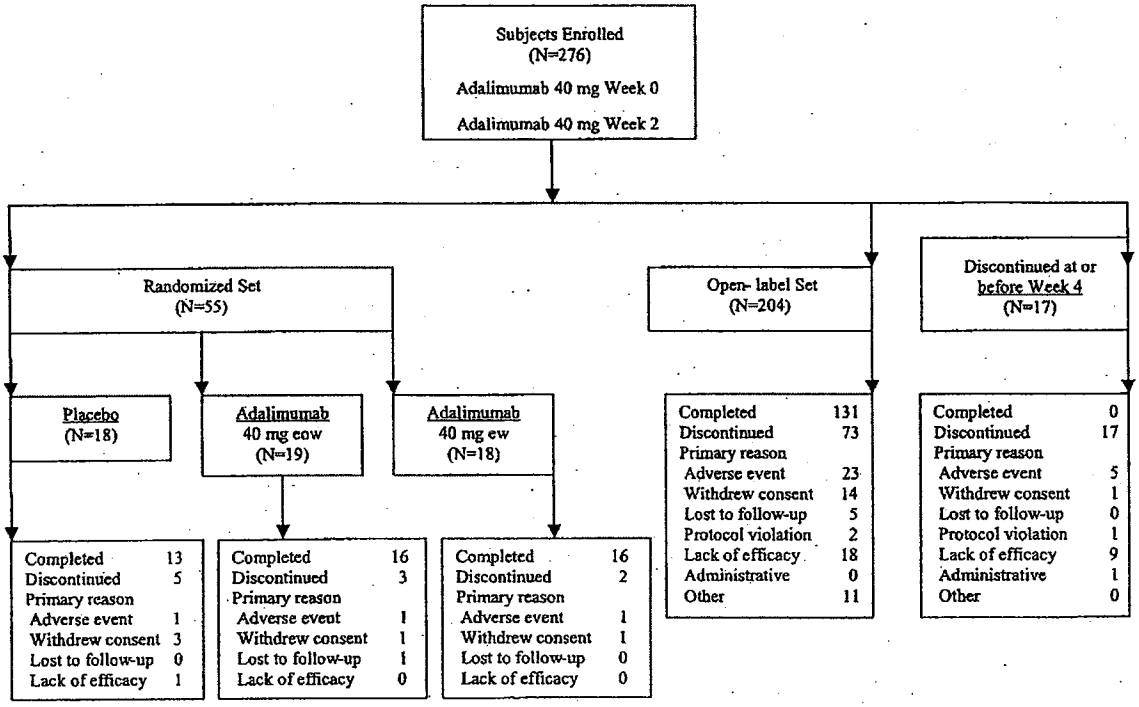
Study M02-433

Study M02-433 was a follow-on study that enrolled subjects only from lead-in Study M02-403 provided that they had completed that study. A total of 276 subjects from the lead-in study enrolled into Study M02-433. All were given adalimumab 40 mg eow x 2 doses and then assessed for clinical remission. Those subjects who were in clinical remission were assigned to be in the "randomized set" (**Figure 7**) where they then were re-randomized to receive either adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo injections and then followed out to Week 56.

Subjects who were not in clinical remission after two doses of adalimumab 40 mg eow were then assigned to be in the "open-label set" and given adalimumab 40 mg eow in open-label fashion

out to Week 56. If these subjects experienced a disease flare, they had their adalimumab doses increased to adalimumab 40 mg ew.

Figure 7: Subject Disposition Schema – Study M02-433



The final status of subjects in Study M02-433 up to Week 56 is displayed in **Table 18**. Of the 276 subjects who entered the follow-on study, 55 were in remission and comprised the randomized analysis set, 204 received open-label adalimumab 40 mg eow therapy, and 17 subjects discontinued at or before Week 4. In the randomized analysis set, 5 of 18 placebo-treated subjects (28%) discontinued the study early. Three of these five subjects discontinued the study due to withdrawal of consent, and one subject each discontinued the study due to an AE or lack of efficacy. Three subjects randomized to the adalimumab 40 mg eow arm discontinued the study due to an AE, withdrawal of consent, and being lost to follow-up, each. Two subjects who received adalimumab 40 mg ew discontinued from the study due to an AE and withdrawal of consent, each. Although the total number of subjects in the randomized analysis set was small (55), more subjects receiving placebo discontinued the randomized portion of this study compared to either adalimumab maintenance regimen.

Of the 204 subjects who were assigned to the open-label analysis set, 36% discontinued the study early (**Table 18**). The primary reasons for these subjects discontinuing early were AE's (11%), lack of efficacy (9%), and withdrawal of consent (7%). Subjects who discontinued the study at or before Week 4 did so due primarily to a lack of efficacy (53%), or an AE (29%).

In total, out of 276 subjects who entered Study M02-433, 64% completed the 56-week study. No deaths occurred, and few subjects discontinued the study due to being lost to follow-up, protocol violations, or administrative reasons.

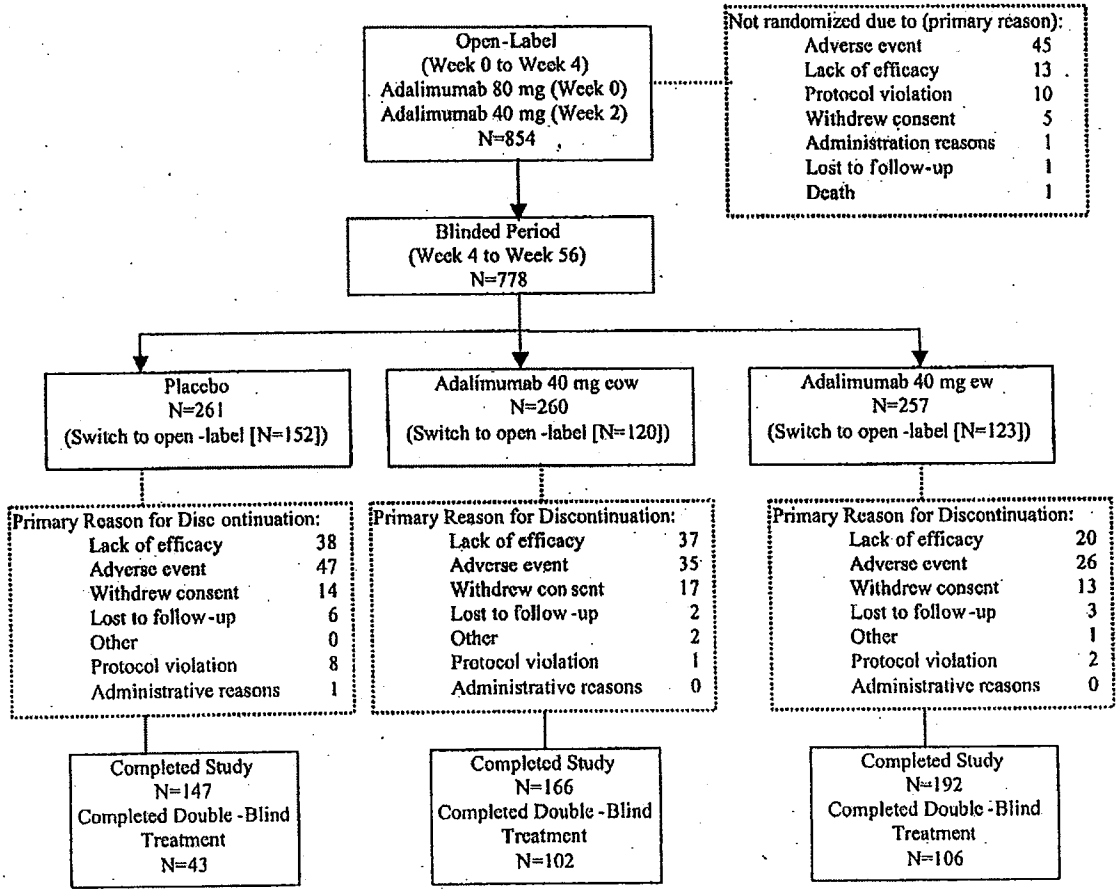
Table 18: Subject Final Status Up to Week 56 – Study M02-433

	Randomized Analysis Set				Open-label Analysis Set		
	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55	Adalimumab 40 mg eow or ew N=204	Discontinued at or before Week 4 N=17	All Subjects N=276
Completed Week 56 Visit (total)	13 (72)	16 (84)	16 (89)	45(82)	131 (64)	0	176 (64)
Completed Week 56 (double-blind)	6 (33)	11 (58)	15 (83)	32(58)	N/A	N/A	N/A
Early Discontinuation	5 (28)	3 (16)	2 (11)	10(18)	73 (36)	17 (100)	100 (36)
Primary reason for discontinuation:							
AE	1 (6)	1 (5)	1 (6)	3 (6)	23 (11)	5 (29)	31 (11)
Withdrawal of consent	3 (17)	1 (5)	1 (6)	5 (9)	14 (7)	1 (6)	20 (7)
Lost to follow-up	0	1 (5)	0	1 (2)	5 (3)	0	6 (2)
Protocol violation	0	0	0	0	2 (1)	1 (6)	3 (1)
Death	0	0	0	0	0	0	0
Lack of efficacy	1 (6)	0	0	1 (2)	18 (9)	9 (53)	28 (10)
Administrative reasons	0	0	0	0	0	1 (6)	1 (<1)
Other	0	0	0	0	11 (5)	0	11 (4)

Study M02-404

Study M02-404 was designed so that all subjects enrolled would receive open-label adalimumab 80 mg at Week 0 and 40 mg at Week 2 (**Figure 8**). The study had two co-primary endpoints 1) the number of subjects who achieved a CR-70 response at Week 4 and clinical remission at Week 26, and 2) the number of subjects who achieved a CR-70 response at Week 4 and clinical remission at Week 56. All of the 854 subjects enrolled received an open-label induction regimen of adalimumab 80 mg/40 mg. At Week 4, 778 subjects entered a blinded period (from Week 4 to Week 56) where they were randomized to receive either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew, regardless of whether they had achieved a CR-70 response or not. These subjects were then followed out to Week 56.

Figure 8: Study Disposition Schema – Study M02-404



A total of 76 out of 854 subjects (9%) discontinued the study before randomization: 45 of these 76 subjects (59%) discontinued due to an AE, and 17% discontinued due to lack of efficacy. Protocol violations accounted for 10 of 76 subjects (13%) discontinuing, and 7% (5 of 76) discontinued due to withdrawal of consent.

The subject disposition after randomization for the 778 randomized subjects is shown in **Table 19**. After the adalimumab 80 mg/40 mg induction regimen at Weeks 0 and 2, 778 subjects were randomized to receive double-blinded placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew maintenance therapy out to Week 56. Out of the 778 randomized subjects, 499 (64%) were found to be clinical responders at Week 4 and 279 (36%) were Week 4 nonresponders. In the group randomized to placebo after the open-label adalimumab induction, 170 of 261 (65%) were found to be Week 4 responders. Of the 260 subjects randomized to adalimumab 40 mg eow after the induction regimen, 172 out of 260 (66%) were Week 4 responders. Lastly, in the group randomized to adalimumab 40 mg ew after the induction period, 157 of 257 (61%) achieved a Week 4 clinical response. These response rates for all randomized subjects were not unexpectedly quite similar since all subjects received the same adalimumab induction regimen of 80 mg at Week 0 and 40 mg at Week 2.

Table 19: Subject Disposition after Randomization – Study M02-404

All subjects given open-label induction **N = 854**						
778 subjects randomized to double-blind therapy for 56 weeks						**76** subjects not randomized (discontinued)
Responders at Week 4 **N=499**			Nonresponders at Week 4 **N=279**			
Placebo	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	Adalimumab 40 mg eow	Adalimumab 40 mg ew	
N=170	**N=172**	**N=157**	**N=91**	**N=88**	**N=100**	
Clinical Remission at Week 26 Assessed						
Clinical Remission at Week 56 Assessed						

The subject final status for Study M02-404 is seen in **Table 20** where 91% of 854 subjects given open-label adalimumab induction therapy were able to continue in the study to be randomized. After randomization, 56% of subjects randomized to placebo completed the study, in contrast to 64% and 75% of subjects randomized to either adalimumab 40 mg eow or 40 mg ew therapy, respectively. The primary reasons for subjects discontinuing the study before Week 56 were lack of efficacy or an adverse event. For both reasons, subjects randomized to placebo had higher proportions of discontinuations compared to either adalimumab group (**Table 20**). Both adalimumab-treated groups had more than a two-fold greater proportion of subjects who were able to complete the double-blind treatment period compared to subjects randomized to placebo.

Table 20: Subject Final Status – Study M02-404

Open-Label Induction	Adalimumab 80 mg (at Week 0), Adalimumab 40 mg (at Week 2) N=854
	n (%)
Number of subjects not randomized	76 (9)
Number of randomized subjects	778 (91)
Not randomized due to primary reason:	
Adverse event	45 (5)
Lack of efficacy	13 (2)
Protocol violation	10 (1)
Withdrew consent	5 (<1)
Administrative reasons	1 (<1)
Lost to follow-up	1 (<1)
Death	1 (<1)

After Randomization	Placebo N=261	Adalimumab eow N=260	Adalimumab ew N=257
	n (%)		
Number of completers	147 (56)	166 (64)	192 (75)
Number who completed double-blind treatment	43 (16)	102 (39)	106 (41)
Number of discontinued subjects	114 (44)	94 (36)	65 (25)
Primary reason for discontinuation			
Lack of efficacy	38 (15)	37 (14)	20 (8)
Adverse event	47 (18)	35 (14)	26 (10)
Withdrew consent	14 (5)	17 (7)	13 (5)
Lost to follow-up	6 (2)	2 (<1)	3 (1)
Other	0	2 (<1)	1 (<1)
Protocol violation	8 (3)	1 (<1)	2 (<1)
Administrative reasons	1 (<1)	0	0

Efficacy Results

6.1.4.4 Study M02-403 Efficacy Results

Primary Endpoint – Study M02-403:

The primary endpoint of clinical remission (CDAI < 150 points) at Week 4 is displayed in **Table 21**. In this four-week study, 299 active CD subjects were randomized to either one of three adalimumab induction dose groups or placebo sc injections given at Weeks 0 and 2. The primary analysis was to compare rates of clinical remission of the two highest adalimumab dose groups against placebo. If this was significant, then pairwise comparisons of each adalimumab dose group vs. placebo were performed. At Week 4, the combined set of adalimumab-treated subjects (80 mg/40 mg group with the 160 mg/80 mg group) had a clinical remission rate of 30% compared to 12% in the placebo arm.

Table 21: Subjects in Clinical Remission at Week 4

Full Analysis Set (N=299)				
Clinical Remission at Time point in study	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	Placebo (N=74) n (%)	Treatment Effect p-value
Week 1	10 (13)	12 (16)	5 (7)	0.214
Week 2	15 (20)	18 (24)	10 (14)	0.277
Week 4	18 (24)	27 (36)	9 (12)	0.004
Week 4 (LOCF)	18 (25)	27 (36)	9 (13)	0.005
Missing data	2[a]	-	2	-

a. Percentage is calculated based on non-missing data.

Pairwise comparison of both adalimumab dose groups (**Table 22**) show that this effect is accounted for primarily by the adalimumab 160 mg/80 mg dose group, with 36% of subjects in this group achieving clinical remission at Week 4 compared to 24% of subjects in the 80 mg/40 mg dose group and 12% of placebo-treated subjects using nonresponder imputation ($p = 0.001$ for adalimumab 160 mg/80 mg vs. placebo comparison). Although the adalimumab 40 mg/20 mg and 80 mg/40 mg dose groups did not individually achieve statistical significance in remission rates compared to the placebo group, a dose-response at Week 4 can be seen among the three adalimumab dose groups. The adalimumab 40 mg/20 mg dose group had 18% of subjects achieving the primary endpoint, compared to 24% of subjects in the 80 mg/40 mg group, and 36% of subjects in the 160 mg/80 mg dose group.

Table 22: Pairwise Comparisons in Induction of Clinical Remission at Week 4

Full Analysis Set (N=299)				
Adalimumab Dose/ Time Point in Study	Adalimumab n (%)	Placebo (N=74) n (%)	Difference[a] (95% CI)	Treatment Effect p-value
40 mg/20 mg (N=74)				
Week 1	12 (16)	5 (7)	9.5 (-0.7, 19.6)	0.071
Week 2	10 (14)	10 (14)	0.0 (-11.0, 11.0)	1.000
Week 4	13 (18)	9 (12)	5.4 (-6.0, 16.8)	0.355
Week 4 (LOCF)	13 (18)	9 (13)	5.3 (-6.3, 16.9)	0.373
80 mg/40 mg (N=75)				
Week 1	10 (13)	5 (7)	6.6 (-3.0, 16.2)	0.182
Week 2	15 (20)	10 (14)	6.5 (-5.5, 18.4)	0.289
Week 4	18 (24)	9 (12)	11.8 (-0.4, 24.0)	0.061
Week 4 (LOCF)	18 (25)	9 (13)	12.2 (-0.3, 24.7)	0.060
160 mg/80 mg (N=76)				
Week 1	12 (16)	5 (7)	9.0 (-1.0, 19.0)	0.081
Week 2	18 (24)	10 (14)	10.2 (-2.2, 22.5)	0.110
Week 4	27 (36)	9 (12)	23.4 (10.3, 36.4)	0.001
Week 4 (LOCF)	27 (36)	9 (13)	23.0 (9.8, 36.2)	0.001
All adalimumab (N=225)				
Week 1	34 (15)	5 (7)	8.4 (1.0, 15.7)	0.064
Week 2	43 (19)	10 (14)	5.6 (-3.7, 14.9)	0.274
Week 4	58 (26)	9 (12)	13.6 (4.2, 23.0)	0.015
Week 4 (LOCF)	58 (26)	9 (13)	13.6 (4.0, 23.2)	0.017

a. Difference refers to the difference between the proportions (%) of adalimumab-treated subjects achieving clinical remission compared with the placebo-treated subjects.

Subgroup Analyses of Primary Endpoint – Study M02-403:

Subgroup analyses of the primary endpoint are consistent with the benefit of the adalimumab 160 mg/80 mg dose as an induction regimen over the adalimumab 80 mg/40 mg and the placebo groups. The proportion of subjects in clinical remission at Week 4 was consistently higher in the 160 mg/80 mg group regardless of which concomitant CD-related medication subjects were on at the Baseline week of Study M02-403.

Table 23: Clinical Remission at Week 4 by Subgroups

Subgroup Parameter	Full Analysis Set (N=299)		
	Adalimumab 80 mg/40 mg n/N (%)	Adalimumab 160 mg/80 mg n/N (%)	Placebo n/N (%)
Sex			
Female	11/50 (22)	16/40 (40)	5/37 (14)
Male	7/25 (28)	11/36 (31)	4/37 (11)
Age			
<40 years	12/40 (30)	19/43 (44)	8/51 (16)
40-64 years	6/34 (18)	8/33 (24)	1/18 (6)
Race			
White	16/64 (25)	23/67 (34)	9/68 (13)
Others	2/11 (18)	4/9 (44)	--
Body weight			
≤ 70 kg	10/38 (26)	14/31 (45)	6/33 (18)
> 70 kg	8/37 (22)	13/45 (29)	3/41 (7)
Baseline use of corticosteroids			
Yes	9/31 (29)	13/22 (59)	5/25 (20)
No	9/44 (21)	14/54 (26)	4/49 (8)
Baseline use of immunosuppressants			
Yes	2/21 (10)	8/22 (36)	2/22 (9)
No	16/54 (30)	19/54 (35)	7/52 (14)
Baseline use of oral aminosalicylates			
Yes	13/41 (32)	16/40 (40)	7/36 (19)
No	5/34 (15)	11/36 (31)	2/38 (5)
Baseline CRP			
< 1 mg/dL	9/42 (21)	15/48 (31)	7/45 (16)
≥ 1 mg/dL	9/33 (27)	12/28 (43)	2/29 (7)
Baseline platelet count			
1st quartile	2/16 (13)	4/17 (24)	4/19 (21)
2nd quartile	5/21 (24)	9/21 (43)	2/17 (12)
3rd quartile	2/19 (11)	11/22 (50)	1/14 (7)
4th quartile	9/19 (47)	3/14 (21)	2/23 (9)
Baseline albumin			
1st quartile	4/20 (20)	10/18 (56)	1/24 (4)
2nd quartile	6/26 (23)	7/30 (23)	3/19 (16)
3rd quartile	5/18 (28)	3/15 (20)	--
4th quartile	3/11 (27)	7/13 (54)	5/15 (33)
Baseline CDAI scores			
220-270 points	8/24 (33)	13/28 (46)	5/30 (17)
271-330 points	6/22 (27)	7/26 (27)	2/21 (10)
331-390 points	3/19 (16)	3/16 (19)	--
391-450 points	1/8 (13)	2/4 (50)	1/8 (13)

Secondary Endpoints – Study M02-403:

Table 24 and **Table 25** show clinical response rates at Week 4 if defined as a decrease in baseline CDAI scores by ≥ 70 points (CR-70), or by ≥ 100 points (CR-100), respectively. As for the results for clinical remission at Week 4, a dose-response for both a CR-70 (**Table 24**) and a

CR-100 (**Table 25**) is seen with increasing adalimumab doses. A total of 60% of subjects in the adalimumab 160 mg/80 mg dose group achieved a CR-70 and 50% achieved a CR-100 at Week 4. These results are meaningful because these subjects had moderately to severely active CD at Baseline despite the use of conventional therapy.

Table 24: Subjects in Clinical Response (Decrease in CDAI Score ≥ 70 points) at Week 4 (nonresponder imputation)

	Full Analysis Set (N=299)				
Time Point in Study	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Week 1	27 (37)	29 (40)	24 (32)	80 (36)	17 (24)
Week 2	32 (44)	40 (55)	33 (45)	105 (48)	21 (30)
Week 4	38 (54)	41 (59)	44 (60)	123 (57)	25 (37)
p-value	0.047	0.010	0.007	0.003	-
Week 4 (LOCF)	38 (52)	41 (56)	44 (58)	123 (55)	26 (36)
p-value	0.053	0.015	0.008	0.004	-

Table 25: Subjects in Clinical Response (Decrease in CDAI Score ≥ 100 points) at Week 4 (nonresponder imputation)

	Full Analysis Set (N=299)				
Time Point in Study	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Week 1	17 (23)	18 (25)	16 (21)	51 (23)	11 (16)
Week 2	15 (21)	27 (37)	23 (31)	65 (30)	10 (15)
Week 4	24 (34)	28 (40)	37 (50)	89 (41)	17 (25)
p-value	0.255	0.060	0.002	0.015	-
Week 4 (LOCF)	24 (33)	28 (38)	37 (49)	89 (40)	17 (24)
p-value	0.215	0.055	0.002	0.011	-

The median changes in CDAI scores from Baseline in Study M02-403 are shown in **Table 26** for each treatment group. All adalimumab dose groups had larger decreases in median CDAI scores compared to the placebo group for each week that the CDAI score was obtained (Weeks 1, 2, and 4). The largest median decrease in CDAI scores compared to Baseline occurred in the adalimumab 160 mg/80 mg dose group at Week 4.

Table 26: Change From Baseline in CDAI Scores

Time Point in Study	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Week 1					
Mean (95% CI)	-50.6 (-66, -35)	-64.7 (-80, -49)	-56.7 (-74, -40)	-57.3 (-66, -48)	-36.4 (-52, -20)
Median	-52.0	-53.0	-42.0	-50.0	-26.0
Week 2					
Mean (95% CI)	-60.1 (-74, -46)	-85.1 (-105, -66)	-78.2 (-99, -58)	-74.5 (-85, -64)	-45.6 (-63, -28)
Median	-58.0	-74.0	-61.0	-64.5	-40.0
Week 4					
Mean (95% CI)	-68.4 (-86, -50)	-93.8 (-115, -72)	-99.9 (-123, -77)	-87.5 (-100, -75)	-51.8 (-69, -35)
Median	-75.0	-90.0	-99.5	-82.0	-45.0
Week 4 (LOCF)					
Mean (95% CI)	-66.5 (-84, -49)	-91.0 (-112, -70)	-98.3 (-121, -76)	-85.4 (-97, -74)	-47.9 (-65, -31)
Median	-71.0	-86.0	-93.5	-79.0	-44.0

The change in IBDQ scores from Baseline for each randomized group in Study M02-403 are displayed in **Table 27**. Median increases in IBDQ scores (indicating improvement in patient-reported quality of life outcomes) were seen in all treatment groups. Week 4 increases in the median IBDQ scores of the adalimumab 80 mg/40 mg and 160 mg/80 mg dose groups were comparable. Although subjects from all three adalimumab dose groups ("all adalimumab") had a higher median increase in the IBDQ score compared to the placebo group, there was no pre-specification in the study protocol as to what would constitute a clinically meaningful change in the IBDQ score.

Table 27: Change From Baseline in IBDQ Scores

Time Point in Study	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Week 1					
Mean (95% CI)	13.8 (9.2, 18.4)	20.8 (15.2, 26.4)	22.3 (16.1, 28.6)	19.1 (15.9, 22.3)	13.8 (8.8, 18.9)
Median	12.0	18.5	15.5	15.0	9.0
Week 2					
Mean (95% CI)	18.0 (13.1, 23.0)	29.5 (22.3, 36.7)	27.4 (20.7, 34.1)	25.0 (21.3, 28.6)	19.5 (13.6, 25.4)
Median	16.0	27.5	21.5	21.0	17.0
Week 4					
Mean (95% CI)	18.2 (10.7, 25.7)	33.8 (25.6, 42.0)	32.8 (24.7, 40.9)	28.6 (23.9, 33.2)	21.1 (14.8, 27.3)
Median	15.0	26.0	26.0	25.0	15.0
Week 4 (LOCF)					
Mean (95% CI)	17.2 (10.3, 24.1)	32.3 (24.2, 40.3)	33.1 (25.2, 41.0)	27.6 (23.1, 32.0)	19.2 (13.2, 25.3)
Median	14.0	25.0	26.0	23.5	14.0

Pairwise comparisons of changes in the Baseline IBDQ scores at Week 4 are shown in **Table 28**. Subjects in the adalimumab 80 mg/40 mg dose group had greater mean increases in their IBDQ scores at Week 4 compared to placebo. However, when all adalimumab dose groups were compared to placebo, there was no statistically significant difference compared to placebo.

While the overall changes in CDAI and IBDQ scores are consistent with and supportive of the primary endpoint, the differences are not substantial enough to include in the labeling.

Table 28: Pairwise Comparison of Change in Baseline IBDQ Scores at Week 4

	Full Analysis Set (N=299)							
	Adalimumab			Placebo (N=74)			Difference (95% CI)	Treatment-effect p-value
Adalimumab Dose/ Time Point in Study	n	Mean	SD	n	Mean	SD		
40 mg/20 mg (N=74)								
Week 1	69	14.2	2.7	70	14.0	2.7	0.25 (-7.3, 7.8)	
Week 2	70	18.7	3.0	67	19.8	3.0	-1.0 (-9.4, 7.3)	
Week 4	63	18.7	3.7	65	22.0	3.7	-3.3 (-13.6, 7.0)	0.5270
Week 4 (LOCF)	71	18.1	3.5	70	19.5	3.5	-1.4 (-11.3, 8.4)	0.7736
80 mg/40 mg (N=75)								
Week 1	72	20.7	2.6	70	14.0	2.7	6.7 (-0.7, 14.1)	
Week 2	70	29.1	3.0	67	19.8	3.0	9.3 (0.9, 17.7)	
Week 4	69	33.3	3.6	65	22.0	3.7	11.4 (1.3, 21.4)	0.0271
Week 4 (LOCF)	72	31.9	3.5	70	19.5	3.5	12.4 (2.6, 22.2)	0.0131
160 mg/80 mg (N=76)								
Week 1	72	21.9	2.7	70	14.0	2.7	7.9 (0.5, 15.4)	
Week 2	70	26.9	3.0	67	19.8	3.0	7.1 (-1.2, 15.5)	
Week 4	69	32.0	3.6	65	22.0	3.7	10.0 (-0.1, 20.1)	0.0518
Week 4 (LOCF)	73	32.4	3.5	70	19.5	3.5	12.9 (3.1, 22.6)	0.0100
All Adalimumab (N=225)								
Week 1	213	19.0	1.6	70	14.0	2.7	5.0 (-1.2, 11.1)	
Week 2	210	24.9	1.7	67	19.8	3.1	5.1 (-1.8, 12.0)	
Week 4	201	28.1	2.1	65	22.2	3.8	5.9 (-2.6, 14.4)	0.1721
Week 4 (LOCF)	216	27.5	2.1	70	19.6	3.6	7.9 (-0.3, 16.1)	0.0581

The number and status of Baseline draining cutaneous fistulas at Week 4 are shown in **Table 29**. It should be noted that Study M02-403 was not designed or powered to study the effect of adalimumab on fistula response. Subjects randomized to the adalimumab 40 mg/20 mg dose group, the 80 mg/40 mg group, and the 160 mg/80 mg group had a total of 4, 10, and 12 fistulas at Baseline, respectively. Subjects randomized to the placebo group reported a total of 10 fistulas. At the Week 4 timepoint, no significant differences in fistula improvement were seen in any adalimumab-treated group compared to the placebo group, but this could have been due to the study being underpowered.

Table 29: Pairwise Comparison of Improvement in Number of Draining Cutaneous Fistulas at Week 4

		Full Analysis Set (N=299)			
Adalimumab Dose/ Time Point in Study	Improvement[a]	Adalimumab n (%)	Placebo (N=10) n (%)	Difference[b] (95% CI)	Treatment-effect p-value
40 mg/20 mg (N=4)					
Week 4	Yes	3 (75)	5 (50)	25.0 (-27.5, 77.6)	0.5804
	No	1 (25)	5 (50)	--	--
Week 4 (LOCF)	Yes	3 (75)	5 (50)	25.0 (-27.5, 77.6)	0.5804
	No	1 (25)	5 (50)	--	--
80 mg/40 mg (N=10)					
Week 4	Yes	2 (20)	5 (50)	-30.0 (-69.7, 9.7)	0.3498
	No	8 (80)	5 (50)	--	--
Week 4 (LOCF)	Yes	2 (18)	5 (50)	-31.8 (-70.3, 6.7)	0.1827
	No	9 (82)	5 (50)	--	--
160 mg/80 mg (N=12)					
Week 4	Yes	1 (8)	5 (50)	-41.7 (-76.4, -7.0)	0.0557
	No	11 (91.7)	5 (50)	--	--
Week 4 (LOCF)	Yes	1 (8)	5 (50)	-41.7 (-76.4, -7.0)	0.0557
	No	11 (92)	5 (50)	--	--
All adalimumab (N=26)					
Week 4	Yes	6 (23)	5 (50)	-26.9 (-61.9, 8.0)	0.2240
	No	20 (77)	5 (50)	--	--
Week 4 (LOCF)	Yes	6 (22)	5 (50)	-27.8 (-62.5, 7.0)	0.1249
	No	21 (78)	5 (50)	--	--

a. Improvement defined as a decrease of $\geq$ 50% in the number of draining cutaneous fistulas at Baseline for at least 2 consecutive visits.
b. Difference refers to the difference between the proportions (%) of adalimumab-treated subjects achieving improvement in the number of cutaneous draining fistulas compared with the placebo-treated subjects.

Median CRP levels at Weeks 1, 2, and 4 are presented for each treatment group in **Table 30**. Baseline CRP levels for all randomized groups were comparable, between 0.7 - 0.9 mg/dL. After blinded treatment was initiated, median CRP levels for all adalimumab-treated groups decreased to 0.2 - 0.3 mg/dL by as early as Week 1 and remained at those levels through Week 4. In contrast, subjects in the placebo group had median CRP levels that remained elevated at Week 2 (0.7 mg/dL) and at Week 4 (0.8 mg/dL).

Table 30: C-Reactive Protein (mg/dL) Values by Visit

Time Point in Study	Full Analysis Set (N=299)				
	Adalimumab 40 mg/20 mg	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	All Adalimumab	Placebo
Baseline					
N	74	75	76	225	74
Mean (95% CI)	1.6 (1.1, 2.0)	2.0 (1.4, 2.7)	1.4 (1.0, 1.8)	1.7 (1.4, 2.0)	1.8 (1.2, 2.4)
Median	0.9	0.9	0.7	0.8	0.9
Week 1					
N	72	72	75	219	72
Mean (95% CI)	0.7 (0.5, 1.0)	0.9 (0.4, 1.4)	0.6 (0.3, 0.8)	0.7 (0.5, 0.9)	1.3 (1.0, 1.7)
Median	0.3	0.3	0.2	0.3	0.8
Week 2					
N	73	73	76	222	69
Mean (95% CI)	0.8 (0.1, 1.1)	1.1 (0.5, 1.8)	0.5 (0.3, 0.7)	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)
Median	0.4	0.3	0.2	0.3	0.7
Week 4					
N	72	72	72	216	67
Mean (95% CI)	1.3 (0.9, 1.7)	1.5 (0.4, 2.5)	0.6 (0.3, 0.8)	1.1 (0.7, 1.5)	1.3 (0.9, 1.7)
Median	0.3	0.4	0.2	0.3	0.8

6.1.4.5 Study M04-691 Efficacy Results

Primary Endpoint – Study M04-691:

The primary endpoint in Study M04-691 was identical to that of Study M02-403: clinical remission at Week 4. This study was designed to determine the effectiveness of adalimumab in inducing clinical remission for moderate to severe CD subjects who had active disease after losing a response to or were intolerant to infliximab therapy. In this four-week study, 325 active CD subjects previously treated with infliximab were randomized to either placebo or adalimumab 160 mg/80 mg therapy at Weeks 0 and 2. Subjects were allowed to continue their CD-related concomitant therapies.

At Week 4, 34 of 159 subjects (21%) randomized to receive adalimumab 160 mg/80 mg were in clinical remission compared to 12 of 166 subjects (7%) randomized to placebo ($p < 0.001$).

Table 31: Clinical Remission at Week 4

	Treatment Group n (%)			
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Difference in Proportions (95% CI)	p-value[a]
Week 4 Visit	12 (7)	34 (21)	14.2 (6.7, 21.6)	<0.001

a. P-value is from Pearson's Chi-square test.

Because there were 11 subjects who did not meet the entry criteria for infliximab failure status, an additional analysis was performed on the proportion of subjects in clinical remission at Week

4. The results of this analysis are shown in **Table 32**, which excludes subjects who did not meet infliximab failure entry criteria. Results of this analysis were similar to those shown in **Table 31** with 22% of the adalimumab-treated subjects achieving clinical remission at Week 4 compared to 8% of those treated with placebo.

Table 32: Clinical Remission at Week 4, Excluding Subjects Who Did Not Meet Infliximab Failure Criteria

	Treatment Group n (%)			
	Placebo (N=161)	Adalimumab 160/80 mg (N=153)	Difference in Proportions (95% CI)	p-value[a]
Week 4 Excluding Subjects Who Did Not Meet Infliximab Failure Criteria (n, %)	12 (8)	33 (22)	14.1 (6.4, 21.8)	<0.001

[a] The p-value is from Pearson's Chi-square test.

Subgroup Analyses

Subgroups that had sample sizes of ≥ 20 subjects and with differences ≥ 10% between treatment arms are shown in **Table 33**. Subjects who were corticosteroid users at Baseline and treated with adalimumab 160 mg/80 mg had 33% of this subgroup in clinical remission at Week 4 compared to 4% treated with placebo. Aminosalicylate non-users had a higher proportion of subjects in remission if treated with adalimumab over placebo. Adalimumab appeared to be as effective for Baseline immunosuppressant users as for non-users.

Table 33: Baseline Predictors of Clinical Remission at Week 4

	Placebo N=166	Adalimumab 160/80 mg N=159
Baseline Predictor	**n (%)**	
Corticosteroid User	3/73 (4)	18/55 (33)
Corticosteroid Non-User	9/93 (10)	16/104 (15)
Aminosalicylates User	6/60 (10)	6/45 (13)
Aminosalicylates Non-User	6/106 (6)	28/114 (25)
CDAI Score		
< 220	0/1	0
≥ 220-270	4/51 (8)	19/43 (44)
> 270-330	8/52 (15)	11/59 (19)
> 330-390	0/34	1/38 (3)
> 390-450	0/27	3/19 (16)
> 450	0/1	0
Immunosuppressant User	6/85 (7)	16/73 (22)
Immunosuppressant Non-User	6/81 (7)	18/86 (21)

The role of being intolerant to infliximab, losing response to infliximab, and the status of human anti-chimeric antibodies (HACA) on clinical remission rates at Week 4 were examined in **Table**

34. Irrespective of whether subjects had a history of loss of response to infliximab or a history of being intolerant to infliximab, a comparable benefit was seen for all subgroups if they were randomized to adalimumab 160 mg/80 mg vs. placebo. Importantly, subjects who were HACA positive or negative from prior infliximab therapy had similar proportions of Week 4 clinical remitters compared to the adalimumab-treated arm as a whole. This suggests that adalimumab is equally effective regardless of prior concomitant "conventional" therapy or prior infliximab history.

Table 34: Intolerance and/or Loss of Response to Infliximab and HACA Status as Predictors of Clinical Remission at Week 4

Baseline Predictor	Placebo N=166	Adalimumab 160/80 mg N=159
	n (%)	
Loss of response to infliximab	7/87 (8)	15/77 (20)
No loss of response to infliximab	5/78 (6)	19/82 (23)
Missing	1	0
Intolerance to infliximab	5/95 (5)	21/95 (22)
No intolerance to infliximab	7/71 (10)	13/64 (20)
Loss of response to and intolerance to infliximab	0/21	3/19 (16)
No loss of response to and intolerance to infliximab	12/144 (8)	31/140 (22)
Missing	1	0
HACA Positive	2/58 (3)	10/48 (21)
HACA Negative	10/101 (10)	21/105 (20)
Missing	7	6

Secondary Endpoints– Study M04-691:

The ranked secondary endpoints for Study M04-691 are presented in this section. CR-70 and CR-100 response rates for each treatment group at Weeks 1, 2, and 4 are presented in **Table 35** and **Table 36**, respectively. The adalimumab-treated group had greater proportions of subjects achieving CR-70 at each week compared to placebo-treated subjects. At Week 4, 52% of adalimumab-treated subjects achieved a CR-70 response vs. 34% of placebo-treated subjects ($p = 0.001$).

Table 35: CR-70 over Time

Visit	Treatment Group n (%)			p-value[a]
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Difference in Proportions (95% CI)	
Week 1	34 (21)	55 (35)	14.1 (4.5, 23.7)	0.004
Week 2	54 (33)	83 (52)	19.7 (9.1, 30.2)	<0.001
Week 4	56 (34)	82 (52)	17.8 (7.3, 28.4)	0.001

a. Pearson's Chi-square test

In Crohn's disease clinical trials, a CR-100 response can be chosen to minimize the placebo effect sometimes seen, despite being a more difficult goal to achieve than a CR-70. In Study M04-691, the adalimumab-treated group had significantly greater proportions of subjects with a CR-100 response at every visit except for Week 1 where the treatment difference compared to the placebo group was 7%, in favor of adalimumab. By Week 4, 38% of adalimumab-treated subjects achieved a CR-100 response compared to 25% of the placebo group. These CR-70 and CR-100 comparisons support the primary endpoint of clinical remission at Week 4.

Table 36: CR-100 over Time

	Treatment Group n (%)			
Visit	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Difference in Proportions (95% CI)	p-value[a]
Week 1	20 (12)	31 (20)	7.4 (-0.5, 15.4)	0.065
Week 2	30 (18)	58 (37)	18.6 (8.9, 27.9)	<0.001
Week 4	41 (25)	61 (38)	13.7 (3.7, 23.7)	0.008

a. Pearson's Chi-square test

The mean changes in IBDQ scores from Baseline at Week 4 for Study M04-691 are presented in **Table 37**. At Week 4, the adalimumab-treated group had greater improvements in the total IBDQ score (mean change of 30 points) compared to the placebo-treated group (mean change of 15 points), with increasing scores indicating greater improvement. Although the adalimumab group had higher mean IBDQ changes in every IBDQ domain score compared to placebo, there was no pre-specification by the Sponsor to indicate what changes in mean IBDQ scores would indicate a clinically meaningful change.

Table 37: Mean Change from Baseline in IBDQ Scores at Week 4

IBDQ Score	Placebo N=161	Adalimumab 160/80 mg N=155	Mean Difference	95% CI	p-value
Total Score					
Baseline Mean ± SD	123.5 ± 27.45	119.7 ± 27.45			
Mean Change ± SD	15.1 ± 26.99	30.2 ± 30.75	14.16	(7.92, 20.41)	<0.001
Social Function					
Baseline Mean ± SD	21.5 ± 7.50	20.4 ± 6.94			
Mean Change ± SD	2.3 ± 5.87	5.3 ± 6.18	2.65	(1.37, 3.92)	<0.001
Systemic System					
Baseline Mean ± SD	15.8 ± 4.58	15.0 ± 4.97			
Mean Change ± SD	2.6 ± 4.95	4.8 ± 6.02	1.97	(0.78, 3.17)	0.001
Emotional Function					
Baseline Mean ± SD	47.6 ± 12.90	46.6 ± 12.63			
Mean Change ± SD	5.6 ± 10.67	10.0 ± 12.14	4.09	(1.68, 6.50)	<0.001
Bowel Symptoms					
Baseline Mean ± SD	38.7 ± 8.21	37.7 ± 8.50			
Mean Change ± SD	4.6 ± 9.23	10.2 ± 9.95	5.34	(3.31, 7.37)	<0.001

Mean changes in SF-36 variables from Baseline at Week 4 are shown in **Table 38**. Statistically greater improvements between the adalimumab and placebo groups were seen for the Physical Component Summary and the Mental Component Summary scores, and in all the SF-36 sub-domains except for physical function, role function, and emotional. While the SF-36 changes are suggestive that adalimumab-treated subjects had higher patient-reported outcome scores compared to placebo, there was no pre-specification (as before in the use of the IBDQ), as to what degree of SF-36 changes would constitute a "clinically meaningful" improvement. In addition, it is unclear whether or not the SF-36 can even be used as an index to measure patient reported outcomes in inflammatory bowel disease trials.

Table 38: Mean Change from Baseline in SF-36 Variables at Week 4

SF-36 Variable	Placebo	Adalimumab 160/80 mg	Mean Difference	95% CI	p-value
Physical Component Summary	N=159	N=153			
Baseline Mean ± SD	35.2 ± 8.02	34.9 ± 7.90			
Mean Change ± SD	3.5 ± 6.76	5.7 ± 8.15	2.12	(0.51, 3.74)	0.010
Mental Component Summary	N=159	N=153			
Baseline Mean ± SD	38.6 ± 11.37	37.4 ± 11.16			
Mean Change ± SD	2.9 ± 10.62	5.9 ± 9.57	2.57	(0.50, 4.64)	0.015
Physical Function	N=160	N=155			
Baseline Mean ± SD	62.6 ± 24.13	60.1 ± 25.83			
Mean Change ± SD	5.7 ± 15.51	9.3 ± 19.34	3.04	(-0.60, 6.68)	0.102
Role Function	N=161	N=154			
Baseline Mean ± SD	17.9 ± 29.10	17.3 ± 27.70			
Mean Change ± SD	17.2 ± 36.15	25.7 ± 42.02	8.19	(-0.09, 16.48)	0.053
Bodily Pain	N=161	N=154			
Baseline Mean ± SD	37.9 ± 18.93	36.6 ± 18.13			
Mean Change ± SD	9.4 ± 20.62	16.7 ± 22.22	6.77	(2.30, 11.25)	0.003
General Health	N=160	N=155			
Baseline Mean ± SD	29.0 ± 16.87	27.5 ± 16.04			
Mean Change ± SD	3.6 ± 12.12	9.7 ± 14.45	5.79	(2.89, 8.69)	<0.001
Vitality	N=160	N=155			
Baseline Mean ± SD	24.1 ± 16.29	23.6 ± 18.31			
Mean Change ± SD	8.6 ± 18.82	14.6 ± 24.41	5.79	(1.25, 10.33)	0.013
Social Function	N=161	N=155			
Baseline Mean ± SD	50.9 ± 22.82	48.5 ± 23.32			
Mean Change ± SD	9.4 ± 22.71	17.1 ± 23.67	6.88	(2.04, 11.72)	0.005
Emotional	N=160	N=153			
Baseline Mean ± SD	49.8 ± 41.63	43.6 ± 40.70			
Mean Change ± SD	7.3 ± 43.22	16.8 ± 39.76	6.52	(-1.67, 14.71)	0.118
Mental Health	N=159	N=155			
Baseline Mean ± SD	56.0 ± 20.09	54.6 ± 20.90			
Mean Change ± SD	4.8 ± 16.96	8.9 ± 16.43	3.59	(0.22, 6.95)	0.037

Another ranked secondary endpoint was the Visual Analog Score scale (VAS), **Table 39**. There was no statically significant difference between the adalimumab and placebo groups for joint pain at Week 4 (p=0.970) using the VAS score. As with the SF-36 score, it is unclear whether the VAS scale for joint pain serves as a validated patient-reported quality of life outcome for CD subjects in IBD trials.

Table 39: Comparison of Change in VAS for Joint Pain from Baseline at Week 4

Visit	Difference of Adalimumab 160/80 mg – Placebo	95% CI	p-value
Week 4	0.10	(-4.99, 5.18)	0.970
Week 4 LOCF	0.28	(-4.79, 5.35)	0.913

Table 40 displays the Baseline number of fistulas per each treatment group and their status at Week 4. There were a total of 25 and 20 fistulas in subjects randomized to either placebo or adalimumab, respectively. In this 4-week study, no differences were seen between the numbers of fistulas that had improved (a decrease in fistula counts from Baseline of at least 50% at the Week 2 and 4 Visits) or were in remission (a complete closure of fistulas at the Week 2 or 4 Visits). No definitive conclusions regarding adalimumab's effectiveness in treating fistulas can be made from Study M04-691 due to the low number of fistulas in the entire study and the study's lack of power to detect differences between treatment groups.

Table 40: Fistula Remission and Improvement at Week 4

	Treatment Group n (%)			
	Placebo (N=25)	Adalimumab 160/80 mg (N=20)	Difference in Proportions (95% CI)	p-value[a]
Fistula Remission[b]	2 (8)	1 (5)	-3.0 (-17.3, 11.3)	1.000
Fistula Improvement[c]	5 (20)	3 (15)	-5.0 (-27.2, 17.2)	0.716

a. P-value is from Fisher's Exact Test.
b. Closure of fistulas at the Week 2 and 4 Visits that were draining at Screening and Baseline.
c. Decrease in fistula counts from Baseline of at least 50% at the Week 2 and 4 Visits.

The mean changes from Baseline CRP levels at Week 4 are seen in **Table 41**. Baseline mean CRP levels were 1.8 mg/dL and 2.0 mg/dL for the placebo group and the adalimumab group, respectively. By Week 4, the mean CRP level change for the placebo group was -0.1, whereas for the adalimumab group, it was -1.1. This decrease was statistically greater than that seen in the placebo group ($p < 0.001$).

Table 41: Change from Baseline in CRP at Week 4

	Treatment Group n (%)			
Week 4 Visit	Placebo (N=159)	Adalimumab 160/80 mg (N=154)	Difference in Mean Proportions (95% CI)	p-value
Baseline Mean ± SD	1.8 ± 3.49	2.0 ± 2.50	--	--
Mean Change ± SD	-0.1 ± 2.67	-1.1 ± 2.36	-0.96 (-1.41, -0.51)	<0.001

Mean changes from Baseline CDAI scores for both treatment groups are shown in **Table 42**. Greater mean decreases in the adalimumab group were seen compared to the placebo group. By Week 4, the mean change in the adalimumab group was a decrease of 87 points on the CDAI score, compared to a decrease of 50 points in the placebo group. Differences in CDAI scores between treatment groups were seen as early as Week 1.

Table 42: Mean Change from Baseline in CDAI Score

Visit	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg	Difference in Mean Proportions (95% CI)	p-value
Week 1	N=161	N=155		
Baseline Mean ± SD	314.7 ± 64.95	311.7 ± 57.22		
Mean Change ± SD	-27.7 ± 60.05	-48.0 ± 58.96	-20.81 (-33.79, -7.83)	0.002
Week 2	N=163	N=156		
Baseline Mean ± SD	313.1 ± 65.77	312.0 ± 57.15		
Mean Change ± SD	-32.3 ± 68.29	-80.2 ± 78.47	-48.15 (-64.11, -32.20)	<0.001
Week 4	N=158	N=153		
Baseline Mean ± SD	314.3 ± 65.89	312.6 ± 57.44		
Mean Change ± SD	-50.1 ± 78.80	-86.5 ± 85.19	-36.72 (-54.79, -18.65)	<0.001

6.1.4.6 Study M02-433 Efficacy Results

Primary Endpoint – Study M02-433:

Study M02-433 was a follow-on study of subjects who completed lead-in Study M02-403. Subjects who were in remission at the end of lead-in Study M02-403 were assigned to the "randomized analysis set" in Study M02-433 where they were randomized to receive either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew therapy. The primary endpoint in Study M02-433 was the proportion of subjects in the randomized analysis set who were in clinical remission at Week 56. By evaluating those randomized subjects as the primary analysis population, the ability of adalimumab to "maintain" clinical benefit could be determined.

In the primary analysis of this study, an initial overall comparison of the three treatment groups was tested. If a significant difference was observed across the three treatment groups, pairwise comparison of each adalimumab dose group vs. placebo was performed.

Subjects with no CDAI data and those who switched to open-label adalimumab therapy before the evaluation were imputed as not being in remission. For last observation carried forward (LOCF) analyses, remission or response status was based on the last observed non-missing evaluation before a subject switched to open-label treatment or discontinued the study.

Randomized Analysis Set

At Week 56, the two adalimumab-treated groups had higher proportions of subjects compared to those in the placebo group (47% and 67% in the adalimumab groups vs. 33% in the placebo group (**Table 43**). These data were not statistically different across the three treatment groups using a nonresponder imputation ($p = 0.142$), but do suggest a dose-response, even with few numbers per treatment arm.

An LOCF analysis in which remission status was based on the last observed non-missing CDAI score before a subject switched to open-label treatment or discontinued the study is also presented in **Table 43**. Using an LOCF approach, Week 56 data show that greater proportions of adalimumab-treated subjects maintained clinical remission at Week 56 than placebo-treated subjects (overall p = 0.029) across treatment groups.

Table 43: Overall Comparison of Subjects in Clinical Remission Up to Week 56 (Randomized Analysis Set)

	Randomized Analysis Set (Up to Week 56)			
	Placebo N=18 n (%)	Adalimumab 40 mg eow N=19 n (%)	Adalimumab 40 mg ew N=18 n (%)	p-value[a]
Study M02-433 Baseline	17 (94)	18 (95)	18 (100)	1.000
Non-Responder Imputation				
Week 2 Ext.	13 (72)	17 (90)	17 (94)	0.190
Week 4 Ext.	16 (89)	18 (95)	18 (100)	0.531
Week 8 Ext.	10 (56)	12 (63)	16 (89)	0.071
Week 12 Ext.	9 (50)	12 (63)	16 (89)	0.039
Week 16 Ext.	10 (56)	12 (63)	14 (78)	0.382
Week 20 Ext.	7 (39)	12 (63)	15 (83)	0.023
Week 24 Ext.	7 (39)	11 (58)	17 (94)	0.001
Week 32 Ext.	5 (28)	11 (58)	17 (94)	<0.001
Week 40 Ext.	6 (33)	11 (58)	16 (89)	0.002
Week 48 Ext.	6 (33)	9 (47)	15 (83)	0.007
Week 56 Ext.	6 (33)	9 (47)	12 (67)	0.142
LOCF Analysis				
Week 2 Ext. LOCF	13 (77)	17 (90)	17 (94)	0.271
Week 4 Ext. LOCF	16 (89)	18 (95)	18 (100)	0.531
Week 8 Ext. LOCF	10 (56)	16 (84)	16 (89)	0.053
Week 12 Ext. LOCF	10 (56)	17 (90)	16 (89)	0.031
Week 16 Ext. LOCF	11 (61)	16 (84)	14 (78)	0.292
Week 20 Ext. LOCF	9 (50)	17 (90)	15 (83)	0.014
Week 24 Ext. LOCF	9 (50)	16 (84)	17 (94)	0.007
Week 32 Ext. LOCF	7 (39)	16 (84)	18 (100)	<0.001
Week 40 Ext. LOCF	8 (44)	16 (84)	17 (94)	0.002
Week 48 Ext. LOCF	8 (44)	14 (74)	17 (94)	0.004
Week 56 Ext. LOCF	8 (44)	15 (79)	15 (83)	0.029

For subjects who switched to open-label therapy, 'no' is assigned to remission status after the switch.
LOCF remission status is based on last observed non-missing CDAI score before subject switched to open label.
[a] P-value is from Fisher's Exact Test across three treatment groups (percentage is calculated based on non-missing data). Missing CDAI score is counted as 'no' to remission, except for LOCF.

Secondary Endpoints – Study M02-433:

Week 24 clinical remission rate for the randomized analysis set was the first major secondary endpoint described in Study M02-433. An initial overall comparison of the three randomized groups was tested. If there was a difference across the three groups, pairwise comparisons of each adalimumab dose group vs. the placebo group was performed.

The adalimumab treatment groups had 28 out of 37 subjects (76%) with clinical remission at Week 24 using non-responder imputation compared to 7 out of 18 (39%) placebo subjects (p=0.001). Using pairwise comparison, a significant difference was seen between the adalimumab 40 mg ew treatment group and the placebo group (94% vs. 39%, p =0.001).

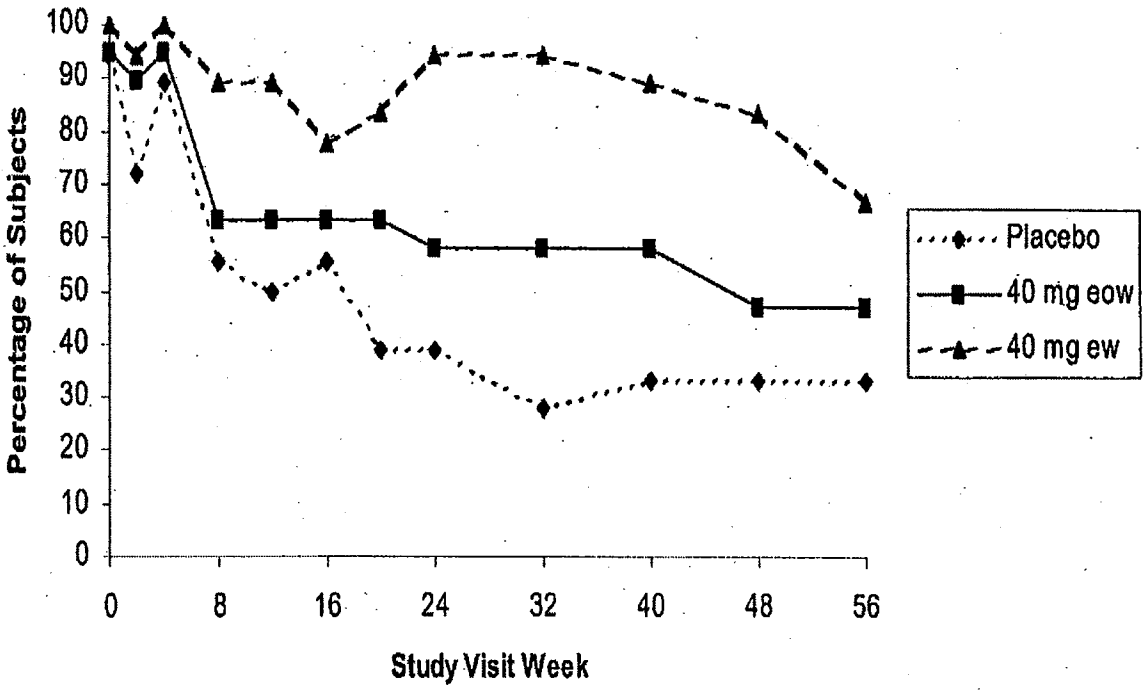
Table 44: Clinical Remission at Week 24

Dose	Placebo N=18 n (%)	All adalimumab N=37 n (%)	Overall p-value[a]	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
40 mg eow (N=19)	7 (39)	11 (58)	0.001	19.0 (-12.6, 50.6)	0.330
40 mg ew (N=18)	7 (39)	17 (94)	0.001	55.6 (30.7, 80.4)	0.001

a. The p-value is from Fisher's Exact test and is across the three treatment groups.
b. The difference is between each adalimumab treatment group and placebo.

Clinical remission rates for each treatment group at every visit in Study M02-433 using non-responder imputation are shown in **Figure 9**. These data points correspond to the non-responder imputation analysis shown on the top half of **Table 43**.

Figure 9: Clinical Remission at Each Visit – Study M02-433



Clinical response rates at Weeks 24 and 56 for the CR-100 and CR-70 analyses are displayed in **Table 45** and **Table 46**, respectively. Adalimumab-treated groups had higher proportions of subjects with Week 24 CR-100 responses (58% in eow group and 94% in the ew group) vs. the placebo group (39%). There was a statistically significant difference between the adalimumab 40 mg ew group and the placebo group (p=0.001). At Week 56, a larger proportion of adalimumab-treated subjects had a CR-100 response compared to the placebo group (47% in eow group and 72% in ew group vs. 33%, respectively). As in Week 56, the adalimumab 40 mg ew group was statistically significant compared to the placebo group (p=0.044).

Table 45: Clinical Response CR-100 at Week 24 and Week 56

Dose	Placebo N=18 n (%)	All adalimumab N=37 n (%)	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
40 mg eow (N=19)				
Week 24	7 (39)	11 (58)	19.0 (-12.6, 50.6)	0.330
Week 56	6 (33)	9 (47)	14.0 (-17.2, 45.3)	0.508
40 mg ew (N=18)				
Week 24	7 (39)	17 (94)	55.6 (30.7, 80.4)	0.001
Week 56	6 (33)	13 (72)	38.9 (8.8, 68.9)	0.044

a. The difference is between each adalimumab treatment group and placebo.
b. The p-value is from Fisher's Exact test to compare each adalimumab treatment group and placebo.

Similar analyses using non-responder imputation show the same pattern of responses among the treatment groups using a CR-70 clinical response cut-off instead of the CR-100 (**Table 46**). The CR-70 response rates in the adalimumab 40 mg ew group was also statistically greater than the placebo group (p=0.003 at Week 24 and p=0.044 at Week 56).

Table 46: Clinical Response CR-70 at Week 24 and Week 56

Dose	Placebo N=18 n (%)	All adalimumab N=37 n (%)	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
40 mg eow (N=19)				
Week 24	8 (44)	13 (68)	24 (-7.1, 55.0)	0.191
Week 56	6 (33)	9 (47)	14.0 (-17.2, 45.3)	0.508
40 mg ew (N=18)				
Week 24	8 (44)	17 (94)	50.0 (24.7, 75.3)	0.003
Week 56	6 (33)	13 (72)	38.9 (8.8, 68.9)	0.044

a. The difference is between each adalimumab treatment group and placebo.
b. The p-value is from Fisher's Exact test to compare each adalimumab treatment group and placebo

Those subjects using Baseline corticosteroids in lead-in Study M02-403 and their ability to discontinue corticosteroids were analyzed in **Table 47**. As per the protocol, these subjects were required to undergo mandatory corticosteroid discontinuation beginning at Week 8. Although the numbers of subjects per the randomized analysis set on Baseline corticosteroids were small, a higher proportion of subjects in both adalimumab treatment groups were able to discontinue corticosteroid use without the development of a clinical relapse compared to placebo-treated subjects.

Table 47: Discontinuation of Corticosteroids at Weeks 24 and 56 for Subjects Taking Corticosteroids at Baseline of Study M02-403

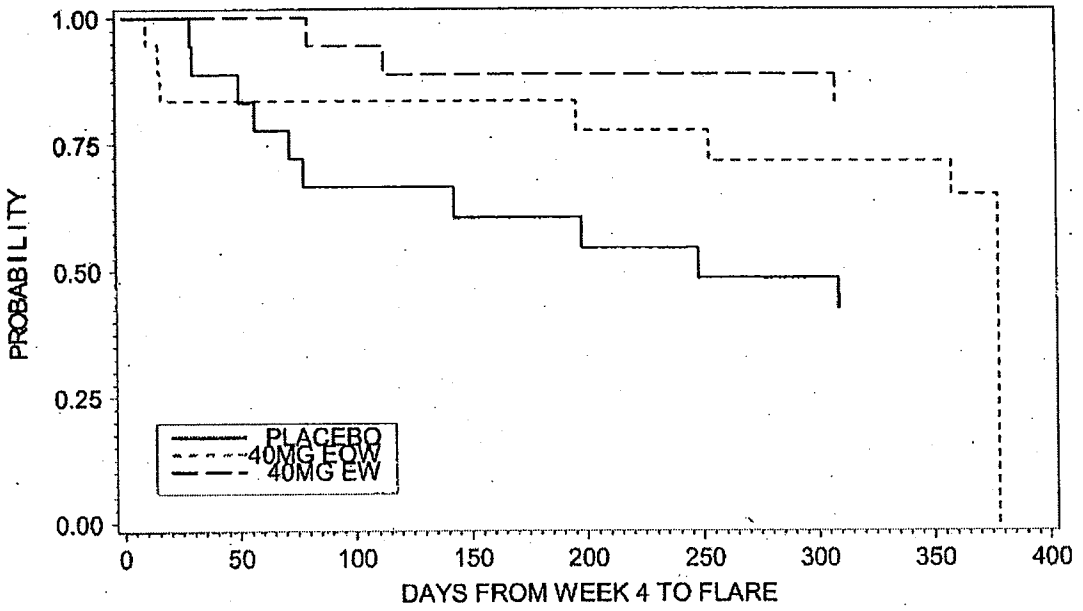
	Randomized Analysis Set		
	Placebo n/N (%)	Adalimumab 40 mg eow n/N (%)	Adalimumab 40 mg ew n/N (%)
Week 24	4/8 (50)	4/6 (67)	7/9 (78)
Week 56	4/7 (57)	4/6 (67)	7/8 (88)

The median times to clinical flare for each treatment group are presented in **Table 48** up to Week 56. Clinical flare was reported in 56%, 37%, and 17% in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively. The median time to flare was 378 days in the adalimumab 40 mg eow group compared to 248 days in the placebo group. The median time to flare in the adalimumab 40 mg ew group was not estimated due to the small numbers of subjects who experienced a clinical flare in 56 weeks (3 out of 18 subjects). These data are depicted in **Figure 10**.

Table 48: Time to Flare Analysis Up to Week 56

Treatment	Number of Subjects	Number of Flare Subjects n (%)	Risk Ratio	p-value	95% CI for Risk Ratio	Median Time to Flare (days)
Placebo	18	10 (56)	--	--	--	248.0
40 mg eow	19	7 (37)	0.518	0.205	(0.19, 1.43)	378.0
40 mg ew	18	3 (17)	0.209	0.018	(0.06, 0.77)	N/A

Figure 10: Time to Flare Analysis



The change in CDAI scores from Study M02-433 compared to Baseline CDAI scores from lead-in Study M02-403 are shown in **Table 49**. The CDAI scores presented excluded those from subjects with missing data or who had switched to open-label therapy prior to the analysis. Subjects across all three randomized treatment arms in Study M02-433 had comparable mean and median CDAI scores at the Baseline of lead-in Study M02-403. At Week 24, subjects in the adalimumab 40 mg ew group had a larger median decrease (227) in CDAI scores than the adalimumab 40 mg eow and placebo groups (157 and 145, respectively). At Week 56 median decreases in the adalimumab groups were 191 in the ew group and 158 in the eow group. The placebo group had a higher mean decrease in CDAI score (211 points) than the adalimumab groups. Limited conclusions can be made regarding the decrease in CDAI scores as they relate to clinical remission and response rates because there were proportionally fewer subjects in the placebo group at Weeks 24 and 56 compared to either adalimumab group. Those placebo subjects who stayed in the study until Week 56 would have likely been the few placebo subjects remaining in the study because they were responding to placebo therapy, explaining the higher median change in CDAI scores for placebo subjects at Week 56.

Table 49: Change in CDAI Score from M02-403 Baseline to Weeks 24 and 56

	Randomized Analysis Set		
	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18
M02-403 Baseline (Week 0)			
N	18	19	18
Mean (95% CI)	289.6 (259.4, 319.8)	266.2 (239.4, 292.9)	291.1 (260.3, 321.8)
Median (range)	268.5 (231 - 437)	245.0 (216 – 432)	285.5 (201 – 424)
M02-433 Baseline			
N	18	19	18
Mean (95% CI)	107.2 (76.2, 138.3)	106.1 (90.1, 122.0)	87.6 (62.5, 112.6)
Median (range)	95.0 (20 – 322)	110.0 (34 - 163)	94.5 (0 – 149)
Week 24			
N	9	14	18
Mean (95% CI)	-166.2 (-242, -90.7)	-164.9 (-211, -119)	-224.3 (-264, -184)
Median (range)	-145.0 (-366 - -40)	-156.5 (-368 - -63)	-226.5 (-352 - -47)
Week 56			
N	6	11	14
Mean (95% CI)	-215.5 (-302, -129)	-169.1 (-245, -92.8)	-200.9 (-250, -152)
Median (range)	-210.5 (-327, -129)	-158.0 (-393, -17)	-190.5 (-371, -65)

A total of five subjects assigned to the randomized analysis set in Study M02-433 (three in the placebo group and two in the adalimumab 40 mg eow group) had draining cutaneous fistulas at Baseline of lead-in Study M02-403 (**Table 50**). At Weeks 24 and 56 of Study M02-433, there was one fewer fistula per group. Conclusions about the efficacy of adalimumab in fistula closure cannot be made due to the small number of fistulas in the randomized analysis set.

Table 50: Number of Draining Cutaneous Fistulas at Week 24 and Week 56

	Randomized Analysis Set	
	Placebo N=3	Adalimumab 40 mg eow N=2
Week 24		
N	2	1
Mean (95% CI)	0.5 (-5.9, 6.9)	0
Median (range)	0.5 (0-1)	0
Week 56		
N	2	1
Mean (95% CI)	0.5 (-5.9, 6.9)	1.0
Median (range)	0.5 (0-1)	1.0 (1-1)

The change in total IBDQ scores in the randomized analysis set in Study M02-433 from Baseline values in Study M02-403 are shown in **Table 51**. All treatment groups in the randomized analysis set had higher IBDQ scores at Weeks 24 and 56, consistent with an improved patient reported outcome. Larger mean increases were seen in both adalimumab treatment groups compared to placebo at Week 24, but this was not consistent at Week 56 where the mean

increase in total IBDQ score for the placebo group (42.2 points) was greater than that in the adalimumab 40 mg ew group (38.7 points). Definitive conclusions about the effect of adalimumab on the IBDQ score cannot be made due to this inconsistency, the small number of subjects in the randomized analysis set, and a lack of pre-specifying what improvement in the total IBDQ score would constitute a clinically meaningful change.

Table 51: Change in Total IBDQ Scores from M02-403 Baseline (Week 0) to Weeks 24 and 56

	Randomized Analysis Set		
	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18
M02-403 Baseline (Week 0)			
N	16	18	18
Mean (95% CI)	137.7 (118.8, 156.6)	133.1 (113.8, 152.4)	140.3 (120.7, 160.0)
Median (range)	136.5 (53 – 189)	135.5 (72 – 200)	146.5 (76 – 218)
M02-433 Baseline			
N	16	18	18
Mean (95% CI)	187.2 (175.4, 199.0)	180.6 (166.8, 194.4)	191.5 (180.5, 202.5)
Median (range)	191.0 (138 – 224)	188.0 (128 – 213)	200.0 (138 – 216)
Week 24			
N	9	13	17
Mean (95% CI)	34.9 (2.4, 67.4)	47.2 (30.5, 64.0)	53.4 (31.2, 75.7)
Median (range)	31.0 (-2 – 123)	43.0 (-2 – 96)	55.0 (-34 – 125)
Week 56			
N	6	11	15
Mean (95% CI)	42.2 (-22.6, 106.9)	49.2 (25.4, 73.0)	38.7 (16.2, 61.1)
Median (range)	19.5 (-16 – 151)	40.0 (11 – 129)	33.0 (-30 – 109)

Note: For subjects who switched to open-label adalimumab, IBDQ score were classified as missing.

Changes in the CRP levels from the Baseline of Study M02-403 at Weeks 24 and 56 are shown in **Table 52**. Subjects with missing data or who had switched to open-label therapy prior to the Week 24 or 56 evaluations were excluded from the analysis. Mean decreases in CRP levels were greater in the adalimumab treatment groups compared to the placebo treatment group which had mean and median CRP levels increase slightly at Weeks 24 and 56. Although the number of evaluable samples decreased by Week 56, no significant difference was seen between the adalimumab treatment groups.

Table 52: Change in CRP (mg/dL) Levels from M02-403 Baseline to Weeks 24 and 56

	Randomized Analysis Set		
	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18
M02-403 Baseline (Week 0)			
N	19	19	18
Mean (95% CI)	0.9 (0.4, 1.4)	3.0 (1.5, 4.4)	2.5 (0.8, 4.1)
Median (range)	0.5 (0.0 – 3.0)	2.2 (0 – 11.3)	0.7 (0.1 – 9.3)
M02-433 Baseline			
N	19	19	18
Mean (95% CI)	0.2 (0.1, 0.3)	0.8 (0.4, 1.2)	0.6 (0.1, 1.0)
Median (range)	0.2 (0.0 – 0.6)	0.5 (0.0 – 2.7)	0.2 (0.0 – 3.6)
Week 24			
N	9	14	18
Mean (95% CI)	0.0 (-0.4, 0.4)	-2.4 (-4.1, -0.7)	-2.1 (-3.7, -0.6)
Median (range)	0.0 (-1.0 – 0.9)	-1.5 (-10.3 – 0.0)	-0.4 (-8.1 – 0.5)
Week 56			
N	6	11	14
Mean (95% CI)	0.1 (-0.2, 0.5)	-2.3 (-4.7, 0.0)	-1.5 (-2.9, - 0.0)
Median (range)	0.2 (-0.4 – 0.5)	-0.5 (-10.3 – 0.7)	-0.2 (-7.5 – 0.3)

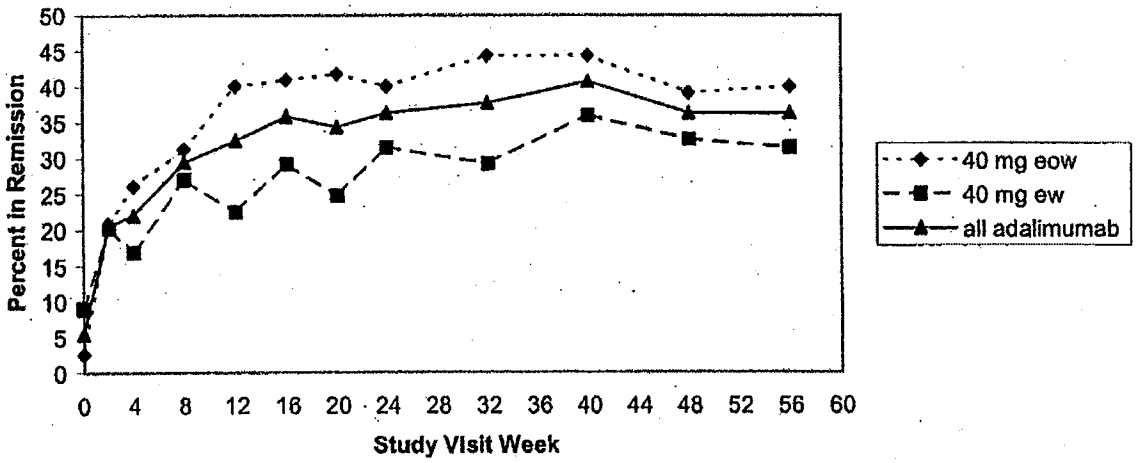
Open-label Analysis Set

The open-label (OL) analysis set of Study M02-433 included subjects who did not achieve clinical remission at Week 0 (Week 4 of Study M02-403) and began receiving OL adalimumab at or after Week 4. Clinical remission rates at Weeks 24 and 56 of Study M02-433 are shown in **Table 53**. A total of 204 subjects entered the OL phase of Study M02-433 and received OL adalimumab 40 mg eow until Week 56. Subjects who experienced a flare while on OL adalimumab 40 mg eow were dose-escalated to 40 mg ew. **Table 53** therefore represents remission rates according to the subject's last administered treatment up to Week 56. Of those whose last administered treatment was adalimumab 40 mg eow, 40% were in clinical remission at both Weeks 24 and 56. Those who dose-escalated to adalimumab 40 mg ew and received this dose as their last administered treatment had a 32% remission rate at both Weeks 24 and 56. Remission data over time are also depicted in **Figure 11**.

Table 53: Clinical Remission at Week 24 and Week 56 (Open-label Analysis Set)

	Open-label Analysis Set (By Last Administered Treatment Up to Week 56)		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Subjects in Clinical Remission at **Week 24**	46 (40)	28 (32)	74 (36)
Subjects in Clinical Remission at **Week 56**	46 (40)	28 (32)	74 (36)

Figure 11: Clinical Remission by Week of Study (Open-label Analysis Set)



Clinical response rates (CR-100) at Weeks 24 and 56 for the open-label analysis set (**Table 54**) were 54% for both adalimumab groups at Week 24, and 50% and 48% for the adalimumab 40 mg eow and ew groups, respectively, at Week 56. In summary, treatment with either adalimumab regimen provided "maintenance" of clinical response from Week 24 out to Week 56 after not being in remission at Week 4. This implies that despite a lack of an initial benefit to induction doses of adalimumab, a significant proportion of active CD subjects could still benefit from long-term adalimumab maintenance therapy. As per **Figure 11**, a peak clinical benefit (remission) may not be seen until 12 to 16 weeks of therapy for subjects who did not initially respond to adalimumab.

Table 54: Clinical Response CR-100 at Week 24 and Week 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Subjects in Clinical Response (CR-100) at **Week 24**	62 (54)	48 (54)	110 (54)
Subjects in Clinical Response (CR-100) at **Week 56**	58 (50)	43 (48)	101 (50)

CR-70 response rates were slightly higher than the CR-100 response rates at Weeks 24 and 56, with 60% of adalimumab-treated subjects achieving a CR-70 at Week 24 and 54% having CR-70 at Week 56 (**Table 55**). As in the CR-100 response rates reported in **Table 54**, there were no significant efficacy differences between the adalimumab 40 mg eow and the 40 mg ew dose groups.

Table 55: Clinical Response CR-70 at Week 24 and Week 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Subjects in Clinical Response (CR-70) at **Week 24**	69 (60)	54 (61)	123 (60)
Subjects in Clinical Response (CR-70) at **Week 56**	62 (54)	48 (54)	110 (54)

Subjects who were using corticosteroids at the Baseline visit in Study M02-403 and were assigned to either the randomized analysis set or OL therapy in Study M02-433 were assessed for the proportion of subjects able to completely withdraw steroid therapy without the development of a relapse. Steroid therapy was optional after Week 8 of Study M02-433. These data are seen in **Table 56**, which excludes subjects with missing data. Results for only the randomized analysis set were previously discussed in **Table 47**. At Week 24 for the open-label analysis set, 56% of adalimumab-treated subjects were able to completely discontinue steroid therapy. At Week 56, this was maintained with 58% of subjects off of corticosteroids without the development of a flare.

Table 56: Evaluation of Corticosteroid Discontinuation at Week 24 and Week 56 for Subjects on Corticosteroids at M02-403 Baseline (All Subjects)

Visit	Complete Steroid Taper?	Randomized Subjects				Open Label	All
		Placebo	40 mg eow	40 mg ew	Total		
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Week 24 Ext.	Yes	4 (50)	4 (67)	7 (78)	15 (65)	22 (56)	37 (60)
	No	4 (50)	2 (33)	2 (22)	8 (35)	17 (44)	25 (40)
	Missing	1	1	0	2	21	23
Week 56 Ext.	Yes	4 (57)	4 (67)	7 (88)	15 (71)	21 (58)	36 (63)
	No	3 (43)	2 (33)	1 (13)	6 (29)	15 (42)	21 (37)
	Missing	2	1	1	4	24	28

Changes in the CDAI scores from the Baseline of lead-in Study M02-403 are shown in **Table 57**. Median changes in CDAI scores decreased by more than half at Week 56. No important differences were seen between the two adalimumab dose groups in the open-label analysis set.

Table 57: Change in CDAI Scores from M02-403 Baseline to Weeks 24 and 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
M02-403 Baseline (Week 0)			
N	115	89	204
Mean (95% CI)	291.7 (282.5, 300.8)	309.2 (297.2, 321.1)	299.3 (291.9, 306.7)
Median (range)	280.0 (209 – 448)	300.0 (218 – 450)	289.0 (209 – 450)
M02-433 Baseline			
N	115	89	204
Mean (95% CI)	237.3 (226.4, 248.3)	255.4 (237.1, 273.7)	245.2 (235.1, 255.3)
Median (range)	244.0 (117 – 402)	267.0 (30 – 492)	237.5 (30 – 492)
Week 24			
N	82	74	156
Mean (95% CI)	-147.7 (-164, -132)	-123.0 (-144, -102)	-136.0 (-149, -123)
Median (range)	-152.5 (-319 - -1)	-132.5 (-362 – 75)	-141.5 (-362 – 75)
Week 56			
N	71	59	130
Mean (95% CI)	-165.2 (-185, -145)	-150.2 (-173, -128)	-158.4 (-173, -144)
Median (range)	-167.0 (-340 – 160)	-163.0 (-333 – 41)	-164.5 (-340 – 160)

A total of 30 subjects assigned to the open-label analysis set had draining fistulas at the Baseline of lead-in Study M02-403. At Week 24 and 56, 24 and 18 subjects were available for analysis. At Study M02-403 Baseline, the mean fistula count was 1.6 and decreased to 0.6 and 0.4 by Weeks 24 and 56, respectively (**Table 58**). No significant difference was seen between the adalimumab dose groups. No firm conclusions can be made concerning the effect of adalimumab on fistula response in this study because of the small number of subjects with fistulas and the lack of a control group for the open-label analysis set.

Table 58: Number of Draining Cutaneous Fistulas at Week 24 and Week 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=17	Adalimumab 40 mg ew N=13	Total N=30
M02-403 Baseline (Week 0)			
N	17	13	30
Mean (95% CI)	1.8 (1.0, 2.6)	1.3 (0.9, 1.7)	1.6 (1.1, 2.0)
Median (range)	1.0 (1 – 7)	1.0 (1 – 3)	1.0 (1 – 7)
Week 24			
N	11	13	24
Mean (95% CI)	0.5 (0.1, 0.8)	0.8 (0.3, 1.2)	0.6 (0.4, 0.9)
Median (range)	0.0 (0 – 1)	1.0 (0 – 2)	1.0 (0 – 2)
Week 56			
N	9	9	18
Mean (95% CI)	0.3 (-0.1, 0.7)	0.6 (0.0, 1.1)	0.4 (0.1, 0.8)
Median (range)	0.0 (0 – 1)	0.0 (0 – 2)	0.0 (0 – 2)

Mean and median changes in total IBDQ scores from the Baseline of Study M02-403 at Weeks 24 and 56 are shown in **Table 59**. Median increases in total IBDQ scores of 52 and 38 points were seen in the adalimumab 40 mg eow and ew dose groups, respectively. While these data do suggest an improvement in patient-reported outcomes due to adalimumab therapy, these data represent open-label experience with no control group. Again, as was discussed for Studies M02-403 and M04-691, no pre-specification of what a clinically meaningful change in total IBDQ scores was discussed.

Table 59: Change in IBDQ Scores from M02-403 Baseline to Weeks 24 and 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
M02-403 Baseline (Week 0)			
N	112	88	200
Mean (95% CI)	126.5 (121.6, 131.7)	124.4 (118.7, 130.2)	125.6 (121.8, 129.4)
Median (range)	127.0 (57 – 181)	125.0 (52 – 185)	126.5 (52 – 185)
Week 24			
N	78	73	151
Mean (95% CI)	44.5 (38.2, 50.7)	34.3 (27.7, 41.0)	39.6 (35.0, 44.2)
Median (range)	50.0 (-27 – 115)	37.0 (-17 – 103)	41.0 (-27 – 115)
Week 56			
N	65	58	123
Mean (95% CI)	49.0 (39.9, 58.2)	39.4 (32.2, 46.5)	44.5 (38.6, 50.3)
Median (range)	52.0 (-71 – 129)	38.0 (-29 – 116)	45.0 (-71 – 129)

Note: Subjects who switched to open-label adalimumab, IBDQ scores were classified as missing.

Mean and median changes in CRP levels from Study M02-403 Baseline at Weeks 24 and 56 are presented in **Table 60** for the open-label analysis set. The OL analysis set had mean decreases of 0.7 and 0.8 mg/dL and median decreases both of 0.3 mg/dL at Weeks 24 and 56, respectively. No significant difference was seen between the adalimumab maintenance regimens.

Table 60: Change in CRP (mg/dL) Levels from M02-403 Baseline (Week 0) to Weeks 24 and 56 (Open-label Analysis Set)

	Open-label Analysis Set		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
M02-403 Baseline (Week 0)			
N	115	89	204
Mean (95% CI)	1.8 (1.2, 2.3)	1.4 (1.1, 1.8)	1.6 (1.3, 1.9)
Median (range)	0.8 (0.0 – 17.3)	0.8 (0.0 – 11.9)	0.8 (0.0 – 17.3)
M02-433 Baseline			
N	113	89	202
Mean (95% CI)	1.2 (0.8, 1.5)	1.4 (0.6, 2.2)	1.3 (0.9, 1.7)
Median (range)	0.5 (0.0 – 13.6)	0.5 (0.0 – 34.0)	0.5 (0.0 – 34.0)
Week 24			
N	83	73	156
Mean (95% CI)	-0.8 (-1.2, -0.4)	-0.6 (-1.1, 0.0)	-0.7 (-1.0, -0.4)
Median (range)	-0.2 (-10.1 – 3.2)	-0.4 (-11.9 – 10.2)	-0.3 (-11.9 – 10.2)
Week 56			
N	70	59	129
Mean (95% CI)	-0.8 (-1.3, -0.2)	-0.8 (-1.3, -0.3)	-0.8 (-1.2, -0.4)
Median (range)	-0.3 (-11.0 – 8.7)	-0.4 (-11.8 – 2.5)	-0.3 (-11.8 – 8.7)

Table 61 displays efficacy results for subjects who underwent dose escalation in Study M02-433 if the Investigator determined that a subject was a non-responder in either the blinded or open-label portions of the study. Subjects in the blinded portion had their therapy changed to open-label adalimumab 40 mg eow. Subjects in the open-label portion who developed a flare while on open-label adalimumab 40 mg eow were allowed to have their dose increased to adalimumab 40 mg ew. Those subjects who were consistent non-responders in the open-label adalimumab 40 mg eow group but did not meet the definition of having a disease flare could also have had their dose increased to 40 mg ew.

Of both the blinded and open-label portions of Study M02-433, a total of 89 subjects underwent dose escalation to either adalimumab 40 mg eow (from the blinded portion), or 40 mg ew (from the open-label portion). Of those that dose escalated, 52% achieved clinical remission up to Week 56. Clinical response rates were 89% and 75% for the CR-70 and CR-100 response cutoffs, respectively. These data show that dose escalation should be considered for subjects that do not initially respond to a maintenance regimen of adalimumab 40 mg eow.

Table 61: Efficacy Results for Subjects Who Underwent Dose Escalation (All Enrolled Subjects Who Dose-Escalated) Up to Week 56

	Randomized and Open-label Analysis Sets Combined
	Subjects Who Dose-Escalated **N=89**
Efficacy Parameter	n (%)
Clinical Remission (CDAI < 150 points)	46 (52)
Clinical Response (CDAI decrease ≥ 70 points)[a]	79 (89)
Clinical Response (CDAI decrease ≥ 100 points)[b]	67 (75)

a. Clinical Response defined as a decrease of ≥ 70 points in Study M02-403 Baseline (Week 0) CDAI score.
b. Clinical Response defined as a decrease of ≥ 100 points in Study M02-403 Baseline (Week 0) CDAI score.
Note: Subjects with missing CDAI scores were counted as not achieving clinical remission or response.

Subgroup Analyses – Study M02-433

Subgroup analyses were performed for the primary endpoint of clinical remission at Week 56 for the subgroups of variables including sex, age group, race/ethnicity, weight, and baseline use of concomitant medications including corticosteroids, immunosuppressants, and aminosalicylates (**Table 62**). Limited conclusions concerning these subgroups can be made because the number of subjects per treatment subgroup was small (usually < 10 subjects) in the randomized analysis set. Overall, however, the proportion of subjects in clinical remission for all adalimumab-treated subjects per subgroup was consistently higher than for subjects treated with placebo. The only exception to this was seen for subjects on baseline corticosteroids in Study M02-403 where 9 of 16 subjects randomized to either adalimumab treatment group had a combined remission rate of 56% compared to 6 of 9 subjects (67%) randomized to placebo (**Table 62**).

Table 62: Subgroup Analyses of Clinical Remission Up to Week 56 by Demographics and Baseline Use of Concomitant Medications (Randomized Analysis Set and Open-label Analysis Set)

Subgroup	Randomized Analysis Set			Open-label Analysis Set		
	Placebo N=18 n/N (%)	Adalimumab 40 mg eow N=19 n/N (%)	Adalimumab 40 mg ew N=18 n/N (%)	Adalimumab 40 mg eow N=115 n/N (%)	Adalimumab 40 mg ew N=89 n/N (%)	Total N=204 n/N (%)
Clinical Remission						
Sex						
Male	4/6 (67)	3/7 (43)	7/9 (78)	27/58 (47)	13/42 (31)	40/100(40)
Female	2/12(17)	6/12 (50)	5/9 (56)	19/57 (33)	15/47 (32)	34/104(33)
Age Group						
< 40 years	5/12(42)	6/13 (46)	8/12 (67)	26/60 (43)	16/47 (34)	42/107(39)
40-64 years	1/5 (20)	3/6 (50)	4/6 (67)	18/49 (37)	11/40 (28)	29/89 (33)
65-74 years	0/1 (0)	NA	NA	2/6 (33)	1/2 (50)	3/8 (38)
Race						
White	5/17(29)	9/17 (53)	10/15 (67)	43/105 (41)	27/77 (35)	70/182(39)
Black	1/1(100)	NA	1/1(100)	1/5(20)	0/3(0)	1/8 (13)
Asian	NA	2/2 (100)	NA	0/1 (0)	NA	0/1 (0)
Hispanic	NA	NA	1/1 (100)	2/3 (67)	1/5 (20)	3/8 (38)
Other	NA	NA	1/1 (100)	0/1 (0)	0/4 (0)	0/5 (0)
Weight Group						
≤ 70 kg	3/10(30)	7/10 (70)	7/12 (58)	17/43 (40)	15/40 (38)	32/83 (39)
> 70 kg	3/8 (38)	2/9 (22)	5/6 (83)	29/72 (40)	13/49 (27)	42/121(35)
Baseline Corticosteroid Use						
Yes	6/9 (67)	4/7 (57)	5/9 (56)	13/32 (41)	9/21 (43)	22/53 (42)
No	0/9 (0)	5/12 (42)	7/9 (78)	33/83 (40)	19/68 (28)	52/151(34)
Baseline Immunosuppressant Use						
Yes	1/3 (33)	3/4 (75)	3/5 (60)	21/37 (57)	6/28 (21)	27/65 (42)
No	5/15(33)	6/15 (40)	9/13 (69)	25/78 (32)	22/61 (36)	47/139(34)
Baseline Aminosalicylate Use						
Yes	4/8 (50)	8/14 (57)	8/12 (67)	30/61 (49)	17/45 (38)	47/106(44)
No	2/10(20)	1/5 (20)	4/6 (67)	16/54 (30)	11/44 (25)	27/98 (28)
CR-70 Response						
Baseline Immunosuppressant Use						
Yes	1/3 (33)	3/4 (75)	4/5 (80)	24/37 (65)	16/28 (57)	40/65 (62)
No	5/15(33)	6/15 (40)	9/13 (69)	38/78 (49)	32/61 (53)	70/139(50)
CD-100 Response						
Baseline Immunosuppressant Use						
Yes	1/3 (33)	3/4 (75)	4/5 (80)	24/37 (65)	14/28 (50)	38/65 (59)
No	5/15(33)	6/15 (40)	9/13 (69)	34/78 (44)	29/61 (48)	63/139(45)

6.1.4.7 Study M02-404 Efficacy Results

Study M02-404 was a long-term study designed to evaluate the efficacy of adalimumab in maintaining clinical remission in moderately to severely active CD subjects. All subjects underwent two portions of the study, an open-label induction period followed by a double-blind

portion in which they were randomized to one of two possible adalimumab maintenance regimens, or placebo. After an induction regimen of adalimumab 80 mg sc at Week 0 and adalimumab 40 mg sc at Week 2, subjects were stratified by responder status and previous anti-TNF use and then randomized to either adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo. Randomized subjects who experienced a disease flare (an increase in the CDAI of $\geq$ 70 points compared to the Week 4 CDAI score and an absolute CDAI score > 220 points) at or after Week 12, they could enter the open-label portion of the study where they would receive OL adalimumab 40 mg sc eow. Subjects who developed a flare on this regimen could then be dose escalated to OL adalimumab 40 mg ew. Those that did not have clinical improvement after dose frequency was increased were withdrawn from the study. Subjects who were consistent non-responders (did not achieve a CDAI decrease $\geq$ 70 points compared to Baseline) at or after Week 12 could be switched to the OL phase of the study after discussion with the study medical monitor.

The M02-404 study protocol pre-specified the following analyzable populations: 1) an "all treated" population was defined as the subjects who received at least one dose of study drug, 2) a "modified intent-to-treat (mITT) population was defined as all treated subjects who achieved a clinical (CR-70) response at Week 4 and were randomized to receive one of three blinded treatments in the second portion of the study – this was the primary analysis population, 3) a "per protocol" population, which excluded all subjects with major protocol deviations from the mITT population.

Primary Endpoint – Study M02-404

This study had two co-primary endpoints which were clinical remission at both Weeks 26 and Week 56 for the population of subjects who were clinical responders at Week 4.

The primary analysis was to be the hypothesis tests for adalimumab treatment effect at Week 26 and Week 56 in the mITT population (this included comparisons of the proportion of responders at Week 4 and in clinical remission at Week 26 or Week 56, with comparison between each adalimumab arm and the placebo treatment group using CMH Chi-square test adjusting for previous anti-TNF use).

Hypothesis testing for the co-primary endpoints was to be carried out in a hierarchical order. The Week 26 remission rate was to be tested first. If the hypothesis test for Week 26 remission rate was rejected, then the Week 56 remission rate was to be tested. Otherwise, testing was to stop.

To be considered a positive trial, adalimumab needed to demonstrate efficacy at both the Week 26 and 56 endpoints. The Hochberg procedure was to be applied to control for multiplicity. If one hypothesis test derived a non-significant p-value ($p \geq 0.05$), then the other hypothesis would be tested against an adjusted 0.025 alpha level. A positive conclusion would still be made if the p-value was significant at the 0.025 alpha level.

Subjects who were consistent non-responders or switched to OL treatment after a flare were to be considered "failures" for all visits post-flare.

For the mITT dataset (**Table 63**), 40% of subjects treated with adalimumab 40 mg eow and 47% of subjects in the adalimumab 40 mg ew treatment group were in clinical remission at Week 26 compared to 17% of subjects treated with placebo. At Week 56, remission rates were 36%, 41%, and 12% for the adalimumab eow, adalimumab ew, and placebo groups, respectively.

Table 63: Clinical Remission at Week 26 and Week 56 (mITT Dataset)

	Placebo N=170	Adalimumab eow N=172	Adalimumab ew N=157
Visit	n (%)		
Week 26	29 (17)	68 (40)	73 (47)
Week 56	20 (12)	62 (36)	65 (41)

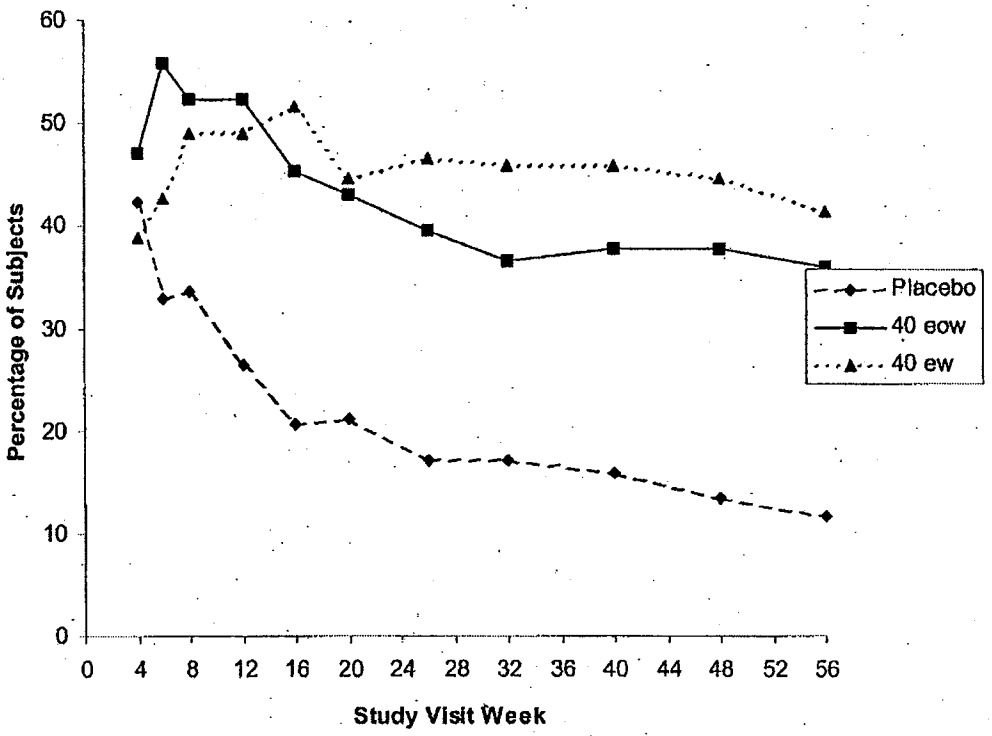
Pairwise comparisons of each adalimumab treatment group vs. placebo are shown in **Table 64**. For both Weeks 26 and 56, each adalimumab treatment regimen yielded significantly greater remission rates when individually compared to placebo ($p < 0.001$ for each individual comparison at Weeks 26 and 56). No significant differences were seen between clinical remission rates for the adalimumab treatment groups.

Table 64: Treatment Comparison of Clinical Remission at Weeks 26 and 56 (mITT Dataset)

Visit	Treatment Comparison	Difference in Proportions	p-value
Week 26	Adalimumab 40 mg eow vs. placebo	23%	<0.001
	Adalimumab 40 mg ew vs. placebo	29%	<0.001
	Adalimumab 40 mg ew vs. adalimumab 40 mg eow	7%	0.220
Week 56	Adalimumab 40 mg eow vs. placebo	24%	<0.001
	Adalimumab 40 mg ew vs. placebo	30%	<0.001
	Adalimumab 40 mg ew vs. adalimumab 40 mg eow	5%	0.344

The proportions of subjects in clinical remission at each study visit for all treatment groups are displayed in **Figure 12**. As early as Week 8 after Baseline (four weeks after randomization), both adalimumab groups have higher rates of clinical remission compared to placebo.

Figure 12: Percentage of Subjects in Clinical Remission at Each Visit (mITT Dataset)



The numeric proportions of subjects in clinical remission for each study visit are displayed in **Table 65**. Clinical remission rates in the placebo-treated group began decreasing as early as Week 6 and continued to decrease to 12% by Week 56. After an initial rise in remission rates for the two adalimumab dose groups with a plateau at approximately Weeks 8 to 12, remission rates for both groups were maintained at approximately 40% up to Week 56.

Table 65: Summary of Proportions of Subjects in Clinical Remission at Any Visit (mITT Dataset)

Visit	Placebo N=170	Adalimumab eow N=172	Adalimumab ew N=157
Week 6	56 (33)	96 (56)	67 (43)
Week 8	57 (34)	90 (52)	77 (49)
Week 12	45 (27)	90 (52)	77 (49)
Week 16	35 (21)	78 (45)	81 (52)
Week 20	36 (21)	74 (43)	70 (41)
Week 26	29 (17)	68 (40)	73 (47)
Week 32	29 (17)	63 (37)	72 (46)
Week 40	27 (16)	75 (38)	72 (46)
Week 48	23 (14)	65 (38)	70 (45)
Week 56	20 (12)	62 (36)	65 (41)

In a different analysis, the proportions of subjects who achieved clinical remission at Week 4 and remained in clinical remission at any study visit thereafter were evaluated and presented in **Figure 13** and **Table 66**. Subjects treated with placebo had rapid decreases in the proportion remaining in clinical remission as soon as Week 6. By Week 56, 8% of placebo-treated subjects remained in clinical remission. In contrast, 28% and 34% of subjects in the adalimumab 40 mg eow and 40 mg ew groups, respectively, remained in clinical remission at Week 56.

Figure 13: Percentage of Subjects Achieving Clinical Remission at Week 4 and Remaining in Clinical Remission at Any Visit (mITT Dataset)

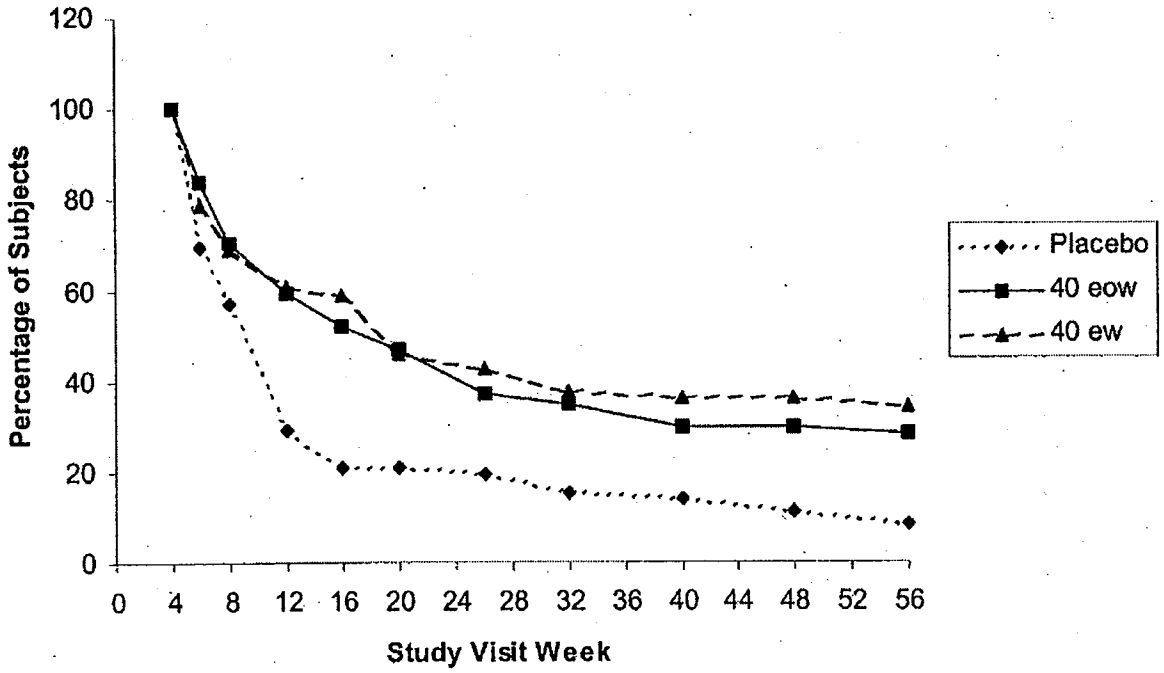


Table 66: Summary of Proportions of Subjects in Clinical Remission at Week 4 and Remaining in Clinical Remission at Any Visit (mITT Dataset)

Visit	Placebo N=72	Adalimumab eow N=81	Adalimumab ew N=61
Week 6	50 (69)	68 (84)	48 (79)
Week 8	41 (57)	57 (70)	42 (69)
Week 12	21 (29)	48 (59)	37 (61)
Week 16	15 (21)	42 (52)	36 (59)
Week 20	15 (21)	38 (47)	28 (46)
Week 26	14 (19)	30 (37)	26 (43)
Week 32	11 (15)	28 (35)	23 (38)
Week 40	10 (14)	24 (30)	22 (36)
Week 48	8 (11)	24 (30)	22 (36)
Week 56	6 (8)	23 (28)	21 (34)

Individual treatment comparisons of each adalimumab dose group vs. placebo for each study visit in Study M02-404 (**Table 67**) were all statistically significant. These data support the use of adalimumab in maintaining clinical remission out to Week 56.

Table 67: Treatment Comparisons of Clinical Remission at Any Visit

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 6	Adalimumab 40 mg eow vs. placebo	15%	(1.2, 27.8)	0.033
Week 12	Adalimumab 40 mg eow vs. placebo	30%	(15.1, 45.1)	<0.001
	Adalimumab 40 mg ew vs. placebo	32%	(15.3, 47.6)	<0.001
Week 16	Adalimumab 40 mg eow vs. placebo	31%	(16.7, 45.4)	<0.001
	Adalimumab 40 mg ew vs. placebo	38%	(22.7, 53.7)	<0.001
Week 20	Adalimumab 40 mg eow vs. placebo	26%	(11.7, 40.4)	<0.001
	Adalimumab 40 mg ew vs. placebo	25%	(9.4, 40.7)	0.002
Week 26	Adalimumab 40 mg eow vs. placebo	18%	(3.7, 31.5)	0.016
	Adalimumab 40 mg ew vs. placebo	23%	(7.8, 38.6)	0.004
Week 32	Adalimumab 40 mg eow vs. placebo	19%	(6.0, 32.6)	0.006
	Adalimumab 40 mg ew vs. placebo	22%	(7.7, 37.2)	0.003
Week 40	Adalimumab 40 mg eow vs. placebo	16%	(3.0, 28.5)	0.019
	Adalimumab 40 mg ew vs. placebo	22%	(7.7, 36.6)	0.003
Week 48	Adalimumab 40 mg eow vs. placebo	19%	(6.2, 30.8)	0.005
	Adalimumab 40 mg ew vs. placebo	25%	(10.9, 39.0)	<0.001
Week 56	Adalimumab 40 mg eow vs. placebo	20%	(8.3, 31.8)	0.002
	Adalimumab 40 mg ew vs. placebo	26%	(12.6, 39.6)	<0.001

a. The p-value is from CMH test stratified by previous anti-TNF use.

Subgroup Analyses

Analysis Based on Previous Anti-TNF Use

A summary of clinical remission rates for subjects with previous anti-TNF use is shown in **Table 68**. At both Weeks 26 and 56, both adalimumab maintenance treatment regimens yielded consistently higher remission rates regardless of whether subjects had a history of prior anti-TNF therapy. Thus, adalimumab appears beneficial for CD subjects whether or not they were previously treated with anti-TNF therapy.

Table 68: Summary of Clinical Remission by Previous Anti-TNF Use (ITT Subjects)

Visit	TNF Use?	Clinical Remission?	Placebo n (%)	Adalimumab Subjects 40 mg EOW n (%)	40 mg EW n (%)	ALL n (%)
Week 26	Yes	Yes	14 (11)	37 (29)	34 (27)	71 (27)
		No	116 (89)	96 (72)	93 (73)	189 (73)
		Total	130	133	127	260
	No	Yes	22 (17)	50 (39)	48 (37)	98 (38)
		No	109 (83)	77 (61)	82 (63)	159 (62)
		Total	131	127	130	257
Week 56	Yes	Yes	9 (7)	31 (23)	31 (24)	62 (24)
		No	121 (93)	102 (77)	96 (76)	198 (76)
		Total	130	133	127	260
	No	Yes	18 (14)	45 (35)	47 (36)	92 (36)
		No	113 (86)	82 (65)	83 (64)	165 (64)
		Total	131	127	130	257

Analyses Based on Baseline Predictors

Baseline predictors for higher clinical remission rates for the adalimumab 40 mg weekly treatment group over the adalimumab 40 mg eow group are presented using two criteria to evaluate whether to present a particular variable (**Table 69**). First, the sample size in each subgroup had to be greater than or equal to 20 subjects. In addition, the difference between adalimumab treatment groups in achieving clinical remission had to be $\geq$ 10%. Using these two criteria, females who received adalimumab 40 mg ew (42%) had Week 56 had a higher proportion of subjects in clinical remission compared to those who received adalimumab 40 mg eow (32%). Also at Week 56, subjects who weighed $\leq$ 70 kg at Baseline and received weekly adalimumab maintenance treatment had a higher proportion of those in clinical remission (51%) compared to those receiving adalimumab every other week. Both At Week 26 and 56, subjects with CRP levels $\geq$ 1.0 mg/dL who were on adalimumab weekly maintenance therapy had higher rates of clinical response (56% at Week 26 and 51% at Week 56) compared those on every other week maintenance therapy.

Table 69: Baseline Predictors of Clinical Remission at Week 26 and Week 56 (mITT Dataset)

Visit	Placebo N=170	Adalimumab 40 mg eow N=172	Adalimumab 40 mg ew N=157
Baseline Predictor	n/N (%)		
Week 56			
Male	6/65 (9)	27/61 (44)	25/62 (40)
Female	14/105 (13)	35/111 (32)	40/95 (42)
Week 56			
< 70 kg	11/102 (11)	37/95 (39)	48/94 (51)
> 70 kg	9/68 (13)	25/77 (33)	17/63 (27)
Week 26			
CRP < 1.0 mg/dL	15/85 (18)	37/95 (39)	31/82 (38)
CRP ≥ 1.0 mg/dL	14/85 (17)	31/76 (41)	42/75 (56)
Week 56			
CRP < 1.0 mg/dL	11/85 (13)	34/95 (36)	27/82 (33)
CRP ≥ 1.0 mg/dL	9/85 (11)	28/76 (37)	38/75 (51)

Analyses Based on Concomitant or Previous Medication Use

Clinical remission rates at Weeks 26 and 56 according to concomitant or previous medication (immunosuppressants and/or anti-TNF) use are presented in **Table 70**. At both timepoints, subjects treated with either of the adalimumab maintenance dosing regimens had consistently higher rates of clinical remission compared to the placebo group whether or not they were on concomitant immunosuppressants or had a history of previous anti-TNF use.

Table 70: Concomitant and/or Previous Medications and Clinical Remission at Week 26 and Week 56 (mITT Dataset)

Visit	Placebo N=170	Adalimumab 40 mg eow N=172	Adalimumab 40 mg ew N=157
Medication	n/N (%)		
Week 26			
Immunosuppressant User[a]	21/131 (16)	53/136 (39)	53/121 (44)
Immunosuppressant Non-User	8/39 (21)	15/36 (42)	20/36 (56)
Week 56			
Immunosuppressant User[a]	15/131 (12)	50/136 (37)	47/121 (39)
Immunosuppressant Non-User	5/39 (13)	12/36 (33)	18/36 (50)
Week 26			
Previous Anti-TNF	13/81 (16)	28/86 (33)	30/71 (42)
Non-Users of Previous Anti-TNF	16/89 (18)	40/86 (47)	43/86 (50)
Week 56			
Previous Anti-TNF	8/81 (10)	26/86 (30)	24/71 (34)
Non-Users of Previous Anti-TNF	12/89 (14)	36/86 (42)	41/86 (48)

[a] Includes previous and concomitant immunosuppressant use.

Secondary Endpoints – Study M02-404:

The proportion of CR-100 responders at Weeks 26 and 56 are shown in **Table 71**. CR-100 clinical response rates at Week 2 of the study were comparable across all randomized responders, with 51% of placebo subjects and 54% of the combined adalimumab treatment group in CR-100 response at Week 2. Clinical response rates peaked at Week 4 with 76% of both the placebo subjects and combined adalimumab group in CR-100 response. By Week 26, the CR-100 response in the placebo group decreased to 27% which was nearly half the 52% rate of the combined adalimumab group. By Week 56, 17% of placebo-treated subjects were still in CR-100 response compared to 44% of the combined adalimumab treatment group.

Table 71: Proportion of Subjects with CR-100 at Weeks 26 and 56 (mITT Dataset)

Visit/ Achieving CR-100	Placebo (N=170) n (%)	Adalimumab Subjects			TOTAL (N=499) n (%)
		40 mg EOW (N=172) n (%)	40 mg EW (N=157) n (%)	ALL (N=329) n (%)	
Week 2	86 (51)	97 (56)	81 (52)	178 (54)	264 (53)
Week 4	129 (76)	134 (78)	117 (75)	251 (76)	380 (76)
Week 6	116 (68)	131 (76)	116 (74)	247 (75)	363 (73)
Week 8	106 (62)	131 (76)	116 (74)	247 (75)	353 (71)
Week 12	87 (51)	120 (70)	108 (69)	228 (69)	315 (63)
Week 16	64 (38)	103 (60)	96 (61)	199 (61)	263 (53)
Week 20	53 (31)	94 (55)	86 (55)	180 (55)	233 (47)
Week 26	45 (27)	89 (52)	82 (52)	171 (52)	216 (43)
Week 32	44 (26)	80 (47)	78 (50)	158 (48)	202 (41)
Week 40	37 (22)	74 (43)	80 (51)	154 (47)	191 (38)
Week 48	33 (19)	74 (43)	78 (50)	152 (46)	185 (37)
Week 56	28 (17)	71 (41)	75 (48)	146 (44)	174 (35)

Table 72 shows the CR-100 clinical response rates for subjects who were considered non-responders after the initial open-label adalimumab 80 mg/40 mg induction regimen was given to all enrollees into Study M02-404. Of the original 854 subjects treated with OL therapy, 279 or 33% were non-responders at the CR-70 level. After stratification at Week 4 for responders/non-responders occurred, non-responder subjects were also randomized to adalimumab 40 mg eow, adalimumab 40 mg ew, or placebo therapy to Week 56. Peak CR-100 response rates for all treatment groups occurred at Weeks 8 and 12 as opposed to Weeks 4 and 6 for the mITT population analysis in **Table 71** above, suggesting that initial non-responders may need to be treated several weeks longer to see a clinical response.

Table 72: Summary of Clinical Response CR-100 for Randomized Non-Responder Subjects

Visit/ Achieving CR-100	Placebo (N=91) n (%)	Adalimumab Subjects			TOTAL (N=279) n (%)
		40 mg EOW (N=88) n (%)	40 mg EW (N=100) n (%)	ALL (N=188) n (%)	
Week 2	12 (13)	10 (11)	10 (10)	20 (11)	32 (12)
Week 6	18 (20)	12 (14)	24 (24)	36 (19)	54 (19)
Week 8	19 (21)	23 (26)	32 (32)	55 (29)	74 (27)
Week 12	14 (15)	24 (27)	30 (30)	54 (29)	68 (24)
Week 16	18 (20)	25 (28)	24 (24)	49 (26)	67 (24)
Week 20	9 (10)	25 (28)	16 (16)	41 (22)	50 (18)
Week 26	9 (10)	24 (27)	18 (18)	42 (22)	51 (18)
Week 32	7 (8)	18 (21)	19 (19)	37 (20)	44 (16)
Week 40	7 (8)	17 (19)	19 (19)	36 (19)	43 (15)
Week 48	8 (9)	18 (21)	15 (15)	33 (18)	41 (15)
Week 56	7 (8)	17 (19)	18 (18)	35 (19)	42 (15)

Time to Clinical Remission

The median times to clinical remission from Week 0 for the ITT and the mITT populations are shown in **Table 73**. In pairwise comparisons against placebo, the adalimumab 40 mg eow treatment group had the lowest median times to remission, with 57 days and 42 days for the ITT and mITT populations, respectively.

Table 73: Median Time to Clinical Remission from Week 0

Population	Treatment	N	Number of Subjects In Remission n (%)	Median Time to Remission (Days)	p-value[a]
Intent-To-Treat	Placebo	261	130 (50)	114	
	40 mg EOW	260	172 (66)	57	0.007
	40 mg EW	257	152 (59)	85	0.217
Modified Intent-To-Treat	Placebo	170	106 (62)	57	
	40 mg EOW	172	135 (79)	42	0.010
	40 mg EW	157	115 (73)	43	0.106

[a] P-values are pairwise comparisons of 40 mg EOW vs. placebo or 40 mg EW vs. placebo by log-rank test

The median times in clinical remission for those subjects who achieved clinical remission are displayed in **Table 74**. Both adalimumab treatment groups had longer periods of time in clinical remission when compared to the placebo group. In the ITT population, the adalimumab 40 mg ew group had a longer median time in remission compared to placebo than the adalimumab 40 mg eow treatment arm. The median times in clinical remission for both adalimumab groups in the mITT population were both significantly longer than the placebo group. The median time in remission for the adalimumab 40 mg ew was unestimable.

Table 74: Median Time in Clinical Remission for Subjects who Achieved Clinical Remission

Population	Treatment	Number of Subjects in Remission	Number of Subjects End Remission n (%)	Median Time in Remission (Days)	p-value[b]
Intent-To-Treat	Placebo	130	66 (51)	124	
	40mgeow	172	78 (45)	338	0.008
	40mg ew	152	66 (43)	366	0.012
Modified Intent-To-Treat	Placebo	106	56 (53)	127	
	40mgeow	135	56 (42)	378	0.002
	40 mg ew	115	45 (39)	85[a]	<0.001

[a] Median time in remission is unestimable, 25th percentile is presented.
[b] p-values are pairwise comparisons of placebo vs. 40 mg eow or placebo vs. 40 mg ew by log-rank test.

Table 75: Median Time in Clinical Remission for Subjects who Achieved Clinical Remission at Week 4

Population	Treatment	Number of Subjects in Remission	Number of Subjects End Remission n (%)	Median Time in Remission (Days)	p-value[b]
Intent-To-Treat	Placebo	73	34 (47)	197	
	40mgEOW	81	28 (35)	146[a]	0.011
	40 mg EW	61	26 (43)	98[a]	0.041
Modified Intent-To-Treat	Placebo	72	34 (47)	197	
	40mgEOW	81	28 (35)	146[a]	0.010
	40 mg EW	61	26 (43)	98[a]	0.039

[a] Median time in remission is unestimable, 25th percentile is presented.
[b] p-values are pairwise comparisons of placebo vs. 40 mg eow or placebo vs. 40 mg ew by log-rank test.

Table 76: Time in Clinical Response CR-70 for Subjects Who Achieved Clinical Response CR-70

Population	Treatment	Number of Subjects with CR-70	Number of Subjects End CR-70 n (%)	Median Time in CR-70 (Days)	p-value[b]
Intent-To-Treat	Placebo	221	159 (72)	87	
	40mgEOW	232	126 (54)	226	<0.001
	40 mg EW	227	123 (54)	222	<0.001
Modified Intent-To-Treat	Placebo	170	121 (71)	94	
	40mgEOW	172	84 (49)	298	<0.001
	40 mg EW	157	75 (48)	381	<0.001

Steroid-Free Clinical Remission

Table 77: Steroid-Free at Least 90 Days and in Clinical Remission at Week 26 and Week 56 (Subjects Receiving Corticosteroids at Baseline in mITT Dataset)

Visit	Placebo	Adalimumab eow	Adalimumab ew
	n (%)		
Week 26[a]	N=66 2 (3)	N=58 11 (19)	N=74 11 (15)
Week 56[a]	N=66 3 (5)	N=58 17 (29)	N=74 15 (20)

[a] Number of mITT subjects on corticosteroids at Baseline.

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[b]
Week 26	Adalimumab 40 mg eow vs. placebo	16%	(5.0, 26.8)	0.006
	Adalimumab 40 mg ew vs. placebo	12%	(2.7, 20.9)	0.019
	Adalimumab 40 mg ew vs. 40 mg eow	-4%	(-17.0, 8.8)	0.639
Week 56	Adalimumab 40 mg eow vs. placebo	25%	(12.0, 37.5)	<0.001
	Adalimumab 40 mg ew vs. placebo	16%	(5.3, 26.2)	0.006
	Adalimumab 40 mg ew vs. 40 mg eow	-9.0	(-23.9, 5.8)	0.306

[b] p-value is from Fisher's Exact test.

Draining Fistulas

Table 78: Proportion of Subjects with Draining Fistulas during Double Blind Period

Analysis Set: Draining Fistulas? (Yes/No)[a]	Placebo n (%)	Adalimumab 40 mg eow n (%)	Adalimumab 40 mg ew n (%)	Adalimumab Total n (%)	p-value[b]
Intent-To-Treat	N=47	N=30	N=40	N=70	
Yes	41 (87)	19 (63)	28 (70)	47 (67)	0.016
No	6 (13)	11 (37)	12 (30)	23 (33)	
Modified ITT	N=28	N=14	N=22	N=36	
Yes	24 (86)	9 (64)	12 (55)	21 (58)	0.027
No	4 (14)	5 (36)	10 (46)	15 (42)	

[a] Subject who had no draining fistulas at the last 2 post baseline evaluations in double-blind period is classified as 'no'. Otherwise, they were classified as 'yes'. If only one post-baseline visit, then subject was classified as 'yes'.
[b] p-value from Fisher's Exact Test to compare placebo with combined 40 mg eow and 40 mg ew groups.

Endoscopic Outcomes

Only 18 of an expected 100 subjects at selected sites enrolled in the endoscopic sub-study, precluding formal analysis of this secondary endpoint.

6.1.6 Efficacy Conclusions

This efficacy supplement was supported by two four-week induction studies (M02-403 and M04-691) and two long-term maintenance studies (M02-433 and M02-404). All studies were conducted in a moderately to severely active adult CD population, defined as having a CDAI of ≥ 220 and ≤ 450 points. Clinical remission was defined as a CDAI score of < 150 points, and clinical responses were defined as CR-70 or CR-100 (decreases in Baseline CDAI score of ≥ 70 points or of ≥ 100 points, respectively).

Study M02-403 was a dose-exploration study of the ability of adalimumab to induce clinical remission in subjects with moderately to severely active CD who were naïve to anti-TNF therapy. The Week 0 and Week 2 doses of adalimumab were 160 mg/80 mg, 80 mg/40 mg, or 40 mg/20 mg, respectively. These doses were compared against a control group given placebo at Weeks 0 and 2. Subjects who received the adalimumab 160 mg/80 mg induction regimen had the greatest number in clinical remission at Week 4, 36%, compared to 12% of subjects who received placebo (p=0.004). A dose-response was seen in this study because the lower dose adalimumab groups had Week 4 remission rates of 18% and 24% in the adalimumab 40 mg/20 mg group and the 80 mg/40 mg group, respectively.

Study M04-691 used the optimal adalimumab dose (160 mg/80 mg) obtained in Study M02-403 and studied this dose in comparison to placebo in active CD subjects who had a previous history of loss of response to or intolerance to infliximab therapy. The primary endpoint was similar to the dose-ranging study, Study M02-403, which was clinical remission at Week 4. In this study of TNF-experienced subjects who still had moderately to severely active CD at Baseline, the adalimumab 160 mg/80 mg group had 21% of subjects in clinical remission at Week 4 compared to 7% in the placebo group after receiving two injections at Week 0 and Week 2.

Study M02-433 was a follow-on study for subjects who completed lead-in Study M02-403. Subjects who were in clinical remission at the end of the lead-in study were enrolled into Study M02-433 and then randomized to one of two adalimumab maintenance regimens (40 mg eow sc or 40 mg ew sc) or placebo ew sc. This "randomized analysis set" served as the primary analysis population for Study M02-433, with a primary endpoint of clinical remission at Week 56. Subjects who were not in remission at the end of lead-in Study M02-403 received open-label adalimumab 40 mg eow sc (the "open-label analysis set") with the option to have their adalimumab dose increased to 40 mg ew sc if they had a disease flare or were consistently in non-response.

In the randomized analysis set of Study M02-433 (55 of the 276 enrolled subjects), higher proportions of subjects in both adalimumab groups demonstrated maintenance of clinical remission at Week 56 when compared to placebo (47% and 67% for the adalimumab 40 mg eow and adalimumab 40 mg ew groups, respectively, vs. 33% for placebo). There was no statistically significant difference for the combined adalimumab groups vs. placebo (p=0.142), but nonetheless these results appeared to be clinically meaningful. At Week 24, the adalimumab 40 mg ew group had a statistically significant greater increase in remission compared to placebo (94% vs. 39%, respectively, p=0.001).

Study M02-404 was conducted to demonstrate maintenance of clinical remission. At the time this study was designed, the results from the dose-ranging induction Study M02-403 were not yet known. Thus, the adalimumab — mg induction regimen was chosen based on PK predictions on steady state concentrations achieved after up to 16 weeks of adalimumab 40 mg eow dosing in rheumatoid arthritis subjects. In this study, a total of 854 subjects with CD were given OL induction doses of adalimumab 80 mg at Week 0 and 40 mg at Week 2. Of all subjects enrolled, 50% had previously received anti-TNF therapy. At Week 4, subjects were stratified by responder status and previous anti-TNF use and then entered the randomized phase of the study to receive adalimumab 40 mg eow, adalimumab 40 mg ew, or placebo. Subjects who developed a disease flare (an increase in CDAI of $\geq$ 70 points compared to Week 4 CDAI score and a CDAI > 220) at or after Week 12 of Study M02-404, they could have been switched to OL adalimumab 40 mg eow. Those who flared on this OL regimen could have switched to OL adalimumab 40 mg ew. There were two co-primary endpoints in this trial for the mITT population which included all treated subjects who achieved a CR-70 response at Week 4 and were randomized to blinded treatment. The first co-primary endpoint was the proportion of subjects in clinical remission at Week 26 and the second co-primary endpoint was the proportion of subjects in clinical remission at Week 56.

b(4)

The proportions of mITT subjects who achieved the endpoints of clinical remission at Weeks 26 and 56 were statistically significantly greater in the adalimumab 40 mg eow (40% and 36%, respectively), and 40 mg ew (47% and 41%, respectively) groups compared to the placebo group (17% and 12%, respectively). No statistical difference was seen between the two adalimumab groups in clinical remission at any timepoint after Week 6 although the adalimumab 40 mg ew group had a numerically higher proportion of subjects in remission at Weeks 26 and 56. The time in clinical remission was greater for each of the adalimumab maintenance groups compared to the placebo group. Clinical remission rates were consistently higher in the adalimumab maintenance groups compared to placebo for subjects who were and were not previously exposed to anti-TNF therapy. Study M02-404 demonstrated the efficacy of both the adalimumab 40 mg eow and 40 mg ew maintenance doses for the maintenance of clinical remission in subjects who previously achieved a CR-70 response after induction therapy.

Results from the two induction studies showed that adalimumab was effective in inducing clinical remission at Week 4 in moderately to severely active CD subjects who were unresponsive to conventional CD therapies and for those who lost response to or were intolerant of infliximab therapy. The two maintenance studies (M02-433 and M02-404) demonstrated that both of the adalimumab maintenance therapies (40 mg eow and 40 mg ew) were effective to maintain clinical remission out to Week 56 in this same population. The secondary endpoints of CR-70 and CR-100 response rates supported results of the primary endpoints for all studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety data for each of the mentioned studies are reviewed in this safety section by reviewing all pertinent safety events that occurred in each pivotal trial.

7.1.1 Deaths

A total of two deaths were reported in the four pivotal (four placebo-controlled and two open-label extension) trials enrolling a combined total of 1478 subjects. These two deaths occurred only in Study M02-404. One death was reported in a 72 y.o. White male who died due to a pulmonary embolism (weakness, loss of consciousness 15 days after the start of open-label induction treatment), with risk factors of a history of pulmonary embolism, hypertension, and atrial fibrillation. This death was reported as probably not related to the study medication. The other reported death was due to a case of leukemia.

In Studies M02-403, M04-691, and M02-433, there were no deaths reported.

Although of concern, these two deaths out of a total of 1478 randomized subjects in the Abbott Crohn's disease development program do not suggest a major new safety signal for adalimumab given the small number of subjects involved and the causes of death specified.

7.1.2 Other Serious Adverse Events

Malignancies

A total of three malignancies were diagnosed during Studies M02-433 and M02-404. In Study M02-433, two subjects (both randomized to placebo) reported a malignancy. One was a 52 y.o. White male who was diagnosed with squamous cell carcinoma 15 days after beginning Study M02-433. The other malignancy reported was in a 32 y.o. White female who reported a labial neoplasm 254 days after beginning study treatment. No lymphomas were reported. In Study M02-404, one breast cancer was reported by a 33 y.o. female who received placebo during double-blind treatment. No malignancies were reported during the open-label induction period or after randomization.

No malignancies were reported in the induction Studies M02-403 or M04-691.

Although any malignancy is concerning, the type and number of malignancies reported in these adult subjects with Crohn's disease do not represent a new cancer signal for adalimumab that is not already mentioned in the current product label. Under the current WARNINGS and PRECAUTIONS section, the HUMIRA® package insert states that "in the controlled portions of

clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients."

It is the opinion of the clinical reviewer that no new language needs to be added to address the above malignancies reported from the Crohn's disease clinical development program.

Serious Adverse Events

The numbers of subjects with treatment-emergent serious adverse events (SAE's) per each pivotal study are presented in this section.

Study M02-403:

In Study M02-403, a four-week dose-ranging induction study, a total of 3% of randomized subjects (8 out of 299) reported nine SAE's during the study, **Table 79**. Three subjects out of 74 treated with placebo (4%) reported an SAE compared to none in the adalimumab 40 mg/20 mg group, 1% in the adalimumab 80 mg/40 mg group, and 5% (4 out of 76) of the adalimumab 160 mg/80 mg treatment group. Although there appears to be a dose-effect for SAE's in this study, the rate of SAE's reported in the placebo group approach that in the highest adalimumab treatment arm. Most of the reported SAE's were CD-related and not unexpected, given the moderately to severely active disease state these subjects had at the time of enrollment.

Table 79: Subjects with Serious Adverse Events (by MedDRA Preferred Terms)-Study M02-403

Subject Number	Adalimumab 40mg/20mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160 mg/80 mg (N=76)	Placebo (N=74)
03405			Fecal impaction Dehydration	
03406				Calculus ureteric
05403				Crohn's disease aggravated Hemorrhoids
06202				Crohn's disease aggravated
04301		Crohn's disease aggravated Crohn's disease		
05102			Pneumonia	
05412			Abdominal pain NOS	
06203			Perianal abscess	

Study M04-691:

In Study M04-691, CD subjects who lost response to infliximab or were intolerant to infliximab were randomized to either placebo therapy or adalimumab 160 mg/80 mg for a four-week treatment period. In this active study population who had already been exposed to infliximab,

more placebo-treated subjects (5%) reported a treatment-emergent SAE compared to those who received adalimumab 160 mg/80 mg induction therapy (1%). The most commonly reported system organ classes from the placebo-treated arm included gastrointestinal disorders and infections and infestations and were not unexpected, **Table 80**. The relatively few SAE's reported from the adalimumab 160 mg/80 mg treatment group do not raise any new concern of SAE's possibly caused by adalimumab administration in CD subjects who previously received infliximab.

Table 80: Subjects with Treatment-Emergent Serious Adverse Events – Study M04-691

System Organ Class MedDRA Preferred Term	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)
Total Subjects (Any SAE)	8 (5)	2 (1)
Gastrointestinal Disorders		
Abdominal pain	2 (1)	0
Crohn's disease	2 (1)	0
Infections and Infestations		
Abdominal abscess	1 (<1)	0
Pelvic abscess	1 (<1)	0
Perianal abscess	1 (<1)	0
Staphylococcal sepsis	1 (<1)	0
Investigations		
Weight decreased	0	1 (<1)
Metabolism and nutrition disorders		
Dehydration	0	2 (1)

Study M02-433:

Study M02-433 was a follow-on study for subjects who completed lead-in Study M02-403. The "randomized analysis set" in Study M02-433 consisted of subjects who had achieved remission after induction therapy from the lead-in study. As a result, the total number of subjects (55) who achieved remission and were randomized to either placebo treatment, adalimumab 40 mg eow, or adalimumab 40 mg ew was a subset of the original 299 subjects enrolled into lead-in Study M02-403. A total of 6% of subjects in the randomized analysis set reported any SAE up to Week 56 of the maintenance portion of Study M02-433 (**Table 81**). There was no dose-response effect for SAE's reported as the maintenance dose of adalimumab increased from 40 mg eow to 40 mg ew. One subject in the adalimumab 40 mg eow maintenance group reported an SAE (5%) up to Week 56.

Table 81: Subjects with Treatment-Emergent SAE's Randomized Analysis Set Up to Week 56 (MedDRA Preferred Terms) – Study M02-433

MedDRA Preferred Term	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55
	n (%)			
Any SAE	2 (11)	1 (5)	0	3 (6)
Coronary artery disease[a]	0	1 (5)	0	1 (2)
Ileal stenosis	1 (6)[b]	0	0	1 (2)
Small intestinal obstruction NOS	1 (6)[b]	0	0	1 (2)
Back pain	1 (6)	0	0	1 (2)

a. Subject had the following risk factors: HTN, Type II Diabetes, and bronchial asthma.
b. SAE's of ileal stenosis and small intestinal obstruction NOS reported in the same placebo subject.

The numbers of treatment-emergent SAE's reported by ≥ 2 subjects in the safety set of Study M02-433 are displayed in **Table 82**. The safety set of subjects consisted of those subjects from lead-in Study M02-403 who were not in remission at the end of the randomized four-week induction therapy but were nevertheless randomized to either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew maintenance treatment up to Week 56 of follow-on Study M02-433 to evaluate the efficacy and safety of randomized maintenance therapy in this group of subjects who did not initially achieve clinical remission. A total of 15% of subjects reported an SAE that occurred in ≥ 2 subjects in the safety set up to Week 56. No dose-response effect for SAE's was observed as the maintenance dose of adalimumab increased. Most of the SAE's reported were related to the gastrointestinal disorders system organ class (SOC).

Table 82: Subjects with Treatment-Emergent SAE's Reported by ≥ 2 Subjects (Safety Set Up to Week 56) – Study M02-433

MedDRA Preferred Term	Placebo N=8	Adalimumab 40 mg eow N=154	Adalimumab 40 mg ew N=114	Total N=276
	n (%)			
Any SAE	1 (13)	28 (18)	11 (10)	40 (15)
Crohn's disease aggravated	0	8 (5)	1 (<1)	9 (3)
Small intestinal obstruction NOS	0	2 (1)	2 (2)	4 (1)
Ovarian cyst	0	1 (<1)	1 (<1)	2 (<1)
Abdominal abscess NOS	0	2 (1)	0	2 (1)
Anemia NOS aggravated	0	1 (<1)	1 (<1)	2 (<1)
Ileal stenosis	0	0	2 (2)	2 (<1)

Table 83 presents the reported SAE's from Study M02-433 in more detail. The majority of reported SAE's were from the gastrointestinal disorders and infections and infestations SOC's. SAE's from other SOC's were mentioned sporadically, with no evidence of dose-response effect. Overall, no new SAE's were identified from Study M02-433 that would necessitate a change in the package insert.

Table 83: Subjects with Treatment-Emergent Serious Adverse Events by MedDRA SOC and Preferred Term (Safety Set Up to Week 56) – Study M02-433

System Organ Class MedDRA Preferred Term	Placebo N=8	Adalimumab 40 mg eow N=154	Adalimumab 40 mg ew N=114	Total N=276
	n (%)			
Total Subjects – Any Adverse Event	1 (13)	28 (18)	11 (10)	40 (15)
Blood and Lymphatic System Disorders				
Anemia NOS aggravated	0	1 (<1)	1 (<1)	2 (<1)
Cardiac Disorders				
Coronary artery disease NOS	0	1 (<1)	0	1 (<1)
Gastrointestinal Disorders				
Crohn's disease aggravated	0	8 (5)	1 (<1)	9 (3)
Diverticulitis NOS	0	1 (<1)	0	1 (<1)
Esophageal ulcer	0	1 (<1)	0	1 (<1)
Gastric ulcer	0	0	1 (<1)	1 (<1)
Ileal stenosis	0	0	2 (2)	2 (<1)
Intestinal stenosis NOS	0	1 (<1)	0	1 (<1)
Pyloric stenosis NOS	0	0	1 (<1)	1 (<1)
Small intestinal obstruction NOS	0	2 (1)	2 (2)	4 (1)
Small intestinal stricture NOS	0	1 (<1)	0	1 (<1)
Vomiting NOS	0	1 (<1)	0	1 (<1)
General Disorders and Administration Site				
Fatigue	0	1 (<1)	0	1 (<1)
Pain NOS	0	1 (<1)	0	1 (<1)
Hepatobiliary Disorders				
Biliary colic	0	1 (<1)	0	1 (<1)
Cholecystitis NOS	0	0	1 (<1)	1 (<1)
Infections and Infestations				
Abdominal abscess NOS	0	1 (<1)	0	1 (<1)
Abscess intestinal	0	1 (<1)	0	1 (<1)
Abscess NOS	0	1 (<1)	0	1 (<1)
Fifth's disease	0	1 (<1)	0	1 (<1)
Gastroenteritis NOS	0	1 (<1)	0	1 (<1)
Lobar pneumonia NOS	0	1 (<1)	0	1 (<1)
Meningitis viral NOS	0	1 (<1)	0	1 (<1)
Nocardiosis	0	1 (<1)	0	1 (<1)
Rectal abscess	0	1 (<1)	0	1 (<1)
Retroperitoneal abscess	0	1 (<1)	0	1 (<1)
Sepsis NOS	0	1 (<1)	0	1 (<1)
Injury, Poisoning and Procedural Complications				
Ankle fracture	0	0	1 (<1)	1 (<1)
Spinal compression fracture	0	0	1 (<1)	1 (<1)
Metabolism and Nutrition Disorders				
Dehydration	0	1 (<1)	0	1 (<1)
Musculoskeletal and Connective Tissue Disorders				
Back pain	1 (13)	0	0	1 (<1)
Intervertebral disc degeneration	0	1 (<1)	0	1 (<1)
Intervertebral disc herniation	0	1 (<1)	0	1 (<1)
Nervous System Disorders				
Dizziness (excluding vertigo)	0	1 (<1)	0	1 (<1)
Headache NOS	0	1 (<1)	0	1 (<1)
Renal and Urinary Disorders				
Calculus renal NOS	0	0	1 (<1)	1 (<1)
Renal failure acute	0	1 (<1)	0	1 (<1)
Reproductive System and Breast Disorders				
Ovarian cyst	0	1 (<1)	1 (<1)	2 (<1)
Skin and Subcutaneous Tissue Disorders				
Sweating increased	0	1 (<1)	0	1 (<1)
Vascular Disorders				
Cerebrovascular accident NOS	0	1 (<1)	0	1 (<1)

Study M02-404:

Study M02-404 was a long-term maintenance study conducted in two phases. First, all 854 enrolled subjects received open-label adalimumab induction therapy of 80 mg and 40 mg at Weeks 0 and 2 respectively. At Week 4, subjects were randomized to receive double-blind placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew maintenance therapy and followed out to Week 56 regardless of whether or not they were in clinical response at the end of Week 4.

Table 84 displays the number of subjects with treatment-emergent SAE's during the open-label induction portion of Study M02-404. Of the 854 subjects enrolled, 1% reported an SAE during the four-week induction period with the majority of SAE's related to the SOC's of gastrointestinal disorders, immune system disorders, or infections and infestations.

Table 84: Number and Percentage of Subjects with Treatment-Emergent SAE's During Open Label Induction by MedDRA SOC and Preferred Term – Study M02-404

	Adalimumab 80/40 mg N=854 n (%)
Total Subjects Any SAE	11 (1)
Gastrointestinal disorders Crohn's disease	7 (<1)
Immune system disorders Serum sickness	1 (<1)
Infections and Infestations Anal abscess Peritoneal abscess	1 (<1) 1 (<1)
Injury, poisoning and procedural complications Anastomotic complication	1 (<1)

Table 85 displays the percentage of subjects who reported treatment-emergent SAE's during the double-blind treatment period of Study M02-404 occurring between Weeks 4 and 56 of the trial. Overall, more placebo-treated subjects (15%) reported SAE's in the double-blind phase compared to subjects who were randomized to adalimumab 40 mg eow (9%), or adalimumab 40 mg ew (8%). Again, as in Study M02-433, the SOC's of gastrointestinal disorders and infections and infestations were the most commonly reported. Other SOC's were reported sporadically, with no new safety signal that would necessitate a new change in the current HUMIRA® package insert.

Table 85: Number and Percentage of Subjects with Treatment-Emergent SAE's During Double-Blind Treatment by MedDRA SOC and Preferred Term

	Placebo N=261	Adalimumab 40 mg eow N=260	Adalimumab 40 mg ew N=257
Total Subjects/Any SAE	40 (15)	24 (9)	21 (8)
Eye disorders			
Visual acuity reduced	0	1 (<1)	0
Gastrointestinal disorders			
Abdominal pain	2 (<1)	1 (<1)	2 (<1)
Abdominal strangulated hernia	1 (<1)	0	0
Anal fistula	1 (<1)	0	1 (<1)
Colonic obstruction	1 (<1)	0	0
Constipation	1 (<1)	0	0
Crohn's disease	17 (7)	4 (2)	3 (1)
Frequent bowel movements	0	0	1 (<1)
Ileal stenosis	1 (<1)	0	0
Intestinal fistula	0	0	1 (<1)
Intestinal obstruction	2 (<1)	0	0
Nausea	0	1 (<1)	0
Pancreatitis	1 (<1)	0	0
Peritonitis	1 (<1)	0	0
Small intestinal obstruction	0	5 (2)	0
Small intestinal stenosis	0	0	1 (<1)
General disorders and administration site			
Chest pain	0	1 (<1)	0
Pain	0	0	1 (<1)
Pelvic mass	1 (<1)	0	0
Pyrexia	0	1 (<1)	0
Hepatobiliary disorders			
Cholelithiasis	0	1 (<1)	0
Portal vein thrombosis	0	1 (<1)	0
Infections and infestations			
Abdominal abscess	2 (<1)	1 (<1)	2 (<1)
Abscess	0	0	1 (<1)
Anal abscess	1 (<1)	0	0
Appendicitis	1 (<1)	0	0
Bacteremia	1 (<1)	0	0
Device related infection	0	1 (<1)	0
Gastroenteritis	1 (<1)	1 (<1)	0
Gastroenteritis viral	0	2 (<1)	0
Perianal abscess	1 (<1)	1 (<1)	2 (<1)
Pneumonia	0	0	1 (<1)
Psoas abscess	1 (<1)	0	0
Scrotal abscess	0	1 (<1)	0
Sinusitis	0	0	1 (<1)
Varicella	1 (<1)	0	0

Table 85 (cont'd): Number and Percentage of Subjects with Treatment-Emergent SAE's During Double-Blind Treatment by MedDRA SOC and Preferred Term

	Placebo N=261	Adalimumab 40 mg eow N=260	Adalimumab 40 mg ew N=257
Total Subjects/Any SAE	40 (15)	24 (9)	21 (8)
Injury, poisoning, and procedural complications			
Injury	0	0	1 (<1)
Intracranial injury	1 (<1)	0	0
Meniscus lesion	1 (<1)	0	0
Road traffic accident	1 (<1)	0	0
Metabolism and nutrition disorders			
Dehydration	0	0	1 (<1)
Hypokalemia	1 (<1)	0	0
Musculoskeletal and connective tissue disorders			
Aseptic necrosis bone	0	0	1 (<1)
Bursitis	0	0	1 (<1)
Rotator cuff syndrome	0	1 (<1)	0
Neoplasms benign, malignant, and unspecified			
Breast cancer	1 (<1)	0	0
Nervous system disorders, autonomic nervous system			
Imbalance	1 (<1)	0	0
Grand mal convulsion	1 (<1)	0	0
Pregnancy, puerperium, and perinatal conditions			
Ectopic pregnancy	0	0	1 (<1)
Psychiatric disorders			
Depression	0	1 (<1)	1 (<1)
Suicide attempt	0	0	1 (<1)
Renal and urinary disorders			
Renal failure	1 (<1)	0	0
Renal failure chronic	1 (<1)	0	0
Reproductive system and breast disorders			
Ovarian cyst	0	0	1 (<1)
Respiratory, thoracic, and mediastinal disorders			
Chronic obstructive pulmonary disease	0	0	1 (<1)
Lung infiltration	0	1 (<1)	0
Pulmonary embolism	0	0	1 (<1)
Skin and subcutaneous tissue disorders			
Erythema nodosum	0	1 (<1)	0
Psoriasis	0	0	1 (<1)
Surgical and medical procedures			
Abortion induced	1 (<1)	0	0
Medical device removal	0	1 (<1)	0
Vascular disorders			
Hematoma	0	0	1 (<1)
Lymphedema	0	1 (<1)	0

Infectious Adverse Events

Infectious adverse events that were reported in each pivotal study are presented in this section of the clinical review.

Study M02-403:

In the four-week induction Study M02-403, most infectious AE's were mild to moderate in intensity (**Table 86**), with two infections (pneumonia NOS and perianal abscess) arising from the adalimumab 160 mg/80 mg treatment group characterized as serious infectious AE's (**Table 87**). One pharyngitis viral NOS infection was characterized as a severe infectious AE, originating from the adalimumab 80 mg/40 mg treatment group. Otherwise, the general profile of upper respiratory infectious AE's reported in this induction study is already represented in the current HUMIRA® package insert.

Table 86: Listing of Infectious Adverse Events - Study M02-403

Treatment	Subject	MedDRA preferred term	Serious AE?	Severity
Placebo				
	003-01	Upper respiratory tract infection NOS	No	Mild
	003-03	Pharyngitis NOS	No	Mild
	023-08	Rhinovirus infection NOS	No	Mod
	039-02	Gastroenteritis NOS	No	Mod
	043-02	Sinusitis NOS	No	Mild
	043-05	Nasopharyngitis	No	Mild
	044-05	Pneumonia NOS	No	Mod
	048-01	Perianal abscess	No	Mod
	053-03	Influenza	No	Mild
	053-09	Influenza	No	Mild
	053-21	Laryngitis NOS	No	Mod
		Laryngitis	No	Mod
	055-03	Vaginitis	No	Mild
Adalimumab 40 mg/20 mg				
	015-14	Sinusitis NOS	No	Mod
		Upper respiratory tract infection NOS	No	Mild
	025-05	Influenza	No	Mod
	031-01	Viral infection NOS	No	Mild
	053-02	Nasopharyngitis	No	Mod
	053-05	Vaginal infection NOS	No	Mod
	053-14	Bacterial infection NOS	No	Mod
	054-14	Nasopharyngitis	No	Mod
	063-01	Pharyngitis NOS	No	Mild
Adalimumab 80 mg/40 mg				
	013-03	Viral infection NOS	No	Mild
	015-11	Staphylococcal infection NOS	No	Mod
	025-04	Nasopharyngitis	No	Mild
		Influenza	No	Mild
		Post-dental extraction infection	No	Mod
	026-05	Fungal rash NOS	No	Mild
	027-02	Pharyngitis streptococcal	No	Mod
	051-04	Nasopharyngitis	No	Mild
	053-01	Stye on eye lid	No	Mild
	053-23	Nasopharyngitis	No	Mod
		Herpes simplex	No	Mod
	054-13	Pharyngitis viral NOS	No	Sev
	057-04	Nasopharyngitis	No	Mild
	062-01	Vaginal candidiasis	No	Mild
	066-03	Influenza	No	Mod
Adalimumab 160 mg/80 mg				
	013-02	Urinary tract infection NOS	No	Mod
	023-05	Vulval abscess	No	Mild
	025-02	Nasopharyngitis	No	Mild
	025-07	Influenza	No	Mod
	043-09	Gastroenteritis NOS	No	Mild
	044-02	Pharyngitis NOS	No	Mild
		Viral infection NOS	No	Mild
	051-02	Pneumonia NOS	Yes	Mod
	052-06	Influenza	No	Mod
	054-15	Fungal infection NOS	No	Mod
	059-03	Nasopharyngitis	No	Mild
	062-03	Eye infection NOS	No	Mild
		Perianal abscess	Yes	Mod
		Pharyngitis NOS	No	Mild
	067-01	Nasopharyngitis	No	Mild
	069-02	Nasopharyngitis	No	Mild

Table 87: Subjects with Treatment-Emergent Serious Infectious Adverse Events Study M02-403

Treatment	Subject	MedDRA preferred term	Serious AE?	Severity
Adalimumab 160 mg/80 mg				
	051-02	Pneumonia NOS	Yes	Mod
	062-03	Perianal abscess	Yes	Mod

Study M04-691:

In Study M04-691, which evaluated active CD subjects who were previously exposed to infliximab therapy, 16% of adalimumab-treated subjects reported an infectious AE compared to 34% of those subjects randomized to receive placebo at Weeks 0 and 2 (**Table 88**). The overall profile of infections reported did not reveal any new safety concern given the multiple, nonspecific nature of the reported infectious AE's. Nasopharyngitis infections accounted for the most common infectious AE's between the adalimumab and placebo treatment groups. These findings suggest that prior infliximab treatment in this study population does not incur an increased risk compared to placebo treatment when adalimumab treatment is initiated.

Table 88: Subjects with Treatment-Emergent Infectious Adverse Events – Study 04-691

System Organ Class MedDRA Preferred Term	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)
Any infectious adverse event	39 (34)	26 (16)
Infections and Infestations		
Abdominal abscess	1 (<1)	0
Anal abscess	1 (<1)	0
Body tinea	0	1 (<1)
Bronchitis	0	2 (1)
Candidiasis	0	1 (<1)
Cystitis	1 (<1)	1 (<1)
Escherichia urinary tract infection	1 (<1)	0
Fungal infection	0	1 (<1)
Gastroenteritis viral	1 (<1)	1 (<1)
Herpes simplex	2 (1)	0
Influenza	3 (2)	1 (<1)
Laryngitis	1 (<1)	0
Nasopharyngitis	7 (4)	7 (4)
Otitis media	0	1 (<1)
Pelvic abscess	1 (<1)	0
Perianal abscess	1 (<1)	0
Pharyngitis streptococcal	1 (<1)	0
Pneumonia	2 (1)	0
Sinusitis	3 (2)	0
Staphylococcal sepsis	1 (<1)	0
Subcutaneous abscess	1 (<1)	0
Tinea pedis	0	1 (<1)
Tooth infection	0	1 (<1)
Upper respiratory tract infection	5 (3)	4 (3)
Urinary tract infection	5 (3)	2 (1)
Vaginal infection	0	2 (1)
Viral infection	2 (1)	1 (<1)
Vulvovaginal mycotic infection	1 (<1)	1 (<1)

Four out of 166 subjects (2%) randomized to placebo induction therapy in Study M04-691 reported a serious infectious AE, compared to no patients in the adalimumab 160 mg/80 mg treatment group (**Table 89**).

Table 89: Subjects with Treatment-Emergent Serious Infectious Adverse Events Study 04-691

System Organ Class MedDRA Preferred Term	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)
Any serious infectious adverse event	4 (2)	0
Infections and Infestations		
Abdominal abscess	1 (<1)	0
Pelvic abscess	1 (<1)	0
Perianal abscess	1 (<1)	0
Staphylococcal sepsis	1 (<1)	0

Study M02-433:

In the follow-on Study M02-433, the most frequently reported (by ≥ 5% of subjects) infectious treatment-emergent AE's are listed in **Table 90**. In the randomized analysis set up to Week 56, more placebo-treated subjects (83%) reported an infectious AE compared to the adalimumab 40 mg eow maintenance group (74%) and the adalimumab 40 mg ew maintenance group (33%). For the most part, upper respiratory illnesses (nasopharyngitis, sinusitis NOS, upper respiratory tract infection NOS, viral infection NOS, influenza, pharyngitis NOS) accounted for the majority of infectious AE's. This profile of infectious AE's is not new in anti-TNF blocker trials in inflammatory bowel disease.

Table 90: Infectious Treatment-Emergent Adverse Events Most Frequently Reported by ≥ 5% of Subjects (Randomized Set, Up to Week 56) – Study M02-433

MedDRA SOC of Infections and Infestations Preferred Term	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55
	n (%)			
Total subjects with an infectious event	15 (83)	14 (74)	6 (33)	35 (64)
Nasopharyngitis	7 (39)	5 (26)	2 (11)	14 (26)
Sinusitis NOS	1 (6)	4 (21)	1 (6)	6 (11)
Upper respiratory tract infection NOS	1 (6)	1 (5)	2 (11)	4 (7)
Viral infection NOS	0	4 (21)	0	4 (7)
Influenza	1 (6)	3 (16)	1 (6)	5 (9)
Pharyngitis NOS	2 (11)	1 (5)	0	3 (6)
Urinary tract infection NOS	2 (11)	0	1 (6)	3 (6)

The infectious AE's that were most frequently reported (by ≥ 5% of subjects) in the safety set population in Study M02-433 are displayed in **Table 91**. A total of 59% of adalimumab-treated subjects reported an infectious AE up to Week 56 compared to 88% of placebo-treated subjects. The most commonly reported infectious AE's in the safety set group mirrors those reported by the randomized analysis set, represented in **Table 90**. No significant differences in the types of infectious AE's were noted between the two safety sets.

Table 91: Infectious Treatment-Emergent Adverse Events Most Frequently Reported by ≥ 5% of Subjects (Safety Set, Up to Week 56) – Study M02-433

MedDRA SOC of Infections and Infestations Preferred Term	Placebo N=8	Adalimumab 40 mg eow N=154	Adalimumab 40 mg ew N=114	Total N=276
	n (%)			
Total subjects with an infectious event	7 (88)	90 (58)	65 (57)	162 (59)
Nasopharyngitis	5 (63)	26 (17)	20 (18)	51 (19)
Sinusitis NOS	1 (13)	16 (10)	9 (8)	26 (9)
Upper respiratory tract infection NOS	0	14 (9)	9 (8)	23 (8)
Influenza	0	12 (8)	7 (6)	19 (7)
Urinary tract infection NOS	0	9 (6)	7 (6)	16 (6)

Study M02-404:

In the open-label (OL) induction phase of Study M02-404, the most commonly reported infectious AE was nasopharyngitis in 12% during the OL period. In the double-blind treatment period, 46% and 44% of subjects who randomized to adalimumab 40 mg eow and 40 mg ew, respectively, reported an infectious AE compared to 37% of placebo-treated subjects. These reported infectious AE's (by ≥ 2% of subjects in any treatment group) are listed in decreasing order of frequency in **Table 92**. The general impression of the profile of infectious AE's reported in Study M02-404 is similar to that discussed for Study M02-433.

Table 92: Commonly Reported (≥ 2% of Subjects in Any Treatment Group) Treatment-Emergent Infectious Adverse Events by MedDRA Preferred Term Double-Blind Treatment (ITT Dataset) – Study M02-404

	Placebo N=261	Adalimumab 40 mg eow N=260	Adalimumab 40 mg ew N=257
	n (%)		
Any infectious adverse event	96 (37)	120 (46)	114 (44)
Nasopharyngitis	18 (7)	29 (11)	31 (12)
Upper respiratory tract infection	16 (6)	12 (5)	16 (6)
Urinary tract infection	4 (2)	11 (4)	15 (6)
Influenza	13 (5)	14 (5)	13 (5)
Sinusitis	6 (2)	11 (4)	12 (5)
Viral infection	4 (2)	5 (2)	7 (3)
Herpes simplex	6 (2)	10 (4)	7 (3)
Bronchitis	7 (3)	6 (2)	4 (2)
Gastroenteritis	3 (1)	10 (4)	6 (2)
Gastroenteritis viral	1 (<1)	6 (2)	1 (<1)

Expressed as the number of infectious AE's per 100 patient-years (100 PYs) of treatment (**Table 93**), the numbers of reported infectious AE's in both adalimumab treatment groups were lower than that reported for subjects randomized to placebo treatment after the OL induction phase (150.1 events/100 PYs and 145.9 events/100 PYs for the adalimumab 40 mg eow and 40 mg ew maintenance groups, respectively) compared to 167.7 infectious AE's/100 PYs for the placebo-

treated group). Again, the general profile of reported infectious AE's in Study M02-404 is similar to that seen in Study M02-433, with nasopharyngitis, upper respiratory infection, UTI, influenza, and sinusitis as the most commonly reported infectious AE's.

Table 93: Treatment-Emergent Infectious Adverse Events per 100 Patient-years by MedDRA Preferred Term for Commonly Reported AE's (≥ 2% of Subjects in Any Treatment Group) – Double-Blind Treatment (ITT Dataset) – Study M02-404

	Placebo N=261 PYs=92.4	Adalimumab 40 mg eow N=260 PYs=143.2	Adalimumab 40 mg ew N=257 PYs=145.3
MedDRA Preferred Term	Number of Events (Events/100 PYs)		
Any infectious adverse event	155 (167.7)	215 (150.1)	212 (145.9)
Nasopharyngitis	25 (27.1)	39 (27.2)	43 (29.6)
Upper respiratory tract infection	16 (17.3)	12 (8.4)	19 (13.1)
Urinary tract infection	6 (6.5)	11 (7.7)	16 (11.0)
Influenza	14 (15.2)	15 (10.5)	15 (10.3)
Sinusitis	11 (11.9)	11 (7.7)	12 (8.3)
Herpes simplex	7 (7.6)	11 (7.7)	9 (6.2)
Viral infection	4 (4.3)	6 (4.2)	8 (5.5)
Gastroenteritis	3 (3.2)	10 (7.0)	7 (4.8)
Bronchitis	7 (7.6)	6 (4.2)	5 (3.4)
Gastroenteritis viral	2 (2.2)	6 (4.2)	1 (0.7)

Serious Infectious Adverse Events

Subjects in Study M02-404 who reported serious infectious AE's are presented in **Table 94**. A total of 11 serious infectious AE's were reported in the 854 subjects (1%) who enrolled in the OL induction phase through Week 4 of the study. The majority of the serious infectious AE's reported were related to the underlying gastrointestinal disorders SOC. Serious infectious AE's reported in the double-blind treatment period of Study M02-404 (**Table 94**) were comparable in number and nature among the three maintenance treatment groups of placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew. Most of the reported serious infectious AE's in Study M02-404 were related to the underlying gastrointestinal disorders SOC except for one case of pneumonia reported from the adalimumab 40 mg ew maintenance group. There was one case of a device-related infection and a scrotal abscess, each, reported from the adalimumab 40 mg eow maintenance treatment group.

**Table 94: Subjects with Serious Infectious Adverse Events
Open-Label Induction and Double-Blind Treatment (Safety Set) – Study M02-404**

Sex	Age	Adverse Event MedDRA Preferred Term	Rx day of onset	Severity
Open-Label Induction Phase				
Adalimumab 80/40 mg				
Male	27	Peritoneal abscess	38	Severe
Male	36	Anal abscess	57	Moderate
Female	38	Abdominal abscess	23	Severe
Female	21	Abscess intestinal	70	Severe
Female	30	Abdominal abscess	55	Severe
		Wound infection	55	Severe
Female	22	Sepsis	53	Severe
Male	31	Abdominal abscess	6	Severe
Male	23	Wound infection	41	Severe
Male	21	Clostridial infection	44	Severe
Female	56	Psoas abscess	29	Moderate
Double-Blind Treatment Phase				
Placebo				
Female	28	Varicella	39	Severe
Male	49	Anal abscess	74	Severe
Male	21	Perianal abscess	62	Moderate
Female	18	Bacteremia	425	Moderate
Male	43	Psoas abscess	147	Severe
Female	26	Abdominal abscess	92	Mild
Female	26	Abdominal abscess	80	Severe
Male	18	Bacteremia	97	Severe
Female	20	Appendicitis	72	Moderate
Male	75	Gastroenteritis	229	Moderate
Adalimumab 40 mg eow				
Female	26	Perianal abscess	65	Severe
Male	55	Device related infection	168	Severe
Female	35	Gastroenteritis	30	Severe
Female	41	Gastroenteritis viral	134	Severe
Female	53	Abdominal abscess	183	Moderate
Male	22	Scrotal abscess	239	Severe
Male	29	Gastroenteritis viral	52	Severe
Adalimumab 40 mg ew				
Male	37	Perianal abscess	204	Severe
Male	50	Pneumonia	99	Severe
Male	33	Abdominal abscess	92	Severe
Male	51	Sinusitis	137	Moderate
Male	46	Abscess	154	Moderate
Female	38	Abdominal abscess	207	Moderate
Female	20	Perianal abscess	69	Severe

Subjects with serious infectious AE's in the open-label treatment period after randomization into double-blind treatment in Study M02-404 are presented in **Table 95**. There was one case of bacteremia in a subject who was randomized to placebo treatment and one case of tuberculosis in a subject randomized to adalimumab 40 mg eow therapy. One case of tuberculosis and

pneumonia, each, was reported in subjects who dose-escalated to adalimumab 40 mg ew open-label therapy after not responding to randomized double-blind treatment.

Table 95: Subjects with Serious Infectious Adverse Events Open-Label (Safety Set After Randomization) – Study M02-404

DB Tx	Sex	Age	Adverse Event MedDRA Preferred Term	Rx day of onset	Severity
Adalimumab 40 mg eow OL					
Placebo	Female	18	Gastroenteritis	351	Severe
			Clostridium colitis	384	Severe
			Gastroenteritis	384	Severe
			Bacteremia	425	Moderate
Placebo	Female	49	Herpes zoster	287	Moderate
40 mg eow	Male	25	Tuberculosis	267	Moderate
40 mg ew	Male	39	Lower respiratory tract infection	185	Mild
			Lower respiratory tract infection	190	Severe
40 mg ew	Female	20	Otitis media	372	Severe
			Clostridial infection	392	Severe
40 mg ew	Female	44	Pyelonephritis	202	Severe
40 mg eow	Female	35	Clostridial infection	307	Severe
Placebo	Male	21	Abdominal abscess	85	Moderate
Adalimumab 40 mg ew OL					
40 mg eow	Female	19	Abdominal abscess	243	Severe
40 mg ew	Female	30	Tuberculosis	429	Moderate
Placebo	Male	29	Postoperative infection	240	Severe
40 mg ew	Male	50	Pneumonia	374	Severe
40 mg ew	Male	33	Abdominal abscess	114	Severe

Tuberculosis and Opportunistic Infections:

Studies M02-403 and M04-691:

No cases of tuberculosis or opportunistic infections were reported in either of these four-week induction studies.

Studies M02-433 and M02-404:

In the long-term maintenance (follow-on) Study M02-433, no cases of tuberculosis or opportunistic infections were reported. In Study M02-404, two cases of tuberculosis were reported in subjects receiving adalimumab maintenance therapy out to Week 56.

The risk of developing frequently disseminated or extrapulmonary tuberculosis, invasive fungal infections, and other opportunistic infections in patients receiving HUMIRA is already addressed in the current full prescribing information for HUMIRA as a Black Box WARNING. The two cases of tuberculosis from Study M02-404 do not warrant additional new language to be added or changed in the WARNING.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The numbers of subjects who terminated from each of the studies in the Crohn's disease development program are displayed in this following section.

7.1.3.2 Adverse events associated with dropouts

Termination from Study

Study M02-403:

Overall in Study M02-403, 284 out of 299 enrolled subjects (95%) completed the four-week induction study. More subjects who were randomized to placebo treatment (8%) in Study M02-403 terminated the study prematurely compared to subjects who received any adalimumab induction treatment (4%) (**Table 96**). The primary reason for discontinuation from Study M02-403 was due to an AE in the placebo-treated group and in the "all adalimumab" treated group. There were no deaths and no subjects lost to follow-up in Study M02-403. There were few study terminations due to protocol violations, withdrawal of consent, or lack of efficacy.

Table 96: Disposition of Subjects by Randomized Treatment Group – Study M02-403

	Full Analysis Set (N=299)				
Result	Adalimumab 40 mg/20 mg (N=74) n (%)	Adalimumab 80 mg/40 mg (N=75) n (%)	Adalimumab 160 mg/80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Completed Screening visit	74 (100)	75 (100)	76 (100)	225 (100)	74 (100)
Completed Baseline (Week 0) visit	74 (100)	75 (100)	76 (100)	225 (100)	74 (100)
Completed Week 1 visit	73 (99)	73 (97)	76 (100)	222 (99)	72 (97)
Completed Week 2 visit	73 (99)	73 (97)	76 (100)	222 (99)	69 (93)
Completed Week 4 visit	72 (97)	70 (93)	74 (97)	216 (96)	68 (92)
Completed Early Termination visit	2 (3)	5 (7)	2 (3)	9 (4)	6 (8)
Completed Follow-up visit	1 (1)	6 (8)	1 (1)	8 (4)	5 (7)
Primary reason for discontinuation:					
Adverse event[a]	1 (1)	1 (1)	0	2 (<1)	2 (3)
Lost to follow-up	0	0	0	0	0
Protocol violation	1 (1)	3 (4)	0	4 (2)	1 (1)
Death	0	0	0	0	0
Withdrawal of consent	0	0	1 (1)	1 (<1)	1 (1)
Lack of efficacy	0	1 (1)	1 (1)	2 (<1)	1 (1)
Administrative reasons	0	0	0	0	0
Other[b]	0	0	0	0	1 (1)

In this study, a total of four subjects out of 299 (1%) had treatment-emergent AE's that resulted in study withdrawal (**Table 97**). Of the four subjects who withdrew from the study due to an AE, most did so due to aggravated Crohn's disease in the gastrointestinal disorders SOC. One subject who received placebo withdrew from the study due to skin and subcutaneous tissue disorders and musculoskeletal and connective tissue disorders reasons (arthralgia). No subject from the adalimumab 160 mg/80 mg dose group withdrew from the study due to an AE.

Table 97: Treatment-Emergent Adverse Events Resulting in Study Withdrawal Study M02-403

Subject Number	Adalimumab 40 mg/20 mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160 mg/80 mg (N=76)	Placebo (N=74)
01001				Gastrointestinal disorders Crohn's disease aggravated
02704				Skin and subcutaneous tissue disorders Skin lesion NOS And Musculoskeletal and connective tissue disorders Arthralgia
03401	Gastrointestinal disorders Crohn's disease			
04301		Gastrointestinal disorders Crohn's disease aggravated		

Study M04-691:

In Study M04-691 where active CD subjects who previously received infliximab therapy and lost response to or were intolerant to infliximab therapy, the number of subjects who discontinued this four-week induction study are presented in **Table 98.** Of those subjects who were randomized to receive adalimumab 160 mg and 80 mg and Weeks 0 and 2, respectively, 3% discontinued the study compared to 6% of subjects randomized to the placebo treatment group. Two of 159 subjects (1%) who received adalimumab 160 mg/80 mg treatment discontinued the study due to an AE compared to four of 166 subjects (2%) who discontinued the study due to an AE, after receiving placebo treatment.

Table 98: Disposition of Subjects - Study M04-691

	Treatment Group n (%)	
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)
Completed study	156 (94)	155 (98)
Number of discontinued subjects	10 (6)	4 (3)
Primary reason for discontinuation		
Adverse event	4 (2)	2 (1)
Withdrew consent	1 (<1)	1 (<1)
Protocol violation	5 (3)	1 (<1)

The two subjects from the adalimumab 160 mg/80 mg treatment group who discontinued Study M04-691 did so due to dehydration and a maculo-papular rash, each (**Table 99**). Of those subjects who received placebo treatment, two discontinued the study due to aggravated Crohn's disease and either an abdominal abscess or a pelvic abscess. The discontinuations due to AE's from Study 04-691 do not reveal any new safety concern for subjects receiving adalimumab 160 mg/80 mg induction therapy compared to receiving placebo therapy in the background of prior treatment with infliximab therapy.

Table 99: Treatment-Emergent Adverse Events Resulting in Study Withdrawal Study M04-691

System Organ Class MedDRA Preferred Term	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)
Total Subjects (Any Adverse Event)	4 (2)	2 (1)
Gastrointestinal disorders		
Crohn's disease	2 (1)	0
Infections and infestations		
Abdominal abscess	1 (<1)	0
Pelvic abscess	1 (<1)	0
Metabolism and nutrition disorders		
Dehydration	0	1 (<1)
Skin and subcutaneous tissue disorders		
Rash maculo-papular	0	1 (<1)

Study M02-433:

In Study M02-433 which was a follow-on 56-week maintenance study of subjects who completed the four-week course of therapy from lead-in Study M02-403, more subjects randomized to placebo maintenance therapy discontinued the study (5 out of 18 subjects, 28%) compared to subjects randomized to one of two possible adalimumab maintenance treatment groups (5 of 37 subjects, 14%) (**Table 100**). The primary reasons for study discontinuation were

AE's and withdrawal of consent. No deaths were reported and few subjects discontinued the study due to being lost to follow-up, a protocol violation, or administrative reasons.

Table 100: Subject Final Status Up to Week 56 – Study M02-433

	Randomized Analysis Set				Open-label Analysis Set		
	Placebo (N=18)	Adalimumab 40 mg eow (N=19)	Adalimumab 40 mg ew (N=18)	Total (N=55)	Adalimumab 40 mg eow or ew (N=204)	Discontinued at or before Week 4 (N=17)	All Subjects (N=276)
Completed Week 56 Visit (total)	13 (72)	16 (84)	16 (89)	45(82)	131 (64)	0	176 (64)
Completed Week 56 (double-blind)	6 (33)	11 (58)	15 (83)	32(58)	N/A	N/A	N/A
Early Discontinuation	5 (28)	3 (16)	2 (11)	10(18)	73 (36)	17 (100)	100 (36)
Primary reason for discontinuation:							
AE	1 (6)	1 (5)	1 (6)	3 (6)	23 (11)	5 (29)	31 (11)
Withdrawal of consent	3 (17)	1 (5)	1 (6)	5 (9)	14 (7)	1 (6)	20 (7)
Lost to follow-up	0	1 (5)	0	1 (2)	5 (3)	0	6 (2)
Protocol violation	0	0	0	0	2 (1)	1 (6)	3 (1)
Death	0	0	0	0	0	0	0
Lack of efficacy	1 (6)	0	0	1 (2)	18 (9)	9 (53)	28 (10)
Administrative reasons	0	0	0	0	0	1 (6)	1 (<1)
Other	0	0	0	0	11 (5)	0	11 (4)

Table 101 lists the number of adalimumab-treated subjects who withdrew from Study M02-433 due to at least a possibly related treatment-emergent AE. For the most part, the AE's listed are non-specific to an SOC or MedDRA Preferred Term and occur in similar proportions among the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew maintenance groups for the randomized analysis set. Of note are one reported case each of nocardiosis infection, systemic lupus erythematosus, lobar pneumonia NOS, and sepsis NOS among subjects who received adalimumab open-label therapy for nonresponse.

Table 101: Listing of Adalimumab-Treated Subjects with at Least Possibly Related Treatment-Emergent Adverse Events Resulting in Study Withdrawal (Safety Set, Up to Week 56) – Study M02-433

Subject Number	Treatment	Age	Sex	MedDRA PT	Days from First Study Drug Dose	Duration of AE (Days)	Relationship to Study Drug (Investigator)
059-03	Placebo	31	F	Adverse drug reaction NOS	99	-	Probably
054-02	Eow	42	F	Sinusitis NOS	2	-	Possibly
014-01	Ew	43	M	Folliculitis	331	42	Possibly
006-01	OL	39	F	Headache NOS	8	22	Possibly
015-03	OL	42	M	Nocardiosis	345	-	Probably
015-06	OL	64	F	Dermatitis NOS	105	53	Probably
015-09	OL	71	F	Rash erythematous	228	68	Probably
				Rash pruritic	228	68	Probably
023-01	OL	36	F	Systemic lupus erythematosus	169	169	Possibly
023-09	OL	33	F	Arrhythmia NOS	5	-	Possibly
034-09	OL	34	F	Rash NOS	26	-	Possibly
040-01	OL	44	F	Crohn's disease aggravated	35	36	Possibly
052-05	OL	25	F	Esophageal ulcer	19	29	Possibly
053-13	OL	47	F	Lobar pneumonia NOS	38	49	Probably
				Sepsis NOS	37	50	Probably
058-01	OL	40	M	Arthritis NOS	132	2	Possibly
069-01	OL	63	F	Heart rate irregular	190	2	Possibly

Study M02-404:

An overview of subjects with treatment-emergent AE's during Study M02-404 is presented in **Table 102**. In this study, 854 active CD subjects were given open-label adalimumab 80 mg at Week 0 and 40 mg at Week 2. At Week 4, subjects with a CR-70 response (CDAI reduction of ≥ 70 points) were randomized to either placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew maintenance therapy. Out of 854 enrolled subjects, 54 (6%) had an AE that led to study discontinuation. A total of 60% of subjects reported an AE, 5% reported an SAE, and 15% reported an infectious AE during open-label induction therapy. No malignancies were reported and there was one AE that resulted in a death.

Table 102: Overview of Subjects with Treatment-Emergent Adverse Events Open-Label Induction (Safety Set) – Study M02-404

	Adalimumab 80 mg/40 mg
	N=854
	n (%)
Any adverse event	508 (60)
Any serious adverse event	45 (5)
Any severe adverse event	69 (8)
Any adverse event leading to study discontinuation[a]	54 (6)
Any adverse event with probable or possible relation to study drug	259 (30)
Any infectious adverse event	130 (15)
Any infectious serious adverse event	10 (1)
Any malignant neoplasm adverse event	0
Any adverse event leading to death	1 (<1)

[a] Denotes subjects who discontinued from the study during OL induction at least in part due to an AE.

An overview of subjects with treatment-emergent AE's in the double-blind treatment period of Study M02-404 is shown in **Table 103**. In this double-blind treatment period, subjects were randomized to placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew from Week 4 to Week 56 of Study M02-404. The proportions of subjects who reported any adverse event were comparable among the three possible maintenance therapies. Fewer adalimumab-treated subjects in the DB period (9% and 8%) reported an SAE compared to those treated with placebo maintenance (15%). Fewer adalimumab-treated subjects (7% and 5%) discontinued the study due to an AE compared to the placebo-treated maintenance group (13%). Higher proportions of adalimumab-treated subjects reported an infectious AE (46% and 44%) compared to those in the placebo-treated group (37%), but the proportion of infectious SAE's per maintenance group was identical (3%). No subjects randomized to either adalimumab-treatment group experienced a malignancy or death in the 56-week study.

Table 103: Overview of Subjects with Treatment-Emergent AE's Double-Blind Treatment (ITT Dataset) – Study M02-404

	Placebo	Adalimumab 40 mg eow	Adalimumab 40 mg ew
	N=261	N=260	N=257
	n (%)		
Any adverse event	221(85)	231 (89)	220 (86)
Any serious adverse event	40 (15)	24 (9)	21 (8)
Any severe adverse event	58 (22)	38 (15)	39 (15)
Any adverse event leading to study discontinuation[a]	35 (13)	18 (7)	12 (5)
Any adverse event with probable or possible relation to study drug	86 (33)	99 (38)	97 (38)
Any infectious adverse event	96 (37)	120 (46)	114 (44)
Any infectious serious adverse event	9 (3)	7 (3)	7 (3)
Any malignant neoplasm adverse event	1 (<1)	0	0
Any adverse event leading to death	0	0	0

[a] Denotes subjects who discontinued from the study during DB treatment at least in part due to an AE.

Those subjects who prematurely discontinued the study drug due to a treatment-emergent AE during the open-label induction period in Study M02-404 are listed in **Table 104**. During the four-week induction period, in which all 854 subjects received open-label adalimumab 80 mg at Week 0 and 40 mg at Week 2, 24 subjects reported 27 AE's that lead to study drug discontinuation. Of the 27 AE's reported, 10 (37%) were related to the gastrointestinal disorders SOC, consistent with the subjects' underlying inflammatory bowel disease. Other reported adverse events that resulted in study drug discontinuation represented various SOC's and did not point to any particular new safety concern.

Table 104: Subjects Who Prematurely Discontinued Study Drug Due to Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug Open-Label Induction (Safety Set)

Open-Label Induction Period – Adalimumab 80/40 mg				
Sex	Age	MedDRA Preferred Term	Rx day of Onset	Severity
Male	38	Crohn's disease	7	Severe
Female	52	Anxiety	29	Moderate
Female	23	Injection site reaction	12	Severe
		Injection site rash	12	Moderate
		Rash	12	Moderate
		Rash maculopapular	12	Moderate
Male	48	Serum sickness	20	Severe
Female	41	Crohn's disease	28	Severe
Female	22	Crohn's disease	26	Severe
Female	22	Injection site pain	16	Severe
Female	28	Diarrhea	22	Moderate
Female	34	Injection site irritation	1	Mild
Male	27	Peritoneal abscess	19	Moderate
Male	35	Diarrhea	1	Mild
Female	46	Serum sickness	19	Moderate
Female	20	Arthralgia	16	Severe
Male	19	Herpes zoster	10	Moderate
Female	38	Rash generalized	10	Moderate
Male	27	Crohn's disease	20	Severe
Male	42	Intestinal obstruction	3	Mild
Female	28	Crohn's disease	16	Severe
Female	45	Fatigue	20	Moderate
Female	42	Menorrhagia	18	Moderate
Male	42	Hypersensitivity	20	Moderate
Female	21	Crohn's disease	6	Severe
Female	49	Rash generalized	7	Mild
Female	20	Injection site reaction	1	Severe

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse event data in the development program

For both of the four-week induction studies, Studies M02-403 and M04-691, subjects had adverse events elicited at the Baseline visit (Week 0), and at Weeks 1, 2, and 4, or at early termination. AE information was also obtained at a 70-day follow-up for all subjects in these two studies.

In the long-term maintenance studies, Studies M02-433 and M02-404, subjects had AE's elicited at the Baseline Week 0 visit, and then every two weeks until Week 4. After the Week 4 visit, adverse event information was collected every four weeks until Week 32. AE's were then elicited every eight weeks from Weeks 32 to 56 or early termination. A 70-day follow-up phone call was conducted after the Week 56 visit, and subjects had the opportunity to have unscheduled adverse event assessments as necessary. In general, blood samples for clinical chemistry and hematology tests, urinalyses, and other laboratory testing procedures were conducted on scheduled visit days.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were deemed appropriate. Treatment-emergent adverse events were reported using the WHOART system-organ class/preferred term classification. Individual AE's for all studies were summarized by system-organ, preferred term, and relationship to study drug as determined by the Investigators.

7.1.5.3 Incidence of common adverse events

The incidence and profile of common adverse events in the four studies presented in this review were comparable to those seen in other TNF-blocker trials for inflammatory bowel disease. Continuing adalimumab for a total of 56 weeks did not significantly increase the number of subjects who reported at least one or more AE's in the long-term maintenance studies (M02-433 and M02-404).

7.1.5.4 Common adverse event tables

Study M04-403

The most frequently reported treatment-emergent adverse events occurring in $\geq$ 5% of any treatment group in Study M02-403 is displayed in **Table 105.** Of the four system organ classes represented (gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and nervous system disorders), the greatest number of AE's arises from the general disorders and administration site conditions, where 13% of all adalimumab-treated subjects reported injection site burning compared to 10% of placebo-treated subjects. Of those subjects who reported an AE in the gastrointestinal disorders SOC, the proportions of

placebo-treated subjects with AE's were comparable to those treated with any adalimumab dose regimen. Nausea was reported in 8% of all adalimumab-treated subjects whereas only 1% of placebo-treated subjects reported this preferred term. Nasopharyngitis and headache NOS accounted for the most commonly reported preferred terms under the SOC's of infections and infestations and nervous system disorders, respectively. As these preferred terms are already reflected in the current package insert for HUMIRA, no changes or additions are required at this time.

Table 105: Subjects with Treatment-Emergent Adverse Events with ≥ 5% Occurrence Study M02-403

MedDRA System Organ Class Preferred Term[a]	Adalimumab 40 mg/ 20 mg (N=74) n (%)	Adalimumab 80 mg/ 40 mg (N=75) n (%)	Adalimumab 160 mg/ 80 mg (N=76) n (%)	All Adalimumab (N=225) n (%)	Placebo (N=74) n (%)
Gastrointestinal disorders					
Nausea	5 (7)	5 (7)	7 (9)	17 (8)	1 (1)
Crohn's disease	4 (5)	2 (3)	3 (4)	9 (4)	2 (3)
Flatulence	2 (3)	2 (3)	4 (5)	8 (4)	3 (4)
Crohn's disease aggravated	2 (3)	3 (4)	2 (3)	7 (3)	4 (5)
Abdominal tenderness	1 (1)	0	4 (5)	5 (2)	1 (1)
General disorders and administration site conditions					
Injection site burning	11 (15)	8 (11)	11 (15)	30 (13)	7 (10)
Injection site reaction NOS	3 (4)	5 (7)	6 (8)	14 (6)	0
Injection site pain	4 (5)	4 (5)	5 (7)	13 (6)	5 (7)
Infections and infestations					
Nasopharyngitis	2 (3)	4 (5)	4 (5)	10 (4)	1 (1)
Nervous system disorders					
Headache NOS	3 (4)	4 (5)	7 (9)	14 (6)	4 (5)

a. The same MedDRA term may appear in more than 1 system organ class. Subjects with multiple occurrences of a preferred term were counted once within the preferred term. Subjects with multiple preferred terms were counted once within the system organ class.

Study M04-691

Adverse events that occurred in ≥ 5% of either the placebo or adalimumab 160 mg/80 mg treatment groups in Study M04-691 are shown in **Table 106**. Not surprisingly, in this study of moderately to severely active CD subjects who lost response to or were intolerant to previous infliximab therapy, abdominal pain was the most commonly reported preferred term, occurring in 7% of placebo subjects and 6% of adalimumab subjects. The proportions of subjects who reported the preferred terms (PT) of arthralgia, headache, injection site irritation, or fatigue were comparable between the two treatment arms. The PT of Crohn's disease was reported in 9% of placebo-treated subjects compared to 1% of adalimumab-treated subjects. As in Study M02-403, these AE's are already discussed in the current package insert and patient information section of the HUMIRA label and no modifications are necessary.

Table 106: Subjects with Treatment-Emergent Adverse Events with ≥ 5% Occurrence in Either Treatment Group* - Study M04-691

MedDRA Preferred Term	Placebo (N=166) n (%)	Adalimumab 160/80 mg (N=159) n (%)
Abdominal pain	12 (7)	9 (6)
Arthralgia	3 (2)	9 (6)
Headache	12 (7)	8 (5)
Injection site irritation	7 (4)	8 (5)
Fatigue	9 (5)	7 (4)
Crohn's disease	15 (9)	2 (1)

* Events are displayed in decreasing order of frequency in the adalimumab 160/80 mg group.

Study M02-433

Treatment-emergent adverse events that occurred in ≥ 5% of subjects in the randomized analysis set in Study M02-433 are presented in **Table 107**. The randomized analysis set in Study M02-433 consisted of a subset of subjects from lead-in Study M02-403 who attained clinical remission after a two-dose induction of one of three possible adalimumab regimens or placebo. As a result, the total number of subjects (N=55) in the randomized analysis set is a small number compared to those who actually enrolled in the lead-in study who subsequently followed on to Study M02-433. All 18 subjects who were treated with placebo reported having an AE compared to 79% and 78% of those subjects who received adalimumab 40 mg eow and 40 mg ew, respectively. The most commonly reported AE's in the whole randomized analysis set were nasopharyngitis, aggravated Crohn's disease, and sinusitis NOS, occurring in 26%, 20%, and 11% of the randomized set. These AE's are already reflected in the current HUMIRA package insert and no new modifications are needed in the safety information section. Other AE's reported up to Week 56 involve the gastrointestinal diseases and infections and infestations SOC's (mainly upper respiratory infections) and have been discussed previously with Studies M02-403 and M04-691.

Table 107: Subjects with Treatment-Emergent Adverse Events with ≥ 5% Occurrence by MedDRA Preferred Term (Randomized Analysis Set), Up to Week 56 – Study M02-433.

MedDRA Preferred Term[a]	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18	Total N=55
	n (%)			
Number of Subjects with AE	18 (100)	15 (79)	14 (78)	47 (86)
Nasopharyngitis	7 (39)	5 (26)	2 (11)	14 (26)
Crohn's disease aggravated	5 (28)	4 (21)	2 (11)	11 (20)
Sinusitis NOS	1 (6)	4 (21)	1 (6)	6 (11)
Constipation	3 (17)	1 (5)	1 (6)	5 (9)
Influenza	1 (6)	3 (16)	1 (6)	5 (9)
Abdominal pain NOS	3 (17)	1 (5)	0	4 (7)
Abdominal tenderness	2 (11)	2 (11)	0	4 (7)
Viral infection NOS	0	4 (21)	0	4 (7)
Dizziness (excluding vertigo)	1 (6)	1 (5)	2 (11)	4 (7)
Arthralgia	1 (6)	2 (11)	1 (6)	4 (7)
Upper respiratory tract infection NOS	1 (6)	1 (5)	2 (11)	4 (7)
Nausea	1 (6)	2 (11)	1 (6)	4 (7)
Pharyngolaryngeal pain	2 (11)	2 (11)	0	4 (7)
Fatigue	2 (11)	1 (5)	1 (6)	4 (7)
Dyspepsia	2 (11)	0	1 (6)	3 (6)
Vomiting NOS	1 (6)	1 (5)	1 (6)	3 (6)
Pharyngitis NOS	2 (11)	1 (5)	0	3 (6)
Urinary tract infection NOS	2 (11)	0	1 (6)	3 (6)
Abrasion NOS	2 (11)	0	1 (6)	3 (6)
Antinuclear factor positive	2 (11)	1 (5)	0	3 (6)
Back pain	2 (11)	0	1 (6)	3 (6)
Epistaxis	0	2 (11)	1 (6)	3 (6)
Rash NOS	0	2 (11)	1 (6)	3 (6)

a. Subjects with multiple occurrences of a PT were counted once within the PT.

Study M02-404

An overview of the treatment-emergent adverse events reported by subjects in the open-label induction period of Study M02-404 is presented in **Table 108.** Of the 854 subjects induced with adalimumab 80 mg/40 mg at Weeks 0 and 2, respectively, 60% reported an AE during the 4-week open-label induction period, 6% reported an AE that lead to study discontinuation, and 15% reported an infectious AE. No malignancies were reported, and there was one AE that resulted in a death.

Table 108: Overview of Subjects with Treatment-Emergent Adverse Events Open-Label Induction (Safety Set) – Study M02-404

	Adalimumab 80/40 mg N=854 n (%)
Any adverse event (AE)	508 (60)
Any serious adverse event (SAE)	45 (5)
Any severe adverse event	69 (8)
Any adverse event leading to study discontinuation[a]	54 (6)
Any AE with probable or possible relation to study drug	259 (30)
Any infectious AE	130 (15)
Any infectious SAE	10 (1)
Any malignant neoplasm AE	0
Any AE leading to death	1 (<1)

[a] Denotes subjects who discontinued from the study during OL induction at least in part due to an AE

The most frequently reported AE's in the open-label induction safety set of subjects in Study M02-404 are displayed in **Table 109.** Headache and nausea occurred in 6% and 5% of subjects, respectively. These AE's are currently reflected in the Adverse Reactions section under the rheumatoid arthritis RA) studies section in the current HUMIRA package insert.

Table 109: Frequently Reported (≥ 5% of All Subjects) Treatment-Emergent AE's by MedDRA Preferred Term – Open-Label Induction (Safety Set) – Study M02-404

MedDRA Preferred Term	Adalimumab 80/40 mg N=854 n (%)
Headache	51 (6)
Nausea	45 (5)

Possibly or probably-related treatment-emergent AE's reported by at least 2% of all subjects in Study M02-404 are presented in **Table 110.** The four commonly reported AE's are nausea, injection site irritation, injection site pain, and headache. Again, as in **Table 109,** these AE's are already discussed in the adverse reactions sections for the RA clinical studies section.

Table 110: Commonly Reported (≥ 2% of All Subjects) Treatment-Emergent AE's Possibly or Probably Related to Study Drug, by MedDRA Preferred Term Open-Label Induction (Safety Set) – Study M02-404

	Adalimumab 80/40 mg N=854 n (%)	
MedDRA Preferred Term	Possibly Related	Probably Related
Nausea	19 (2)	6 (<1)
Injection site irritation	1 (<1)	38 (4)
Injection site pain	1 (<1)	38 (4)
Headache	22 (3)	5 (<1)

Reviewing the common adverse events tables overall, there were no new safety signals or increased rates of AE's that arose out of comparisons between adalimumab-treated subjects vs. the placebo group that would necessitate in a change in the current package insert.

7.1.5.5 Identifying common and drug-related adverse events

No new adverse events by system organ class or by preferred term were identified that would necessitate a change in the adalimumab package insert.

7.1.6 Less Common Adverse Events

Less common but clinically significant adverse events are discussed in section 7.1.2 of this review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

General laboratory testing was performed according to the schedule outlined in section 7.1.5.1.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Both Studies M02-403 and M04-691 were randomized, blinded, placebo-controlled trials that allowed for the direct comparison of laboratory values for subjects with active CD who received adalimumab vs. placebo treatment.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.5 Special assessments

No special laboratory assessments were performed in the Abbott Crohn's disease development program.

7.1.8 Vital Signs

Vital signs were collected according to the schedule outlined in section 7.1.5.1. No pattern of abnormal vital signs was observed.

7.1.8.4 Additional analyses and explorations

N/A. Adalimumab is an approved product and its safety has previously been well characterized.

7.1.9 Electrocardiograms (ECG's)

ECG's were performed at the Screening visit for all subjects. ECG's were not repeated at Follow-up unless a clinically significant abnormality was noted on the initial ECG. Adalimumab is an approved product with no known effects on ECG findings.

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenomena and/or abuse potential issues identified with this product to date.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies with adalimumab have been conducted in pregnant women. Prescribers and patients are encouraged to call a pregnancy registry established by Abbott Labs if pregnant women receive adalimumab therapy.

7.1.15 Assessment of Effect on Growth

No data are available to adequately assess the product's effect on growth.

7.1.16 Overdose Experience

The maximum tolerated dose of HUMIRA® has not been established in humans although the OVERDOSAGE section of the HUMIRA package insert states "Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities." There are no known signs or symptoms of adverse reactions or effects resulting from overdosage.

7.1.17 Postmarketing Experience

There is no new information from spontaneous AE reports that would require modification of the **Adverse Reaction Information from Spontaneous Reports** section.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

N/A. The Sponsor provided primary source data with data collected from studies under the Sponsor's IND. No secondary data sources were used.

7.2.3 Adequacy of Overall Clinical Experience

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing provided to subjects was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No new potential AE's were identified and there are no new recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on extensive prior experience, the use of adalimumab is associated with a number of adverse events that appear drug related which are fully described in the current package insert. In this submission, there were no specific adverse events identified that are not already appropriately reflected in the package insert.

8 ADDITIONAL CLINICAL ISSUES

8.4 Pediatrics

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

Recommend approval of the efficacy supplement with revisions to the label.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management plan is required.

9.3.2 Required Phase 4 Commitments

The Applicant is currently committed to conduct a randomized, controlled clinical trial to assess the safety and efficacy in pediatric patients with moderately to severely active Crohn's disease, and also plans to conduct a five-year, 5000-patient registry.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

9.5 Comments to Applicant

There are no comments to convey to the applicant.

10 APPENDICES

Appendix 1: Study Criteria

Inclusion Criteria - Study M02-403

1. Males and females ≥ 18 and ≤ 75 years of age.

2. Female subjects who:

   - Utilized a highly-effective method of birth control throughout the study and for 70 days after study completion, or
   - Were not of childbearing potential, defined as postmenopausal at least 2 years, surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy or hysterectomy).

3. Diagnosis of Crohn's disease for > 4 months.

4. Diagnosis of Crohn's disease confirmed by endoscopy or radiologic evaluation.

5. Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 points.

6. Ability and willingness to give written informed consent and to comply with the requirements of the protocol.

7. Adequate cardiac, renal, and hepatic function, as determined by Investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results within normal limits.

Exclusion Criteria – Study M02-403

1. History of cancer or lymphoproliferative disease other than a successfully and completely treated squamous cell or basal cell carcinoma.

2. History of active tuberculosis (TB), *Listeria* or human immunodeficiency virus (HIV).

3. Ulcerative colitis.

4. Symptomatic obstructive strictures.

5. Surgical bowel resection in the past 6 months or any resection planned at any time while enrolled in the study.

6. Ostomies.

7. Extensive bowel resection (total of >100 cm) or short bowel syndrome.

8. Current receipt of total parenteral nutrition (TPN).

9. Any investigational chemical agent in the past 30 days or 5 half-lives prior to Screening, (whichever was longer).

10. Any investigational biological agent in the past 4 months or 5 half-lives prior to Screening (whichever was longer).

11. Antibiotic treatment within 3 weeks prior to Screening for all non-Crohn's related infections.

12. Pregnant or breast-feeding female subjects.

13. History of clinically significant drug or alcohol abuse in the previous year.

14. Poorly controlled medical condition, including diabetes with documented history of recurrent infections or cerebrovascular accidents (within 3 months).

15. Previous use of infliximab or any anti-TNF therapy.

16. Positive *Clostridium difficile* stool assay.

17. Demonstration of clinically significant deviations in any laboratory parameters, including the Following:
    - Electrocardiogram (ECG) with clinically significant abnormalities,
    - Hemoglobin $\leq$ 8.5 g/dL,
    - Total white blood cell (WBC) count < 3000/mm^3,
    - Platelet count < 100,000/mm^3,
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.75 x the upper limit of the reference range,
    - Total bilirubin $\geq$ 3 mg/dL,
    - Serum creatinine > 1.6 mg/dL.

18. Regarding Prior or Concurrent Therapies:

    Current treatment with Imuran (azathioprine), 6-MP or MTX, but not on stable doses of these medications for at least 12 weeks prior to Screening,

Current treatment with 5-aminosalicylic acid (5-ASA), mesalamine, sulfasalazine, or Crohn's related antibiotics, but not on stable doses of these medications for at least 4 weeks prior to Screening,

Treatment with azathioprine, 6-MP, or MTX, with discontinuation of these medications within 12 weeks of Screening,

Treatment with 5-ASA, sulfasalazine, or Crohn's related antibiotics, with discontinuation of these medications within 4 weeks of Screening,

Current treatment with prednisone > 20 mg/day (or equivalent), but not on a stable dose for 2 weeks prior to Screening,

Discontinuation of prednisone (or equivalent) within 2 weeks of Screening,

Current treatment with budesonide > 9 mg/day, but not on a stable dose for at least 2 weeks prior to Screening,

Discontinuation of budesonide within 2 weeks of Screening,

Current treatment with both budesonide and prednisone (or equivalent),

Use of enemas within 2 weeks prior to Screening,

Treatment with cyclosporine or tacrolimus within 8 weeks of Screening.

For subjects entering the study on stable doses of Imuran (azathioprine), 6-MP, MTX, prednisone (or equivalent), or budesonide, doses were to remain stable during the entire study.

Inclusion Criteria – Study M04-691

A subject was eligible for enrollment if all of the following criteria were met:

1. Subject had a diagnosis of Crohn's disease confirmed by endoscopy or radiologic evaluation.

2. Subject had a CDAI score of ≥ 220 and ≤ 450.

3. Males and females > 18 and < 75 years of age at Screening.

4. If female, subject was either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and practiced 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; or had been using oral or parenteral contraceptives for 3 months prior to study drug administration; or a vasectomized partner.

5. If female, subject was not breast-feeding throughout the study and for 150 days after the last dose.

6. Subject was able and willing to give written informed consent and comply with the requirements of the study protocol.

7. Subject had adequate cardiac, renal, and hepatic function as determined by principal Investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results that were within normal limits.

8. Subjects must have previously been administered infliximab and discontinued use due to a loss of response or intolerance to infliximab therapy.

Exclusion Criteria – Study M04-691

Subjects were to be excluded from the study for any of the following reasons:

1. Subject had a history of cancer or lymphoproliferative disease other than a successfully and completed treated cutaneous squamous cell or basal cell carcinoma or carcinoma-in-situ of the cervix.

2. Subject had a history of listeria, human immunodeficiency virus, central nervous system demyelinating disease, or untreated tuberculosis (TB).

3. Subject had ulcerative colitis.

4. Subject had symptomatic known obstructive strictures.

5. Subject had surgical bowel resections within the past 6 months or any resection was planned at any timepoint while enrolled in the study.

6. Subject had an ostomy or ileoanal pouch.

7. Subject had short bowel syndrome as determined by the Investigator.

8. Subject was currently receiving total parenteral nutrition.

9. Female subjects who were pregnant or breast-feeding.

10. Subject had received any investigational chemical agent in the past 30 days or 5 half-lives prior to Screening (whichever was longer).

11. Subject had received any investigational biological agent in the past 3 months or 5 half-lives prior to Screening (whichever was longer).

12. Subject had received systemic antibiotic, antiviral, or antifungal treatment(s) within 3 weeks prior to Screening for any non-Crohn's-related infections.

13. Subject had a history of clinically significant drug or alcohol abuse in the last year.

14. Subject with a poorly controlled medical condition such as: uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents, or any other condition which, in the opinion of the Investigator or the Sponsor, would put the subject at risk by participation in the protocol.

15. Subject had positive *C. difficile* stool assay.

16. Subject had previously used infliximab and had never clinically responded as determined by the Investigator unless primary non-response was due to a treatment limiting reaction to infliximab.

17. Subject had previously used infliximab within 8 weeks of Screening.

18. Subject had previous treatment with adalimumab or previous participation in an adalimumab clinical study.

19. Subject had Screening laboratory and other analyses showing any of the following abnormal results:

- Electrocardiogram (ECG) with clinically significant abnormalities;
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.75 x the upper limit of the reference range;
- Total bilirubin ≥ 3 mg/dL;
- Serum creatinine > 1.6 mg/dL.

20. Subject was on Imuran® (azathioprine), 6-MP, or MTX, and had not been on stable doses of these medications for at least 4 weeks prior to Screening. For subjects on those medications, doses were to remain stable during the entire course of the study. In addition, subjects taking azathioprine, 6-MP, or MTX should have been on these medications for at least 12 weeks prior to Screening. Moreover, subjects who had discontinued azathioprine, 6-MP, or MTX within 12 weeks of Screening were excluded.

21. Subject was on 5-aminosalicylic acid (5-ASA), mesalamine, sulfasalazine, or Crohn's-related antibiotics and had not been on stable doses of these medications for at least 4 weeks prior to Screening. In addition, subjects who had discontinued 5-ASA, sulfasalazine or Crohn's related antibiotic treatment within 4 weeks of Screening were excluded.

22. Subject was on prednisone > 40 mg/day (or equivalent) and subjects who were not on stable doses for 2 weeks prior to entry into study. In addition, subjects who discontinued prednisone (or equivalent) within 2 weeks of Screening were excluded.

23. Subject was on budesonide > 9 mg/day and subjects who were not on stable doses of budesonide for at least 2 weeks prior to Screening. In addition, subjects who discontinued budesonide within 2 weeks of Screening were excluded.

24. Subject was currently taking both budesonide and prednisone (or equivalent).

25. Subject had undergone therapeutic enemas within 2 weeks prior to Screening.

26. Subject had been on cyclosporine (intravenous, oral), tacrolimus (any form), or mycophenolate mofetil within 8 weeks of Screening.

27. Subject had known hypersensitivity to the excipients of adalimumab as stated in the label.

28. Subject was not in compliance with concomitant therapy.

29. Subject with any prior exposure to Tysabri® (natalizumab).

Inclusion Criteria – Study M02-433

1. Subjects were required to have successfully enrolled in and completed the lead-in study, Study M02-403.

2. Female subjects must have:

    - Continued to utilize a highly-effective method of birth control throughout the study and for 150 days after the last dose of study drug,
    - Not been of childbearing potential, defined as postmenopausal at least 2 years, surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), and
    - Practiced an acceptable form of birth control, which could include hormonal contraceptives (i.e., oral, skin patch, injection, or implant), contraceptive foam with barrier, intra-uterine contraceptive device, condom, or diaphragm with spermicidal cream or jelly.

3. Subjects must have been able and willing to give written informed consent and to comply with the requirements of the protocol.

4. Subjects must have had adequate cardiac, renal, and hepatic function, as determined by the Investigator and demonstrated by Screening laboratory evaluations, questionnaires, and physical examination results within normal limits.

Exclusion Criteria – Study M02-433

A subject was excluded from Study M02-433 if he/she was excluded from Study M02-403, or did not complete Study M02-403.

Inclusion Criteria – Study M02-404

A subject was eligible for enrollment if all of the following criteria were met:

1. Subject had a diagnosis of Crohn's disease for > 4 months.

2. Subject had a diagnosis of Crohn's disease confirmed by endoscopy or radiologic evaluation.

3. Subject had a CDAI score of $\geq$ 220 and $\leq$ 450.

4. Males and females between 18 and 75 years of age, inclusive.

5. If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and practiced 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, or had been using oral or parenteral contraceptives for $\geq$ 3 months prior to study drug administration.

6. If female, subject was not breast-feeding throughout the study and for 150 days after the last dose.

7. Subject or his/her legal representative had voluntarily signed and dated an informed consent approved by and compliant with the requirements of this study protocol that had been approved by an IRB or IEC.

8. Subject must have been able to self-inject study medication or had a designee or healthcare professional who could inject the study medication.

9. Subject was included if he/she used infliximab or any anti-TNF agent and had a) responded and then stopped the agent, b) responded and lost their response, c) responded and became intolerant, or d) did not tolerate the anti-TNF agent.

Exclusion Criteria – Study M02-404

Subjects were to be excluded from the study for any of the following reasons:

1. Subject had a history of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma-in-situ of the cervix.

2. Subject had a history of listeria, human immunodeficiency virus, central nervous system demyelinating disease, or untreated tuberculosis (TB).

3. Subject had ulcerative colitis.

4. Subject had symptomatic known obstructive strictures.

5. Subject had surgical bowel resections within the past 6 months or any resection was planned at any timepoint while enrolled in the study.

6. Subject had an ostomy.

7. Subject had received extensive small bowel resection or had short bowel syndrome.

8. Subject was currently receiving total parenteral nutrition.

9. Female subject who was pregnant or breast-feeding.

10. Subject had received any investigational chemical agent in the past 30 days or 5 half-lives prior to Screening (whichever was longer).

11. Subject had received any investigational biological agent in the past 3 months or 5 half-lives prior to Screening (whichever was longer).

12. Subject had received antibiotic treatment within 3 weeks prior to Screening for any non-Crohn's-related infection.

13. Subject had a history of clinically significant drug or alcohol abuse in the last year.

14. Subject had any abscess or a history of a poorly controlled medical condition, e.g., a subject with diabetes with documented history of recurrent infections.

15. Subject had previously used infliximab or any anti-TNF agent and had not clinically responded.

16. Subject had previously used infliximab or any anti-TNF within 12 weeks of Screening.

17. Subject had previous treatment with adalimumab or previous participation in an adalimumab clinical study.

18. Subject had positive *C. difficile* stool assay.

19. Subject had Screening laboratory and other analyses showing any of the following abnormal results:

- Electrocardiogram (ECG) with clinically significant abnormalities;
- Hemoglobin $\leq$ 8.5 g/dL for males; $\leq$ 8.0 g/dL for females
- Total white blood cell (WBC) count < 3000/mm^3;
- Platelet count < 100,000/mm^3;
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.75 x the upper limit of the reference range;
- Total bilirubin $\geq$ 3 mg/dL;
- Serum creatinine > 1.6 mg/dL

20. Subject was on Imuran® (azathioprine), 6-MP, or MTX, and had not been on stable doses of these medications for at least 4 weeks prior to Screening. For subjects on those medications, doses were to remain stable during the entire course of the study. In addition, subjects taking azathioprine, 6-MP, or MTX should have been on these medications for at least 12 weeks prior to screening. Moreover, subjects who had discontinued azathioprine, 6-MP, or MTX within 12 weeks of Screening were excluded.

21. Subject was on 5-aminosalicylic acid (5-ASA), mesalamine, sulfasalazine, or Crohn's-related antibiotics and had not been on stable doses of these medications for at least 4 weeks prior to Screening. In addition, subjects who had discontinued 5-ASA, sulfasalazine or Crohn's-related antibiotic treatment within 4 weeks of Screening, were excluded.

22. Subject was on prednisone > 30 mg/day (or equivalent) and subjects who were not on stable doses for 2 weeks prior to entry into study. In addition, subjects who discontinued prednisone (or equivalent) within 2 weeks of Screening were excluded.

23. Subject was on budesonide > 9 mg/day and subjects who were not on stable doses of budesonide for at least 2 weeks prior to Screening. In addition, subjects who discontinued budesonide within 2 weeks of Screening were excluded.

24. Subject was currently taking both budesonide and prednisone (or equivalent).

25. Subject had undergone therapeutic enemas within 2 weeks prior to Screening (enemas prior to endoscopy were permitted).

26. Subject had been on cyclosporine (intravenous, oral), mycophenolate mofetil, or tacrolimus (any form) within 8 weeks of Screening.

27. Subject was not in compliance with concomitant medications and/or prohibited medications.

Appendix 2: Schedule of Assessments

Study M02-403

Assessment	Screening	Baseline (Week 0)	Week 1	Week 2	Week 4/ Early Termination	Follow-Up
Eligibility requirements (inclusion/exclusion criteria)	X					
Written informed consent	X					
Demographic data	X					
Medical/surgical history,[a] including Crohn's disease history	X	X				
Past and current tobacco and alcohol use	X					
Vital signs	X	X	X	X	X	X
Physical examination[b]	X	X	X	X	X	X
Fistula counts	X	X	X	X	X	X
CXR[c]	X					X[b]
ECG[d]	X					X[c]
Tuberculin PPD skin test	X					
Samples for clinical chemistry and hematology lab tests	X	X	X	X	X	X
Sample for urinalysis (dipstick and microscopic)[e] test	X	X		X	X	X
Sample for pregnancy test[f]	X	X				X
Sample for *C difficile* stool test	X					
Sample for C-reactive protein test	X	X	X	X	X	X
Samples for HBsAg and HCV Ab serologies	X					
Previous and concomitant medications	X					

Assessment	Screening	Baseline (Week 0)	Week 1	Week 2	Week 4/ Early Termination	Follow-Up
Sample for measurement of adalimumab concentration		X	X	X	X	X
Sample for AAA testing		X	X	X	X	X
Sample for ANA test		X			X	
Sample for anti-dsDNA antibody[g] test		X			X	
Concomitant medication changes		X	X	X	X	X
CDAI information		X	X	X	X	X
IBDQ information		X	X	X	X	X
Adverse event information		X	X	X	X	X
Study drug administration		X		X		

CXR: chest X-ray; ECG: electrocardiogram; PPD: purified protein derivative; HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; AAA: anti-adalimumab antibody; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA; CDAI: Crohn's Disease Activity Index; IBDQ: Inflammatory Bowel Disease Questionnaire

a. A detailed medical history with respect to TB exposure was also documented, including *Bacille Calmette-Guérin* (BCG) vaccination, cohabitation with individuals who had TB, and residence or work in TB endemic locations.
b. Height was measured at Screening only.
c. A follow-up CXR was performed only for subjects not entering the M02-433 study.
d. An ECG was performed at Screening for all subjects. An ECG was performed at Follow-up, only if clinically significant abnormalities were present on the previous ECG.
e. A microscopic urinalysis was performed at Screening and at other visits, if the dipstick urinalysis was abnormal (*i.e.*, protein, blood, ketones or glucose results were greater than trace).
f. A serum pregnancy test was performed on all women at Screening and at Follow-up. A urine pregnancy test was performed at Baseline (Week 0).
g. An anti-dsDNA antibody test was performed only if the ANA result was positive.

Study M04-691

	Screening	Baseline	Week 1	Week 2	Week 4/ Early Term	70 Day Follow-up Phone Call
Inclusion/exclusion criteria	X					
Informed consent	X					
Medical/surgical history (including Crohn's medical/surgical history)	X	X				
Previous and concomitant medications	X					
Concomitant medication changes		X	X	X	X	
Vital signs[a]	X	X	X	X	X	
Purified protein deriviative skin test[b]	X					
Chest x-ray (posteroanterior and Lateral)	X					
Physical examination	X	X	X	X	X	
Electrocardiogram	X					
Pregnancy test[c]	X	X				
General laboratory tests[d]	X	X	X[d]	X[d]	X	
C-reactive protein	X	X			X	
HACA to infliximab blood samples		X				
PK blood sampling		X			X	
Anti-adalimumab antibodies		X			X	
Antinuclear antibodies		X			X	
Anti-dsDNA[e]		X			X	
Urinalysis (dipstick and microscopic)[f]	X	X			X	
C. difficile	X					
CDAI		X	X	X	X	
IBDQ		X			X	
Visual analogue scale		X			X	
SF-36		X			X	
Adverse events		X	X	X	X	X
Study drug administration		X		X		

CDAI = Crohn's Disease Activity Index; dsDNA = double-stranded DNA; HACA = human anti-chimeric antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; PK = pharmacokinetic; SF-36 = 36-Item Short Form

a. Height was measured at Screening only.

b. Read by the Investigator or a qualified delegate during the period between 48 and 72 hours after injection

c. Performed on all women of childbearing potential - serum test at Screening and a urine test at Baseline.

d. At Weeks 1 and 2, hematology (no differential) only was required.

e. Performed only if antinuclear antibody result was positive.

f. Microscopic urinalysis was performed at Screening. A microscopic urinalysis was also assessed at the Baseline and/or Week 4/early termination Visits if dipstick urinalysis results were abnormal, where abnormal was defined as a ketone, protein, blood or glucose value of greater than a trace.

Study M02-433

Assessment	Baseline (Week 0)	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 56	Early Termination	Follow-Up	Unscheduled	70 Day Phone Follow-Up
Eligibility requirements (inclusion/exclusion criteria)	X															
Written informed consent	X															
ECG	X													X[a]		
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X				
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination including weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fistula counts		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Samples for clinical chemistry and hematology lab tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sample for urinalysis (dipstick and microscopic)[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sample for CRP test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CDAI and IBDQ information		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE information		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Baseline (Week 0)	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 56	Early Termination	Follow-Up	Unscheduled	70 Day Phone Follow-Up
Sample for measurement of adalimumab concentration and AAA testing[c]			X					X				X	X			
CXR[d]				X										X		
Urine pregnancy test[e]				X				X		X				X		
Prednisone and Budesonide discontinuation start				X												
Sample for ANA test								X				X	X			
Sample for anti-dsDNA antibody test[f]								X				X	X			

ECG: electrocardiogram; CDAI: Crohn's Disease Activity Index; IBDQ: Inflammatory Bowel Disease Questionnaire; AAA: anti-adalimumab antibody; CXR: chest X-ray; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA

a. An ECG was to be performed at Follow-up, only if clinically significant abnormalities were present on the previous ECG.

b. A microscopic urinalysis was to have been performed, if the dipstick urinalysis was abnormal (*i.e.*, protein, blood, ketones or glucose results were greater than trace).

c. For any disease flare occurring prior to Week 56, a sample was to be collected for adalimumab and AAA testing. Samples were to have been collected prior to study drug dosing. Samples for adalimumab and AAA testing were to be collected at Early Termination, only for subjects withdrawing from the study prior to Week 56.

d. A CXR was to be performed at Week 8, only for subjects with positive tuberculin purified protein derivative (PPD) skin tests at Screening in the Study M02-403.

e. A urine pregnancy test was to be performed on all female subjects, except women who were surgically sterile or postmenopausal for at least 2 years.

f. An anti-dsDNA antibody test was to be performed only if the ANA result was positive.

Study M02-404

Procedures	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 26	Week 32	Week 40	Week 48	Week 56/ Early Term	Follow-up	70-Day Follow-up Phone Call
Inclusion/exclusion	X															
Informed consent	X															
Medical/surgical hx (including Crohn's)	X	X														
Previous and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Purified protein derivative	X															
Chest x-ray[a]	X									X						
Electrocardiogram	X															
Pregnancy test[b]	X	X													X	
C. difficile testing	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
General lab tests[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis (dipstick and microscopic)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-nuclear antibodies[e]		X														
CDAI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IBDQ, SF-36		X		X			X			X				X		

Procedures	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 26	Week 32	Week 40	Week 48	Week 56/ Early Term	Follow-up	70-Day Follow-up Phone Call
Global Rating of Change Questionnaire		X		X			X			X				X		
FACIT-Fatigue Scale		X		X			X			X				X		
Zung Depression Self-Rating Scale		X		X			X			X				X		
Nutritionals, Productivity and Pain Questionnaire		X		X			X			X				X		
Prednisone Start Taper[f]						X										
Budesonide Start Taper[f]						X										
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing[g]		X[g]	X	X	X	X	X[g]	X	X	X	X	X	X			
Endoscopy[h]		X					X							X		

CDAI = Crohn's Disease Activity Index; FACIT = Functional Assessment of Chronic Illness Therapy; IBDQ – Inflammatory Bowel Disease Questionnaire; SF-36 = Short Form-36

a. See 9.5.1.2.3.
b. See 9.5.1.2.5.
c. Blood draws were to be performed after questionnaires, pain assessment, and vital sign determinations and before study drug administration.
d. Microscopic urinalysis (UA) was to be performed at Screening and other visits if dipstick UA was abnormal (*i.e.*, protein, blood, ketones or glucose were greater than trace).
e. Double stranded deoxyribonucleic acid (dsDNA) testing was to be performed automatically if antinuclear antibody (ANA) result was positive.
f. Randomized subjects could begin a taper if qualifications were met.
g. For subjects in the endoscopy sub-study, study medication was to be administered the day after the colonoscopy.
h. Endoscopy was to be performed at Baseline, Week 12, and Week 56 in approximately 100 subjects at selected sites.

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2006.002.A.00109
APPLICATION TYPE	BLA 125057/89
LETTER DATE	August 28, 2006
STAMP DATE	August 28, 2006
PDUFA GOAL DATE	February 28, 2007
DATE OF CONSULT REQUEST	October 30, 2006
REVIEW DIVISION	Division of Gastroenterology Products (DGP)
MEDICAL REVIEWER	Li Liang
REVIEW DIVISION PM	Thomas Moreno
SEALD REVIEWER(S)	Ann Marie Trentacosti/Laurie Burke
REVIEW COMPLETION DATE	February 6, 2007
ESTABLISHED NAME	Humira
TRADE NAME	Adalimumab
THERAPEUTIC CLASS	Recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF)
APPLICANT	Abbott Laboratories
ENDPOINT(S) CONCEPT(S)	Quality of Life
INSTRUMENT(S)	Inflammatory Bowel Disease Questionnaire (IBDQ); SF-36; Visual Analog (VAS) Scale
FORMULATION	Solution for subcutaneous injection
INDICATION	Treatment of moderately to severely active disease in adult patients: ➢ who have had an inadequate response to conventional therapy ➢ who have lost response to or are intolerant to infliximab
INTENDED POPULATION(S)	Patients with moderately to severely active Crohn's Disease

- Asking patients how happy or pleased they are about their personal life as proposed is a question which encompasses all aspects of a patient's "quality of life" (i.e. economic and/or marital status) and is not adequate to evaluate HRQOL specific to patients with Crohn's disease.

- The IBDQ requires patients average and recall their symptoms over a 2 week period and in some questions compare their state to a previous non-quantified time period. The choice of recall period and averaging of symptoms has the propensity to increase error and jeopardize the validity of the data.

In addition, we have the following comments:

- Although a statistical improvement in IBDQ scores with adalimumab treatment compared to placebo was reported by the sponsor, we do not know how to interpret this result. For example, in study MO2-403, only the total IBDQ scores are compared between treatment groups. Results for all of the domains have not been provided to ascertain if the results for the total score were consistent with those for all four IBDQ domains (i.e., it would be important to know whether any of the domains worsened with adalimumab therapy).

- The sponsor has not provided evidence to support the fact that the IBDQ has been translated or culturally adapted from the original Canadian English into acceptable versions to support use in their international clinical trials (i.e. Poland, Czech Republic and South Africa).

SF-36 Physical Component Summary (PCS)/ SF-36 Mental Component Summary (MCS):

The SF-36 Physical Component Summary (PCS) was utilized as a secondary endpoint in studies M04-691 and MO4-404 and the SF-36 Mental Component Summary (MCS) was utilized as a secondary endpoint in study M04-691. However, the sponsor has not proposed any additions to the adalimumab label based upon the observed changes in these scales with treatment. It should be noted, however, that neither instrument is useful in describing the impact of treatment in labeling, since they include items which are unrelated to the concept implied by the score name (physical or mental functioning).

Visual Analog Scale (VAS) for Joint Pain:

The VAS evaluating joint pain was utilized as a secondary endpoint in study M04-691. Since a copy of the instrument has not been provided in the BLA, we cannot comment about the acceptability of the instrument. In study M04-691, no statistically significant difference between the adalimumab and placebo groups was observed for mean change from Baseline in VAS score for joint pain at Week 4 ($p = 0.970$). In addition, the sponsor has not proposed any additions to the adalimumab label based upon the observed changes in the symptom scale with treatment.

reflects better HRQL). The total IBDQ score is more likely to describe physical symptoms and effects of IBDQ due to the larger number of items retained that relate to the physical impact of IBD (10 bowel and 5 systemic items). Higher scores for domains and total scores are assumed to reflect better HRQL. The IBDQ is included in Appendix 1.

Although the initial qualitative work involving patient interviews to ascertain clinically meaningful items to evaluate the HRQOL in IBD patients is important, the overall content validity of the IBDQ has not been adequately determined in order to support labeling claims. This point can be illustrated by several examples.

The IBDQ requires patients average and recall their symptoms over a 2 week period and in some questions, compare their state to a previous non-quantified time period (i.e. Question: How frequent have your bowel movements been over the last two weeks? Response: Bowel movements as or more frequent than they have ever been.) The choice of recall period and averaging of symptoms has the propensity to increase error and jeopardize the validity of the data.. It is usually better to ask patients to describe their current state rather than compare their current state with an earlier period or average their experiences over time.

Many of the questions in the IBDQ are double-barreled in that they combine two or more issues in a single question. For example, asking patients if they have a problem "maintaining or getting to a desired weight" is essentially combing the concept of weight gain with weight stability into a single question.

Posing a question concerning the extent bowel habits limits sexual activity, makes the underlying assumption that the patient is sexually active. This question would not be appropriate for a patient who in not sexually active. Asking patients how happy or pleased they are about their personal life is a question which encompasses all aspects of a patient's "quality of life" (i.e. economic and/or marital status) and is not adequate to evaluate HRQOL in Crohn's disease patients.

In addition, the sponsor has not provided evidence to support the fact that the IBDQ has been translated or culturally adapted from the original Canadian English into other versions to support use in their international clinical trials (i.e. Poland, Czech Republic and South Africa).

Validity, reliability, and responsiveness of the IBDQ were accessed by Irvine et al.[2] in 350 patients with Crohn's disease receiving cyclosporine or placebo for 18 months. Concordance of IBDQ scores was tested in 280 stable subjects. IBDQ and dimensional scores (bowel, social, systemic, and emotional) were correlated with Crohn's Disease Activity Index (CDAI), Harvey-Bradshaw Index, Patient-Reported Global Assessment and Physician Reported Global Assessment. Linear regression evaluated change in IBDQ scores over time. Matrices of the Pearson product-moment correlation coefficients for baseline scores and score differences at 8-week follow-up are presented in Table 1.

Visual Analog Scale (VAS) for Joint Pain:

The VAS evaluating joint pain was utilized as a secondary endpoint in study M04-691. Since a copy of the instrument has not been provided in the BLA, we cannot comment about the acceptability of the instrument. In study M04-691, no statistically significant difference between the adalimumab and placebo groups was observed for mean change from Baseline in VAS score for joint pain at Week 4 (p = 0.970). In addition, the sponsor has not proposed any additions to the adalimumab label based upon the observed changes in the symptom scale with treatment.

3 BACKGROUND

Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody that contains exclusively human sequences, binds specifically to TNF, and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

BLA 125057 SE89 was submitted on August 28, 2006 by Abbott Laboratories in order to seek FDA approval for a new indication for adalimumab. Based upon the efficacy and safety data submitted in this application, Abbott has proposed the addition of the following indication to the adalimumab label:

Humira is indicated for treatment of moderately to severely active Crohn's disease in adult patients who:

- *have had an inadequate response to conventional therapy as treatment or*
- *have lost response to or are intolerant to infliximab*

The adalimumab clinical development program to support the above indication included both short-term and long-term studies in order to demonstrate safety and efficacy for use in the induction and maintenance of therapy in patients with moderately to severely active Crohn's disease. Induction of clinical remission (defined as CDAI <150) was evaluated in two randomized, double-blind, placebo-controlled studies: M02-403 (CLASSIC I) and M04-691 (GAIN). Two long-term randomized studies, M02-404 (CHARM) and M02-433, compared the efficacy of adalimumab vs. placebo for the maintenance of clinical remission.
A brief description of each study is provided below.

MO2-403:
Title: A Multi-Center, Randomized, Double -Blind, Placebo -Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Crohn's Disease

Site: The study was conducted in the United States, Canada, Poland, Belgium, the Netherlands, and the Czech Republic

Objectives: The objectives of this study were:

- To demonstrate the efficacy of adalimumab in the treatment of subjects with Crohn's disease;
- To delineate the safety of adalimumab when administered to subjects with Crohn's disease; and

the placebo group who withdrew from the study early compared to subjects who withdrew from the study early in the 160 mg/ 80 mg adalimumab group. For the 40 mg/ 20 mg adalimumab dose, the p - values were not statistically significant (i. e., the p-values were > 0.05).

The summary statistics for pairwise comparison of IBDQ scores for the full set of analysis is presented in Table 2.

Table 2. Study MO2-403: Summary Statistics for Pairwise Comparison of IBDQ Score (Full Set Analysis)

SUMMARY STATISTICS FOR PAIRWISE COMPARISON OF IBDQ SCORE
FULL ANALYSIS SET SUBJECTS

DOSE / TIME POINT	PLACEBO (N=74)		ADALIMUMAB		DIFFERENCE^(95% CI)	P-VALUES@
	n	MEAN# (S.D.)	n	MEAN# (S.D.)		
20 MG (N=74)						
WEEK 1	70	141.02 (2.7)	70	141.27 (2.7)	0.25 (-7.3, 7.8)	
WEEK 2	67	147.67 (3.0)	71	146.65 (3.0)	-1.02 (-9.4, 7.3)	
WEEK 4	65	149.44 (3.7)	64	146.13 (3.7)	-3.31 (-13.6, 7.0)	0.5270
WEEK 2 (LOCF)	70	145.81 (3.0)	72	146.10 (3.0)	0.29 (-8.1, 8.7)	
WEEK 4 (LOCF)	70	146.68 (3.5)	72	145.25 (3.5)	-1.44 (-11.3, 8.4)	0.7736
40 MG (N=75)						
WEEK 1	70	141.02 (2.7)	73	147.73 (2.6)	6.70 (-0.7, 14.1)	
WEEK 2	67	147.67 (3.0)	71	156.96 (3.0)	9.30 (0.9, 17.7)	
WEEK 4	65	149.44 (3.7)	70	160.81 (3.6)	11.37 (1.3, 21.4)	0.0271
WEEK 2 (LOCF)	70	145.81 (3.0)	73	155.46 (3.0)	9.65 (1.3, 18.0)	
WEEK 4 (LOCF)	70	146.68 (3.5)	73	159.10 (3.5)	12.41 (2.6, 22.2)	0.0131
80 MG (N=76)						
WEEK 1	70	141.02 (2.7)	74	148.94 (2.7)	7.92 (0.5, 15.4)	
WEEK 2	67	147.67 (3.0)	71	154.78 (3.0)	7.12 (-1.2, 15.5)	
WEEK 4	65	149.44 (3.7)	70	159.45 (3.6)	10.01 (-0.1, 20.1)	0.0518
WEEK 2 (LOCF)	70	145.81 (3.0)	75	154.40 (3.0)	8.59 (0.3, 16.9)	
WEEK 4 (LOCF)	70	146.68 (3.5)	75	159.54 (3.5)	12.86 (3.1, 22.6)	0.0100
ALL ADALIMUMAB (N=225)						
WEEK 1	70	140.92 (2.7)	217	145.87 (1.6)	4.95 (-1.2, 11.1)	
WEEK 2	67	147.57 (3.1)	213	152.69 (1.7)	5.12 (-1.8, 12.0)	
WEEK 4	65	149.27 (3.8)	204	155.19 (2.1)	5.92 (-2.6, 14.4)	0.1721
WEEK 2 (LOCF)	70	145.75 (3.0)	220	151.91 (1.7)	6.16 (-0.7, 13.1)	
WEEK 4 (LOCF)	70	146.64 (3.6)	220	154.55 (2.1)	7.90 (-0.3, 16.1)	0.0581

MEAN = LEAST SQUARE MEAN, ADJUSTED FOR BASELINE; MEAN AND THE CORRESPONDING 95% CONFIDENCE INTERVAL ARE FROM ANCOVA MODEL.
^ DIFFERENCE OF ADJUSTED MEANS BETWEEN ADALIMUMAB AND PLACEBO (ADALIMUMAB - PLACEBO).
@ P-VALUE IS FROM ANCOVA MODEL COMPARING THE DIFFERENCE BETWEEN ADALIMUMAB AND PLACEBO, ADJUSTED FOR BASELINE VALUE.
LOCF - LAST OBSERVATION CARRIED FORWARD

Summary statistics for the pairwise comparisons of change in Baseline (Week 0) IBDQ scores for the per-protocol set revealed minimal differences in change in Baseline (Week 0) IBDQ scores between the full analysis set and the per-protocol set. However, for the per-protocol set, a statistically significant p-value was not obtained for the 80 mg/ 40 mg adalimumab dose for the Week 4 observed data (p = 0.0669).

MO4-691:

Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects

Sites: United States, Canada, Belgium, and France

Objectives: The objectives of this study were to demonstrate the efficacy of adalimumab in the treatment of subjects with Crohn's disease who either initially responded to administration of infliximab but stopped responding or were intolerant to infliximab; to delineate the safety of adalimumab when administered to subjects with Crohn's disease; and to assess the pharmacokinetics of adalimumab following subcutaneous administration.

Table 3. Study M04-691: Mean Change From Baseline in IBDQ Scores at Week 4 (Full Analysis Set)

IBDQ Score	Placebo N=161	Adalimumab 160/80 mg N=155	LS Mean Difference	95% CI	p-value
Total Score					
Baseline Mean ± SD	123.5 ± 27.45	119.7 ± 27.43			
Mean Change ± SD	15.1 ± 26.99	30.2 ± 30.75	14.16	7.92, 20.41	< 0.001
Social Function					
Baseline Mean ± SD	21.5 ± 7.50	20.4 ± 6.94			
Mean Change ± SD	2.3 ± 5.87	5.3 ± 6.18	2.65	1.37, 3.92	< 0.001
Systemic System					
Baseline Mean ± SD	15.8 ± 4.58	15.0 ± 4.97			
Mean Change ± SD	2.6 ± 4.95	4.8 ± 6.02	1.97	0.78, 3.17	0.001
Emotional Function					
Baseline Mean ± SD	47.6 ± 12.90	46.6 ± 12.63			
Mean Change ± SD	5.6 ± 10.67	10.0 ± 12.14	4.09	1.68, 6.50	< 0.001
Bowel Symptoms					
Baseline Mean ± SD	38.7 ± 8.21	37.7 ± 8.50			
Mean Change ± SD	4.6 ± 9.23	10.2 ± 9.95	5.34	3.31, 7.37	< 0.001

Note: LS mean (adalimumab 160/80 mg - placebo), confidence intervals, and p-values are from ANCOVA model using treatment as factor and Baseline value as covariate.

According to the sponsor, the mean change from Baseline in SF-36 PCS score at Week 4, the sixth ranked secondary variable, and mean change from Baseline in SF-36 Mental Component Summary (MCS) score at Week 4, the tenth ranked secondary variable, were analyzed using the ANCOVA model. Statistically significant differences between the adalimumab and placebo groups were observed for mean change from Baseline to Week 4 in PCS, MCS, and all of the SF-36 sub-domains except physical function, role function, and emotional. In each case, greater mean increases from Baseline, were observed in the adalimumab group compared to the placebo group.

The mean change from Baseline in VAS score for joint pain at Week 4, the seventh ranked secondary variable, was analyzed using the ANCOVA model. No statistically significant difference between the adalimumab and placebo groups was observed for mean change from Baseline in VAS score for joint pain at Week 4 ($p = 0.970$). A mean decrease of 9.0 and 9.1, respectively, in the placebo and adalimumab groups was observed. Results were similar for the PP Analysis Set.

MO2-404:

Title: Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Crohn's Disease

Sites: Europe, United States, Canada, Australia, and South Africa

40 mg eow group), with greater improvements observed in the adalimumab groups than the placebo group. None of the differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups were statistically significant. Treatment groups had similar mean scores at Baseline.

A summary of the treatment differences from placebo in IBDQ variables at week 56 is presented in Table 4.

Table 4. Study MO2-404: Summary of the Treatment Differences from Placebo in IBDQ Variables at Week 56

Variable	Placebo	Adalimumab eow	Adalimumab ew
Total Score	N=32	N=77	N=81
Baseline Mean (SD)	127.4 (26.78)	128.0 (30.26)	126.7 (28.02)
Mean Change (SD)	45.9 (31.90)	59.8 (29.64)	59.7 (32.27)
Domain Score (Social Function)	N=32	N=77	N=80
Baseline Mean (SD)	22.8 (6.71)	22.0 (7.66)	22.4 (7.62)
Mean Change (SD)	6.8 (6.39)	10.7 (7.36)	9.9 (6.68)
Domain Score (Systemic Function)	N=32	N=77	N=81
Baseline Mean (SD)	15.4 (4.37)	17.1 (5.32)	16.3 (4.98)
Mean Change (SD)	8.8 (6.40)	9.6 (5.89)	9.2 (7.23)
Domain Score (Emotional Function)	N=32	N=77	N=81
Baseline Mean (SD)	49.2 (13.06)	49.3 (12.97)	49.0 (12.90)
Mean Change (SD)	15.8 (12.73)	21.2 (12.53)	20.2 (13.44)
Domain Score (Bowel Symptoms)	N=32	N=77	N=81
Baseline Mean (SD)	40.2 (7.95)	39.6 (7.94)	39.1 (8.88)
Mean Change (SD)	14.6 (10.80)	18.3 (9.05)	20.3 (11.36)

Variable	Treatment Comparison	Difference in Means	95% CI	p-value[a]
Total Score	Adalimumab 40 mg eow *vs.* placebo	14.36	(4.20, 24.52)	0.006
	Adalimumab 40 mg ew *vs.* placebo	13.26	(3.17, 23.35)	0.010
Social Function	Adalimumab 40 mg eow *vs.* placebo	3.36	(1.65, 5.07)	< 0.001
	Adalimumab 40 mg ew *vs.* placebo	2.86	(1.16, 4.56)	0.001
Systemic Function	Adalimumab 40 mg eow *vs.* placebo	2.08	(-0.20, 4.37)	0.074
	Adalimumab 40 mg ew *vs.* placebo	1.13	(-1.13, 3.39)	0.326
Emotional Function	Adalimumab 40 mg eow *vs.* placebo	5.49	(1.30, 9.69)	0.011
	Adalimumab 40 mg ew *vs.* placebo	4.24	(0.07, 8.41)	0.046
Bowel Symptoms	Adalimumab 40 mg eow *vs.* placebo	3.35	(-0.07, 6.77)	0.055
	Adalimumab 40 mg ew *vs.* placebo	4.95	(1.55, 8.34)	0.005

eow = every other week; ew = weekly; CI = confidence interval

a. Mean, confidence intervals, and p-values are from ANCOVA model with factors for treatment, Baseline value, previous anti-TNF use, and Week 4 responder status.

Note: Evaluations after discontinuation of DB study drug were excluded from analysis. Week 56 data include subjects receiving DB treatment.

Baseline (Week 0) of Study M02- 403. Subjects in the blinded treatment groups who met these criteria could be switched to OL adalimumab 40 mg eow and subjects receiving adalimumab 40 mg eow who met these criteria could potentially receive OL adalimumab 40 mg ew. Subjects receiving OL 40 mg adalimumab ew who developed another flare, or who continued to be a non-responder, could be withdrawn from the study. If a subject did not meet the disease flare definition, but was a consistent non- responder while receiving OL.

Efficacy variable: The primary efficacy variable was the maintenance of clinical remission at Week 56. This was defined as the proportion of subjects who were in clinical remission (CDAI score of < 150 points) at Week 56 who were also in remission at Study M02- 433 Baseline (Week 0) and Week 4. The secondary efficacy variable included the Changes in Baseline (Week 0) Inflammatory Bowel Disease Questionnaire (IBDQ) scores at Week 24 and Week 56;

Statistical Analysis: The primary efficacy endpoint was the proportion of randomized subjects with clinical remission, defined as achievement of a CDAI score < 150 points, at Week 56 between each adalimumab dose group and placebo group using Pearson's Chi-square test or Fisher's Exact test if more than 20% expected cell count < 5. Subjects without Week 56 evaluations and subjects who switched to OL adalimumab were classified as not being in remission (imputed analysis). The two-sided 95% confidence interval for the difference in proportion was also provided. An initial overall comparison of the three treatment groups, adalimumab 40 mg eow, adalimumab 40 mg ew, and placebo, was tested.

Summary statistics were to be conducted for many of the secondary efficacy variables including changes in Baseline (Week 0) IBDQ scores at Week 24 and Week 56.

Efficacy results: The protocol- specified primary endpoint was the proportion of subjects in clinical remission at Week 56. For the randomized cohort, greater proportions of subjects in the two adalimumab treatment groups demonstrated maintenance of clinical remission at Week 56 compared to placebo (47.4% eow and 66.7% ew vs. 33.3%). No statistically significant treatment group differences were observed. At Week 24, a statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group (94.4% vs. 38.9%, respectively; p = 0.001). The clinical remission rate for adalimumab 40 mg eow was 57.9% at Week 24.

In the OL Analysis Set, 36.3% of subjects were in clinical remission at Week 24 and 36.3% were in clinical remission at Week 56. No clinically important difference was observed in clinical remission rates between subjects whose last administered treatment was adalimumab 40 mg eow or ew.

Subjects randomized to the adalimumab groups had greater mean increases in IBDQ scores from M02 - 403 Baseline (Week 0) to Week 24 than subjects in the placebo group (53.4 ew and 47.2 eow vs. 34.9 placebo). At Week 56, the adalimumab dose groups did not have consistently greater mean increases in IBDQ scores than placebo (38.7 ew, 49.2 eow, and 42.2 placebo).

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from
   1 ALL OF THE TIME
   2 MOST OF THE TIME
   3 A GOOD BIT OF THE TIME
   4 SOME OF THE TIME
   5 A LITTLE OF THE TIME
   6 HARDLY ANY OF THE TIME
   7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from
   1 ALL OF THE TIME
   2 MOST OF THE TIME
   3 A GOOD BIT OF THE TIME
   4 SOME OF THE TIME
   5 A LITTLE OF THE TIME
   6 HARDLY ANY OF THE TIME
   7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from
   1 ALL OF THE TIME
   2 MOST OF THE TIME
   3 A GOOD BIT OF THE TIME
   4 SOME OF THE TIME
   5 A LITTLE OF THE TIME
   6 HARDLY ANY OF THE TIME
   7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from
   1 NO ENERGY AT ALL
   2 VERY LITTLE ENERGY
   3 A LITTLE ENERGY
   4 SOME ENERGY
   5 A MODERATE AMOUNT OF ENERGY
   6 A LOT OF ENERGY
   7 FULL OF ENERGY

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
    1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
    2 A LOT OF DIFFICULTY
    3 A FAIR BIT OF DIFFICULTY
    4 SOME DIFFICULTY
    5 A LITTLE DIFFICULTY
    6 HARDLY ANY DIFFICULTY
    7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from
    1 A MAJOR PROBLEM
    2 A BIG PROBLEM
    3 A SIGNIFICANT PROBLEM
    4 SOME TROUBLE
    5 A LITTLE TROUBLE
    6 HARDLY ANY TROUBLE
    7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
    1 ALL OF THE TIME
    2 MOST OF THE TIME
    3 A GOOD BIT OF THE TIME
    4 SOME OF THE TIME
    5 A LITTLE OF THE TIME
    6 HARDLY ANY OF THE TIME
    7 NONE OF THE TIME

28. To what extent has <u>your bowel problem</u> limited sexual activity during the last 2 weeks? Please choose an option from
    1 NO SEX AS A RESULT OF BOWEL DISEASE
    2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
    3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
    4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
    5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
    6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
    7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125057/89
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Applicant:	Abbott Laboratories.
Date(s):	Received August 28, 2006 PDUFA: February 28, 2007
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Clinical Team:	Li Liang, M.D. (HFD-180)
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

1.1.1 Induction Studies

Two induction studies, Studies M02-403 and M04-691), were conducted to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease (CD). Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691 was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

Study M02-403 demonstrated that adalimumab was statistically significant in inducing clinical remission (achievement of a Crohn's Disease Activity Index score < 150 points) at Week 4 at doses of 80 mg/40 mg and 160 mg/80 mg as compared to placebo. Superiority of adalimumab compared to placebo was also shown in major secondary efficacy endpoints: clinical response CR-70 (a decrease from baseline in CDAI score ≥ 70) and clinical response CR-100 (a decrease from baseline CDAI score ≥ 100). The CR-70 endpoint comparisons showed superiority for both 80 mg/40 mg and 160 mg/80 mg doses groups; while CR-100 endpoint showed superiority for the 160 mg/80 mg dose group.

For subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab, Study M04-691 demonstrated the proportion of subjects who achieved clinical remission at Week 4 was statistically significant greater in the adalimumab 160 mg/80 mg group compared to the placebo group. For 9 of 11 major secondary efficacy endpoints, adalimumab showed statistical significance or near-significance compared to placebo.

1.1.2 Maintenance Studies

Two studies, Studies M02-404 and M02-433, were conducted to evaluate adalimumab as maintenance therapy for moderate to severe Crohn's disease. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

In a second supportive maintenance study (Study M02-433), the extension study to Study M02-403, the primary evaluation was the maintenance of remission through year one in subjects who had achieved remission. The sponsor submitted this study as a supportive study.

Study M02-404 demonstrated that the proportion of all randomized subjects who achieved clinical response at Week 4 (a decrease from baseline in CDAI score ≥ 70)

achieved clinical remission (CDAI < 150) at Week 26 and Week 56 (co-primary efficacy endpoints), were statistically significantly greater in the adalimumab 40 mg every other week (eow) and 40 mg every week (ew) groups compared to the placebo group. Superiority of adalimumab groups over placebo was also shown in secondary efficacy endpoints, clinical response CR-70 (decrease from baseline in CDAI score ≥ 70 points) at Weeks 26 and 56, and clinical response CR-100 (decrease from baseline in CDAI score ≥ 100 points) at Weeks 26 and 56.

Study M02-433, the supportive, extension study to Study M02-403, showed that a numerically greater proportion of subjects in the two adalimumab treatment groups (40 mg eow and 40 mg ew) demonstrated maintenance of remission (CDAI score < 150) at Week 56 compared to placebo. However, due to small sample size, statistical significance was not achieved across the three treatment groups. For the secondary efficacy endpoints, clinical remission at Week 24, CR-70 at Week 24 and Week 56 and CR-100 at Week 24 and Week 56, numerically greater proportion of subjects responded in the adalimumab treatment groups compared to the placebo treatment group.

1.2 Brief Overview of Clinical Studies

1.2.1 Induction Studies

The two studies designed to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease are Studies M02-403 and M04-691. Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

1.2.1.1 Study M02-403

This study was a randomized, double-blind, placebo-controlled, international multi-center (55 sites), efficacy, safety and pharmacokinetic study designed to demonstrate the effectiveness of adalimumab as induction therapy for the treatment for Crohn's disease in subject with moderate to severely active Crohn's disease.

Subjects having a diagnosis of Crohn's disease for greater than 4 months with confirmation by endoscopic or radiologic evaluation and Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 and having met exclusion criteria were randomized to adalimumab 80, 40, 20 mg or placebo treatment arms. All study treatment was administered subcutaneously. During baseline visit (Week 0), subject received a loading dose of adalimumab. The loading dose was two times dose of each treatment arm (40, 80, 160 mg, or placebo). The treatment dose (20, 40, 80 mg or placebo) was administered at Week 2.

Subjects could continue their doses of azathioprine, 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been

stable for at least 12 weeks prior to screening. Subject could continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening. Concomitant therapy was to remain stable during the entire study.

The primary efficacy variable was the induction of clinical remission, defined as a CDAI score of < 150 at Week 4 for the 160 mg/80 mg and 80 mg/40 mg dose groups and placebo group. A CDAI score was calculated from a subject diary at baseline, Week 1, Week 2, Week 4, and follow-up.

Secondary efficacy variables were:

(1) clinical response defined as a decrease in baseline CDAI score ≥ 70 points at Week 4;
(2) clinical response defined as a decrease in baseline CDAI score ≥ 100 points at Week 4;
(3) change in baseline IBDQ scores at Week 4;
(4) improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of ≥ 50% in the number of draining fistula for at least 2 consecutive visits);
(5) fistula remission at Week 4 (defined as closure of all fistulas that were draining at baseline for at least two consecutive visits);
(6) achievement of clinical remission (defined as CDAI < 150) in the 20 mg dose arm at Week 4;
(7) achievement of clinical response in the 20 mg dose arm (defined as a decrease in baseline CDAI score ≥ 70 points) at Week 4.

The primary efficacy analyses (Pearson's Chi-square test) were to be conducted in the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study drug. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations.

The sponsor assumed a 20% of clinical remission in the placebo arm and a 45% clinical remission in the active arms. Fifty four (54) subjects per treatment provided 80% power in the test of comparing two treatment groups with a 2-sided alpha of 0.05. Assuming 20% of subjects would drop out before Week 4, the sponsor stipulated that a total of 272 subjects was adequate with equally allocated to adalimumab 20, 40, 80 mg and placebo groups. Type I error control was not pre-specified for the secondary efficacy endpoint comparisons.

A total of 390 subjects were screened, 299 subjects were randomized (74 in Adalimumab 40 mg/20mg, 75 in Adalimumab 80 mg/40mg, 76 in Adalimumab 160 mg/80mg and 74 in placebo). A total of 284 subjects completed the study.

1.2.1.2 Study M04-691

This study was a randomized, double-blind, placebo-controlled, international multi-center (52 sites), efficacy and safety study designed to demonstrate the effectiveness of adalimumab in the treatment of Crohn's disease in subjects with moderately to severely active Crohn's disease who either initially responded to administration of infliximab but stopped responding or were intolerant to infliximab.

Subjects having a diagnosis of Crohn's disease with confirmation by endoscopic or radiologic evaluation and Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450, previously been administered infliximab and discontinued use due to a loss of response or intolerance to infliximab therapy and having met exclusion criteria were randomized to adalimumab 160 mg/80 mg or placebo treatment arms.

All study treatment was administered subcutaneously. During baseline visit (Week 0), subject received a loading dose of adalimumab. The loading dose was two times dose of each treatment arm (160 mg or placebo). The treatment dose (80 mg or placebo) was administered at Week 2.

Subjects could continue their doses of azathioprine, 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been stable for at least 4 weeks prior to screening. Subject could continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening. Concomitant therapy was to remain stable during the entire study.

Subject who qualified was given the opportunity to roll over into M04-690, a study of the Long-term Safety and Tolerability of Repeated Administration of Adalimumab.

The primary efficacy variable was the induction of clinical remission, defined as a CDAI score of < 150 at Week 4. A CDAI score was calculated from a subject diary at baseline, Week 1, Week 2, and Week 4/early termination (ET).

Secondary efficacy variables were:

(1) clinical response defined as a decrease in baseline CDAI score ≥ 70 points at Week 4;
(2) clinical response defined as a decrease in baseline CDAI score ≥ 100 points at Week 4;
(3) change in baseline IBDQ scores at Week 4;
(4) improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of $\geq 50\%$ in the number of draining fistula that were draining at Screening and Baseline for at least 2 consecutive visits);
(5) fistula remission at Week 4 (where remission was defined as closure of all fistulas that were draining at Screening and Baseline for at least two consecutive visits).

The primary efficacy analyses (Pearson's Chi-square test) were conducted in the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study drug. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations.

The sponsor assumed 20% of clinical remission in the placebo arm and a 33% clinical remission in the active arms. One Hundred twenty-three (123) subjects per treatment provided 80% power in the test of comparing two treatment groups with a 2-sided alpha of 0.05. Assuming 5% of subjects would drop out before Week 4, a total of 300 subjects was adequate and was equally allocated to adalimumab 160 mg/80 mg and placebo groups. Type I error control was not pre-specified for the secondary efficacy endpoint comparisons.

A total of 325 subjects participated the study and were randomized (159 in adalimumab 160 mg/80 mg and 166 in placebo). Of 325 subjects, a total 14 subjects (4 in adalimumab 160 mg/80 mg and 10 in placebo) was prematurely discontinued from the study.

1.2.2 Maintenance Studies

Two studies were designed to evaluate adalimumab as maintenance therapy for moderate to severe Crohn's disease: Studies M02-404 and M02-433. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

In a second supportive maintenance Study M02-433, the extension study to Study M02-403, the primary evaluation was the maintenance of remission through one year in subjects who had achieved remission.

1.2.2.1 Study M02-404

This study was a randomized, double-blind, placebo-controlled, multi-center (92 sites), efficacy and safety study designed to demonstrate the effectiveness of adalimumab in the induction and maintenance of clinical remission in subjects with moderate to severe Crohn's disease.

Subjects having a diagnosis of Crohn's disease for greater than 4 months with confirmation by endoscopic or radiologic evaluation and CDAI score of ≥ 220 and ≤ 450 and having met exclusion criteria were eligible for study participation.

Study medication was administered by sc injection. At baseline, all subjects received open-label 80 mg adalimumab sc at baseline (Week 0) followed by a 40 mg dose at Week 2. At Week 4, subjects were evaluated for clinical response. All subjects were then randomized to receive sc injection of adalimumab 40 mg weekly, or 40 mg eow sc or placebo and treated for up to 52 additional weeks.

The Week 4 randomization was stratified by subjects' responder status and previous anti-TNF use. If subjects in the randomized portion of the study experienced a disease flare at or after Week 12 and was between scheduled visits, they could be switched to an open-label portion of study where they would receive 40 mg weekly sc eow. If subjects flared on this dose scheduled, they might switch to open-label 40 mg weekly sc dose. If after the dose frequency was increased, subjects continued to demonstrate a lack of improvement, they would be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders at or after Week 12, they might also switch to the open-label portion of the study after a discussion with the sponsor's medical monitor.

Subjects were not allowed to decrease Crohn's specific concomitant medications. Subjects could continue their doses of Imuran (azathioprine), 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been stable for at least 4 weeks prior to screening. Doses were to remain stable during the entire course of the study (Week 60). Subject could continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening. Doses were to remain stable during the entire course of the study (Week 60).

The duration of the study was up to 62 weeks, which included a 2-week screening and a 4-week follow-up period. Study visit from baseline through Week 8 occurred every 2 weeks. Study visits from Week 8 through Week 20 occurred every 4 weeks. Study visits from Week 20 through Week 32 occurred very 6 weeks. Study visits from Week 32 through Week 56 occurred every 8 weeks. A CDAI score was calculated from a subject diary and appropriate laboratory values at all study visits beginning at baseline.

The primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT), which was defined as all treated subjects who achieved clinical response (CDAI decrease $\geq$ 70) at Week 4 and were randomized to receive one of the three blind treatments. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations in the modified ITT population. This was the additional analysis population for primary efficacy variables.

The primary efficacy variable was clinical remission (CDAI< 150). The first co-primary endpoint was the proportion of subjects in clinical remission at Week 26 who had at least a clinical response (decrease in CDAI scores $\geq$ 70 points when compared to baseline) at Week 4, and the second co-primary endpoint was the proportion of subjects in clinical remission at Week 56 who had at least a clinical response at Week 4. Treatment comparisons were to be done with Cochran-Manatel-Haenszel (CMH) test stratified by previous anti-TNF use.

There were four subset populations that were analyzed in this study. They were:

(1) Week 4 non-responder subset of all treated population;

(2) subjects with previous and/or concomitant use of other Crohn's medications

subset of the modified ITT population;
(3) the subset of all treated population with endoscopic evaluation;
(4) subjects with baseline CRP values of $\geq$ 1.0 mg/dL.

These subset populations were subjected to primary and secondary analyses, as appropriate; however, these results are to be considered exploratory as no control over type I error, sample size and power were pre-specified.

The secondary efficacy variables were clinical response (CDAI decrease by 70 and 100 points), clinical remission (CDAI < 150), IBDQ score, fistula counts, steroid use, Crohn's Disease Endoscopic Index of Severity (CDEIS) scores, simple endoscopic score for Crohn's disease (SES-CD) and ulcer counts.

The secondary efficacy endpoints were:
(1) the proportion of subjects in clinical remission at Week 60;
(2) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score $\geq$ 70 points) at Weeks 26, 56 and 60;
(3) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score $\geq$ 100 points) at Weeks 26, 56 and 60;
(4) changes from baseline in IBDQ scores at Weeks 26 and 56;
(5) proportion of subjects with improvement in the number of draining fistulas (where improvement was defined as a decrease from baseline in the number of draining fistulas of $\geq$ 50% for at least 2 consecutive visits);
(6) proportion of subjects with fistula remission (where fistula remission was defined as a closure of all fistulas that were draining at baseline for least 2 consecutive visits);
(7) steroid sparing at Weeks 26 and 56 (the proportion of subjects at Weeks 26 and 56 in clinical remission [CDAI< 150] able to discontinue steroid use);
(8) of those with a clinical response (CDAI decrease $\geq$ 70 points) at Week 4, time to flare, up to and including Week 56 (where flare was defined as a recurrence of very active disease, specifically an increase in the CDAI when compared to the Week 4 baseline, of $\geq$ 70 points and a CDAI above 220).

The sponsor assumed 58% of subject would achieve clinical response at Week 4, and approximately 830 subjects at the study baseline allowed 160 subjects to be equally allocated to the adalimumab 40 mg weekly, 40 mg eow, and the placebo groups at Week 4. If the actual response rate at Week 4 was higher or lower than the anticipated rate then subject enrollment could be shorten or extended, respectively. As a result, the total number of subjects at baseline could vary accordingly.

A total of 854 subjects participated in the 4-week open-label (OL) induction phase of study (adalimumab 80 mg followed by adalimumab 40 mg). Of these, 778 went on to participate in the double-blind (DB) phase of the study (261 in placebo, 260 in adalimumab 40 mg eow, and 257 in adalimumab 40 mg ew), and 505 subjects (147 in placebo, 166 in adalimumab 40 mg eow, and 192 in adalimumab 40 mg ew) completed Week 56. Week 56 completers either rolled over to Study M04-690 or continued in this

study for the 4-week follow-up period. Nine additional subjects prematurely discontinued from the study, but their final study visit fell within the Week 56 window for analysis. Therefore, a total of 514 subjects participated in the Week 56 Visit.

1.2.2.2 Study M02-433

The objective of this study was to demonstrate the efficacy and safety adalimumab in the maintenance of clinical remission of subjects with Crohn's disease who participated in Protocol M02-403.

All subjects received 40 mg eow open label study drug at the Baseline and Week 2 visits. Subjects previously in remission in the M02-403 study were evaluated at Week 4 visit. If they continued to be in remission, they were randomized to receive to weekly injection of 40 mg weekly, 40 mg eow, or placebo. Subjects not in remission at the Week 4 study visit of M02-403 and at Week 4 of this clinical trial received 40 mg eow open-label. After Week 56 subjects from the blinded portion of the study would be switched to 40 mg eow open-label therapy. In case of a flare or non-response, the subject might be switched to 40 mg weekly dosing.

All subjects received 40 mg of adalimumab subcutaneously at Baseline and Week 2. Subjects were randomized at Week 4 in the M02-433 trial based upon their clinical remission status at Baseline and Week 4. The first cohort was comprised of subjects who achieved clinical remission (defined as a CDAI < 150) at the end of Study M02-403, and remained in clinical remission at Week 4 of Study M02-433. These subjects were randomized to receive weekly injection of either adalimumab 40 mg weekly, 40 mg every other week (eow), or placebo. If the subjects in this randomized portion of the study developed a disease flare, they could be switched to the open-label portion of the study after a discussion with the Abbott Medical Monitor. Subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

The second cohort was comprised of subjects who did not achieve clinical remission (CDAI score of ≥ 150) at Week 4 of M02-403/M02-443 Baseline or those subjects who were no longer in remission at Week 4 of M02-433. These study subjects, regardless of any future response, were not randomized into the double-blind portion of the study.

These subjects received 40 mg eow of open-label adalimumab starting at the baseline visit. From Week 4 onward, subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg

weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

When entering the extension portion of this study at Week 56, subjects who were in the blinded cohort would be assigned to open-label adalimumab 40 mg every other week (eow). From Week 4 onward, subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

The primary efficacy variable was the maintenance of clinical remission at Week 56. This is defined as the proportion of subjects who have CDAI score of < 150 at Week 56, who were in remission at baseline and at Week 4 of this study. A CDAI score would be calculated at all study visits (Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and Week 56).

Secondary efficacy variables were:

(1) clinical remission : CDAI score < 150 at Week 24;
(2) clinical remission: CDAI score < 150 at Week 56 for subjects who were not in remission at Baseline or Week 4 of this study;
(3) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 70 points at Week 24 and Week 56;
(4) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 100 points at Week 24 and at Week 56, respectively;
(5) change in baseline of M02-403 IBDQ scores at Week 24 and Week 56;
(6) steroid taper at Week 24 and Week 56 (complete withdrawal of steroid therapy with a development of relapse); and
(7) time to flare (where flare is defined as the first recurrence of very active disease, specifically the 1st increase in the CDAI when compared to their M02-433 Week 4 values, of ≥70 points and a CDAI above 220).

The primary efficacy analyses (Fisher's exact test) were conducted in the intent-to-treat (ITT) population of the randomized population at Week 4. Intent-to-treat population was defined as all randomized subjects who received at least one dose of study drug.

Subjects who fully completed the M02-403 study were eligible and potentially participate in this study. Approximately 90% (270 subjects) of subjects from M02-403 were expected to enroll.

A total of 276 subjects participated in the study. All subjects, irrespective of remission status from Study M02-403, were to receive adalimumab 40 mg eow at Weeks 0 and 2. At Week 4, 55 subjects who had achieved clinical remission (CDAI score < 150 points) at Baseline (Week 0) and Week 4 of Study M02-433 were randomized one of three treatment groups; 18 placebo, 19 adalimumab 40 mg eow, and 18 adalimumab 40 mg ew. A total of 204 subjects were not randomized and received OL adalimumab 40 mg eow. Seventeen (17) were discontinued at or before Week 4.

1.3 STATISTICAL ISSUES AND FINDINGS

1.3.1 Induction Studies

Two induction studies (M02-403 and M04-691) were conducted to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease. Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691 was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

Study M02-403 demonstrated that adalimumab was statistically significant better in inducing clinical remission (defined as an achievement of a CDAI score < 150 points) at Week 4, primary efficacy endpoint, at dose of 80 mg/40 mg and 160 mg/80 mg as compared to placebo.

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. The sponsor's analysis was the "worst" case analysis. This reviewer performed sensitivity analyses including "best" case and observed case (OC) analyses. In the observed case analysis, only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals. In the "best" case analysis, any patients with missing data who was randomized to active treatment was classified as 'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'. For both OC and "best" case analyses, adalimumab160 mg/80 mg was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 as compared to placebo.

These analyses indicated that the efficacy conclusion favoring adalimumab 160 mg/ 80 mg in inducing clinical remission (defined as an achievement of a CDAI score < 150 points) at Week 4 was not sensitive to imputation strategy.

For the secondary efficacy endpoints, for clinical response CR-70 (defined as a decrease CDAI score ≥ 70), pairwise comparisons between each adalimumab group and the placebo group demonstrated that both 80 mg/40 mg and 160 mg/80 mg adalimumab doses achieved statistically significance superiority. For clinical response CR-100 (defined as a decrease CDAI score ≥ 70), pairwise comparisons between each adalimumab group and the placebo group demonstrated that 160 mg/80 mg adalimumab dose achieved statistically significance superiority. The 80 mg/40 adalimumab dose showed a favorable trend but was not statistical significant.

For subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab, Study M04-691 demonstrated the proportion of subjects who achieved clinical remission (defined as an achievement of a CDAI score < 150 points) at Week 4, primary efficacy endpoint, was statistically significant greater in the adalimumab 160 mg/80 mg group compared to the placebo group. The superiority was replicated in 9 of 11 secondary efficacy endpoints, although such results were not adjusted for multiplicity.

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. As noted above, this reviewer performed "best" case and observed case (OC) analyses. For the OC analysis, adalimumab 160 mg/80 mg was statistically significantly better in inducing clinical remission at Week 4 as compared to placebo.

1.3.2 Maintenance Studies

Two studies, Studies M02-404 and M02-433, were conducted to evaluate adalimumab as maintenance therapy for moderate to severe CD. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

Study M02-404 demonstrated that the proportion of all randomized subjects who achieved clinical response at Week 4 (decrease from baseline in CDAI ≥ 70) achieved clinical remission (CDAI < 150) at Week 26 and Week 56 (co-primary efficacy endpoints) were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group. Superiority of adalimumab groups over placebo was also shown in major secondary efficacy endpoints, clinical response CR-70 (decrease from baseline in CDAI ≥ 70) at Week 26 and Week 56, and clinical response CR-100 (decrease from baseline in CDAI ≥ 100) at Week 26 and Week 56.

The protocol stated that the primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT) population, which was defined as all treated subjects who achieved clinical response (CDAI decrease ≥ 70) at Week 4 and were randomized to receive one of the three blind treatments.

In general, the mITT population was similar to the ITT population for demographic and baseline characteristics with exception of use of corticosteroids. In general, the mITT was similar to the ITT for demographic and baseline characteristics with exception of use of corticosteroids at baseline. In the mITT, there were more subjects with use of corticosteroids at baseline in the adalimumab ew as compared to adalimumab eow and placebo group (47% vs. 34% and 39%). Because of this imbalance, results from a subgroup analysis of steroid free remission might be unreliable and difficult to interpret.

This reviewer performed exploratory ITT analyses for more stringent efficacy endpoints: sustained clinical remission (CDAI < 150) at weeks 4 and 56, sustained clinical remission at weeks 4, 26, and 56, sustained clinical response CR 70 (decrease from baseline in CDAI $\geq$ 70) at weeks 4 and 26, sustained clinical response CR 70 at weeks 4, 26, and 56, sustained clinical response CR-100 (decrease from baseline in CDAI $\geq$ 100) at weeks 4 and 26, and sustained clinical response CR-100 at weeks 4, 26, and 56.

Results from these analyses indicated that adalimumab treatment groups were superior to placebo with regard to sustained clinical remission, sustained clinical responses (decrease from baseline in CDAI $\geq$ 70) and sustained clinical response (decrease from baseline in CDAI $\geq$ 100) at both weeks 4 and 26 and at weeks 4, 26, and 56. There were no differences between adalimumab 40 mg ew and 40 mg eow treatment groups – although the study was not powered to show a difference in dose regimens.

Study M02-433, the extension study to Study M02-403, demonstrated that greater proportion of subjects in the two adalimumab treatment groups (40 mg eow and 40 mg ew) demonstrated maintenance of remission (CDAI score < 150) at Week 56 compared to placebo. However, no statistical significant difference was observed across the three treatment groups due to insufficient sample size.

Study M02-433 was a rollover study the lead-in study, Study M02-403. So, it did not have sample size determination. A total of 67 subjects had induction of clinical remission at week 4 in Study M02-403. It was expected that about 60 subjects who would achieve clinical remission at Week 4 and were randomized to one of three treatment groups. The sample size per arm would be about 20. Considering 20% subjects who did not complete Week 56 (double-blind), about 16 subjects per arm could be evaluable for the randomized set. Sixteen subjects per arm were too few to draw any meaningful statistical conclusion. So, this study and the results should be considered exploratory by design.

2. INTRODUCTION

2.1 Overview

Adalimumab is a human-derived monoclonal antibody to tumor necrosis factor-alpha (TNF-α). It binds only to TNF and has a half-life of approximately 2 weeks. Adalimumab is currently approved in the U.S. for treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

The current efficacy supplement has been submitted to show efficacy and safety of adalimumab therapy in inducing clinical remission in moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy, and, who have lost response to or are intolerant to infliximab therapy and in maintaining clinical remission in moderately to severely active Crohn's disease in adult patients. The sponsor has conducted two clinical remission induction studies and two long-term maintenance studies, enrolling a total of 1459 subjects. This statistical review primarily addresses the adalimumab efficacy results for the induction and maintenance studies.

2.2 Data Sources

This BLA supplement included two Phase III studies (M02-403 and M04-691) for the induction of clinical remission. It also included two long-term studies (M02-404 and M02-433) for the maintenance of clinical remission. These four studies were:

M02-403: A multiple-center, randomized, double-blind, placebo-controlled study of the Human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with Crohn's disease.

M02-404: A multiple-center, randomized, double-blind, placebo-controlled study of the Human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn's disease.

M04-691: A multiple-center, randomized, double-blind, placebo-controlled study of the Human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with moderate to severe Crohn's disease who have lost response or are intolerant to infliximab.

M02-433: A multiple-center, randomized, double-blind, placebo-controlled study of the Human anti-TNF monoclonal antibody adalimumab for the maintenance of clinical remission in subjects with Crohn's disease.

Data from all these studies were submitted in electronically.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Induction Studies

The two studies designed to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease are Studies M02-403 and M04-691. Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691

was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

3.1.1.1 Study M02-403

3.1.1.1.1 Study Design

This study was a randomized, double-blind, placebo-controlled, multi-center (55 sites), efficacy, safety and pharmacokinetic study designed to demonstrate the effectiveness of adalimumab in treatment of Crohn's disease in subject with moderate to severely active Crohn's disease.

The objective of this study was to demonstrate the efficacy of adalimumab in the treatment of subjects with Crohn's disease.

Subjects having a diagnosis of Crohn's disease for greater than 4 months with confirmation by endoscopic or radiologic evaluation and Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 and having met exclusion criteria were randomized to adalimumab 80, 40, 20 mg or placebo treatment arms.

All study treatment was administered subcutaneously. During baseline visit (Week 0), subject received a loading dose of adalimumab. The loading dose was two times dose of each treatment arm (40, 80, 160 mg, or placebo). The treatment dose (20, 40, 80 mg or placebo) was administered at Week 2.

Subjects could continue their doses of azathioprine, 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been stable for at least 12 weeks prior to screening.

Subject could continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening.

Corticosteroids ≤ 20 mg/day of prednisone were permitted provided subjects were on stable doses for at least two weeks prior to entry into study.

Budesonide ≤ 9 mg/day was permitted provided subjects were on stable doses for at least two weeks prior to screening.

Concomitant therapy was to remain stable during the entire study.

A CDAI score was calculated from a subject diary at baseline, Week 1, Week 2, Week 4, and follow-up.

Subject completed Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline, Week 1, Week 2, Week 4, and follow-up.

A Drug Safety Monitoring (DSMB) met to discuss unblinded data from the study every four months and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC) made final decisions based on DSMB recommendations.

Subject who qualified was given the opportunity to roll over into M02-433, a follow-up maintenance of remission/response study.

The primary efficacy variable was the induction of clinical remission, defined as a CDAI score of < 150 at Week 4.

Secondary efficacy variables were:

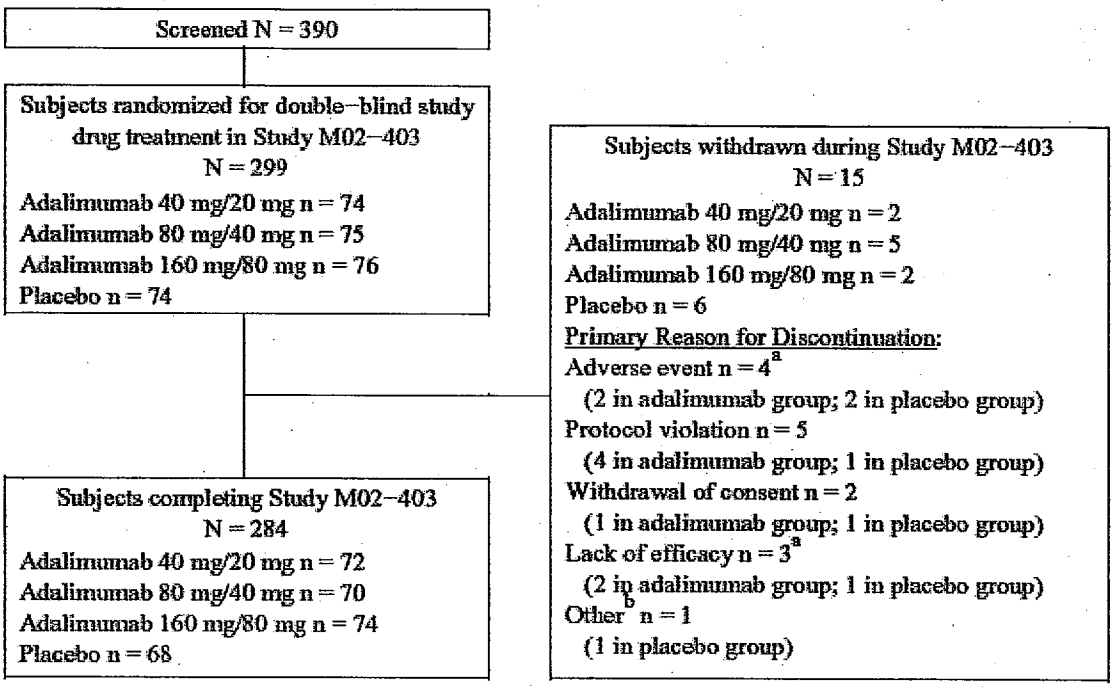
(1) clinical response defined as a decrease in baseline CDAI score ≥ 70 points at Week 4;
(2) clinical response defined as a decrease in baseline CDAI score ≥ 100 points at Week 4;
(3) change in baseline IBDQ scores at Week 4;
(4) improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of ≥ 50% in the number of draining fistula for at least 2 consecutive visits);
(5) fistula remission at Week 4 (defined as closure of all fistulas that were draining at baseline for at least two consecutive visits);
(6) achievement of clinical remission (defined as CDAI < 150) in the 20 mg dose arm at Week 4;
(7) achievement of clinical response in the 20 mg dose arm (defined as a decrease in baseline CDAI score ≥ 70 points) at Week 4.

Assuming a 20% of clinical remission in the placebo arm and a 45% clinical remission in the active arms, 54 subjects per treatment provided 80% power in the test of comparing two treatment groups with a 2-sided alpha of 0.05. Assuming 20% of subjects would drop out before Week 4, a total of 272 subjects was adequate and was equally allocated to adalimumab 20, 40, 80 mg and placebo groups.

3.1.1.1.2 Sponsor Analysis

A total of 390 subjects were screened, 299 subjects were randomized (74 in Adalimumab 40 mg/20mg, 75 in Adalimumab 80 mg/40mg, 76 in Adalimumab 160 mg/80mg and 74 in placebo). A total of 284 subjects completed the study.

The disposition of subjects who entered the study is summarized below.



a. Subject 06202 is not counted as an AE withdrawal in this figure. Although the occurrence of an AE was noted as a reason for discontinuation for this subject in some of the statistical tables, it was not the primary reason for discontinuation. Per Appendix 16.2__1.2, the primary reason for premature discontinuation for Subject 06202 was lack of efficacy, which is the reason indicated in this figure.

b. Per Appendix 16.2__1.2, the subject did not receive study drug at Week 2 due to an inability to come in for the clinic visit; therefore, study participation was prematurely terminated.

Cross Reference: Section 14, Table 14.1__1, Table 14.1__2, and Table 14.1__4

A total of 15 of 299 subjects prematurely withdrew from the study. Of those subjects who discontinued study participation, 4 subjects (2 in adalimumab and 2 in placebo) withdrew due to an AE, 5 subjects (4 in adalimumab and 1 in placebo) withdrew due to a protocol violation, 2 subjects (1 in adalimumab and 1 in placebo) withdrew due to withdrawal of consent, 3 subjects (2 in adalimumab and 1 in placebo) withdrew due to lack of efficacy, and 1 subject withdrew due to other reasons.

A total of 54 of 299 subjects had at least 1 major protocol deviation. A total of 299 subjects were in the full analysis set and 269 subjects (64 in placebo, 68 in 20 mg, 66 in 40 mg and 71 in 80 mg) were in per-protocol set.

3.1.1.1.2.1 Planned Analysis

The primary efficacy analyses were conducted in the intent-to-treat (ITT), which was defined as all randomized subjects who received at least one dose of study drug. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations.

All statistical test was two-sided and was conducted at an α=0.05 level.

Demographic and baseline characteristics among the four treatment groups were summarized and compared. Continuous variables were compared using the Kruskal-Wallis test, and discrete variables were compared using the Pearson's chi-square test.

The primary efficacy analysis was the comparison the induction of clinical remission (achievement of a CDAI < 150) of adalimumab 40 mg and 80 mg vs. placebo at Week 4. Those with missing primary endpoint data at Week 4 was classified in the "no induction of clinical remission" category. An assessment was performed using the Pearson's Chi-square test.

Adjustment for multiple testing was done following the closed testing procedure. An initial overall comparison of the three treatment groups (adalimumab 40, 80 mg, and placebo) was tested. If this was significant, pairwise comparisons of each adalimumab dose group (40 mg and 80 mg) vs. placebo was performed. A supportive analysis of the primary efficacy variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values at Week 4.

The proportion of clinical response CR-70 (a decrease in baseline CDAI score $\geq$ 70 points) at Week 4 was compared using the Pearson's Chi-square test between adalimumab dose group and placebo, if the primary endpoint was significant. The sponsor stated that no adjustments for alpha level were needed for each testing.

For other secondary efficacy variables, summary statistics was conducted.

Summary statistics for efficacy was performed by subgroups: sex, age [<65 years $\geq$65 years], and ethnicity, weight [$\leq$70 kg > 70 kg], and use of corticosteroid or immune modifier [yes, no].

3.1.1.1.2.2 Treatment Group Comparability

A summary of the demographic characteristics at baseline, baseline Crohn's disease characteristics, and Crohn's related mediation use by treatment are presented in Appendix Table 1.

As seen from Appendix Table 1, overall, demographic characteristics at baseline and baseline Crohn's disease characteristics were similar across four treatment groups.

3.1.1.1.2.3 Sponsor's Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was the induction of clinical remission, defined as a CDAI score of 150 points at Week 4. Those with missing primary endpoint data at Week 4 were classified in the "no induction of clinical remission" category. An assessment was performed using the Pearson's Chi-square test.

A summary of subjects with clinical remission at Week 4 is given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M02-403

Analysis	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo	overall p-value	Adalim 80mg/40mg vs. Plac p-value	Adalim 160mg/80mg vs. Plac p-value
	18/75 (24.0%)	27/76 (35.5%)	9/74 (12.2%)	0.004	0.061	0.001
LOCF	18/73 (24.7%)	27/76 (35.5%)	9/72 (12.5%)	0.005	0.060	0.001

Complied from Tables 20 and 21.

As seen from table above, adalimumab was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 at doses of 80 mg/40 mg and 160 mg/80mg adalimumab, in comparison to placebo. Pairwise comparisons between each adalimumab group the placebo group demonstrated that 160 mg/80 mg adalimumab dose achieved statistically significance superiority. The 80 mg/40 adalimumab dose was close to statistical significance.

3.1.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Endpoints

Secondary efficacy variables were:

(1) clinical response defined as a decrease in baseline CDAI score ≥ 70 points at Week 4;
(2) clinical response defined as a decrease in baseline CDAI score ≥ 100 points at Week 4;
(3) change in baseline IBDQ scores at Week 4;
(4) improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of ≥ 50% in the number of draining fistula for at least 2 consecutive visits);
(5) fistula remission at Week 4 (defined as closure of all fistulas that were draining at baseline for at least two consecutive visits);
(6) achievement of clinical remission (defined as CDAI < 150) in the 20 mg dose arm at Week 4;
(7) achievement of clinical response in the 20 mg dose arm (defined as a decrease in baseline CDAI score ≥ 70 points) at Week 4.

3.1.1.1.2.4.1 Clinical Response CR-70 (Decrease in Baseline CDAI Score ≥ 70 Points) at Week 4

A summary of subjects with clinical response CR-70, defined as a decrease CDAI score ≥ 70 points at Week 4 is given below.

Clinical Response CR-70 (Decrease in Baseline CDAI Score ≥ 70 Points) at Week 4
Fully Analysis Set
Protocol M02-403

Analysis	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo	Adalim 80mg/40mg vs. Plac p-value	Adalim 160mg/80mg vs. Plac p-value
	41/70 (58.6%)	44/74 (59.5%)	25/68 (36.8%)	0.010	0.007
LOCF	41/73 (56.2%)	44/76 (57.9%)	26/72 (36.1%)	0.015	0.008

Complied from Tables 22 and 23.

As seen from table above, for clinical response CR-70, pairwise comparisons between each adalimumab group and the placebo group demonstrated that both 80 mg/40 mg and 160 mg/80 mg adalimumab doses achieved statistically significance superiority.

3.1.1.1.2.4.2 Clinical Response CR-100 (Decrease in Baseline CDAI Score ≥100 Points) at Week 4

A summary of subjects with clinical response CR-100, defined as a decrease CDAI score ≥ 100 points at Week 4 is given below.

Clinical Response CR-100 (Decrease in Baseline CDAI Score ≥ 100 Points) at Week 4
Fully Analysis Set
Protocol M02-403

Analysis	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo	Adalim 80mg/40mg vs. Plac p-value	Adalim 160mg/80mg vs. Plac p-value
	28/70 (40.0%)	37/74 (50.0%)	17/68 (25.0%)	0.060	0.002
LOCF	28/73 (38.4%)	37/76 (48.7%)	17/72 (23.6%)	0.055	0.002

Complied from Tables 24 and 25.

As seen from table above, for clinical response CR-100, pairwise comparisons between each adalimumab group and the placebo group demonstrated that 160 mg/80 mg adalimumab dose achieved statistically significance superiority. The 80 mg/40 adalimumab dose was close to statistical significance.

3.1.1.1.2.4.3 Change in Baseline CDAI Scores at Week 4

Summary statistics of change from baseline in CDAI scores for the full analysis set are given Appendix Table 2.

As seen from Appendix Table 2, based on the observed data, subjects treated with placebo had a mean change in CDAI score from Baseline to Week 4 of -51.8 The mean change observed for the subjects treated with adalimumab was greater than the mean

change for placebo (-68.4, -93.8 and -99.9 in 40 mg/ 20 mg, 80 mg/40 mg and 160 mg/80 mg, respectively). The LOCF data also demonstrated similar results.

3.1.1.1.2.4.4 Change in Baseline IBDQ Scores at Week 4

Summary statistics of change from baseline in CDAI scores for the full analysis set are given Appendix Table 3.

As seen from Appendix Table 3, based on the observed data, subjects treated with placebo had a mean change in IBDQ score from Baseline to Week 4 of 21.1, with subjects in the 40 mg/20 mg adalimumab group having a similar mean change of 18.2. The greatest mean changes were in the 80 mg/40 mg adalimumab and 160 mg/80 mg adalimumab groups, with mean changes of 33.8 and 32.8, respectively. The LOCF data also demonstrated similar results.

3.1.1.1.3 Reviewer's Comments and Evaluation

3.1.1.1.3.1 Reviewer's Comments on Study Design

The lower dose (adalimumab 40 mg/20 mg) was not included in primary efficacy analysis. Efficacy of the lower dose against placebo was assessed as a secondary efficacy endpoint. So, efficacy analysis of the lower dose against placebo should be considered as exploratory.

The study design without the lower dose would have been a better design.

3.1.1.1.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

Adalimumab 40 mg and placebo had more subjects who were discontinued from study as compared to adalimumab 80 mg (5 and 6 for adalimumab 40 mg and placebo, respectively vs. 2 for adalimumab 80 mg).

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. The sponsor's analysis was the "worst" case analysis. This reviewer performed sensitivity analyses including the "best" case and observed case analyses. Two sensitivity analyses were performed were:

OC - only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals.

"Best" Case - any patients with missing data who was randomized to active treatment was classified as 'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'.

3.1.1.1.3.2.1 Sensitivity Analysis

Summary of results for reviewer sensitivity is given below

Induction of Clinical Remission at Week 4
Reviewer's Sensitivity Analysis
Protocol M02-403

Analysis	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo	overall p-value	Adalim 80mg/40mg vs. Plac p-value	Adalim 160mg/80mg vs. Plac p-value
OC	18/70 (25.7%)	27/74 (36.5%)	9/68 (13.2%)	0.0065	0.0857	0.0018
Best	18/75 (24.0%)	27/76 (35.5%)	15/74 (20.3%)	0.0875	0.1349	0.0169

Complied by this reviewer.

As seen from table above, for both OC and "best" case analyses, adalimumab 80 mg was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 as compared to placebo,

3.1.1.1.3.2.2 Subgroup Analysis

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M02-403

Category	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo
Country			
Belgium		0/2 (0.0%)	1/2 (50.0%)
Canada	4/15 (26.7%)	6/19 (31.6%)	1/17 (5.9%)
Czechoslovakia	4/7 (57.1%)	4/7 (57.1%)	1/4 (25.0%)
Netherland	0/1 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Poland	2/3 (66.7%)	1/1 (100.0%)	2/3 (66.7%)
USA	8/49 (16.3%)	16/46 (34.8%)	4/46 (8.7%)
Gender			
Male	7/25 (28.0%)	11/36 (30.6%)	4/37 (10.8%)
Female	11/50 (22.0%)	16/40 (40.0%)	5/37 (13.5%)
Age			
< 40 years	12/40 (30%)	19/43 (44.2%)	8/51 (15.7%)
40-64	6/34 (17.4%)	8/33 (24.2%)	1/18 (5.6%)
65-74	0/1 (0.0%)		
Body weight			
≤ 70 kg	10/38 (26.3%)	14/31 (45.2%)	6/33 (18.2%)
> 70 kg	8/37 (21.6%)	13/45 (28.9%)	3/41 (7.3%)

Tobacco use			
Never used	7/30 (23.3%)	11/27 (40.7%)	3/34 (8.8%)
Current user	9/32 (28.1%)	12/32 (37.5%)	3/28 (10.7%)
Ex-user	2/13 (15.4%)	4/17 (23.5%)	3/12 (25.0%)
Alcohol use			
Non-drinker	8/31 (25.8%)	12/30 (40.0%)	4/27 (14.8%)
Drinker	9/38 (23.7%)	15/43 (34.9%)	3/39 (7.7%)
Ex-drinker	1/6 (16.7%)	0/3 (0.0%)	2/8 (25.0%)
Use of Corticosteroids at baseline			
Yes	9/31 (29.0%)	13/22 (59.1%)	5/25 (20.0%)
No	9/44 (20.5%)	14/54 (25.9%)	4/49 (8.2%)
Use of immunosuppressants at baseline			
Yes	2/21 (9.5%)	8/22 (36.4%)	2/22 (9.1%)
No	16/54 (29.6%)	19/54 (35.2%)	7/52 (13.5%)
Use of oral aminosalicylates at baseline			
Yes	13/41 (31.7%)	16/40 (40.0%)	7/36 (19.4%)
No	5/34 (14.7%)	11/36 (30.6%)	2/38 (5.3%)
Baseline CRP			
< 1 mg/dL	9/42 (21.4%)	15/48 (31.3%)	7/45 (15.6%)
≥ 1 mg/dL	9/33 (27.3%)	12/28 (42.9%)	2/29 (6.9%)
Baseline CDAI scores			
220-270 points	8/24 (33.3%)	13/28 (46.4%)	5/30 (16.7%)
271-330 points	6/22 (27.3%)	7/26 (26.9%)	2/21 (9.5%)
331-390 points	3/19 (15.8%)	3/16 (18.8%)	0/14 (0.0%)
391-450 points	1/8 (12.5%)	2/4 (50.0%)	1/8 (12.5%)

Complied by this reviewer.

As seen from table above, proportion of subjects in induction of clinical remission at Week 4 was consistent for subgroups of country, gender, age, body weight, alcohol use, use of immunosuppressant, use corticosteroids, use of oral aminosalicylates, and baseline CDAI scores. But, it was not consistent for subgroup of tobacco use.

3.1.1.1.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints

There were seven secondary efficacy endpoints pre-specified in the protocol, but no adjustments were prospectively defined for analyses of secondary efficacy endpoints. So, the p-values reported by sponsor were not adjusted and results of these analyses should be considered as "exploratory."

3.1.1.2 Study M04-691

3.1.1.2.1 Study Design

This study was a randomized, double-blind, placebo-controlled, multi-center (52 sites), efficacy, and safety study designed to demonstrate the effectiveness of adalimumab in the treatment of Crohn's disease in subjects with moderately to severely active Crohn's disease who either initially responded to administration of infliximab but stopped responding or were intolerant to infliximab.

The objective of this study was to demonstrate the efficacy of adalimumab in the treatment of Crohn's disease in subjects with moderately to severely active Crohn's disease who either initially responded to administration of infliximab but stopped responding or were intolerant to infliximab.

Subjects having a diagnosis of Crohn's disease with confirmation by endoscopic or radiologic evaluation and Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450, previously been administered infliximab and discontinued use due to a loss of response or intolerance to infliximab therapy and having met exclusion criteria were randomized to adalimumab 160 mg/80 mg or placebo treatment arms.

All study treatment was administered subcutaneously. During baseline visit (Week 0), subject received a loading dose of adalimumab. The loading dose was two times dose of each treatment arm (160 mg or placebo). The treatment dose (80 mg or placebo) was administered at Week 2.

Subjects could continue their doses of azathioprine, 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been stable for at least 4 weeks prior to screening.

Subject could continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening.

Corticosteroids ≤ 40 mg/day of prednisone were permitted provided subjects were on stable doses for at least two weeks prior to entry into study.

Budesonide ≤ 9 mg/day was permitted provided subjects were on stable doses for at least two weeks prior to screening.

Concomitant therapy was to remain stable during the entire study.

A CDAI score was calculated from a subject diary at baseline, Week 1, Week 2, and Week 4/early termination (ET).

Subject completed Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline and Week 4/ET.

Subjects completed a Visual Analog Scale (VAS) to assess joint pain at baseline and Week4/ET.

Subjects completed the SF-36 36-Item Short Form (SF-36) questionnaire at baseline and Week 4/ET.

Subject who qualified was given the opportunity to roll over into M04-690, a study of the Long-term Safety and Tolerability of Repeated Administration of Adalimumab.

The primary efficacy variable was the induction of clinical remission, defined as a CDAI score of < 150 at Week 4.

Secondary efficacy variables were:

(1) clinical response CR-70 defined as a decrease in baseline CDAI score ≥ 70 points at Week 4;
(2) clinical response CR-100 defined as a decrease in baseline CDAI score ≥ 100 points at Week 4;
(3) change in baseline IBDQ scores at Week 4;
(4) improvement in the number of draining fistulas at Week 4 (where improvement was defined as a decrease of ≥ 50% in the number of draining fistula that were draining at Screening and Baseline for at least 2 consecutive visits);
(5) fistula remission at Week 4 (where remission was defined as closure of all fistulas that were draining at Screening and Baseline for at least two consecutive visits).

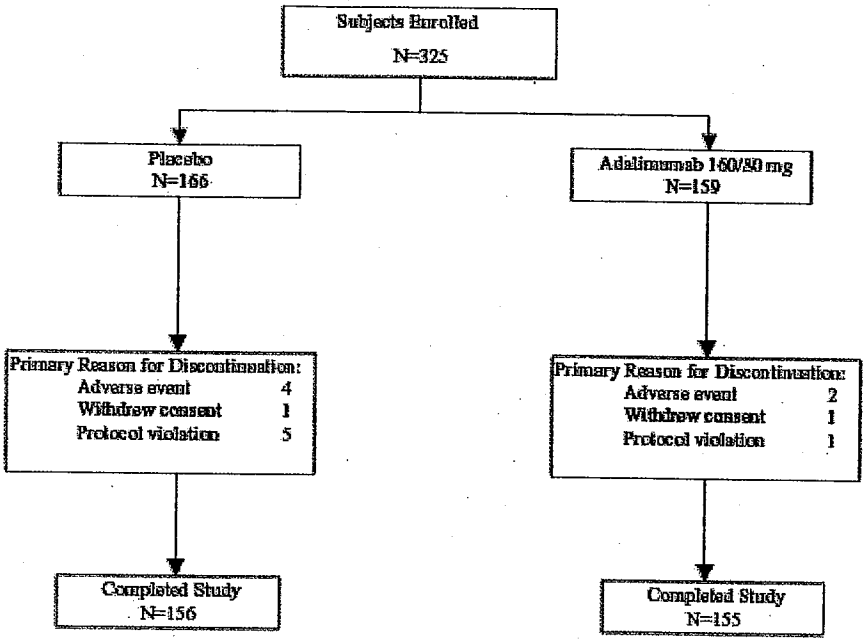
Assuming a 20% of clinical remission in the placebo arm and a 33% clinical remission in the active arms, 123 subjects per treatment provided 80% power in the test of comparing two treatment groups with a 2-sided alpha of 0.05. Assuming 5% of subjects would drop out before Week 4, a total of 300 subjects was adequate and was equally allocated to adalimumab 160 mg/80 mg and placebo groups.

3.1.1.2.2 Sponsor's Analysis

A total of 325 subjects participated the study and were randomized (159 in adalimumab 160 mg/80 mg and 166 in placebo). Of 325 subjects, a total 14 subjects (4 in adalimumab 160 mg/80 mg and 10 in placebo) was prematurely discontinued from the study. One adalimumab 160 mg/ 80 mg subject (42104) who completed the study, but did not roll over to Study M04-690.

The disposition of subjects who entered the study is summarized below.

Figure 3. **Flowchart of the Number of Subjects**



Cross Reference: Section 14, Table 14.1__1 and Table 14.1__3.1.

A total of 23 subjects (9 in adalimumab 160 mg/ 80 mg and 14 in placebo) were excluded in the Per Protocol Analysis Set.

3.1.1.2.2.1 Planned Analysis

The primary efficacy analyses were conducted in the intent-to-treat (ITT), which was defined as all randomized subjects who received at least one dose of study drug. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations.

All statistical testing was two-sided and was conducted at an α=0.05 level.

Demographic and baseline characteristics among the four treatment groups were summarized and compared. Continuous variables were compared using the Wilcoxon/Mann-Whitney test, and discrete variables were compared using the Pearson's chi-square test.

The primary efficacy analysis was the comparison the induction of clinical remission (achievement of a CDAI <150) of adalimumab 160 mg/80 mg vs. placebo at Week 4. Those with missing primary endpoint data at Week 4 was classified in the "no induction of clinical remission" category. An assessment was performed using the Pearson's chi-square test.

A supportive analysis of the primary efficacy variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values at Week 4.

Subset analyses were completed for subjects that participated in this study. All primary and secondary efficacy analyses were performed on these subsets. The additional subsets consisted of ; 1) subjects with Baseline CRP value of $\geq$ 1.0 mg/dL, 2) subjects with a Baseline CRP value of < 1.0 mg/dL, 3) subjects who were intolerant to infliximab, and 4) subjects who had lost response to previous infliximab use.

Secondary efficacy analyses were conducted on Week 4 LOCF data and included the following: (1) the proportions of clinical response CR-70 (a decrease in Baseline CDAI score $\geq$ 70 points) at Week 4 was compared using the chi-square test between adalimumab group and placebo.

Summary statistics was conducted for the following efficacy variables: (2) clinical response CR-100 (a decrease in Baseline CDAI score $\geq$ 100 points); (3) changes in Baseline IBDQ scores.

Summary statistics for efficacy was performed by subgroups: sex, age [< 65 years, $\geq$ 65 years], and ethnicity, weight [$\leq$ 70 kg, > 70 kg], and use of corticosteroid or immune modifier [yes, no], smoker, present or past [yes or no], and subjects with a Baseline CRP $\geq$ 1 mg/dL and < 1 mg/dL.

3.1.1.2.2.2 Treatment Group Comparability

A summary of the demographic characteristics at baseline, baseline Crohn's disease characteristics, and Crohn's related mediation use by treatment are presented in Appendix Table 4.

As seen from Appendix Table 4, overall, demographic characteristics at baseline and baseline Crohn's disease characteristics were similar between two treatment groups exception of height and corticosteroids use.

There were 11 subjects (5 placebo and 6 adalimumab 160/80 mg) enrolled in the study that did not meet entry criteria for infliximab failure status. No statistically significant difference was observed in the proportion of subjects with intolerance and/or loss of response to infliximab.

Treatment groups were comparable in regard to mean CDAI scores at baseline, concomitant corticosteroid use, concomitant immunosuppressant use, and concomitant aminosalicylate use.

3.1.1.2.2.3 Sponsor's Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects achieving clinical remission (CDAI < 150) at Week 4.

A summary of the proportion of subjects who achieved clinical remission at Week 4 is given below.

Clinical Remission at Week 4
Full Analysis Set
Protocol M04-691

	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg	Difference in	
Visit	N=166	N=159	Proportions (95% CI)	p-value[a]
Week 4	12 (7.2)	34 (21.4)	14.2 (6.7, 21.6)	< 0.001

a. The p-value is from Pearson's Chi-square test.

Cross Reference: Section 14, Table 14.2__1.1.1.1.

As seen from table above, the proportion of subjects in the Full Analysis Set who achieved clinical remission at Week 4 was statistically significant greater in the adalimumab 160 mg/80 mg group compared to the placebo group.

Two additional analyses were performed on clinical remission at Week 4. One involved excluding data from the 11 subjects who did not meet the entry criteria for infliximab failure status and the other excluded subjects from Site 418. After completion of the study and following the data base lock, one investigator (Dr. Kim, site 418) was found to be noncompliant with Good Clinical Practice (GCP).

Results of both analyses are summarized in Appendix Table 5.

As seen from Appendix Table 5, results of both analyses were similar to those of the overall analysis set.

Results were similar for the PP Analysis Set.

3.1.1.2.2.4 Sponsor's Analysis of Secondary Efficacy Endpoints

Secondary efficacy variable were divided into two groups. The first group included major secondary endpoints, where ranked by importance as specified by the SAP. The second group included all other secondary variables.

3.1.1.2.2.4.1 Major Secondary Endpoints

The following table listed the sections in which the results of the ranked secondary endpoints were presented.

Major Secondary Endpoints
Full Analysis Set
Protocol M04-691

Ranked Secondary Variables	Rank	p-value 160/80 mg vs. Placebo	Section
Proportion of subjects with CR-100 at Week 4	1	0.008	3.1.1.2.2.4.2
Proportion of subjects with CR-70 at Week 4	2	0.001	3.1.1.2.2.4.3
Change from Baseline in IBDQ total Score at Week 4	3	<0.001	3.1.1.2.2.4.4
Proportion of subjects with CR-70 at Week 2	4	<0.001	3.1.1.2.2.4.3
Proportion of subjects with CR-70 at Week 1	5	0.004	3.1.1.2.2.4.3
Change from Baseline in SF-36 PCS Score at Week 4	6	0.010	3.1.1.2.2.4.5
Change from Baseline in VAS score for Joint pain at Week 4	7	0.970	3.1.1.2.2.4.6
Proportion of subjects with no draining Fistulas at last two evaluations	8	1.000	3.1.1.2.2.4.7
Change from Baseline in CRP at Week 4	9	<0.001	3.1.1.2.2.4.8
Change from Baseline in SF-36 Mental Component Summary score at Week 4	10	0.015	3.1.1.2.2.4.5
Proportion of subjects with remission at Week 2	11	<0.001	3.1.1.2.2.4.9

Copied from table in page 112.

3.1.1.2.2.4.2 Proportion of Subjects with CR-100 at Over Time

A summary of the proportion of subjects who achieved CR-100 over time is given below.

CR-100 Over Time
Full Analysis Set
Protocol M04-691

	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg	Difference in	
Visit	N=166	N=159	Proportions (95% CI)	p-value[a]
Week 1	20 (12.0)	31 (19.5)	7.4 (-0.5, 15.4)	0.065
Week 2	30 (18.1)	58 (36.5)	18.4 (8.9, 27.9)	< 0.001
Week 4	41 (24.7)	61 (38.4)	13.7 (3.7, 23.7)	0.008

CR-100 response is defined as a decrease from Baseline in CDAI score ≥ 100 points.

a. The p-value is from Pearson's Chi-square test.

Cross Reference: Section 14, Table 14.2__1.4.1.

As seen from table above, the proportion of subjects in the full analysis set achieving CR-100 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group. A statistically significant difference was also observed at Week 2. Results of the LOCF analysis were similar to those of the OC analysis.

3.1.1.2.2.4.3 Proportion of Subjects with CR-70 at Over Time

A summary of the proportion of subjects who achieved CR-70 over time is given below.

CR-70 Over Time
Full Analysis Set
Protocol M04-691

	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg	Difference in	
Visit	N=166	N=159	Proportions (95% CI)	p-value[a]
Week 1	34 (20.5)	55 (34.6)	14.1 (4.5, 23.7)	0.004
Week 2	54 (32.5)	83 (52.2)	19.7 (9.1, 30.2)	< 0.001
Week 4	56 (33.7)	82 (51.6)	17.8 (7.3, 28.4)	0.001

CR-70 response is defined as a decrease from Baseline in CDAI score ≥ 70 points.

a. The p-value is from Pearson's Chi-square test.

Cross Reference: Section 14, Table 14.2__1.3.1.

As seen from table above, the proportion of subjects in the full analysis set achieving CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group. Statistically significant differences were also observed at Weeks 1 and 2. Results of the LOCF analysis were similar to those of the OC analysis.

3.1.1.2.2.4.4 Change from Baseline in IBDQ Total Score at Week 4

A summary of change from Baseline in IBDQ scores at Week 4 for full analysis set is given Appendix Table 6.

As seen from Appendix Table 6, statistical significant differences between the adalimumab and placebo groups were observed at Week 4 for mean change from Baseline in IBDQ total score and each IBDQ domain score (social function, systemic system, emotional function, and bowel symptoms). Results of the LOCF analysis were similar to those of the OC analysis.

3.1.1.2.2.4.5 Change from Baseline in SF-36 PCS Score at Week 4

A summary of the mean change from Baseline in SF-36 variables at Week 4 is given in Appendix Table 7.

As seen from Appendix Table 7, statistical significant differences between the adalimumab and placebo groups were observed for mean change from Baseline to Week 4 in PCS, MCS, all of the SF-36 sub-domains except physical function, role function, and emotional.

3.1.1.2.2.4.6 Mean Change from Baseline to Week 4 in VAS Score for Joint Pain

A summary of the mean change from Baseline to Week 4 in VAS score for joint pain is given in Appendix Table 8.

As seen from Appendix Table 8, no statistically significant difference between adalimumab and placebo groups was observed for mean change from Baseline in VAS score for joint pain at Week 4. A mean decrease of 9.0 and 9.1, respectively, in the placebo and adalimumab groups was observed.

3.1.1.2.2.4.7 Fistula Improvement and Remission at Week 4

A summary of the fistula remission and improvement at Week 4 is given in Appendix Table 9.

As seen from Appendix Table 9, no statistically significant difference between the adalimumab and placebo groups was observed for the proportion of subjects with either remission or improvement at Week 4

3.1.1.2.2.4.8 Change from Baseline in CRP at Week 4

Results of changes from Baseline in CRP at Week are summarized in Appendix Table 10.

As seen from Appendix Table 10, a statistically significant difference between the adalimumab and placebo was observed at Week 4 for change from Baseline in CRP.

3.1.1.2.2.4.9 Clinical Remission at Week 2

A summary of clinical remission at Week 2 is given in Appendix Table 11.

As seen from Appendix Table 11, the proportion of subjects who achieved clinical remission (CDAI < 150) at Week 2 was statistically significant greater in the adalimumab 160/80 mg group compared to the placebo group.

3.1.1.2.3 Reviewer's Comments and Evaluation

More subjects in placebo were early withdrawn as compared to adalimumab 160 mg/80 mg (10 vs. 4, p=0.1194).

3.1.1.2.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

Placebo had more subjects who were discontinued from study as compared to adalimumab 80 mg (10 for placebo and 4 for adalimumab 160 mg/80 mg).

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. The sponsor's analysis was the "worst" case analysis. This reviewer performed sensitivity analyses including the "best" case and observed case analyses. Two sensitivity analyses were performed were:

OC - only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals.

"Best" Case - any patients with missing data who was randomized to active treatment was classified as 'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'.

3.1.1.2.3.1.1 Sensitivity Analysis

Summary of results for reviewer sensitivity is given below

Induction of Clinical Remission at Week 4
Reviewer's Sensitivity Analysis
Protocol M04-691

Analysis	Adalimumab 160 mg/80 mg	Placebo	Difference	95% C.I.	Chj-square p-value
OC	34/155 (21.9%)	12/156 (7.7%)	14.2%	(6.5%, 22.0%)	0.0004
Best	34/159 (21.4%)	22/166 (13.3%)	8.1%	(-0.07%, 16.3%)	0.0910

Complied by this reviewer.

As seen from table above, for the OC case analysis, adalimumab 160 mg/80 mg was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 as compared to placebo,

3.1.1.2.3.1.2 Subgroup Analysis

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M04-691

Category	Adalimumab 160 mg/80 mg	Placebo	Difference	95% C. I.
Country				
Belgium	9/18 (50.0%)	2/18 (11.1%)	38.9%	(11.6%, 66.2%)
Canada	7/25 (28.0%)	0/28 (0.0%)	28.0%	(10.4%, 45.6%)
France	2/5 (40.0%)	0/6 (0.0%)	40.0%	(-3.0%, 82.0%)
USA	16/111 (14.4%)	10/114 (8.8%)	5.6%	(-2.7%, 14.0%)
Gender				
Male	10/50 (20.0%)	5/65 (7.7%)	12.3%	(-0.5%, 25.2%)
Female	24/109 (22.0%)	7/101 (6.9%)	15.1%	(5.9%, 24.3%)
Age				
<40 years	20/88 (22.7%)	9/102 (8.8%)	13.9%	(3.6%, 24.2%)
40-64	13/68 (19.1%)	3/60 (5.0%)	14.1%	(3.3%, 25.0%)
65-74	1/2 (50.0%)	0/3 (0.0%)	50.0%	(-19.3%, 100%)
≥ 75	0/1 (0.0%)	0/1 (0.0%)		
Body weight				
≤70 kg	19/91 (20.9%)	6/91 (6.6%)	14.3%	(4.5%, 24.1%)
>70 kg	15/68 (22.1%)	6/75 (8.0%)	14.1%	(2.4%, 25.7%)
Tobacco Use				
User	13/55 (23.6%)	4/56 (7.1%)	16.5%	(3.4%, 29.6%)
Ex-User	8/39 (20.5%)	1/45 (2.2%)	18.3%	(4.9%, 31.7%)
Never	13/65 (20.0%)	7/65 (10.8%)	9.2%	(-3.1%, 21.5%)
Alcohol Use				
Drinker	22/77 (28.6%)	8/86 (9.3%)	19.3%	(7.5%, 31.1%)
Ex-Drinker	1/14 (7.1%)	2/19 (10.5%)	-3.4%	(-22.7%, 15.9%)
Never	11/68 (16.2%)	2/61 (3.3%)	12.9%	(3.1%, 22.7%)
HACA to Infliximab				
Positive	10/48 (20.8%)	2/58 (3.4%)	17.4%	(5.0%, 29.8%)
Negative	21/105 (20.0%)	10/101 (9.9%)	10.1%	(0.5%, 19.7%)
Missing	3/6 (50.0%)	0/7 (0.0%)	50.0%	(10.0%, 90.0%)
Use of Corticosteroids at baseline				
Yes	18/55 (32.7%)	3/73 (4.1%)	28.6%	(15.4%, 41.8%)
No	16/104 (15.4%)	9/93 (9.7%)	5.7%	(-3.5%, 14.9%)
Use of immunosuppressants at baseline				

Yes	16/73 (21.9%)	6/85 (7.1%)	14.9%	(3.9%, 25.8%)
No	18/86 (20.9%)	6/81 (7.4%)	13.5%	(3.2%, 23.8%)
Use of oral aminosalicylates at baseline				
Yes	6/45 (13.3%)	6/60 (10.0%)	3.3%	(-9.2%, 15.8%)
No	28/114 (24.6%)	6/106 (5.7%)	18.9%	(9.9%, 27.9%)
Baseline CRP				
<1 mg/dL	15/82 (18.3%)	7/98 (7.1%)	11.1%	(1.3%, 21.1%)
≥1 mg/dL	19/77 (24.7%)	5/68 (7.4%)	17.3%	(5.9%, 28.8%)
Intolerance to Infliximab				
Yes	21/95 (22.1%)	5/95 (5.3%)	16.8%	(7.4%, 26.3%)
No	13/64 (20.3%)	7/71 (9.9%)	10.5%	(-1.6%, 22.5%)
Lost response to previous Infliximab				
Yes	15/77 (19.5%)	7/87 (8.0%)	11.4%	(0.9%, 22.0%)
No	19/82 (23.2%)	5/78 (6.4%)	16.8%	(6.1%, 27.4%)
Missing		0/1 (0.0%)		
Baseline CDAI scores				
< 220		0/1 (0.0%)		
220-270 points	19/43 (44.2%)	4/51 (7.8%)	36.3%	(19.8%, 52.9%)
271-330 points	11/59 (18.6%)	8/52 (15.4%)	3.3%	(-10.7%, 17.2%)
331-390 points	1/38 (2.6%)	0/34 (0.0%)	2.6%	(-2.5%, 7.7%)
391-450 points	3/19 (15.8%)	0/27 (0.0%)	15.8%	(-6.1%, 32.2%)
>450		0/1 (0.0%)		

Complied by this reviewer.

As seen from table above, proportion of subjects in induction of clinical remission at Week 4 was consistent for subgroups of gender, age, body weight, tobacco use, use of immunosuppressant, baseline CRP, intolerance to infliximab, and lost response to previous infliximab. But, it was not consistent for subgroups of country, alcohol use, use of corticosteroids, use of aminosalicylates, and baseline CDAI scores.

3.1.1.2.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints

Secondary efficacy variable were divided into two groups. The first group included 11 major secondary endpoints, where ranked by importance as specified by the SAP. The second group included all other secondary variables. But no adjustments were prospectively defined for analyses of secondary efficacy endpoints. So, the p-values reported by sponsor were not adjusted and results of these analyses should be considered as "exploratory."

3.1.1.2.3.3 Reviewer's Comments on Change from Baseline in IBDQ Total Score at Week 4

Results from sponsor's analysis of change from baseline in IBDQ total score at Week 4 demonstrated statistical significance in favor of Adalimumab 160 mg/80 mg over placebo; but treatment difference (LS mean differences) was about 14.2 for total score and ranged from 1.97 to 5.34 for components of IBDQ. Treatment differences might not be clinical meaningful.

3.1.2 Maintenance Studies

The two studies designed to evaluate adalimumab as maintenance therapy for moderate to severe Crohn's disease were Studies M02-404 and M02-433. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

In a second supportive Maintenance Study M02-433, the extension study to Study M02-403, the primary evaluation was the maintenance of remission through year one in subjects who had achieved remission.

3.1.2.1 Study M02-404

3.1.2.1.1 Study Design

This study was a randomized, double-blind, placebo-controlled, multi-center (92 sites), efficacy and safety study designed to demonstrate the effectiveness of adalimumab in the induction and maintenance of clinical remission in subjects with moderate to severe Crohn's disease.

The objective of this study was to assess the efficacy and safety of 40 mg weekly or 40 mg every other week (eow) sc doses of adalimumab for the induction and maintenance of clinical remission in subjects with moderate to severe Crohn's disease.

Subjects having a diagnosis of Crohn's disease for greater than 4 months with confirmation by endoscopic or radiologic evaluation and Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 and having met exclusion criteria were eligible for study participation.

Study medication was administered by sc injection. At baseline, all subjects received open-label 80 mg adalimumab sc at baseline (Week 0) followed by a 40 mg dose at Week 2. At Week 4, subjects were evaluated for clinical response. All subjects were then randomized to receive sc injection of adalimumab 40 mg eow, or adalimumab 40 mg ew or placebo and treated for up to 52 additional weeks.

The Week 4 randomization was stratified by subjects' responder status and previous anti-TNF use. If subjects in the randomized portion of the study experienced a disease flare (defined as a recurrence of very active disease, specifically an increase in CDAI when compared to Week 4 of $\geq$ 70 points and a CDAI above 220) at or after Week 12 and was between scheduled visits, they could be switched to an open-label portion of study where they would receive 40 mg weekly sc eow. If subjects flared on this dose scheduled, they might switch to open-label 40 mg weekly sc dose. If after the dose frequency was increased, subjects continued to demonstrate a lack of improvement, they would be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders (do not attain a CDAI decrease of $\geq$ 70 points compared to baseline) at or after Week 12, they might also switch to the open-label portion of the study after a discussion with the sponsor's medical monitor.

Subjects were not allowed to decrease Crohn's specific concomitant medications.

Subjects might continue their doses of Imuran (azathioprine), 6-MP, and MTX provided they were on these medications for at least 12 weeks prior to screening and that doses had been stable for at least 4 weeks prior to screening. Doses were to remain stable during the entire course of the study (Week 60).

Subject might continue doses of 5-ASA, sulfasalazine, mesalamine, or Crohn's related antibiotics provided they had been on stable doses of these medications for at least 4 weeks prior to screening. Doses were to remain stable during the entire course of the study (Week 60).

No escalation of Crohn's related concomitant treatments were allowed. No reductions in concomitant therapy would be allowed except for corticosteroids and Crohn's treatment-related toxicities (e.g Leukopenia) of Grade 3 or higher.

Corticosteroids ($\leq$ 30 mg/day of prednisone [or equivalent]) were permitted provided subjects were on stable doses for at least 2 weeks prior to screening.

Budesonide $\leq$ 9 mg/day was permitted provided subjects were on stable doses for at least 2 weeks prior to screening.

Subjects might not be on both budesonide and prednisone (or equivalent) simultaneously.

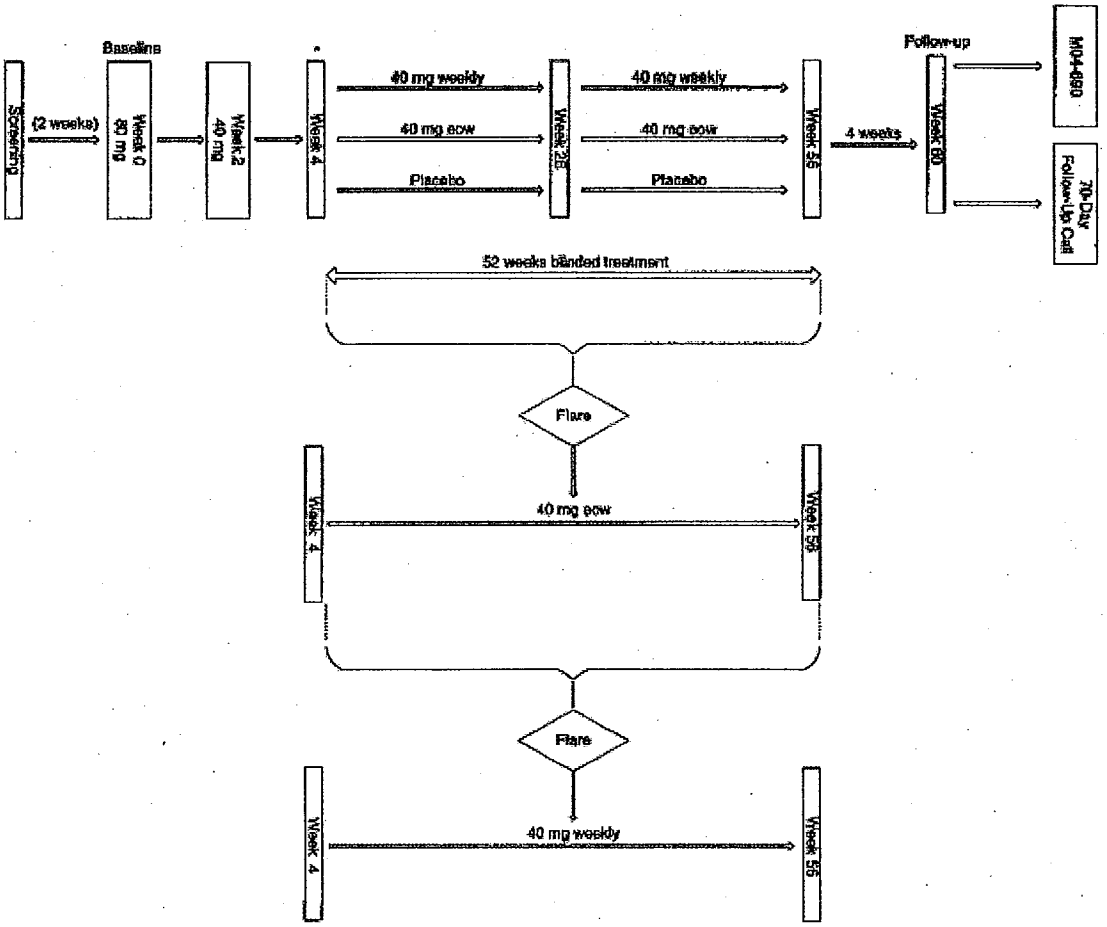
Live vaccine should not be given concurrently while on study drug.

Infliximab or any other anti-TNF was prohibited within 12 weeks before screening and during the study. Cyclosporine, mycophenolate mofetil, tacrolimus, and enemas (except enemas related to routine colonoscopy) were prohibited during the study.

Subjects taking cyclosporine, mycophenolate mofetil and tacrolimus needed to discontinue use 8 weeks prior to enrollment.

The duration of the study was up to 62 weeks, which included a 2-week screening and a 4-week follow-up period. Study visit from baseline through Week 8 occurred every 2 weeks. Study visits from Week 8 through Week 20 occurred every 4 weeks. Study visits from Week 20 through Week 32 occurred very 6 weeks. Study visits from Week 32 through Week 56 occurred every 8 weeks. The visit window was + or -7 days for the time period between screening and baseline. The visit window was + or -3 days for all visits from baseline through Week 8. The visit window was + or -7 days for all visits from Week 12 through follow up.

The schematic of the study design is shown below.



*All subjects will be randomized at Week 4. However, the co-primary endpoints will be the proportion of subjects who were at least clinical responders (CDAI decrease of ≥70 when compared to baseline) at Week 4 who are in clinical remission at Week 26 and Week 56.

A CDAI score was calculated from a subject diary and appropriate laboratory values at all study visits beginning at baseline.

Subjects completed Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline, Weeks 4, 12, 26, and 56/early termination.

36-Item Short Form (SF-36), Global Rating of Change Questionnaire, Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale, Zung Depression Self-Rating Scale and a Nutritionals, Productivity and Pain Questionnaire were completed by the subject at baseline, Weeks 4, 12, 26, and 56/early termination.

A Drug Safety Monitoring (DSMB) met to discuss unblinded data from the study twice a year and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC) made final decisions based on DSMB recommendations.

The primary efficacy variable was clinical remission (CDAI< 150). The first co-primary endpoint was the proportion of subjects in clinical remission at Week 26 who had at least a clinical response (decrease in CDAI scores ≥ 70 points when compared to baseline) at Week 4, and the second co-primary endpoint was the proportion of subjects in clinical remission at Week 56 who had at least a clinical response at Week 4,

The secondary efficacy variables were clinical response (CDAI decrease by 70 and 100 points), clinical remission (CDAI < 150), IBDQ score, fistula counts, steroid use, Crohn's Disease Endoscopic Index of Severity (CDEIS) scores, simple endoscopic score for Crohn's disease (SES-CD) and ulcer counts.

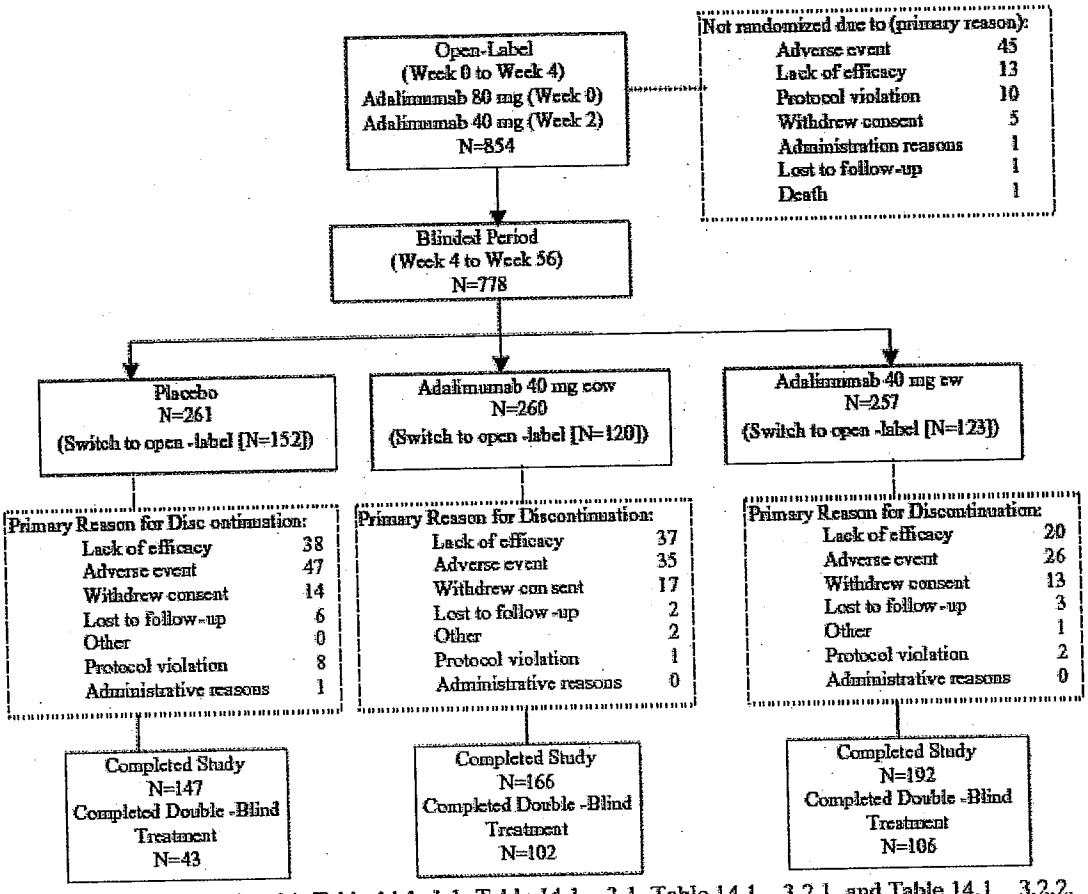
Assuming a 14% of clinical remission in the placebo arm and a 28% clinical remission in the adalimumab arms at Week 56, 160 subjects per treatment arm provided 87% power at 0.05 alpha level and 80% power at adjusted 0.025 alpha level. It provided more than 90% power to test clinical remission rate at Week 26. Thus, a total of 480 subjects were needed for the primary analysis for Week 4 responders.

Assuming 58% of subject would achieve clinical response at Week 4, approximately 830 subjects at the study baseline allowed 160 subjects to be equally allocated to the adalimumab 40 mg weekly, 40 mg eow, and the placebo groups at Week 4. If the actual response rate at Week 4 was higher or lower than the anticipated rate then subject enrollment might be shorten or extended, respectively. As result, the total number of subjects at baseline may vary accordingly.

3.1.2.1.2 Sponsor's Analysis

A total of 854 subjects participated in the 4-week open-label (OL) induction phase of study (adalimumab 80 mg followed by adalimumab 40 mg). Of these, 778 went on to participate in the double-blind (DB) phase of the study (261 in placebo, 260 in adalimumab 40 mg eow, and 257 in adalimumab 40 mg ew), and 505 subjects (147 in placebo, 166 in adalimumab 40 mg eow, and 192 in adalimumab 40 mg ew) completed Week 56. Week 56 completers either rolled over to Study M04-690 or continued in this study for the 4-week follow-up period. Nine additional subjects prematurely discontinued from the study, but their final study visit fell within the Week 56 window for analysis. Therefore, a total of 514 subjects participated in the Week 56 Visit based on subjects who had evaluation of vital signs or CDAI score.

A flowchart showing the disposition of subjects is present below.



Cross Reference: Section 14, Table 14.1_1.1, Table 14.1__3.1, Table 14.1__3.2.1, and Table 14.1__3.2.2.

The rate of premature discontinuation from the study was 8.9% (76/854) during the 4-week OL induction with adalimumab and 35.1% (273/778) during the randomization phase.

Statistically significantly greater proportions of subjects randomized to placebo and adalimumab 40 mg eow (43.7% and 36.2%, respectively) prematurely discontinued from the study compared to adalimumab 40 mg ew (25.3%; $p<0.001$ and $p\leq0.008$, respectively).

During both OL induction and randomization phase, the most common reason for discontinuation was an AE.

Of these 514 subjects who participated in the Week 56 visit, 251 subjects (49.7%) remained on their randomized DB treatment (43 placebo, 102 adalimumab 40 mg eow, and 106 adalimumab 40 mg ew).

The proportion of subjects who experienced a disease flare or non-response in the DB phase and were switched to received OL adalimumab was greater in placebo subjects

(58.2%) compared to adalimumab 40 mg eow and adalimumab 40 mg ew subjects (46.2% and 47.9%, respectively).

The ITT, mITT, PP, RNR, and endoscopy datasets were used to analyze efficacy while safety dataset was used to analyze safety. Summary of datasets by treatment group is given below.

In the randomized non-responder (RNR) dataset, a statistically significantly greater proportion of placebo subjects (59.3%) prematurely discontinued from the DB or OL phases compared to adalimumab 40 mg eow and adalimumab 40 mg ew subjects (42.0% and 39.0%, respectively; p=0.025 and p=0.006, respectively).

A summary of datasets by treatment group is given below.

Datasets by Treatment Group

	Treatment Group n (%)			Not Randomized
	Placebo	Adalimumab eow	Adalimumab ew	
	N=261	N=260	N=257	N=76
ITT Dataset	261 (100.0)	260 (100.0)	257 (100.0)	0
mITT Dataset	170 (65.1)	172 (66.2)	157 (61.1)	0
RNR Dataset	91 (34.9)	88 (33.8)	100 (38.9)	0
Per Protocol Dataset	142 (54.4)	147 (56.5)	138 (53.7)	0
Endoscopic Dataset	4 (1.5)	7 (2.7)	8 (3.1)	-
Safety Dataset	261 (100.0)	260 (100.0)	257 (100.0)	76 (100.0)

eow = every other week; ew = weekly; ITT = intent-to-treat; mITT = modified intent-to-treat; RNR = randomized non-responder

Cross Reference: Section 14, Table 14.1__1.1, Table 14.1__2.1, and Table 14.2__7.1.1.

The ITT dataset included all randomized subjects who received at least one dose of randomized study drug, while the safety dataset included all subjects who received at least one dose of any study drug (including OL induction).

The modified intent-to-treat (mITT) included all randomized subjects who received at least one dose of randomized study drug and achieved clinical response at Week 4 (defined as a CDAI decrease $\geq$ 70 compared to the Baseline CDAI).

The per-protocol (PP) included all subjects in the mITT population who had no major protocol deviations.

The RNR dataset included all randomized subjects who failed to achieve a clinical response at Week 4.

The endoscopic dataset included all ITT subjects who underwent endoscopy.

3.1.2.1.2.1 Planned Analysis

The primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT), which was defined as all treated subjects who achieved clinical response (CDAI decrease ≥ 70) at Week 4 and were randomized to receive one of the three blind treatments. Additional analyses were performed on the "per-protocol" population, which excluded all subjects with major protocol deviations in the modified ITT population. This was the additional analysis population for primary efficacy variables.

The primary efficacy variable was clinical remission (CDAI< 150). The first co-primary endpoint was the proportion of subjects in clinical remission at Week 26 who had at least a clinical response (decrease in CDAI scores ≥ 70 points when compared to baseline) at Week 4, and the second co-primary endpoint was the proportion of subjects in clinical remission at Week 56 who had at least a clinical response at Week 4,

There were four subset populations that were analyzed in this study. They were:

(1) Week 4 non-responder subset of all treated population;
(2) subjects with previous and/or concomitant use of other Crohn's medications subset of the modified ITT population;
(3) the subset of all treated population with endoscopic evaluation;
(4) subjects with baseline CRP values of ≥ 1.0 mg/dL.

These subset populations were subjected to primary and secondary analyses, as appropriate.

The secondary efficacy variables were clinical response (CDAI decrease by 70 and 100 points), clinical remission (CDAI < 150), IBDQ score, fistula counts, steroid use, Crohn's Disease Endoscopic Index of Severity (CDEIS) scores, simple endoscopic score for Crohn's disease (SES-CD) and ulcer counts.

The secondary efficacy endpoints were:

(1) the proportion of subjects in clinical remission at Week 60;
(2) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score ≥ 70 points) at Weeks 26, 56 and 60;
(3) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score ≥ 100 points) at Weeks 26, 56 and 60;
(4) changes from baseline in IBDQ scores at Weeks 26 and 56;
(5) proportion of subjects with improvement in the number of draining fistulas (where improvement was defined as a decrease from baseline in the number of draining fistulas of ≥ 50% for at least 2 consecutive visits);
(6) proportion of subjects with fistula remission (where fistula remission was defined as a closure of all fistulas that were draining at baseline for least 2 consecutive visits);
(7) steroid sparing at Weeks 26 and 56 (the proportion of subjects at Weeks 26 and 56 in clinical remission [CDAI< 150] able to discontinue steroid use);
(8) of those with a clinical response (CDAI decrease ≥ 70 points) at Week 4, time to

flare, up to and including Week 56 (where flare was defined as a recurrence of very active disease, specifically an increase in the CDAI when compared to the Week 4 baseline, of $\geq$ 70 points and a CDAI above 220).

Proportion of all subjects who achieved clinical response or remission was summarized at Week 4. Comparisons of Week 26 and 56 remission rates between treatment groups were also tested in the subject(s) with previous and/or concomitant use of other Crohn's medications and in subjects with baseline CRP values of $\geq$1.0 mg/dL.

All statistical test was two-sided and was conducted at an α=0.05 level (2-sided).

Demographic and baseline characteristics among the three treatment groups were summarized and compared by previous anti-TNF. Continuous variables were compared using the stratum-adjusted Kruskal-Wallis test, and discrete variables were compared using the Cochran-Mantel-Haenszel (CMH) Chi-square test adjusted for previous anti-TNF use.

The primary analysis was the hypothesis tests for adalimumab treatment effect at Weeks 26 and 56 in the modified ITT population. It encompassed the comparisons of the proportion of subjects who were responders at Week 4 and in clinical remission at Week 26 or 56 between each adalimumab arm and placebo treatment group using the CMH Chi-square test adjusting for previous anti-TNF use. Subjects without CDAI assessments at Week 26 or 56 were classified as remission "failure." Consistent non-responders after Week 12 were reviewed by the sponsor's medical monitor on a case-by-case basis, and might be classified as "failures" as appropriate.

Hypothesis testing for the co-primary endpoints was carried out in a hierarchical order. The Week 26 remission rate was tested first. If the hypothesis test Week 26 remission rate was rejected then the Week 56 remission rate would be tested. Otherwise, testing would stop.

While testing the hypothesis for the 2 dose arms at the Week 26 remission, the Hochberg procedure would be applied to control for multiplicity. Each adalimumab dose group would be compared with the placebo group in the proportion of subjects in clinical remission at Week 26. If both p-values were smaller than 0.05, then the individual null hypotheses (no treatment difference between adalimumab and the placebo) would be rejected and the hypothesis test for Week 56 remission could be continued. If one p-value did not show significance at 0.05 alpha level, then the hypothesis test for this dose at Week 56 had to stop and the hypothesis test for the other dose would be subjected at an adjusted 0.025 alpha level.

If the null hypothesis was rejected at Week 26, then the Week 56 remission rate would be tested using the same testing procedure as for the Week 26 remission rate.

In an effort to assess the impact of subjects who dropped of the trial, data would be analyzed as observed as well as last observation carried forward (LOCF) post baseline.

The sponsor stated that no adjustment for alpha level would be needed for the secondary efficacy analyses.

In the analysis of secondary efficacy endpoints, continuous variable would be compared using the analysis of covariance (ANCOVA) adjusting for baseline value. Discrete variables would be compared using the Chi-square test. Statistical summaries would be displayed for subjects in clinical response, improvement in the number of draining fistulas, steroid taper, and fistula remission. Time to flare (Weeks 4 to 56) would be plotted using the Kaplan-Meier survival analysis and would be analyzed with log-rank test for the comparison between treatment groups.

Summary statistics for the primary and secondary endpoints would be provided for four subset populations.

In addition to the summary statistics for the Week 4 non-responder subgroup population, time to first response would be compared between each adalimumab group and the placebo by the Kaplan-Meier survival analysis.

3.1.2.1.2.2 Treatment Group Comparability

Summaries of the demographic characteristics at baseline and baseline Crohn's disease characteristics by treatment are presented in Appendix Tables 12 and 13 for ITT and mITT, respectively.

As seen from Appendix Tables 12 and 13, overall, demographic characteristics at baseline and baseline Crohn's disease characteristics were similar across three treatment groups for ITT and mITT .

3.1.2.1.2.3 Sponsor's Analysis of Primary Efficacy Endpoint

The co-primary efficacy endpoints, the proportion of mITT subjects who achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were compared between each of the adalimumab group and placebo using the CMH test stratified by previous anti-TNF use. Summary of clinical remission at Week 26 and Week 56 for mITT for observed case analysis given below. For observed case analysis, subjects who discontinued DB treatment were classified as not in clinical remission (response) after discontinuation DB treatment.

A summary of the proportion of subjects who achieved clinical remission at Weeks 26 and 56 for mITT dataset for observed case analysis is given below.

Clinical Remission at Week 26 and Week 56
mITT Dataset
Observed Case Analysis
Protocol M02-404

Visit	Placebo N=170 n (%)	Adalimumab eow N=172 n (%)	Adalimumab ew N=157 n (%)
Week 26	29 (17.1)	68 (39.5)	73 (46.5)
Week 56	20 (11.8)	62 (36.0)	65 (41.4)

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 26	Adalimumab 40 mg eow *vs.* placebo	22.5	(13.2, 31.7)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* placebo	29.4	(19.8, 39.1)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* adalimumab 40 mg eow	7.0	(-3.7, 17.7)	0.220
Week 56	Adalimumab 40 mg eow *vs.* placebo	24.3	(15.6, 32.9)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* placebo	29.6	(20.5, 38.7)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* adalimumab 40 mg eow	5.4	(-5.2, 15.9)	0.344

eow = every other week; ew = weekly; CI = confidence interval

a. The p-value is from CMH test stratified by previous anti-TNF use.

Note: Subjects without CDAI assessments at Weeks 26 or 56 were to be classified as remission "failures."

Cross Reference: Section 14, Table 14.2__1.1.2.

As seen from table above, the proportion of mITT subjects who achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

3.1.2.1.2.4 Sponsor's Analysis of Secondary Efficacy Endpoint

The secondary efficacy endpoints were:

(1) the proportion of subjects in clinical remission at Week 60;
(2) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score ≥ 70 points) at Weeks 26, 56 and 60;
(3) the proportion of subjects with a clinical response (defined as a decrease from baseline in CDAI score ≥ 100 points) at Weeks 26, 56 and 60;
(4) changes from baseline in IBDQ scores at Weeks 26 and 56;
(5) proportion of subjects with improvement in the number of draining fistulas (where improvement was defined as a decrease from baseline in the number of draining fistulas of ≥ 50% for at least 2 consecutive visits);
(6) proportion of subjects with fistula remission (where fistula remission was defined as a closure of all fistulas that were draining at baseline for least 2 consecutive visits);
(7) steroid sparing at Weeks 26 and 56 (the proportion of subjects at Weeks 26 and 56 in clinical remission [CDAI< 150] able to discontinue steroid use);

(8) of those with a clinical response (CDAI decrease ≥ 70 points) at Week 4, time to flare, up to and including Week 56 (where flare is defined as a recurrence of very active disease, specifically an increase in the CDAI when compared to the Week 4 baseline, of ≥ 70 points and a CDAI above 220).

3.1.2.1.2.4.1Clinical Response (CR-70) at Weeks 26 and 56

A summary of the proportion of subjects who achieved clinical response (CR-70) at Weeks 26 and 56 for mITT dataset for observed case analysis is given below.

Proportion of Subjects With Clinical Response (CR-70)
mITT Dataset
Observed Cases Analysis
Protocol M02-404

	Placebo	Adalimumab eow	Adalimumab ew
	N=170	N=172	N=157
Visit	n (%)		
Week 26	48 (28.2)	93 (54.1)	88 (56.1)
Week 56	30 (17.6)	74 (43.0)	77 (49.0)

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 26	Adalimumab 40 mg eow *vs.* placebo	25.8	(15.8, 35.9)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* placebo	27.8	(17.5, 38.1)	< 0.001
Week 56	Adalimumab 40 mg eow *vs.* placebo	25.4	(16.0, 34.7)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* placebo	31.4	(21.7, 41.1)	< 0.001

OC = observed cases; eow = every other week; ew = weekly; CI = confidence interval

a. The p-value is from CMH test stratified by previous anti-TNF use.

Cross Reference: Section 14, Table 14.2__3.2.2.

As seen from table above, the difference between each of the adalimumab groups and the placebo group in the proportion of mITT subjects achieving clinical response (CR-70) were statistically significant at Week 26 and Week 56 in observed cases (OC) analysis.

3.1.2.1.2.4.2 Clinical Response (CR-100) at Weeks 26 and 56

A summary of the proportion of subjects who achieved clinical response (CR-100) at Weeks 26 and 56 for mITT dataset for observed case analysis is given below.

Proportion of Subjects with Clinical Response (CR-100)
mITT Dataset
Observed Cases Analysis
Protocol M02-404

	Placebo	Adalimumab eow	Adalimumab ew
	N=170	N=172	N=157
Visit		n (%)	
Week 26	45 (26.5)	89 (51.7)	82 (52.2)
Week 56	28 (16.5)	71 (41.3)	75 (47.8)

Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 26	Adalimumab 40 mg eow *vs.* placebo	25.3	(15.3, 35.3)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* placebo	25.8	(15.5, 36.0)	< 0.001
Week 56	Adalimumab 40 mg eow *vs.* placebo	24.8	(15.6, 34.0)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* placebo	31.3	(21.7, 40.9)	< 0.001

OC = observed cases; eow = every other week; ew = weekly; CI = confidence interval

a. The p-value is from CMH test stratified by previous anti-TNF use.

Cross Reference: Section 14, Table 14.2__2.2.2.

As seen from table above, the difference between each of the adalimumab groups and the placebo group in the proportion of mITT subjects achieving clinical response (CR-100) was statistically significant at Week 26 and Week 56 in observed cases (OC) analysis.

3.1.2.1.2.4.3 Changes from Baseline in IBDQ Scores at Weeks 26 and 56

Summary of treatment differences from placebo in IBDQ variables at Week 56 is given in Appendix Table 14.

As seen from Appendix Table 14, in the OC analyses of the mITT dataset, statistically significant differences were observed between each of the adalimumab groups and the placebo group for the mean change from Baseline to Week 56 for IBDQ total score.

3.1.2.1.3 Reviewer's Comments and Evaluation

3.1.2.1.3.1 Reviewer's Comments on Study Design

Week 4 randomization was stratified by the subjects' responder status and previous anti-TNF use. So, subjects who had a clinical response (decrease in CDAI scores $\geq$ 70 points when compared to baseline) at Week 4 were randomized to received sc injection of adalimumab 40 mg eow, or adalimumab 40 mg ew or placebo. Primary analyses were performed in the modified ITT population instead of 'true" ITT population.

3.1.2.1.3.2 Sample Size Determination

Although not specified as a co-primary analysis, there was inadequate sample size to test of the difference between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at Weeks 26 and 56.

3.1.2.1.3.3 Assessment of IVRS Misclassification

The sponsor noted that among ITT subjects, examining the agreement between CRF (where investigators recorded the CDAI) and Interactive Voice Response System (IVRS) responder stratification, Some deviations were found. Deviations included 1.7% of subjects classified as responders by CRF and non-responders by IVRS and 11.2% of all subjects classified as non-responders by CRF and responders by IVRS. In the mITT dataset, 2.6% of subjects were classified as responders by CRF and non-responders by IVRS and no subjects were classified as non-responders by CRF and responders by IVRS.

When compared to the mITT dataset, dataset based on IVRS Week 4 responder status had slightly lower remission rates in each group (see Table below). This issue as identified until the database was locked.

A summary of the proportion of subjects who achieved clinical remission at Weeks 26 and 56 for mITT dataset and for IVRS Week 4 response status stratification for observed case analysis is given below.

Clinical Remission by mITT Dataset and by IVRS Week 4 Responder Status Stratification at Week 26 and Week 56 Observed Cases Analysis Protocol M02-404

Analysis	Placebo	Adalimumab eow	Adalimumab ew
Visit		n (%)	
mITT Dataset	**N=170**	**N=172**	**N=157**
Week 26	29 (17.1)	68 (39.5)	73 (46.5)
Week 56	20 (11.8)	62 (36.0)	65 (41.4)
IVRS Week 4 Responder Status	**N=192**	**N=191**	**N=189**
Week 26	32 (16.7)	72 (37.7)	74 (39.2)
Week 56	22 (11.5)	64 (33.5)	70 (37.0)

eow = every other week; ew = weekly

Note: Subjects without CDAI assessments at Weeks 26 or 56 were to be classified as remission "failures."

Cross Reference: Section 14, Table 14.2__1.1.2 and Table 14.2__1.1.4.

3.1.2.1.3.4 Clinical Remission at Weeks 26 and 56 by IVRS Week 4 Response Status Stratification

The sponsor noted that among ITT subjects, some deviation in the agreement between CRF (where investigators recorded the CDAI) and IVRS responder stratification were found. This reviewer performed analyses of clinical remission at Weeks 26 and 56 for subjects who achieved IVRS response.

A summary of clinical remission by IVRS Week 4 response status stratification is listed below.

Induction of Clinical Remission at Weeks 26 and 56 by IVRS Week 4 Responder Status Protocol M02-404

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	72/191 (37.7%)	74/189 (39.2%)	32/192 (16.7%)	<0.0001	<0.0001	<0.0001
56	64/191 (33.5%)	70/189 (37.0%)	22/192 (11.5%)	<0.0001	<0.0001	<0.0001

Complied by this reviewer.

As seen from table above, the proportion of subjects who achieved IVRS Week 4 response and achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

3.1.2.1.3.5 Population Difference between ITT and mITT Populations

In general, the mITT was similar to the ITT for demographic and baseline characteristics with exception of use of corticosteroids at baseline. In the mITT, there were more subjects with use of corticosteroids at baseline in the adalimumab ew as compared to adalimumab eow and placebo group (47% vs. 34% and 39%; p=0.0440). Because of this imbalance of use of corticosteroids at baseline for mITT population, results from subgroup analysis of steroid free remission might be biased and might be not reliable. The results have difficulty to be interpreted.

3.1.2.1.3.6 Reviewer's Comments on mITT Population

The Week 4 randomization was stratified by subjects' responder status and previous anti-TNF use.

The protocol stated that the primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT), which was defined as all treated subjects who achieved clinical response (CDAI decrease ≥ 70) at Week 4 and were randomized to receive one of the three blind treatments.

This reviewer found that for the mITT population, statistically significantly greater proportions of subjects randomized to placebo and adalimumab 40 mg eow (33.3% and 33.1%, respectively) prematurely discontinued from the study compared to adalimumab 40 mg ew (16.6%; $p<0.001$).

It was also found that for the mITT population, statistically significantly greater proportions of subjects randomized to placebo and switched to open label at Week 12 as compared to adalimumab 40 mg eow and adalimumab 40 mg ew (58.8% for placebo and about 40% for adalimumab treatment groups; $p<0.001$).

3.1.2.1.3.7 Reviewer's Sponsor's Analyses for Secondary Efficacy Endpoint

Statistical Analysis Plan was submitted on 13 September 2005 for review, discussed with FDA on 16-17 November 2005, and finalized on 2 December 2005. A formal review of the SAP was not conducted at the time.

In the SAP, for analyses of secondary efficacy endpoints it stated:

The secondary endpoints are divided into two groups. The first group includes major secondary efficacy endpoints which are ranked by importance in the order described below. The second group includes all other secondary efficacy endpoints and special assessments (listed in Sections 3.2.3, 3.3.4 and 3.2.5) which may be of interest to assess the effectiveness of adalimumab treatment.

Major Secondary Efficacy Endpoints:

Comparisons of adalimumab 40 mg EW versus placebo

- **Proportion of subjects with a clinical response CR-100 at Weeks 26 and 56 (mITT population)**
- **Proportion of subjects with a clinical response CR-70 at Weeks 26 and 56 (mITT population)**

Comparisons of adalimumab 40 mg EOW versus placebo

- **Proportion of subjects with a clinical response CR-100 at Weeks 26 and 56 (mITT population)**
- **Proportion of subjects with a clinical response CR-70 at Weeks 26 and 56 (mITT population)**

The comparison of adalimumab 40 mg EW versus placebo will be made for the following secondary endpoints in the stated order until the comparison is not statistically significant. Following the previous assessment, the comparison of adalimumab 40 mg EOW versus placebo will made for the following secondary endpoints in the stated order until the comparison is not statistically significant.

- **Time in response (CR-70) (mITT population)**

- **Proportion of subject who discontinue steroid use and remain steroid-free and in clinical remission for at least 90 days at Week 56 (mITT population)**
- **Time in remission (mITT population)**
- **Change from baseline in IBDQ total score at Weeks 26 and 56 (mITT population)**
- **Change from baseline in SF-36 Physical Component Summary at Weeks 26 and 56 (mITT population)**
- **Proportion of subjects with no draining fistulas at last 2 evaluations (ITT population)**
- **Proportion of subjects with complete healing of ulcers at Week 12 and Week 56 (Endoscopic population)**

All other secondary endpoints except changes from baseline in IBDQ scores at Weeks 26 and 56 and proportion of subjects with no draining fistulas at last 2 evaluations were not pre-specified in the protocol. The testing in a hierarchical order described above was not pre-specified in the protocol.

3.1.2.1.3.7.1 Steroid-Free Remission

Proportion of patients in steroid-free remission exceeding 90 days at Weeks 26 and Week 56 was not pre-specified in the protocol as one of the secondary efficacy endpoints or subgroup analysis. Steroid sparing at Weeks 26 and 56 was pre-specified in the protocol as one of secondary efficacy endpoints. Proportion of patients in steroid-free remission exceeding 90 days at Week 56 was included as one of secondary endpoints in the SAP. It was the fourth ranked secondary endpoint in hierarchical order.

In the mITT, there were significantly fewer numbers of steroid-free subjects at baseline in the placebo and adalimumab eow arms as compared to the adalimumab ew arm (39% and 34% vs. 47%; p=0.0440). This shows a potential imbalance across treatment groups that likely compromises inference.

The observed results for steroid free remission for $\geq$ 90 day at Week 26 and Week 56 are also likely misleading. The percent of patients in steroid free remission at Week 56 was higher than those at Week 26 (3%, 19%, and 15% at Week 26 and 5%, 29%, and 20% at Week 56, for placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew, respectively).

These percentages are also inconsistent with those observed for percent of patients with steroid free remission for the mITT population. Percents at Week 26 were 34%, 30%, and 3% for adalimumab 40 mg eow, adalimumab 40 mg ew and placebo, respectively. Percents of patients in steroid free remission at Week 56 for mITT were 30%, 23%, and 6% for adalimumab 40 mg eow, adalimumab 40 mg ew and placebo, respectively.

3.1.2.1.3.7.2 Time in Remission

Time in remission was not pre-specified in the protocol as one of the secondary efficacy endpoints. But, it was included as one of secondary endpoints in the SAP. It was the fourth ranked secondary endpoint in hierarchical order.

The sponsor performed two tests. One was for the time in remission among mITT population. The other was for the time in remission among subjects achieving clinical remission at Week 4 in the mITT population.

At baseline, all subjects received open-label 80 mg adalimumab sc at baseline (Week 0) followed by a 40 mg dose at Week 2. At Week 4, subjects were evaluated for clinical response. All subjects were then randomized to receive sc injection of adalimumab 40 mg eow, or adalimumab 40 mg ew or placebo and treated for up to 52 additional weeks. So, for the time in remission among mITT population endpoint, it included subjects who achieving clinical remission before Week 4.

The figures (378 days for adalimumab 40 mg eow and 127 days for placebo) for the median time in days cited in the clinical report was for the time in remission among mITT subjects who achieved clinical remission but not for the time in remission among subjects achieving clinical remission at Week 4 stated in sponsor's stated in proposed label for time in remission.

This reviewer performed analysis of time in remission for subjects achieving clinical remission at Week 4 in the mITT population using sponsor's program, *effi09.sas* - median *time in clinical remission for subjects who achieved clinical remissio*n, for using Kaplan-Meier method. .It was found that the median time in remission could be not estimated in both adalimumab groups because more than 50% remained in clinical remission at the end of study. The median time in remission for placebo was 197 days. The p-values for overall comparison and pairwise comparison are given below.

P-values for Testing Homogeneity of Survival Curve to Time in Remission (Subjects Achieving Clinical Remission at Week 4) mITT Population

Analysis	Comparison	Log-Rank	Wilcoxon
mITT			
	Overall	0.0254	0.1137
	40 mg eow vs. placebo	0.0106	0.0513
	40 mg ew vs. placebo	0.0406	0.1452
PP			
	Overall	0.0750	0.2517
	40 mg eow vs. placebo	0.0339	0.1234
	40 mg ew vs. placebo	0.0815	0.2459

Prepared by this reviewer.

As seen table above, the difference between each of the adalimumab group and the placebo group did not achieve statistical significance by the Wilcoxon test even with

adjustment for multiplicity. Since the Wilcoxon test gives more weight to early times than to late times, it is less sensitive than the log-rank test to differences between groups that occur at later points in time. So, the results on time in remission for subjects achieving clinical remission at Week 4 might not be robust. The time in remission for subjects achieving clinical remission at Week 4 was sensitive to various kinds of departures from that hypothesis (e.g. proportional hazards assumption).

3.1.2.1.3.8 LOCF Analysis of Primary Efficacy Endpoint

This reviewer performed LOCF analyses of clinical remission at Weeks 26 and 56 by for mITT population. The results are summarized below.

Induction of Clinical Remission at Weeks 26 and 56
mITT Population
LOCF Analysis
Protocol M02-404

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	81/171 (47.4%)	77/155 (49.7%)	40/168 (23.8%)	<0.0001	<0.0001	<0.0001
56	78/171 (45.6%)	70/155 (45.2%)	35/168 (20.8%)	<0.0001	<0.0001	<0.0001

Complied by this reviewer. P-values were obtained using Chi-square test.

As seen from table above, for the LOCF analysis, the proportion of mITT subjects who achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

3.1.2.1.3.9 LOCF Analyses of Clinical Responses CR-70 and CR-100

This reviewer performed LOCF analyses of clinical responses CR-70 and CR-100 at Weeks 26 and 56 by for mITT population. The results are summarized below.

Induction of Clinical Response (CR-70) at Weeks 26 and 56
mITT Population
LOCF Analysis
Protocol M02-404

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	123/171 (71.9%)	109/155 (70.3%)	91/168 (54.2%)	0.0008	0.0007	0.0028
56	112/171 (65.5%)	102/155 (65.8%)	84/168 (50.0%)	0.0034	0.0039	0.0041

Complied by this reviewer. P-values were obtained using Chi-square test.

Induction of Clinical Response (CR-100) at Weeks 26 and 56
mITT Population
LOCF Analysis
Protocol M02-404

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	113/171 (66.1%)	96/155 (61.9%)	74/168 (44.1%)	<0.0001	<0.0001	0.0013
56	103/171 (60.2%)	91/155 (58.7%)	68/168 (40.5%)	0.0003	0.0003	0.0011

Complied by this reviewer. P-values were obtained using Chi-square test.

As seen from tables above, for the LOCF analyses, the proportion of mITT subjects who achieved clinical responses CR-70 and CR-100 at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

3.1.2.1.3.10 Induction of Clinical Remission at Weeks 26 and 56 by Switch Status

This reviewer performed an analysis of clinical remission at Weeks 26 and 56 by switch status for mITT population. The results are summarized below.

Induction of Clinical Remission at Weeks 26 and 56
mITT Population by Switch Status
Protocol M02-404
Switch=0

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	63/104 (60.6%)	68/94 (72.3%)	23/70 (32.9%)	<0.0001	0.0003	<0.0001
56	70/104 (67.3%)	64/94 (68.1%)	24/70 (34.3%)	<0.0001	<0.0001	<0.0001

Switch=1

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	5/68 (7.4%)	5/63 (7.9%)	6/100 (6.0%)	0.8816	0.7279	0.6313
56	20/68 (29.4%)	13/63 (20.6%)	21/100 (21.0%)	0.3748	0.2128	0.9555

Complied by this reviewer. P-values were obtained using Chi-square test.

As seen from tables above, the proportion of subjects of mITT achieved clinical remission (CDAI < 150) at Weeks 26 and 56 for mITT subjects who stayed in blinded phase after Week 12 (Switch=0) were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

For mITT subjects who switched to open label phase, the proportion of subjects achieved clinical remission (CDAI < 150) at Weeks 26 and 56 was similar among treatment groups. Proportion of subjects achieved clinical remission was increased from about 7% at Week 26 to about 20% Week 56.

3.1.2.1.3.11 ITT Analysis of Induction of Clinical Remission at Weeks 26 and 56

This reviewer performed ITT analysis included all randomized patients. In this analysis, those subjects who had missing values at Week 26 or Week 56 were assumed as failures.

A summary of clinical remission at Weeks 26 and 56 for ITT analysis is listed below.

Induction of Clinical Remission at Weeks 26 and 56
ITT Population
Protocol M02-404

Week	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo	overall p-value	Adalim 40 mg eow vs. Plac p-value	Adalim 40 mg ew vs. Plac p-value
26	87/260 (33.5%)	82/257 (31.9%)	36/261 (13.8%)	<0.0001	<0.0001	<0.0001
56	76/260 (29.2%)	78/257 (30.4%)	27/261 (10.4%)	<0.0001	<0.0001	<0.0001

Complied by this reviewer. P-values were obtained using Chi-square test.

As seen from table above, the proportion of ITT subjects who achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

This reviewer tabulated subjects with clinical remission at Week 56 for ITT population by countries. Results are summarized below.

Induction of Clinical Remission at Week 56
ITT Dataset
Protocol M02-404

Country	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Austria	11/25 (44.0%)	7/22 (31.8%)	1/25 (4.0%)
Belgium	6/19 (31.6%)	12/24 (50.0%)	3/14 (21.4%)
Canada	18/69 (26.1%)	22/81 (27.2%)	8/78 (10.3%)
German	1/3 (33.3%)	1/4 (25.0%)	0/3 (0.0%)
Denmark	7/12 (58.3%)	3/6 (50.0%)	1/11 (9.1%)
Spain	1/2 (50.0%)	0/1 (0.0%)	1/4 (25.0%)
France	3/13 (23.1%)	5/13 (38.5%)	0/9 (0.0%)
Great Britain	0/4 (0.0%)	3/9 (33.3%)	1/9 (11.1%)
Hungary	0/2 (0.0%)	2/4 (50.0%)	0/5 (0.0%)
Italy	1/5 (20.0%)	1/5 (20.0%)	3/6 (50.0%)
Netherland	2/7 (28.6%)		0/7 (0.0%)
Norway			0/2 (0.0%)
Poland	2/7 (28.6%)	5/6 (83.3%)	0/2 (0.0%)
Sweden	1/3 (33.3%)	1/2 (50%)	0/2 (0.0%)

USA	16/79 (20.3%)	13/72 (18.1%)	8/75 (10.7%)
South Africa	7/10 (70.0%)	3/8 (37.5%)	1/9 (11.1%)

Complied by this reviewer.

As seen from table above, proportion of subjects in induction of clinical remission clinical remission (CDAI < 150 points) at Week 56 for ITT dataset was consistent for countries except Italy.

3.1.2.1.3.12 Subgroup Analyses of Primary Efficacy Endpoint

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Weeks 26 and 56 by treatment group for mITT dataset are given below.

Induction of Clinical Remission at Week 26
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Gender			
Male	28/61 (45.9%)	30/62 (48.4%)	12/65 (18.5%)
Female	40/111 (36.0%)	43/95 (45.3%)	17/105 (16.2%)
Age			
<40 years	43/106 (40.6%)	45/93 (48.4%)	19.105 (18.1%)
≥40	25/66 (37.9%)	28/64 (43.8%)	10/65 (15.4%)
Body weight			
≤70 kg	41/95 (43.2%)	49/94 (52.1%)	15/102 (14.7%)
>70 kg	27/77 (35.1%)	24/63 (38.1%)	14/68 (20.6%)
Tobacco Use			
User	26/62 (41.9%)	16/51 (31.4%)	8/63 (12.7%)
Ex-User	13/33 (39.4%)	27/48 (56.3%)	7/43 (16.3%)
Never	29/77 (37.7%)	30/58 (51.7%)	14/64 (21.9%)
Alcohol Use			
Drinker	40/98 (40.8%)	43/84 (51.2%)	14/90 (15.6%)
Ex-Drinker	5/6 (83.3%)	3/8 (37.5%)	3/8 (37.5%)
Never	23/68 (33.8%)	27/64 (42.2%)	12/72 (16.7%)
Use of Previous and concomitant other Crohn's medications			
Yes	62/161 (38.5%)	71/151 (47.0%)	25/160 (15.6%)
No	6/11 (54.5%)	2/6 (33.3%)	4/10 (40%)
Use of Corticosteroids at baseline			
Yes	24/58 (41.4%)	30/74 (40.5%)	7/66 (10.6%)
No	44/114 (38.6%)	43/83 (51.8%)	22/104 (21.2%)
Use of immunosuppressants			

at baseline			
Yes	32/77 (41.6%)	32/79 (40.5%)	14/83 (16.9%)
No	36/95 (37.9%)	41/78 (52.6%)	15/87 (17.2%)
Previous Use of Anti-TNF			
Yes	27/86 (31.4%)	31/75 (41.3%)	15/83 (18.1%)
No	41/86 (47.7%)	42/82 (51.2%)	14/87 (16.1%)
Use of oral aminosalicylates			
Yes	31/66 (47.0%)	31/61 (50.8%)	10/78 (12.8%)
No	37/106 (34.9%)	42/96 (43.8%)	19/92 (20.7%)
Baseline CRP			
<1 mg/dL	37/95 (38.9%)	31/82 (37.8%)	15/85 (17.6%)
≥1 mg/dL	31/76 (40.8%)	42/75 (56.0%)	14/85 16.5%)
Baseline CDAI scores			
< 220		0/1 (0.0%)	
220-270 points	22/47 (46.8%)	25/44 (56.8%)	13/41 (31.7%)
271-330 points	25/57 (43.9%)	26/61 (42.6%)	7/63 (11.1%)
331-390 points	17/46 (37.0%)	15/30 (50.0%)	6/32 (18.8%)
391-450 points	4/22 (18.2%)	7/21 (33.3%)	3/31 (9.7%)
≥ 451			0/3 (0.0%)

Complied by this reviewer.

Induction of Clinical Remission at Week 56
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Gender			
Male	27/61 (44.3%)	25/62 (40.3%)	6/65 (9.2%)
Female	35/111 (31,5%)	40/95 (42.1%)	14/105 (13.3%)
Age			
< 40 years	39/106 (36.8%)	38/93 (40.9%)	10/105 (9.5%)
≥ 40	23/66 (34.8%)	27/64 (42.2%)	10/65 (15.4%)
Body weight			
≤ 70 kg	37/95 (38.9%)	48/94 (51.1%)	11/102 (10.8%)
> 70 kg	25/77 (32.5%)	17/63 (27.0%)	9/68 (13.2%)
Tobacco Use			
User	22/62 (35.5%)	16/51 (31.4%)	7/63 (11.1%)
Ex-User	15/33 (45.5%)	24/48 (50.0%)	8/43 (18.6%)
Never	25/77 (32.5%)	25/58 (43.1%)	15/64 (7.8%)
Alcohol Use			
Drinker	42/98 (42.9%)	37/84 (44.1%)	8/90 (8.9%)
Ex-Drinker	2/6 (33.3%)	3/8 (37.5%)	3/8 (37.5%)
Never	18/68 (26.5%)	25/64 (39.1%)	9/72 (12.5%)
Use of Previous and concomitant other Crohn's			

medicationa			
Yes	56/161 (34.8%)	63/151 (41.7%)	16/160 (10.0%)
No	6/11 (54.5%)	2/6 (33.3%)	4/10 (40%)
Use of Corticosteroids at baseline			
Yes	20/58 (34.5%)	24/74 (32.4%)	6/66 (9.1%)
No	42/114 (36.8%)	41/83 (49.4%)	14/104 (13.5%)
Use of immunosuppressants at baseline			
Yes	30/77 (39.0%)	28/79 (35.4%)	10/83 (12.1%)
No	32/95 (33.7%)	37/78 (47.4%)	10/87 (11.5%)
Previous Use of Anti-TNF			
Yes	26/86 (30.2%)	25/75 (33.3%)	9/83 (10.8%)
No	36/86 (41.9%)	40/82 (48.8%)	11/87 (12.6%)
Use of oral aminosalicylates			
Yes	29/66 (43.9%)	29/61 (47.5%)	7/78 (9.0%)
No	33/106 (31.1%)	36/96 (37.5%)	13/92 (14.1%)
Baseline CRP			
<1 mg/dL	34/95 (35.8%)	27/82 (32.9%)	11/85 (12.9%)
≥1 mg/dL	28/76 (36.8%)	38/75 (50.7%)	9/85 (10.6%)
Baseline CDAI scores			
< 220		1/1 (100%)	
220-270 points	17/47 (36.2%)	23/44 (52.3%)	7/41 (17.1%)
271-330 points	24/57 (42.1%)	22/61 (36.1%)	7/63 (11.1%)
331-390 points	16/46 (34.8%)	14/30 (46.7%)	4/32 (12.5%)
391-450 points	5/22 (22.7%)	5/21 (23.8%)	2/31 (6.5%)
≥ 451			0/3 (0.0%)

Complied by this reviewer.

As seen from tables above, proportion of subjects in induction of clinical remission (CDAI < 150 points) at Weeks 26 and 56 for mITT dataset was consistent for subgroups of gender, age, body weight, tobacco use, alcohol use, use of immunosurppressant, use of corticosteroids, use of aminosalicylates, previous use of anti-TNF, baseline CRP, and baseline CDAI scores.

3.1.2.1.3.13 ITT Analyses of Sustained Clinical Remission and Sustained Clinical Responses

As suggested by Dr. Welch, this reviewer performed exploratory analyses for more stringent endpoints: sustained remission at weeks 4 and 56, sustained remission at weeks 4, 26, and 56, sustained clinical response CR-70 at weeks 4 and 26, sustained clinical response CR-70 at weeks 4, 26, and 56, sustained clinical response CR-100 at weeks 4 and 26, and sustained clinical response CR-100 at weeks 4, 26, and 56. Sustained remission and sustained were used in studies for Remicade. In Remicade studies the sustained remission and sustained response were based on Mayo scores.

3.1.2.1.3.13.1 ITT Analyses of Sustained Clinical Remission

In these analyses, subjects who switched to open-label were considered as "failure."

The results of exploratory analyses of sustained clinical remission at weeks 4 and 26 and clinical sustained remission at weeks 4, 26, and 56 are given below.

Sustained Clinical Remissions
(ITT Population)
Protocol M02-404

Sustained Remission	Adalimumab 40 mg eow	Adalimumab 40 mg ew	placebo	Overall p-value
Clinical remission at both Week 4 and 26	40/260 (15%)	36/257 (14%)	22/261 (8%)	0.0404
Clinical remission at Weeks 4, 26 and 56	32/260 (12%)	30/257 (12%)	9/261 (3%)	0.0005

Complied by this reviewer. p-values were obtained using Chi-square test.

As seen from table above, there were no differences between adalimumab 40 mg ew and adalimumab 40 mg eow treatment groups with regard clinical remission, both adalimumab treatment groups were superior to placebo. The treatment difference between adalimumab and placebo treatment group for mITT analysis tended to be large compared those given in ITT analysis.

3.1.2.1.3.13.2 ITT Analyses of Sustained Clinical Responses CR-70 and CR-100

The results of exploratory analyses of sustained clinical response CR-70 at weeks 4 and 26, sustained clinical response CR-70 at weeks 4, 26, and 56, sustained clinical response CR-100 at weeks 4 and 56, and sustained clinical response CR-100 at weeks 4, 26, and 56 are given below.

Sustained Clinical Response CR-70 and CR-100
(ITT Population)
Protocol M02-404

Sustained Response	Adalimumab 40 mg eow	Adalimumab 40 mg ew	placebo	Overall p-value
CR-70				
at both Week 4 and 26	91/260 (35%)	88/257 (34%)	48/261 (18%)	<0.0001
at Weeks 4, 26 and 56	71/260 (27%)	73/257 (28%)	30/261 (11%)	<0.0001

CR-100				
at both Week 4 and 26	69/260 (27%)	63/257 (25%)	38/261 (15%)	0.0019
at Weeks 4, 26 and 56	51/260 (20%)	52/257 (20%)	22/261 (8%)	0.0002

Complied by this reviewer. p-values were obtained using Chi-square test.

As seen from table above, there were no differences between adalimumab 40 mg ew and adalimumab 40 mg eow treatment groups with regard clinical responses CR-70 and CR-100 at both weeks 4 and 26 and at weeks 4, 26, and 56. Adalimumab treatment groups were superior to placebo. The treatment difference between adalimumab and placebo treatment groups for mITT analysis tended to be large compared those given in ITT analysis.

3.1.2.2 Study M02-433

3.1.2.2.1 Study Design

The objective of this study was to demonstrate the efficacy and safety adalimumab in the maintenance of clinical remission of subjects with Crohn's disease who participated in Protocol M02-403.

All study treatments were administered subcutaneously. All subjects received 40 mg eow open label study drug at the Baseline and Week 2 visits. Subjects previously in remission in the M02-403 study were evaluated at Week 4 visit. If they continued to be in remission, they were randomized to receive to weekly injection of 40 mg weekly, 40 mg eow, or placebo. Subjects not in remission at the Week 4 study visit of M02-403 and at Week 4 of this clinical trial received 40 mg eow open-label. After Week 56 subjects from the blinded portion of the study would be switch to 40 mg eow open-label therapy. In case of a flare or non-response, the subject might be switched to 40 mg weekly dosing.

A flare was defined as a recurrence of very active disease, specifically in increase in CDAI when compared to their M02-433 Week 4 value of 70 or more points and a CDAI above 220.

A non-responder was defined as not attaining CDAI decrease of $\geq$ 70 points compared to Study M02-403 Baseline.

All subjects received 40 mg of adalimumab subcutaneously at Baseline and Week 2. Subjects were randomized at Week 4 in the M02-433 trial base upon their clinical remission status at Baseline and Week 4. The first cohort was comprised of subjects who achieved clinical remission (defined as a CDAI < 150) at the end of Study M02-403, and remained in clinical remission at Week 4 of Study M02-433. These subjects were randomized to receive weekly injection of either adalimumab 40 mg weekly, 40 mg every other week (eow), or placebo. If the subjects in this randomized portion of the study

developed a disease flare, they could be switched to the open-label portion of the study after a discussion with the Abbott Medical Monitor. Subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

The second cohort was comprised of subjects who did not achieve clinical remission (defined as those subjects who did not achieve a CDAI score of < 150) at Week 4 of M02-403/M02-443 Baseline or those subjects who were no longer in remission at Week 4 of M02-433. These study subjects, regardless of any future response, were not randomized into the double-blind portion of the study. These subjects received 40 mg eow of open-label adalimumab starting at the baseline visit. From Week 4 onward, subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

When entering the extension portion of this study at Week 56, subjects who were in the blinded cohort would be assigned to open-label adalimumab 40 mg every other week (eow). From Week 4 onward, subjects who developed a flare of Crohn's disease while receiving 40 mg eow of adalimumab might have their dose frequency increased to 40 mg weekly. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg eow, they might also have their dose of study medication increased to 40 mg weekly after a discussion with the Abbott Medical Monitor. Subjects receiving 40 mg weekly dosing who continued to have a disease flare or developed another flare might be withdrawn from the study. In addition, if subjects did not meet the definition of flare, but were consistent non-responders while receiving 40 mg weekly, might be withdrawn from the study after a discussion with the Abbott Medical Monitor.

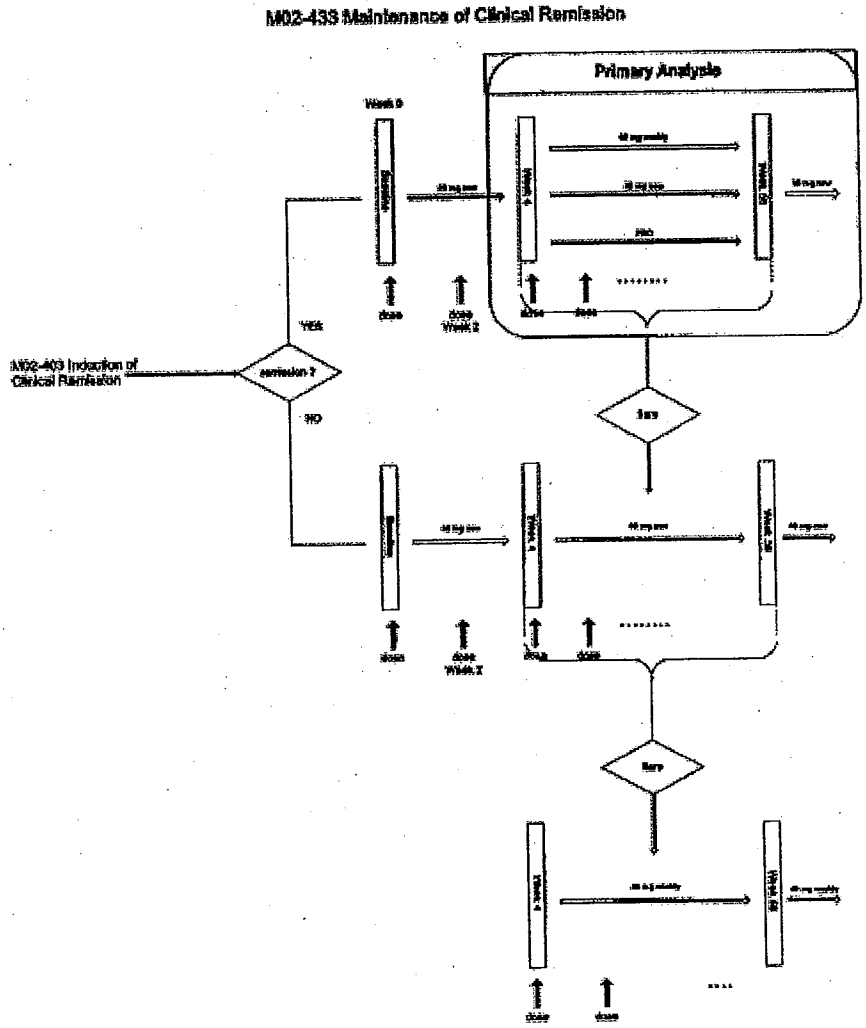
Reduction in concomitant therapy was allowed for Crohn's treatment related tociities of Grade 3 or higher.

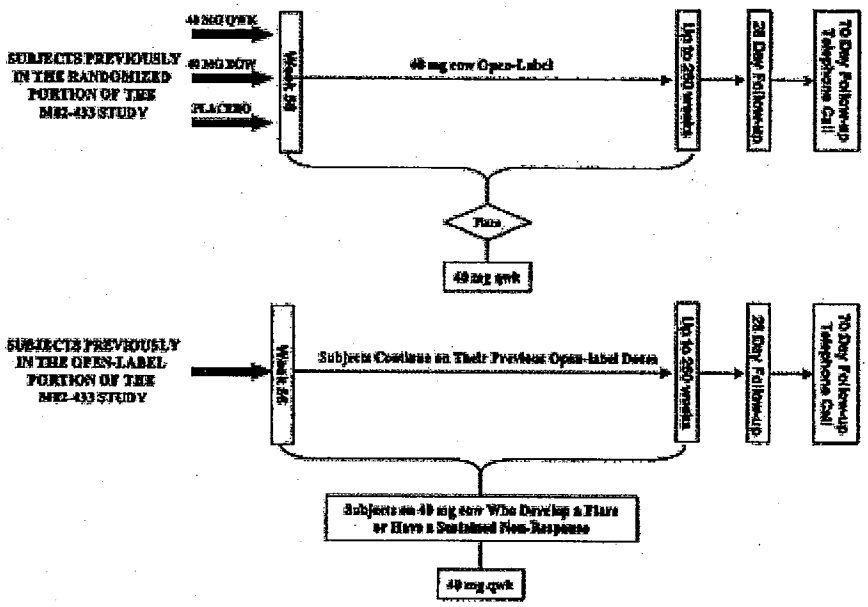
Subjects were allowed to adjust Crohn's specific concomitant medications if the criteria were met.

Subjects were allowed to decrease prednisore and budesonide. If criteria were met a mandatory taper was required.

The duration of the study could last up to 264 weeks, which included a 4-week follow-up period. A phone call would be made 70 days after dose of study medication for all subjects to obtain follow-up information on any ongoing or on any new adverse events.

A schematic of the study design is given below.





A CDAI score would be calculated from a subject diary and appropriate laboratory values at all study visits (Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and Week 56).

Subjects would complete Inflammatory Bowel Disease Questionnaire (IBDQ) at study entry/baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 80, 104, 128, 152, 176, 200, 224, 248, early termination, if applicable and the follow-up visits.

The primary efficacy variable was the maintenance of clinical remission at Week 56. This is defined as the proportion of subjects who have CDAI score of < 150 at Week 56, who were in remission at baseline and at Week 4 of this study.

Secondary efficacy variables were:

(1) clinical remission : CDAI score < 150 at Week 24;
(2) clinical remission: CDAI score < 150 at Week 56 for subjects who were not in remission at Baseline or Week 4 of this study;
(3) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 70 points at Week 24 and Week 56;
(4) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 100 points at Week 24 and at Week 56, respectively;
(5) change in baseline of M02-403 IBDQ scores at Week 24 and Week 56;
(6) steroid taper at Week 24 and Week 56 (complete withdrawal of steroid therapy with a development of relapse); and
(7) time to flare (where flare is defined as the first recurrence of very active disease, specifically the 1st increase in the CDAI when compared to their M02-433 Week 4 values, of ≥70 points and a CDAI above 220).

Clinical assessment of CDAI scores and other efficacy measures for maintenance of clinical response and remission during the open-label extension period following year

one (1) would be evaluated. Quality of Life parameters, including IBDQ would also be summarized.

A Data Monitoring Committee (DMC) met to discuss unblended data from the study every four months or at a frequency determined by the DMC and rendered their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in the study, would make the final decisions based on DMC recommendations.

Subjects who fully completed the M02-403 study were eligible and potentially participate in this study. Approximately 90% (270 subjects) of subjects from M02-403 were expected to enroll.

3.1.2.2.2 Sponsor's Analysis

This study, Study M02-433, was a rollover study the lead-in study, Study M02-403.

A total of 276 subjects participated in the study. All subjects, irrespective of remission status from Study M02-403, were to receive adalimumab 40 mg eow at Weeks 0 and 2. At Week 4, 55 subjects who had achieved clinical remission (CDAI score < 150 points) at Baseline (Week 0) and Week 4 of Study M02-433 were randomized one of three treatment groups; 18 placebo, 19 adalimumab 40 mg eow, and 18 adalimumab 40 mg ew.

A total of 204 subjects were not randomized and received OL adalimumab 40 mg eow. Seventeen (17) were discontinued at or before Week 4.

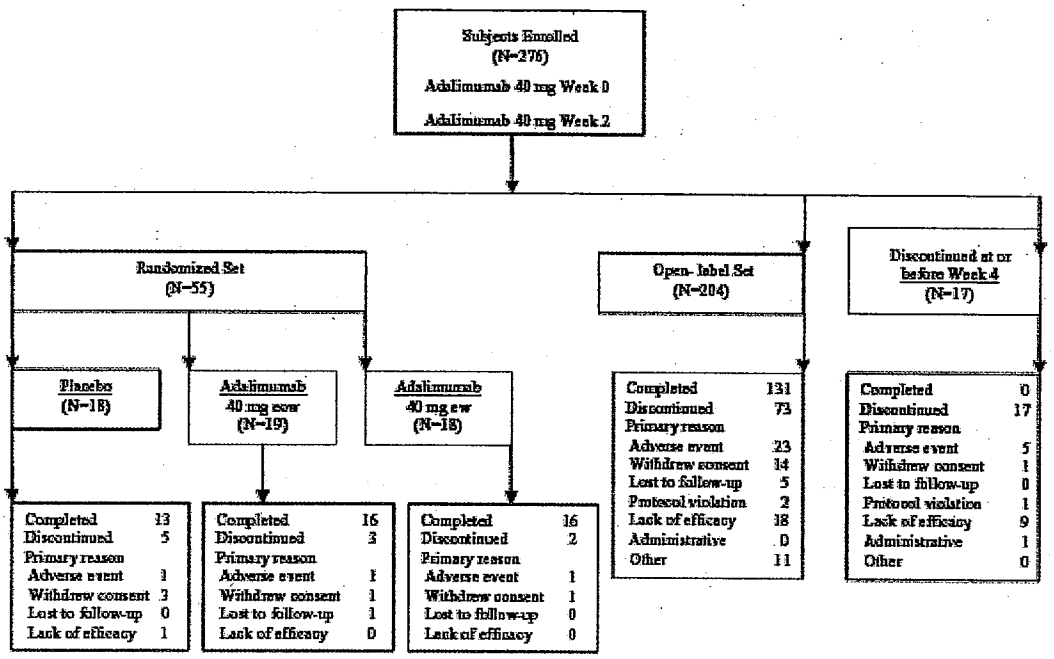
A total of 18.2% (10) of randomized subjects discontinued from the study. The highest percentage of subjects discontinued due to primary reasons of withdrawal of consent (9.1%) and AE (5.5%). A greater proportion of subjects discontinued from the study in the placebo group (27.8%, 5) than in the adalimumab 40 mg eow (15.8%, 3) and adalimumab 40 mg ew (11.1%, 2) groups.

A total of 35.8% (73) of subject in the OL analysis set discontinued from the study. Subjects discontinued in the greatest numbers due to primary reasons of AE (11.3%) and lack of efficacy (8.8%).

The randomized analysis set included all subjects who were randomized to the placebo-controlled cohort and received at least one study drug injection (N=55). All randomized subjects, with the exception of one each from the placebo and adalimumab 40 mg eow treatment groups, had achieved clinical remission at Baseline and Week 4. These two subjects were misrandomized due to an error in CDAI calculation. All efficacy analyses included these two misrandomized subjects.

The OL analysis set included all subjects who were not included in the randomized analysis set and received study drug at or after Week 4 (N=204)

Subject disposition is illustrated below.



3.1.2.2.2.1 Planned Analysis

The primary efficacy analyses were conducted in the intent-to-treat (ITT) population of the randomized population at Week 4. Intent-to-treat population was defined as all randomized subjects who received at least one dose of study drug.

All statistical tests were two-sided and were conducted at an α=0.05 level (2-sided).

Demographic and baseline characteristics among the randomized treatment groups were summarized and compared. Continuous variables were compared using the Kruskal-Wallis test, and discrete variables were compared using the Pearson's chi-square test.

The primary analysis was the comparison of the proportion of subjects maintaining clinical remission (maintaining a CDAI < 150) from Week 4 and Week 56 between treatment groups using Pearson's chi-square test or Fisher's exact test if more than 20% expected cell count <5. Subjects without Week 56 evaluations were classified as "failure." An adjustment for multiple testing was done following the closed testing procedure. An initial overall comparison of the three treatment groups (adalimumab 40 mg eow, adalimumab 40 mg weekly, and placebo) was tested. If this was significant, pairwise comparisons of each adalimumab dose group vs. placebo would be performed.

Summary statistics included point estimates of the maintenance rate of clinical remission rate for each treatment group, the difference in proportion between each adalimumab dose group and placebo, and the corresponding 95% confidence intervals.

A supportive analysis of the primary variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values.

No adjustments for alpha level were needed for the secondary efficacy analyses.

The proportion of subjects achieving a clinical remission (CDAI score <150points) at Week 24 was compared using the Chi-square test. Summary statistics were displayed as the frequency and proportion of subjects who achieved clinical remission in each treatment group, the difference in clinical remission rates between each adalimumab dose group and placebo, and the corresponding 95% confidence intervals of the difference.

3.1.2.2.2.2 Treatment Group Comparability

A summary of the demographic characteristics at baseline, baseline Crohn's disease characteristics, and Crohn's related mediation use by treatment are presented in Appendix Table 15.

As seen from Appendix Table 15, overall, demographic characteristics at baseline were similar across three treatment groups in subjects in the randomized analysis set. The demographic characteristics of subjects in the OL analysis set were similar to those of the randomized analysis set.

3.1.2.2.2.3 Sponsor's Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of randomized subjects with clinical remission, defined as achievement of a CDAI score < 150 points, at Week 56.

Subjects without Week 56 evaluation and subjects who switched to OL adalimumab before the evaluation were classified as not being in remission or response (imputed analysis). An initial overall comparison of the three treatment groups was tested. If a significant difference was observed across the three treatment groups, pairwise comparisons of each adalimumab dose group vs. placebo was performed.

The result of imputed analysis of primary efficacy endpoint is given below.

Number of Subjects in Clinical Remission at Week 56
Randomized Analysis Set Up to Week 56
Imputed Analysis
Protocol M02-433

	Randomized Analysis Set (Up to Week 56)			
	Placebo N = 18	Adalimumab 40 mg eow N = 19	Adalimumab 40 mg ew N = 18	
	n (%)			p-value[a]
Week 56	6 (33.3)	9 (47.4)	12 (66.7)	0.142

eow = every other week; ew = every week

a. The p-value is from Fisher's Exact test for the comparison across the three treatment groups.

Cross Reference: Section 14, Table 14.2__3.1.1

As seen from table above, greater proportion of subjects in the two adalimumab treatment groups demonstrated maintenance of remission (CDAI score < 150) at Week 56 compared to placebo. However, no statistical significant difference was observed across the three treatment groups.

3.1.2.2.2.3.1 LOCF Analysis

The sponsor also performed a sensitivity analysis using the LOCF approach. For LOCF analyses, remission or response status was based on the last observed non-missing CDAI score before a subject switched to OL treatment or discontinued the study.

The result of LOCF analysis of primary efficacy endpoint is given in Appendix Table 16.

As seen from Appendix Table 16, the Week 56 LOCF analysis demonstrated that greater proportion of subjects from the adalimumab treatment groups maintenance of clinical remission at Week 56 than did subjects from the placebo treatment group. The overall p-value was 0.029 across treatment groups.

3.1.2.2.2.4 Sponsor's Analyses of Secondary Efficacy Endpoints

Secondary efficacy variables were:

(1) clinical remission : CDAI score < 150 at Week 24;
(2) clinical remission: CDAI score < 150 at Week 56 for subjects who were not in remission at Baseline or Week 4 of this study;
(3) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 70 points at Week 24 and Week 56;
(4) clinical response defined as decrease in baseline of M02-403 CDAI score ≥ 100 points at Week 24 and at Week 56, respectively;
(5) change in baseline of M02-403 IBDQ scores at Week 24 and Week 56;

(6) steroid taper at Week 24 and Week 56 (complete withdrawal of steroid therapy with a development of relapse); and
(7) time to flare (where flare is defined as the first recurrence of very active disease, specifically the 1st increase in the CDAI when compared to their M02-433 Week 4 values, of ≥70 points and a CDAI above 220).

3.1.2.2.2.4.1 Clinical Remission at Week 24

The result of imputed analyses of clinical remission at Week 24 is given in below.

Number of Subjects in Clinical Remission at Week 24
Randomized Analysis Set
Imputed Analysis
Protocol M02-433

	Randomized Analysis Set				
	Placebo N=18	Adalimumab N=37	Overall p-value[a]	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
	n (%)				
Imputed Analysis					
40 mg eow (N=19)	7 (38.9)	11 (57.9)	0.001	19.0 (-12.6, 50.6)	0.330
40 mg ew (N=18)	7 (38.9)	17 (94.4)	0.001	55.6 (30.7, 80.4)	0.001

eow = every other week; ew = every week

a. The p-value is from Fisher's Exact test and is across the three treatment groups.

b. The difference is between each adalimumab treatment group and placebo.

Cross Reference: Section 14, Table 14.2__3.1.2 and 14.2__3.1.1

As seen from table above, greater proportion of subjects in the adalimumab treatment groups maintained clinical remission at Week 24 than did subjects from the placebo treatment group with a statistically significant difference observed across treatment groups (overall p-value=0.001). Upon pairwise comparison, a statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group.

3.1.2.2.2.4.2 Clinical Response CR-70 (Defined as Decrease in Baseline of M02-403 CDAI score ≥ 70 points) at Weeks 24 and 56

The results of imputed analyses of clinical response CR-70 (defined as decrease in Baseline of M02-403 CDAI score ≥70 points) at Week 24 and Week 56 are given in below.

Clinical Response CR-70 at Week 24 and Week 56
Randomized Analysis Set
Imputed Analysis
Protocol M02-433

	Randomized Analysis Set			
	Placebo N=18	Adalimumab N=37	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
	n (%)			
Imputed Analysis				
40 mg eow (N = 19)				
Week 24	8 (44.4)	13 (68.4)	24.0 (-7.1, 55.0)	0.191
Week 56	6 (33.3)	9 (47.4)	14.0 (-17.2, 45.3)	0.508
40 mg ew (N=18)				
Week 24	8 (44.4)	17 (94.4)	50.0 (24.7, 75.3)	0.003
Week 56	6 (33.3)	13 (72.2)	38.9 (8.8, 68.9)	0.044

eow = every other week; ew = every week

a. The difference is between each adalimumab treatment group and placebo.

b. The p-value is from Fisher's Exact test to compare each adalimumab treatment group and placebo.

Cross Reference: Section 14, Table 14.2__14.1

As seen from table above, greater proportion of subjects in the adalimumab treatment groups demonstrated clinical response C-70 at Week 24 than did subjects from the placebo treatment group. Upon pairwise comparison, a statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group.

Greater proportion of subjects in the adalimumab treatment groups demonstrated clinical response C-70 at Week 56 than did subjects from the placebo treatment group. Upon pairwise comparison, a slightly statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group.

3.1.2.2.2.4.3 Clinical Response CR-100 (Defined as Decrease in Baseline of M02-403 CDAI score ≥ 100 points) at Weeks 24 and 56

The results of imputed analyses of clinical response CR-100 (defined as decrease in Baseline of M02-403 CDAI score ≥100 points) at Week 24 and Week 56 are given in below.

Clinical Response CR-100 at Week 24 and Week 56
Randomized Analysis Set
Imputed Analysis
Protocol M02-433

	Randomized Analysis Set			
	Placebo N=18	Adalimumab N=37	Difference[a] (95% CI)	Pairwise Comparison p-value[b]
	n (%)			
Imputed Analysis				
40 mg eow (N=19)				
Week 24	7 (38.9)	11 (57.9)	19.0 (-12.6, 50.6)	0.330
Week 56	6 (33.3)	9 (47.4)	14.0 (-17.2, 45.3)	0.508
40 mg ew (N=18)				
Week 24	7 (38.9)	17 (94.4)	55.6 (30.7, 80.4)	0.001
Week 56	6 (33.3)	13 (72.2)	38.9 (8.8, 68.9)	0.044

eow = every other week; ew = every week

a. The difference is between each adalimumab treatment group and placebo.

b. The p-value is from Fisher's Exact test to compare each adalimumab treatment group and placebo.

Cross Reference: Section 14, Table 14.2__14.2

As seen from table above, greater proportion of subjects in the adalimumab treatment groups demonstrated clinical response C-100 at Week 24 than did subjects from the placebo treatment group. Upon pairwise comparison, a statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group.

Greater proportion of subjects in the adalimumab treatment groups demonstrated clinical response C-100 at Week 56 than did subjects from the placebo treatment group. Upon pairwise comparison, a slightly statistically significant difference was observed between the adalimumab 40 mg ew treatment group and the placebo treatment group.

3.1.2.2.2.4.4 Change in Baseline of M02-403 IBDQ Scores at Weeks 24 and 56

Summary of change in IBDQ scores from M02-403 Baseline (Week 0) to Week 24 and Week 56 is given Appendix Table 17.

As seen from Appendix Table 17, all randomized treatment groups demonstrated mean increases in IBDQ at Weeks 24 and 56. Subjects in the adalimumab treatment groups had greater mean increases in IBDQ scores from M02-403 Baseline (Week 0) to Week 24 than subjects in the placebo treatment group. At Week 56, the adalimumab dose groups did not have consistently greater mean increases in IBDQ scores than placebo.

3.1.2.2.2.4.5 Open-label Analysis Set

The OL analysis set included subjects who failed to achieve clinical remission at Week 0 and Week 4 and received OL adalimumab at or after Week 4.

Summary of analysis of clinical remission at Week 24 and Week 56 is given Appendix Table 18.

Summary of analyses of clinical responses CR-70 and CR-100 at Week 24 and Week 56 are given Appendix Table 19.

Summary of change in IBDQ scores from M02-403 Baseline (Week 0) to Week 24 and Week 56 is given Appendix Table 20.

3.1.2.2.2.4.6 Subjects who Underwent Dose Escalation

A total of 89 subjects underwent dose escalation to either OL adalimumab 40 mg eow (from blinded treatment) or OL adalimumab 40 mg ew (from OL adalimumab 40 mg eow).

A summary of efficacy results for subjects who underwent dose escalation (all enrolled subjects who dose escalated) (Up to Week 56) is given below.

Efficacy Results for Subjects Who Underwent Dose Escalation
All Enrolled Subjects Who Dose Escalated (Up to Week 56)
Study M02-433

	Randomized and Open-label Analysis Sets
	Subjects Who Dose Escalated N = 89
Efficacy Parameter	n (%)
Clinical remission (CDAI < 150 points)	46 (51.7)
Clinical response (CDAI ≥ 70 points)[a]	79 (88.8)
Clinical response (CDAI ≥ 100 points)[b]	67 (75.3)

a. Clinical response is defined as a decrease ≥ 70 points in M02-403 Baseline (Week 0) CDAI score.

b. Clinical response is defined as a decrease ≥ 100 points in M02-403 Baseline (Week 0) CDAI score.

Note: Subjects with missing CDAI scores were counted as not achieving clinical remission or response.

Cross Reference: Section 14, Table 14.2__11

3.1.2.2.3 Reviewer's Comments and Evaluation

3.1.2.2.3.1 Reviewer's Comments on Study Design

This study, Study M02-433, was a rollover study the lead-in study, Study M02-403. So,

it did not have sample size determination. This study was supposed to run up 248 weeks (close 5 years). Among 284 subjects who completed Study M02-403, 276 subjects were enrolled in this study. All subjects were to receive adalimumab 40 mg eow at Week 0 and 2. At Week 4, 55 subjects (20%) who had achieved clinical remission and were randomized one of three treatment groups. But, most of subjects (80%) who had not achieved clinical remission were included in open-label set.

In the study M02-403, a total of 67 subjects had induction of clinical remission at week in Study M02-403. It was expected that about 60 subjects who would achieve clinical remission at Week 4 and were randomized to one of three treatment groups. The sample size per arm would be about 20. Considering that 20% subjects who did not complete Week 56 (double-blind), about 16 subjects per arm could be evaluable for the randomized set. Sixteen subjects per arm were just too few to draw any meaningful statistical conclusion. So, this study should be considered as an "exploratory" by design.

Furthermore, due to small sample size, the results tend to not reliable. Subgroup analyses could not be performed.

3.1.2.2.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints

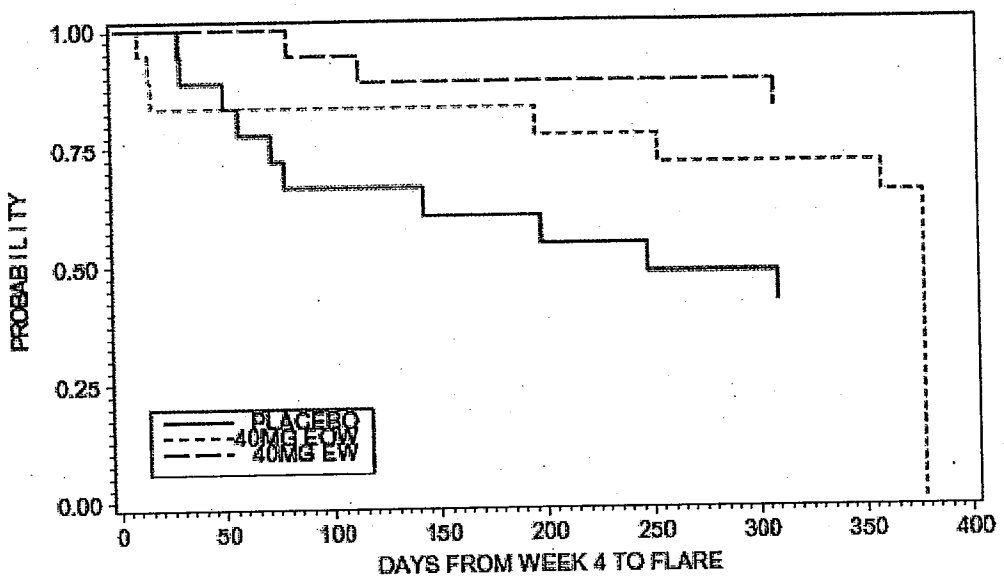
There were seven secondary efficacy endpoints pre-specified in the protocol, but no adjustments were prospectively defined for analyses of secondary efficacy endpoints. So, the p-values reported by sponsor were not adjusted and results of these analyses should be considered as "exploratory.

3.1.2.2.3.3 Time to Flare (Where Flare is Defined as the First Recurrence of Very Active Disease, Specifically the 1st Increase in the CDAI when Compared to Their M02-433 Week 4 Values, of $\geq$ 70 Points and a CDAI above 220)

Flare was experienced by 10 subjects (55.6%), 7 subject (36.8%), and 3 subjects (16.7%) in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively.

The figure of plots of time to flare from Week 4 is given below.

Time to Flare from Week 4



ANALYSIS OF TIME TO FLARE [A]
RANDOMIZED ANALYSIS SET SUBJECTS (UP TO WEEK 56)

TREATMENT	NUMBER OF SUBJECTS	NUMBER OF FLARE SUBJECTS n (%)	RISK RATIO [B]	P-VALUE [C]	95% C.I. FOR RISK RATIO	MEDIAN TIME TO FLARE (DAYS)
PLACEBO	18	10 (55.6)	.	.		248.0
40 MG EOW	19	7 (36.8)	0.518	0.205	(0.19, 1.43)	378.0
40 MG WKLY	18	3 (16.7)	0.209	0.018	(0.06, 0.77)	N/A

As seen from figure above, this reviewer found that the plot for the adalimumab 40 mg eow treatment group crossed the plot for placebo treatment group. The adalimumab 40 mg ew treat group was better than placebo treatment group.

3.1.2.2.3.4 Reviewer's Comments on Open-label Analysis Set

The sponsor's open-label analysis set excluded 17 subjects who received OL adalimumab (adalimumab 40 mg eow) and were discontinued at or before Week 4. If 17 subjects were included as "failure", then clinical remission at Week 56 for adalimumab eow would be 34.8% instead of 40.0%. The difference between adalimumab 40 mg eow and adalimumab 40 mg ew would be 3.3% instead of 8.5%.

3.1.2.2.3.5. Reviewer's Comments on Sponsor's Analysis of Subjects who Underwent Dose Escalation

For subjects who underwent dose escalation, this reviewer statistical analysis using sponsor's dataset. It was found that for open-label set, a total of 89 subjects underwent dose escalation to OL adalimumab 40 mg ew from OL adalimumab 40 mg eow. For randomized set, 10 subjects underwent dose escalation to either OL adalimumab 40 mg

eow or OL adalimumab 40 mg ew from placebo and 3 subjects to OL adalimumab 40 mg ew from OL adalimumab 40 mg eow.

A summary of efficacy results for subjects who underwent dose escalation (all enrolled subjects who dose escalated) (Up to Week 56) is given below.

Efficacy Results for Subjects Who Underwent Dose Escalation
All Enrolled Subjects Who Dose Escalated (Up to 56)
Randomized and Open-label Analysis Sets
Study M02-433
Reviewer's Analysis

Efficacy Parameter	Rate
Clinical remission	28/102 (27.5%)
CR-70	48/102 (47.1%)
CR-100	43/102 (42.2%)

Compiled by this reviewer.

As seen from table above, contrary to sponsor's finding, the rates for clinical remission, clinical response CR-70, and clinical response CR-100 were much smaller than those given by the sponsor.

3.2 Evaluation of Safety

3.2.1 Induction Studies

3.2.1.1 Study M02-403

A total of 213 (71.2%) of 299 subjects reported a treatment-emergent AE, with 50 subjects in the 40 mg/20 mg adalimumab group, 51 subjects in the 80 mg/40 mg adalimumab group, 57 subjects in the 160 mg/80 mg adalimumab group, and 55 subjects in the placebo group.

There were no AEs leading to death. The most commonly reported treatment-emergent AE in all group was injection site burning (12.4%), followed by injection site pain (6.0%), headache NOS (6.0%), nausea (6.0%), injection site reaction NOS (4.7%), Crohn's disease (3.7%), Crohn's disease aggravated (3.7%), flatulence (3.7%), nasopharyngitis (3.7%), and pyrexia (3.3%).

In general, the majority of the most frequently reported treatment-emergent AEs showed comparable incidence between the groups. Nausea, injection site burning, injection site reaction NOS, and nasopharyngitis were reported by more subjects in all the adalimumab group vs. the placebo group.

3.2.1.2 Study M04-691

The overall incidence of treatment-emergent AE was statistically significantly greater in the placebo group compared with the adalimumab 160/80 mg group (72.9% vs. 57.2%; p=0.004). The most frequently reported treatment-emergent AEs included abdominal pain, arthralgia, headache, injection site irritation, fatigue, and Crohn's disease. A statistically significantly greater proportion of placebo subjects reported the treatment-emergent AE of Crohn's disease compared with adalimumab 160/80 mg subjects (9.0% vs. 1.3%; p=0.002)

The proportion of subjects who reported a treatment-related AE was 31.9% in the placebo group and 27.0% in the adalimumab 160/80 mg group.

There were no cases of treatment-emergent malignant neoplasm during the study. The incidence of infectious AEs was 23.5% in the placebo group and 16.4% in the adalimumab 160/80 mg group.

3.2.2 Maintenance Study

3.2.2.1 Study M02-404

During Open-Label induction (Week 0 to Week 4), all subjects received OL adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. One subject died due to pulmonary embolism. A total 45 (5.3%) subjects reported a SAE. A total of 54% (6.3%) subjects reported AEs that at least in part led to premature discontinuation from the study.

The overall incidence of treatment-emergent AEs was 59.5%. The most frequently reported treatment-emergent AEs were headache and nausea. There were no reported cases of malignant neoplasma. A total of 130 (15.2%) subjects reported infectious AEs. During Double-Blind treatment (Week 4 to Week 56), no deaths occurred. The overall incidence of treatment-emergent AEs was 84.7%, 88.8%, and 85.6% in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively.

There was one reported case of malignant neoplasm (breast cancer) in a placebo subject. The incidence of infectious AEs were 36.8%, 46.2%, and 44.4% in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew groups, respectively. The most frequently reported treatment-emergent AEs included Crohn's disease, arthralgia, tract infection, injection site reaction, urinary tract infection, influenza, diarrhoea, and pharyngolaryngeal pain.

Refer to Medical Officer's review for more detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Induction Studies

4.1.1.1 Study M02-403

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M02-403

Category	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo
Gender			
Male	7/25 (28.0%)	11/36 (30.6%)	4/37 (10.8%)
Female	11/50 (22.0%)	16/40 (40.0%)	5/37 (13.5%)
Age			
< 40 years	12/40 (30%)	19/43 (44.2%)	8/51 (15.7%)
40-64	6/34 (17.4%)	8/33 (24.2%)	1/18 (5.6%)
65-74	0/1 (0.0%)		

Compiled by this reviewer.

As seen from table above, proportions of subjects in clinical remission at Week 4 were consistent for subgroups of gender and age.

4.1.1.2 Study M04-691

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M04-691

Category	Adalimumab 160 mg/80 mg	Placebo	Difference	95% C. I.
Gender				
Male	10/50 (20.0%)	5/65 (7.7%)	12.3%	(-0.5%, 25.2%)
Female	24/109 (22.0%)	7/101 (6.9%)	15.1%	(5.9%, 24.3%)
Age				
<40 years	20/88 (22.7%)	9/102 (8.8%)	13.9%	(3.6%, 24.2%)
40-64	13/68 (19.1%)	3/60 (5.0%)	14.1%	(3.3%, 25.0%)

65-74	1/2 (50.0%)	0/3 (0.0%)	50.0%	(-19.3%, 100%)
≥ 75	0/1 (0.0%)	0/1 (0.0%)		

Compiled by this reviewer.

As seen from table above, proportions of subjects in clinical remission at Week 4 were consistent for subgroups of gender and age.

4.1.2 Maintenance Studies

4.1.2.1 Study M02-404

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Weeks 26 and 56 by treatment group for mITT dataset are given below.

Induction of Clinical Remission at Week 26
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Gender			
Male	28/61 (45.9%)	30/62 (48.4%)	12/65 (18.5%)
Female	40/111 (36.0%)	43/95 (45.3%)	17/105 (16.2%)
Age			
<40 years	43/106 (40.6%)	45/93 (48.4%)	19.105 (18.1%)
≥40	25/66 (37.9%)	28/64 (43.8%)	10/65 (15.4%)

Compiled by this reviewer.

Induction of Clinical Remission at Week 56
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Gender			
Male	27/61 (44.3%)	25/62 (40.3%)	6/65 (9.2%)
Female	35/111 (31,5%)	40/95 (42.1%)	14/105 (13.3%)
Age			
< 40 years	39/106 (36.8%)	38/93 (40.9%)	10/105 (9.5%)
≥ 40	23/66 (34.8%)	27/64 (42.2%)	10/65 (15.4%)

Compiled by this reviewer.

As seen from table above, proportions of subjects in clinical remission at Weeks 26 and 56 were consistent for subgroups of gender and age.

4.2 Other Special/Subgroup populations

4.2.1 Induction Studies

4.2.1.1 Study M02-403

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M02-403

Category	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Placebo
Country			
Belgium		0/2 (0.0%)	1/2 (50.0%)
Canada	4/15 (26.7%)	6/19 (31.6%)	1/17 (5.9%)
Czecholovakia	4/7 (57.1%)	4/7 (57.1%)	1/4 (25.0%)
Netherland	0/1 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Poland	2/3 (66.7%)	1/1 (100.0%)	2/3 (66.7%)
USA	8/49 (16.3%)	16/46 (34.8%)	4/46 (8.7%)
Body weight			
≤ 70 kg	10/38 (26.3%)	14/31 (45.2%)	6/33 (18.2%)
> 70 kg	8/37 (21.6%)	13/45 (28.9%)	3/41 (7.3%)
Tobacco use			
Never used	7/30 (23.3%)	11/27 (40.7%)	3/34 (8.8%)
Current user	9/32 (28.1%)	12/32 (37.5%)	3/28 (10.7%)
Ex-user	2/13 (15.4%)	4/17 (23.5%)	3/12 (25.0%)
Alcohol use			
Non-drinker	8/31 (25.8%)	12/30 (40.0%)	4/27 (14.8%)
Drinker	9/38 (23.7%)	15/43 (34.9%)	3/39 (7.7%)
Ex-drinker	1/6 (16.7%)	0/3 (0.0%)	2/8 (25.0%)
Use of Corticosteroids at baseline			
Yes	9/31 (29.0%)	13/22 (59.1%)	5/25 (20.0%)
No	9/44 (20.5%)	14/54 (25.9%)	4/49 (8.2%)
Use of immunosuppressants at baseline			
Yes	2/21 (9.5%)	8/22 (36.4%)	2/22 (9.1%)
No	16/54 (29.6%)	19/54 (35.2%)	7/52 (13.5%)
Use of oral aminosalicylates at baseline			
Yes	13/41 (31.7%)	16/40 (40.0%)	7/36 (19.4%)
No	5/34 (14.7%)	11/36 (30.6%)	2/38 (5.3%)
Baseline CRP			
< 1 mg/dL	9/42 (21.4%)	15/48 (31.3%)	7/45 (15.6%)

≥ 1 mg/dL	9/33 (27.3%)	12/28 (42.9%)	2/29 (6.9%)
Baseline CDAI scores			
220-270 points	8/24 (33.3%)	13/28 (46.4%)	5/30 (16.7%)
271-330 points	6/22 (27.3%)	7/26 (26.9%)	2/21 (9.5%)
331-390 points	3/19 (15.8%)	3/16 (18.8%)	0/14 (0.0%)
391-450 points	1/8 (12.5%)	2/4 (50.0%)	1/8 (12.5%)

Complied by this reviewer.

As seen from table above, proportion of subjects in induction of clinical remission at Week 4 was consistent for subgroups of country, body weight, alcohol use, use of immunosuppressant, use of corticosteroids, use of oral aminosalicylates, and baseline CDAI scores. But, it was not consistent for subgroup of tobacco use.

4.2.1.2 Study M04-691

Summary of subgroup analyses of clinical remission (CDAI < 150 points) at Week 4 are given below.

Induction of Clinical Remission at Week 4
Fully Analysis Set
Protocol M04-691

Category	Adalimumab 160 mg/80 mg	Placebo	Difference	95% C. I.
Country				
Belgium	9/18 (50.0%)	2/18 (11.1%)	38.9%	(11.6%, 66.2%)
Canada	7/25 (28.0%)	0/28 (0.0%)	28.0%	(10.4%, 45.6%)
France	2/5 (40.0%)	0/6 (0.0%)	40.0%	(-3.0%, 82.0%)
USA	16/111 (14.4%)	10/114 (8.8%)	5.6%	(-2.7%, 14.0%)
Gender				
Male	10/50 (20.0%)	5/65 (7.7%)	12.3%	(-0.5%, 25.2%)
Female	24/109 (22.0%)	7/101 (6.9%)	15.1%	(5.9%, 24.3%)
Age				
<40 years	20/88 (22.7%)	9/102 (8.8%)	13.9%	(3.6%, 24.2%)
40-64	13/68 (19.1%)	3/60 (5.0%)	14.1%	(3.3%, 25.0%)
65-74	1/2 (50.0%)	0/3 (0.0%)	50.0%	(-19.3%, 100%)
≥ 75	0/1 (0.0%)	0/1 (0.0%)		
Body weight				
≤70 kg	19/91 (20.9%)	6/91 (6.6%)	14.3%	(4.5%, 24.1%)
>70 kg	15/68 (22.1%)	6/75 (8.0%)	14.1%	(2.4%, 25.7%)
Tobacco Use				
User	13/55 (23.6%)	4/56 (7.1%)	16.5%	(3.4%, 29.6%)
Ex-User	8/39 (20.5%)	1/45 (2.2%)	18.3%	(4.9%, 31.7%)
Never	13/65 (20.0%)	7/65 (10.8%)	9.2%	(-3.1%, 21.5%)
Alcohol Use				
Drinker	22/77 (28.6%)	8/86 (9.3%)	19.3%	(7.5%, 31.1%)

Ex-Drinker	1/14 (7.1%)	2/19 (10.5%)	-3.4%	(-22.7%, 15.9%)
Never	11/68 (16.2%)	2/61 (3.3%)	12.9%	(3.1%, 22.7%)
HACA to Infliximab				
Positive	10/48 (20.8%)	2/58 (3.4%)	17.4%	(5.0%, 29.8%)
Negative	21/105 (20.0%)	10/101 (9.9%)	10.1%	(0.5%, 19.7%)
Missing	3/6 (50.0%)	0/7 (0.0%)	50.0%	(10.0%, 90.0%)
Use of Corticosteroids at baseline				
Yes	18/55 (32.7%)	3/73 (4.1%)	28.6%	(15.4%, 41.8%)
No	16/104 (15.4%)	9/93 (9.7%)	5.7%	(-3.5%, 14.9%)
Use of immunosuppressants at baseline				
Yes	16/73 (21.9%)	6/85 (7.1%)	14.9%	(3.9%, 25.8%)
No	18/86 (20.9%)	6/81 (7.4%)	13.5%	(3.2%, 23.8%)
Use of oral aminosalicylates at baseline				
Yes	6/45 (13.3%)	6/60 (10.0%)	3.3%	(-9.2%, 15.8%)
No	28/114 (24.6%)	6/106 (5.7%)	18.9%	(9.9%, 27.9%)
Baseline CRP				
<1 mg/dL	15/82 (18.3%)	7/98 (7.1%)	11.1%	(1.3%, 21.1%)
≥1 mg/dL	19/77 (24.7%)	5/68 (7.4%)	17.3%	(5.9%, 28.8%)
Intolerance to Infliximab				
Yes	21/95 (22.1%)	5/95 (5.3%)	16.8%	(7.4%, 26.3%)
No	13/64 (20.3%)	7/71 (9.9%)	10.5%	(-1.6%, 22.5%)
Lost response to previous Infliximab				
Yes	15/77 (19.5%)	7/87 (8.0%)	11.4%	(0.9%, 22.0%)
No	19/82 (23.2%)	5/78 (6.4%)	16.8%	(6.1%, 27.4%)
Missing		0/1 (0.0%)		
Baseline CDAI scores				
< 220		0/1 (0.0%)		
220-270 points	19/43 (44.2%)	4/51 (7.8%)	36.3%	(19.8%, 52.9%)
271-330 points	11/59 (18.6%)	8/52 (15.4%)	3.3%	(-10.7%, 17.2%)
331-390 points	1/38 (2.6%)	0/34 (0.0%)	2.6%	(-2.5%, 7.7%)
391-450 points	3/19 (15.8%)	0/27 (0.0%)	15.8%	(-6.1%, 32.2%)
>450		0/1 (0.0%)		

Complied by this reviewer.

As seen from table above, proportion of subjects in induction of clinical remission at Week 4 was consistent for subgroups of gender, age, body weight, tobacco use, use of immunosurppressant, baseline CRP, intolerance to infliximab, and lost response to

previous infliximab. But, it was not consistent for subgroups of country, alcohol use, use of corticosteroids, use of aminosalicylates, and baseline CDAI scores.

4.2.2 Maintenance Studies

4.2.2.1 Study M02-404

Induction of Clinical Remission at Week 26
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Body weight			
≤70 kg	41/95 (43.2%)	49/94 (52.1%)	15/102 (14.7%)
>70 kg	27/77 (35.1%)	24/63 (38.1%)	14/68 (20.6%)
Tobacco Use			
User	26/62 (41.9%)	16/51 (31.4%)	8/63 (12.7%)
Ex-User	13/33 (39.4%)	27/48 (56.3%)	7/43 (16.3%)
Never	29/77 (37.7%)	30/58 (51.7%)	14/64 (21.9%)
Alcohol Use			
Drinker	40/98 (40.8%)	43/84 (51.2%)	14/90 (15.6%)
Ex-Drinker	5/6 (83.3%)	3/8 (37.5%)	3/8 (37.5%)
Never	23/68 (33.8%)	27/64 (42.2%)	12/72 (16.7%)
Use of Previous and concomitant other Crohn's medications			
Yes	62/161 (38.5%)	71/151 (47.0%)	25/160 (15.6%)
No	6/11 (54.5%)	2/6 (33.3%)	4/10 (40%)
Use of Corticosteroids at baseline			
Yes	24/58 (41.4%)	30/74 (40.5%)	7/66 (10.6%)
No	44/114 (38.6%)	43/83 (51.8%)	22/104 (21.2%)
Use of immunosuppressants at baseline			
Yes	32/77 (41.6%)	32/79 (40.5%)	14/83 (16.9%)
No	36/95 (37.9%)	41/78 (52.6%)	15/87 (17.2%)
Previous Use of Anti-TNF			
Yes	27/86 (31.4%)	31/75 (41.3%)	15/83 (18.1%)
No	41/86 (47.7%)	42/82 (51.2%)	14/87 (16.1%)
Use of oral aminosalicylates			
Yes	31/66 (47.0%)	31/61 (50.8%)	10/78 (12.8%)
No	37/106 (34.9%)	42/96 (43.8%)	19/92 (20.7%)
Baseline CRP			
<1 mg/dL	37/95 (38.9%)	31/82 (37.8%)	15/85 (17.6%)
≥1 mg/dL	31/76 (40.8%)	42/75 (56.0%)	14/85 16.5%)

Baseline CDAI scores			
< 220		0/1 (0.0%)	
220-270 points	22/47 (46.8%)	25/44 (56.8%)	13/41 (31.7%)
271-330 points	25/57 (43.9%)	26/61 (42.6%)	7/63 (11.1%)
331-390 points	17/46 (37.0%)	15/30 (50.0%)	6/32 (18.8%)
391-450 points	4/22 (18.2%)	7/21 (33.3%)	3/31 (9.7%)
≥ 451			0/3 (0.0%)

Complied by this reviewer.

Induction of Clinical Remission at Week 56
mITT Dataset
Protocol M02-404

Category	Adalimumab 40 mg eow	Adalimumab 40 mg ew	Placebo
Body weight			
≤ 70 kg	37/95 (38.9%)	48/94 (51.1%)	11/102 (10.8%)
> 70 kg	25/77 (32.5%)	17/63 (27.0%)	9/68 (13.2%)
Tobacco Use			
User	22/62 (35.5%)	16/51 (31.4%)	7/63 (11.1%)
Ex-User	15/33 (45.5%)	24/48 (50.0%)	8/43 (18.6%)
Never	25/77 (32.5%)	25/58 (43.1%)	15/64 (7.8%)
Alcohol Use			
Drinker	42/98 (42.9%)	37/84 (44.1%)	8/90 (8.9%)
Ex-Drinker	2/6 (33.3%)	3/8 (37.5%)	3/8 (37.5%)
Never	18/68 (26.5%)	25/64 (39.1%)	9/72 (12.5%)
Use of Previous and concomitant other Crohn's medicationa			
Yes	56/161 (34.8%)	63/151 (41.7%)	16/160 (10.0%)
No	6/11 (54.5%)	2/6 (33.3%)	4/10 (40%)
Use of Corticosteroids at baseline			
Yes	20/58 (34.5%)	24/74 (32.4%)	6/66 (9.1%)
No	42/114 (36.8%)	41/83 (49.4%)	14/104 (13.5%)
Use of immunosuppressants at baseline			
Yes	30/77 (39.0%)	28/79 (35.4%)	10/83 (12.1%)
No	32/95 (33.7%)	37/78 (47.4%)	10/87 (11.5%)
Previous Use of Anti-TNF			
Yes	26/86 (30.2%)	25/75 (33.3%)	9/83 (10.8%)
No	36/86 (41.9%)	40/82 (48.8%)	11/87 (12.6%)
Use of oral aminosalicylates			
Yes	29/66 (43.9%)	29/61 (47.5%)	7/78 (9.0%)
No	33/106 (31.1%)	36/96 (37.5%)	13/92 (14.1%)
Baseline CRP			

<1 mg/dL	34/95 (35.8%)	27/82 (32.9%)	11/85 (12.9%)
≥1 mg/dL	28/76 (36.8%)	38/75 (50.7%)	9/85 (10.6%)
Baseline CDAI scores			
< 220		1/1 (100%)	
220-270 points	17/47 (36.2%)	23/44 (52.3%)	7/41 (17.1%)
271-330 points	24/57 (42.1%)	22/61 (36.1%)	7/63 (11.1%)
331-390 points	16/46 (34.8%)	14/30 (46.7%)	4/32 (12.5%)
391-450 points	5/22 (22.7%)	5/21 (23.8%)	2/31 (6.5%)
≥ 451			0/3 (0.0%)

Complied by this reviewer.

As seen from tables above, proportion of subjects in induction of clinical remission clinical remission (CDAI < 150 points) at Weeks 26 and 56 for mITT dataset was consistent for subgroups of body weight, tobacco use, alcohol use, use of immunosuppressant, use of corticosteroids, use of aminosalicylates, previous use of anti-TNF, baseline CRP, and baseline CDAI scores.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Induction Studies

For induction studies, two studies (M02-403 and M04-691), were conducted to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease. Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691 was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

For subjects who were naïve to anti-tumor necrosis factor (TNF) therapy, Study M02-403 demonstrated that adalimumab was statistically significant better in inducing clinical remission (defined as an achievement of a CDAI score < 150 points) at Week 4, primary efficacy endpoint, at dose of 80 mg/40 mg and 160 mg/80 mg as compared to placebo.

However, it was found that adalimumab 80/40 mg and placebo had more subjects who were discontinued from study as compared to adalimumab 160/80 mg (5 and 6 for adalimumab 80/40 mg and placebo, respectively vs. 2 for adalimumab 160/80 mg).

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. The sponsor's analysis was the "worst" case analysis. This reviewer performed sensitivity analyses including "best" case and observed case (OC) analyses. In the observed case analysis, only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals. In the "best" case analysis, any patients with missing data who was randomized to active treatment was classified as

'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'. For both OC and "best" case analyses, adalimumab 160 mg/80 mg was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 as compared to placebo.

So, efficacy results favoring adalimumab 160 mg/80 in inducing clinical remission (defined as an achievement of a CDAI score < 150 points) at Week 4 were robust.

For the efficacy secondary endpoints, for clinical response CR-70 (defined as a decrease CDAI score ≥ 70), pairwise comparisons between each adalimumab group and the placebo group demonstrated that both 80 mg/40 mg and 160 mg/80 mg adalimumab doses achieved statistically significance superiority. For clinical response CR-100 (defined as a decrease CDAI score ≥ 70), pairwise comparisons between each adalimumab group and the placebo group demonstrated that 160 mg/80 mg adalimumab dose achieved statistically significance superiority. The 80 mg/40 adalimumab dose was close to statistical significance.

For subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab, Study M04-691 demonstrated the proportion of subjects who achieved clinical remission (defined as a achievement of a CDAI score < 150 points) at Week 4, primary efficacy endpoint, was statistically significant greater in the adalimumab 160 mg/80 mg group compared to the placebo group. The superiority was replicated in 9 of 11 major secondary endpoints.

However, it was found that placebo had more subjects who were discontinued from study as compared to adalimumab 160 mg/80 mg (10 for placebo and 4 for adalimumab 160 mg/80 mg).

In the sponsor's analysis, those subjects with missing primary endpoint data at Week 4 were classified in the 'no induction of clinical remission" category. The sponsor's analysis was the "worst" case analysis. This reviewer performed sensitivity analyses including "best" case and observed case (OC) analyses. In the observed case analysis, only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals. In the "best" case analysis, any patients with missing data who was randomized to active treatment was classified as 'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'. For the OC and analysis, adalimumab 160 mg/80 mg was statistically significantly better in inducing clinical remission (defined as achievement of a CDAI score < 150 points) at Week 4 as compared to placebo.

5.1.2 Maintenance Studies

Two studies, Studies M02-404 and M02-433, were conducted to evaluate adalimumab as maintenance therapy for moderate to severe CD. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF

agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

Study M02-404 demonstrated that the proportion of all randomized subjects who achieved clinical response at Week 4 (defined as CDAI decrease ≥ 70 compared to the Baseline CDAI) achieved clinical remission (CDAI < 150) at Week 26 and Week 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group. Superiority of adalimumab groups over placebo was also shown in secondary efficacy endpoints, clinical response (defined as a decrease from baseline in CDAI score ≥ 70 points) at Weeks 26 and 56, clinical response (defined as a decrease from baseline in CDAI score ≥ 100 points) at Weeks 26 and 56, and mean change of IBDQ baseline to Weeks 24 and 56.

Furthermore, the sponsor noted that among ITT subjects, examining the agreement between CRF (where investigators recorded the CDAI) and IVRS responder stratification, some deviations were found. Deviations included 1.7% of subjects classified as responders by CRF and non-responders by IVRS and 11.2% of all subjects classified as non-responders by CRF and responders by IVRS. In the mITT dataset, 2.6% of subjects were classified as responders by CRF and non-responders by IVRS and no subjects were classified as non-responders by CRF and responders by IVRS.

When compared to the mITT dataset, dataset based on IVRS Week 4 responder status had slightly lower remission rates in each group. This issue was identified until the database was locked.

This reviewer performed analyses of clinical remission at Weeks 26 and 56 for subjects who achieved IVRS response. It was observed that the proportion of subjects who achieved IVRS Week 4 response and achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

In general, the mITT population was similar to the ITT population for demographic and baseline characteristics with exception of use of corticosteroids. In general, the mITT was similar to the ITT for demographic and baseline characteristics with exception of use of corticosteroids at baseline. In the mITT, there were more subjects with use of corticosteroids at baseline in the adalimumab ew as compared to adalimumab eow and placebo group (47% vs. 34% and 39%; p=0.0440). Because of this imbalance, results from a subgroup analysis of steroid free remission might be unreliable and difficult to interpret.

The protocol stated that the primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT), which was defined as all treated subjects who achieved clinical response (CDAI decrease ≥ 70) at Week 4 and were randomized to receive one of the three blind treatments.

This reviewer found that for the mITT population, statistically significantly greater proportions of subjects randomized to placebo and adalimumab 40 mg eow (33.3% and 33.1%, respectively) prematurely discontinued from the study compared to adalimumab 40 mg ew (16.6%; $p<0.001$).

It was also found that for the mITT population, statistically significantly greater proportions of subjects randomized to placebo and switch to open label at Week 12 as compared to adalimumab 40 mg eow and adalimumab 40 mg ew (58.8% for placebo and about 40% for adalimumab treatment groups; $p<0.001$).

This reviewer performed ITT analysis included all randomized patients. In this analysis, those subjects who were non-responders at Week 4 or had missing values at Week 26 or Week 56 were assumed failures. It was demonstrated that the proportion of ITT subjects who achieved clinical remission (CDAI < 150) at Weeks 26 and 56, were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew groups compared to the placebo group.

As suggested by Dr. Welch, this reviewer performed exploratory ITT analyses for more stringent efficacy endpoints: sustained clinical remission (CDAI < 150)at weeks 4 and 56, sustained clinical remission at weeks 4, 26, and 56, sustained clinical response CR-70 (decrease from baseline CDAI $\geq$ 70) at weeks 4 and 26, sustained clinical response CR-70 at weeks 4, 26, and 56, sustained clinical response CR-100 (decrease from baseline CDAI $\geq$ 100) at weeks 4 and 26, and sustained clinical response CR-100 at weeks 4, 26, and 56.

Results from these analyses indicated that adalimumab treatment groups were superior to placebo with regard to sustained clinical remission, sustained clinical responses (defined as a CDAI decrease $\geq$ 70 compared to the Baseline CDAI) and sustained clinical response (defined as a CDAI decrease $\geq$ 100 compared to the Baseline CDAI) at both weeks 4 and 26 and at weeks 4, 26, and 56. There were no differences between adalimumab 40 mg ew and 40 mg eow treatment groups. They also revealed that the treatment difference between adalimumab and placebo treatment groups for sponsor's analyses for mITT population tended to be large compared those given in reviewer's ITT analyses.

Study M02-433, the extension study to Study M02-403, demonstrated that greater proportion of subjects in the two adalimumab treatment groups (40 mg eow and 40 mg ew) demonstrated maintenance of remission (CDAI score < 150) at Week 56 compared to placebo. However, no statistical significant difference was observed across the three treatment groups due to insufficient sample size.

Furthermore, this study, Study M02-433, was a rollover study the lead-in study, Study M02-403. So, it did not have sample size determination. A total of 67 subjects had induction of clinical remission at week in Study M02-403. It was expected that about 60 subjects who would achieve clinical remission at Week 4 and were randomized to one of three treatment groups. The sample size per arm would be about 20. Considering 20% subjects who did not complete Week 56 (double-blind), about 16 subjects per arm could

be evaluable for the randomized set. Sixteen subjects per arm were just too few to draw any meaningful statistical conclusion. So, this study should be considered an "exploratory" by design.

5.2 Conclusions and Recommendations

5.2.1 Induction Studies

Two induction studies, Studies M02-403 and M04-691), were conducted to evaluate adalimumab as induction therapy for moderate to severe Crohn's disease (CD). Study M02-403 evaluated a range of adalimumab induction regimens (40/20 mg, 80/40 mg. and 160/80 mg) in subjects who were naïve to anti-tumor necrosis factor (TNF) therapy. Study M04-691 was conducted using subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab.

Study M02-403 demonstrated that adalimumab was statistically significant in inducing clinical remission (achievement of a Crohn's Disease Activity Index score < 150 points) at Week 4 at doses of 80 mg/40 mg and 160 mg/80 mg as compared to placebo. Superiority of adalimumab compared to placebo was also shown in major secondary efficacy endpoints: clinical response CR-70 (a decrease from baseline in CDAI score ≥ 70) and clinical response CR-100 (a decrease from baseline CDAI score ≥ 100). The CR-70 endpoint comparisons showed superiority for both 80 mg/40 mg and 160 mg/80 mg doses groups; while CR-100 endpoint showed superiority for the 160 mg/80 mg dose group.

For subjects previously treated with infliximab who either lost response to infliximab or who had intolerance to infliximab, Study M04-691 demonstrated the proportion of subjects who achieved clinical remission at Week 4 was statistically significant greater in the adalimumab 160 mg/80 mg group compared to the placebo group. For 9 of 11 major secondary efficacy endpoints, adalimumab showed statistical significance or near-significance compared to placebo.

5.2.2 Maintenance Studies

Two studies, Studies M02-404 and M02-433, were conducted to evaluate adalimumab as maintenance therapy for moderate to severe Crohn's disease. In the large pivotal study, Study M02-404, the primary evaluation was the maintenance of remission in subjects who had initially responded to an adalimumab induction regimen. Subjects were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were permitted to enroll in this study.

In a second supportive maintenance study (Study M02-433), the extension study to Study M02-403, the primary evaluation was the maintenance of remission through year one in subjects who had achieved remission. The sponsor submitted this study as a supportive study.

Study M02-404 demonstrated that the proportion of all randomized subjects who achieved clinical response at Week 4 (a decrease from baseline in CDAI score ≥ 70) achieved clinical remission (CDAI < 150) at Week 26 and Week 56 (co-primary efficacy endpoints), were statistically significantly greater in the adalimumab 40 mg every other

week (eow) and 40 mg every week (ew) groups compared to the placebo group. Superiority of adalimumab groups over placebo was also shown in secondary efficacy endpoints, clinical response CR-70 (decrease from baseline in CDAI score $\geq$ 70 points) at Weeks 26 and 56, and clinical response CR-100 (decrease from baseline in CDAI score $\geq$ 100 points) at Weeks 26 and 56.

Study M02-433, the supportive, extension study to Study M02-403, showed that a numerically greater proportion of subjects in the two adalimumab treatment groups (40 mg eow and 40 mg ew) demonstrated maintenance of remission (CDAI score < 150) at Week 56 compared to placebo. However, due to small sample size, statistical significance was not achieved across the three treatment groups. For the secondary efficacy endpoints, clinical remission at Week 24, CR-70 at Week 24 and Week 56 and CR-100 at Week 24 and Week 56, numerically greater proportion of subjects responded in the adalimumab treatment groups compared to the placebo treatment group.

Appendix

Table 1 Summary of Demographic and Baseline Characteristics --- Randomized Population --- Protocol M02-403

Characteristics	Adalimumab 40mg/20 mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160mg/80mg (N=76)	Placebo (N=74)	p-value
Sex					0.0815
Male	39 (52.7%)	25 (33.3%)	36 (47.4%)	37 (50.0%)	
Female	35 (47.3%)	50 (66.7%)	40 (52.6%)	37 (50.0%)	
Race					0.2271
White	67 (90.5%)	64 (85.3%)	67 (88.2%)	68 (91.9%)	
Black	2 (2.7%)	7 (9.3%)	3 (3.9%)	2 (2.7%)	
Hispanic	0 (0.0%)	4 (5.3%)	3 (3.9%)	2 (2.7%)	
Asian	2 (2.7%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	
Other Races	3 (4.1%)	0 (0.0%)	2 (2.6%)	2 (2.7%)	
Age (months)					0.7614
Mean (SD)	39.2 (12.6)	38.3 (11.6)	38.5 (11.1)	37.1 (13.3)	
Age					0.0249
< 40 years	39 (52.7%)	40 (53.3%)	43 (56.6%)	51 (68.9%)	
40 - 64 years	32 (43.2%)	34 (45.3%)	33 (43.4%)	18 (24.3%)	
65-74 years	3 (4.1%)	1 (1.3%)	0 (0.0%)	5 (6.8%)	
Height (cm)					0.3846
Mean (SD)	171.3 (9.5)	169.1 (9.1)	171.3 (7.5)	170.5 (10.1)	
Weight (kg)					0.6568
Mean (SD)	74.8 (16.3)	74.3 (19.7)	77.5 (17.7)	74.3 (19.4)	
Weight					0.6567
≤ 70 kg	32 (43.2%)	38 (50.7%)	31 (40.8%)	33 (44.6%)	
>70 kg	42 (56.8%)	37 (49.3%)	45 (59.2%)	41 (55.4%)	
Tobacco use					0.4975
Never used	28 (37.8%)	30 (40.0%)	27 (35.5%)	34 (46.0%)	
Current user	25 (33.8%)	32 (42.7%)	32 (42.1%)	28 (37.8%)	
Ex-user	21 (28.4%)	13 (17.3%)	17 (22.4%)	12 (16.2%)	
Alcohol use					0.5445
Non-drinker	23 (31.1%)	31 (41.3%)	30 (39.5%)	27 (36.5%)	
Drinker	42 (56.8%)	38 (50.7%)	43 (56.6%)	39 (52.7%)	
Ex-drinker	9 (12.2%)	6 (8.0%)	3 (4.0%)	8 (10.8%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 1 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol M02-403 (Continued)

Characteristics	Adalimumab 40mg/20 mg (N=74)	Adalimumab 80 mg/40 mg (N=75)	Adalimumab 160mg/80mg (N=76)	Placebo (N=74)	p-value
Location of Crohn's disease at screening					
Colonic	23 (31.1%)	17 (22.7%)	22 (29.0%)	14 (19.0%)	
Ileal	45 (69.8%)	48 (64.0%)	41 (54.0%)	50 (67.6%)	
Ileocolonic	5 (6.8%)	9 (12.0%)	9 (11.8%)	10 (13.5%)	
Perianal		1 (1.3%)	1 (1.3%)		
Small bowel	1 (1.4%)		2 (2.6%)		
Unclassifiable			1 (1.3%)		
CDAI score at baseline					0.9145
N	73	75	76	74	
Mean (SD)	298.7 (57.3)	301.1 (60.5)	295.2 (51.9)	295.7 (59.9)	
Baseline CDAI scores					0.8429
N	74	73	74	73	
<220	1 (1.4%)				
220-270 points	27 (36.5%)	24 (32.9%)	28 (37.8%)	30 (41.1%)	
271-330 points	25 (33.8%)	22 (30.1%)	26 (35.1%)	21 (28.8%)	
331-390 points	16 (21.6%)	19 (26.0%)	16 (21.6%)	14 (19.2%)	
391-450 points	5 (6.8%)	8 (11.0%)	4 (5.4%)	8 (11.0%)	
IBDQ					0.7655
N	68	69	71	66	
Mean (SD)	129.5 (27.5)	126.1 (31.2)	124.9 (31.4)	129.1 (31.0)	
CRP Level at baseline					0.0006
N	72	72	72	67	
<1 mg/L	26 (36.1%)	15 (20.8%)	8 (11.1%)	25 (37.3%)	
≥1 mg/L	46 (63.9%)	57 (79.2%)	64 (88.9%)	42 (62.7%)	
Corticosteroids					0.0434
Yes	15 (20.3%)	31 (41.3%)	22 (29.0%)	25 (33.8%)	
No	59 (79.7%)	44 (58.7%)	54 (71.0%)	49 (66.2%)	
Immunosuppressants					0.9803
Yes	23 (31.1%)	21 (28.0%)	22 (29.0%)	22 (29.7%)	
No	51 (68.9%)	54 (72.0%)	54 (71.0%)	52 (70.3%)	
Oral Aminosalicylates					0.9037
Yes	38 (51.4%)	41 (54.7%)	40 (52.6%)	36 (48.7%)	
No3	36 (48.7%)	34 (45.3%)	36 (47.4%)	38 (51.4%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 2 Change in Baseline (Week 0) CDAI Score at Week 4

Change in Baseline (Week 0) CDAI Score at Week 4
Full Analysis Set
Protocol M02-403

	Full Analysis Set (N = 299)				
Time Point in Study	Adalimumab 40 mg/20 mg (N = 74)	Adalimumab 80 mg/40 mg (N = 75)	Adalimumab 160 mg/80 mg (N = 76)	All Adalimumab (N = 225)	Placebo (N = 74)
Week 4					
N	71	70	74	215	68
Mean (95% CI)	-68.4 (-86, -50)	-93.8 (-115, -72)	-99.9 (-123, -77)	-87.5 (-100, -75)	-51.8 (-69, -35)
SD	75.7	90.8	98.4	89.6	71.0
Median	-75.0	-90.0	-99.5	-82.0	-45.0
(Range)	(-253.0–112.0)	(-398.00–171.0)	(-375.0–115.0)	(-398.0–171.0)	(-345.0–106.0)
Week 4 (LOCF)					
N	73	73	76	222	72
Mean (95% CI)	-66.5 (-84, -49)	-91.0 (-112, -70)	-98.3 (-121, -76)	-85.4 (-97, -74)	-47.9 (-65, -31)
SD	75.7	90.1	97.6	89.1	72.9
Median	-71.0	-86.0	-93.5	-79.0	-44.0
(Range)	(-253.0–112.0)	(-398.0–171.0)	(-375.0–115.0)	(-398.0–171.0)	(-345.0–128.0)

CI: confidence interval; SD: standard deviation; LOCF: last observation carried forward

Cross Reference: Section 14, Table 14.2__2.1

Table 3 Change in Baseline (Week 0) IBDQ Score at Week 4

Change in Baseline (Week 0) IBDQ Score at Week 4
Full Analysis Set
Protocol M02-403

	Full Analysis Set (N = 299)				
Time Point in Study	Adalimumab 40 mg/20 mg (N = 74)	Adalimumab 80 mg/40 mg (N = 75)	Adalimumab 160 mg/80 mg (N = 76)	All Adalimumab (N = 225)	Placebo (N = 74)
Week 4					
N	63	69	69	201	65
Mean (95% CI)	18.2 (10.7, 25.7)	33.8 (25.6, 42.0)	32.8 (24.7, 40.9)	28.6 (23.9, 33.2)	21.1 (14.8, 27.3)
SD	29.8	34.2	33.7	33.3	25.2
Median	15.0	26.0	26.0	25.0	15.0
(Range)	(-59.0–95.0)	(-27.0–134.0)	(-11.0–185.0)	(-59.0–185.0)	(-27.0–144.0)
Week 4 (LOCF)					
N	71	72	73	216	70
Mean (95% CI)	17.2 (10.3, 24.1)	32.3 (24.2, 40.3)	33.1 (25.2, 41.0)	27.6 (23.1, 32.0)	19.2 (13.2, 25.3)
SD	29.2	34.4	33.9	33.3	25.4
Median	14.0	25.0	26.0	23.5	14.0
(Range)	(-59.0–95.0)	(-27.0–134.0)	(-11.0–185.0)	(-59.0–185.0)	(-27.0–144.0)

CI: confidence interval; SD: standard deviation; LOCF: last observation carried forward.
Cross Reference: Section 14, Table 14.2__9.1

Table 4 Summary of Demographic and Baseline Characteristics --- Randomized Population --- Protocol M04-691

Characteristics	Adalimumab 160mg/80mg (N=159)	Placebo (N=166)	p-value
Sex			0.1462
Male	50 (31.4%)	65 (39.2%)	
Female	109 (68.6%)	101 (60.8%)	
Race			0.4431
White	147 (92.5)	160 (96.4%)	
Black	6 (3.8%)	3 (1.8%0	
Hispanic	2 (1.3%)	2 (1.2%)	
Asian	2 (1.3%)	1 (0.6%)	
Other Races	2 (1.3%)		
Age (months)			0.1488
Mean (SD)	39.4 (11.9)	37.4 (11.9)	
Age			0.6636
<40 years	88 (55.4%)	102 (61.5%)	
40-64 years	68 (42.8%)	60 (36.1%)	
65-74 years	2 (1.3%)	3 (1.8%)	
≥75 years	1 (0.6%)	1 (0.6%)	
Height (cm)			0.0428
Mean (SD)	167.8 (10.0)	169.5 (10.0)	
Weight (kg)			0.9341
Mean (SD)	71.7 (19.0)	71.9 (19.2)	
Weight			0.6613
≤ 70 kg	91 (57.2%)	91 (54.8%)	
> 70 kg	68 (42.8%)	75 (45.2%)	
Tobacco use			0.8663
Never	65 (40.9%)	65 (39.2%)	
User	55 (34.6%)	56 (33.7%)	
Ex-user	39 (24.5%)	45 (27.1%)	
Alcohol use			0.4761
Never	68 (42.8%)	61 (36.7%)	
Drinker	77 (48.4%)	86 (51.8%)	
Ex-drinker	14 (8.8%)	19 (11.4%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 4 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol M04-691 (Continued)

Characteristics	Adalimumab 160mg/80mg (N=159)	Placebo (N=166)	p-value
CDAI score at baseline			0.8575
N			
Mean (SD)	312.5 (57.5)	313.2 (65.5%)	
Baseline CDAI scores			0.4683
<220		1 (0.6%)	
220-270 points	43 (27.0%)	51 (30.7%)	
271-330 points	59 (37.1%)	52 (31.3%)	
331-390 points	38 (23.9%)	34 (20.5%)	
391-450 points	19 (12.0%)	27 (16.3%)	
>450 points	0 (0.0%)	1 (0.6%)	
IBDQ			0.2282
N	158	166	
Mean (SD)	119.7 (27.2)	124.0 (27.6)	
CRP Level at baseline			0.1760
<1 mg/L	82 (51.6%)	98 (59.0%)	
≥1 mg/L	77 (48.4%)	68 (41.0%)	
Intolerant to Infliximab			0.6450
Yes	95/159 (59.7%)	95/166 (57.2%)	
No	64/159 (40.3%)	71/166 (42.8%)	
Lost response to previous Infliximab			0.4390
Yes	77/159 (48.4%)	87/165 (52.7%)	
No	82/159 (51.6%)	78/165 (47.3%)	
Intolerant and lost response to infliximab			0.8316
Yes	19/159 (11.9%)	21/166 (12.7%)	
No			
Corticosteroids			0.0835
Yes	55/159 (34.6%)	73/166 (44.0%)	
No	104/159 (65.4%)	93/166 (56.0%)	
Immunosuppressants			0.3399
Yes	73/159 (45.9%)	85/166 (51.2%)	
No	86/159 (54.1%)	81/166 (48.8%)	
Oral Aminosalicylates			0.1307
Yes	45/159 (28.3%)	60/166 (36.1%)	
No	114/159 (71.7%)	106/166 (63.9%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 5 Clinical Remission at Week 4 – Results Excluding Site 418 and Excluding Subjects who Did Not Meet Infliximab Failure Criteria

Clinical Remission at Week 4 - Results Excluding Site 418 and Excluding Subjects who Did Not Meet Infliximab Failure Criteria
Protocol M04-691

Treatment Group n (%)			
Placebo	Adalimumab 160/80 mg	Difference in Proportions (95% CI)	p-value[a]
Week 4 Excluding Site 418 Subjects (n, %)			
N = 166	N = 159		
12 (7.4)	34 (21.8)	14.4 (6.8, 22.1)	< 0.001
Week 4 Excluding Subjects Who Did Not Meet Infliximab Failure Criteria (n, %)			
N = 161	N = 153		
12 (7.5)	33 (21.6)	14.1 (6.4, 21.8)	< 0.001

a. The p-value is from Pearson's Chi-square test.

Cross Reference: Section 14, Table 14.2__1.1.1.2 and Table 14.2__1.1.1.3.

Table 6 Mean Change from Baseline in IBDQ Scores at Week 4

Mean Change from Baseline in IBDQ Scores at Week 4
Full Analysis Set
Protocol M04-691

IBDQ Score	Placebo N=161	Adalimumab 160/80 mg N=155	LS Mean Difference	95% CI	p-value
Total Score					
Baseline Mean ± SD	123.5 ± 27.45	119.7 ± 27.43			
Mean Change ± SD	15.1 ± 26.99	30.2 ± 30.75	14.16	7.92, 20.41	< 0.001
Social Function					
Baseline Mean ± SD	21.5 ± 7.50	20.4 ± 6.94			
Mean Change ± SD	2.3 ± 5.87	5.3 ± 6.18	2.65	1.37, 3.92	< 0.001
Systemic System					
Baseline Mean ± SD	15.8 ± 4.58	15.0 ± 4.97			
Mean Change ± SD	2.6 ± 4.95	4.8 ± 6.02	1.97	0.78, 3.17	0.001
Emotional Function					
Baseline Mean ± SD	47.6 ± 12.90	46.6 ± 12.63			
Mean Change ± SD	5.6 ± 10.67	10.0 ± 12.14	4.09	1.68, 6.50	< 0.001
Bowel Symptoms					
Baseline Mean ± SD	38.7 ± 8.21	37.7 ± 8.50			
Mean Change ± SD	4.6 ± 9.23	10.2 ± 9.95	5.34	3.31, 7.37	< 0.001

Note: LS mean (adalimumab 160/80 mg - placebo), confidence intervals, and p-values are from ANCOVA model using treatment as factor and Baseline value as covariate.

Cross Reference: Section 14, Table 14.2__2.1.1 and Table 14.2__2.2.1.

Table 7 Mean Change from Baseline to Week 4 in SF-36 Variables

Mean Change from Baseline to Week 4 in SF-36 Variables
Full Analysis Set
Protocol M04-691

SF-36 Varinble	Placebo	Adalimumab 160/80 mg	LS Mean Difference	95% CI	p-value
Physical Component Summary	N=159	N=153			
Baseline Mean ± SD	35.2 ± 8.02	34.9 ± 7.90			
Mean Change ± SD	3.5 ± 6.76	5.7 ± 8.15	2.12	0.51, 3.74	0.010
Mental Component Summary	N=159	N=153			
Baseline Mean ± SD	38.6 ± 11.37	37.4 ± 11.16			
Mean Change ± SD	2.9 ± 10.62	5.9 ± 9.57	2.57	0.50, 4.64	0.015
Physical Function	N=160	N=155			
Baseline Mean ± SD	62.6 ± 24.13	60.1 ± 25.83			
Mean Change ± SD	5.7 ± 15.51	9.3 ± 19.34	3.04	-0.60, 6.68	0.102
Role Function	N=161	N=153			
Baseline Mean ± SD	17.9 ± 29.10	17.3 ± 27.70			
Mean Change ± SD	17.2 ± 36.15	25.7 ± 42.02	8.19	-0.09, 16.48	0.053
Bodily Pain	N=161	N=154			
Baseline Mean ± SD	37.9 ± 18.93	36.6 ± 18.13			
Mean Change ± SD	9.4 ± 20.62	16.7 ± 22.22	6.77	2.30, 11.25	0.003
General Health	N=160	N=155			
Baseline Mean ± SD	29.0 ± 16.87	27.5 ± 16.04			
Mean Change ± SD	3.6 ± 12.12	9.7 ± 14.45	5.79	2.89, 8.69	< 0.001
Vitality	N=160	N=155			
Baseline Mean ± SD	24.1 ± 16.29	23.6 ± 18.31			
Mean Change ± SD	8.6 ± 18.82	14.6 ± 24.41	5.79	1.25, 10.33	0.013
Social Function	N=161	N=155			
Baseline Mean ± SD	50.9 ± 22.82	48.5 ± 23.32			
Mean Change ± SD	9.4 ± 22.71	17.1 ± 23.67	6.88	2.04, 11.72	0.005
Emotional	N=160	N=153			
Baseline Mean ± SD	49.8 ± 41.63	43.6 ± 40.70			
Mean Change ± SD	7.3 ± 43.22	16.8 ± 39.76	6.52	-1.67, 14.71	0.118
Mental Health	N=159	N=155			
Baseline Mean ± SD	56.0 ± 20.09	54.6 ± 20.90			
Mean Change ± SD	4.8 ± 16.96	8.9 ± 16.43	3.59	0.22, 6.95	0.037

Note: LS mean (adalimumab 160/80 mg - placebo), confidence intervals, and p-values are from ANCOVA model using treatment as factor and Baseline value as covariate.

Cross Reference: Section 14, Table 14.2__8.1.1 and Table 14.2__8.2.1.

Table 8 Summary of Mean Change from Baseline to Week 4 in VAS Score for Joint Pain

COMPARISON OF CHANGE IN VAS FOR JOINT PAIN FROM BASELINE AT WEEK 4
FULL ANALYSIS SET

VISIT	LS MEAN DIFFERENCE [A] (ADALIMUMAB 160/80 MG - PLACEBO)	95% CI [A]	P-VALUE [A]
WEEK 4	0.10	(-4.59 , 5.18)	0.970
WEEK 4(LOCF)	0.28	(-4.79 , 5.35)	0.913

SUMMARY STATISTICS OF VAS FOR JOINT PAIN BY VISIT
FULL ANALYSIS SET

VISIT / TREATMENT	N	BASELINE MEAN	BASELINE SD	VISIT MEAN	VISIT SD	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE SD	MEDIAN	MIN	MAX
BASELINE										
PLACEBO	160	41.5	28.53							
ADALIMUMAB 160/80 MG	154	41.5	28.69							
WEEK 4										
PLACEBO	153	41.5	28.31	32.5	28.07	-9.0	23.69	-8.0	-76.0	77.0
ADALIMUMAB 160/80 MG	149	41.9	28.75	32.9	28.00	-9.1	26.82	-4.0	-98.0	77.0
WEEK 4(LOCF)										
PLACEBO	155	41.7	28.35	32.4	27.93	-9.3	24.04	-8.0	-76.0	77.0
ADALIMUMAB 160/80 MG	150	42.0	28.66	32.9	27.90	-9.1	26.74	-4.0	-98.0	77.0

Table 9 Fistula Remission and Improvement at Week 4

Fistula Remission and Improvement at Week 4
Full Analysis Set
Protocol M04-691

	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg		
	N=25	N=20	Difference (95% CI)	p-value[a]
Fistula Remission[b]	2 (8.0)	1 (5.0)	-3.0 (-17.3, 11.3)	1.000
Fistula Improvement[c]	5 (20.0)	3 (15.0)	-5.0 (-27.2, 17.2)	0.716

a. The p-value is from Fisher's Exact test.

b. Closure of fistulas at the Week 2 and 4 Visits that were draining at Screening and Baseline.

c. Decrease in fistula counts from Baseline of at least 50% at the Week 2 and 4 Visits.

Cross Reference: Section 14, Table 14.2__3 and Table 14.2__4.

Table 10 Mean Change from Baseline in CRP at Week 4

Mean Change from Baseline in CRP at Week 4
Full Analysis Set
Protocol M04-691

Week 4					
Baseline Mean ± SD	1.8 ± 3.49	2.0 ± 2.50			
Mean Change ± SD	-0.1 ± 2.67	-1.1 ± 2.36	-0.96	-1.41, -0.51	< 0.001

Note: LS mean (adalimumab 160/80 mg - placebo), confidence intervals, and p-values are from ANCOVA model using treatment as factor and Baseline value as covariate.
Cross Reference: Section 14, Table 14.2__7.1.1 and Table 14.2__7.2.1.

Table 11 Clinical Remission at Week 2

Clinical Remission Over Time
Full Analysis Set
Protocol M04-691

	Treatment Group n (%)			
	Placebo	Adalimumab 160/80 mg	Difference in	
Visit	N=166	N=159	Proportions (95% CI)	p-value[a]
Week 1	6 (3.6)	10 (6.3)	2.7 (-2.0, 7.4)	0.265
Week 2	10 (6.0)	33 (20.8)	14.7 (7.5, 22.0)	< 0.001

a. The p-value is from Pearson's Chi-square test.

Cross Reference: Section 14, Table 14.2__1.2.1.

Table 12 Summary of Demographic and Baseline Characteristics --- Randomized Population --- Protocol M02-404

Characteristics	Total (N=854)	Placebo (N=261)	Adalim eow (N=260)	Adalim ew (N=257)	p-value
Sex					0.9310
Male	326 (38.2%)	99 (37.9%)	97 (37.3%)	100 (38.9%)	
Female	528 (61.8%)	162 (62.1%)	163 (62.7%)	157 (50.0%)	
Race					0.4662
White	796 (93.2%)	246 (94.3%)	245 (94.2%)	231 (89.8%)	
Black	27 (3.2%)	8 (3.1%)	7 (2.7%)	12 (4.7%)	
Hispanic	5 (0.6%)	0 (0.0%)	1 (0.4%)	3 (1.2%)	
Asian	14 (1.6%)	3 (1.1%)	4 (1.5%)	7 (2.7%)	
Other Races	12 (1.4%)	4 (1.5%)	3 (1.2%)	4 (1.6%)	
Age (months)					0.6901
Mean (SD)	37.1 (11.9)	36.9 (11.4)	36.8 (11.5)	37.8 (12.1)	
Age					0.6641
< 40 years	514 (60.2%)	155 (59.4%)	162 (62.3%)	149 (58.0%)	
40 - 64 years	323 (37.8%)	102 (39.1%)	96 (36.9%)	101 (39.3%)	
65-74 years	14 (1.6%)	3 (1.1%)	2 (0.8%)	6 (2.3%)	
≥ 75	3 (0.4%)	1 (0.4%)		1 (0.4%)	
Height (cm)					0.9654
Mean (SD)	168.9 (9.5)	168.9 (9.8)	168.9 (9.3)	169.0 (9.2)	
Weight (kg)					0.9963
Mean (SD)	70.5 (17.8)	71.1 (18.4)	70.5 (16.9)	71.0 (18.5)	
Weight					0.7023
≤ 70 kg	491 (57.5%)	153 (58.6%)	143 (55.0%)	147 (57.2%)	
>70 kg	363 (42.5%)	108 (41.4%)	117 (45.0%)	110 (42.8%)	
Tobacco use					0.5910
Never used	303 (35.5%)	96 (36.8%)	92 (35.4%)	89 (34.6%)	
Current user	208 (24.4%)	63 (24.1%)	59 (22.7%)	73 (28.4%)	
Ex-user	343 (40.2%)	102 (39.1%)	109 (41.9%)	95 (37.0%)	
Alcohol use					0.5760
Non-drinker	329 (38.5%)	96 (36.8%)	104 (40.0%)	101 (38.7%)	
Drinker	477 (55.9%)	152 (58.2%)	146 (56.2%)	137 (53.3%)	
Ex-drinker	46 (5.4%)	13 (5.0%)	10 (3.8%)	17 (6.6%)	
Unkown	2 (0.2%)			2 (0.8%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 12 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol M02-404 (Continued)

Characteristics	Total (N=854)	Placebo (N=261)	Adalim eow (N=260)	Adalim ew (N=257)	p-value
Crohn's disease location					
Leum	621 (72.7%)	180 (69.0%)	196 (75.4%)	195 (75.9%)	
Colon	640 (74.9%)	200 (76.6%)	192 (73.8%)	189 (73.5%)	
Gastroduodenum	43 (5.0%)	8 (12.0%)	19 (7.3%)	13 (5.1%)	
Other	129 (15.1%)	40 (15.3%)	36 (13.8%)	36 (14.0%)	
CDAI score at baseline					0.4679
Mean (SD)	313.1 (62.0)	315.8 (65.7)	309.6 (60.7)	308.2 (55.3)	
Baseline CDAI scores					0.1322
<220	6 (0.7%)	2 (0.8%)		1 (0.4%)	
220-270 points	240 (28.1%)	69 (26.4%)	83 (31.9%)	75 (29.2%)	
271-330 points	304 (35.6%)	93 (35.6%)	85 (32.7%)	102 (39.7%)	
331-390 points	184 (21.5%)	53 (20.3%)	62 (23.9%)	51 (19.8%)	
391-450 points	116 (13.6%)	41 (15.7%)	30 (11.5%)	28 (10.9%)	
≥ 451	4 (0.5%)	3 (1.2%)			
IBDQ					0.3762
Mean (SD)	121.8 (27.8)	122.9 (28.3)	124.5 (27.2)	120.6 (27.4)	
CRP Level at baseline					0.3423
N	852	261	258	257	
<1 mg/L	445 (52.2%)	130 (49.8%)	140 (54.3%)	144 (56.0%)	
≥1 mg/L	407 (47.8%)	131 (50.2%)	118 (45.7%)	113 (44.0%)	
Corticosteroids					0.6785
Yes	376 (44.0%)	107 (41.0%)	99 (38.1%)	107 (41.6%)	
No	478 (56.0%)	154 (59.0%)	161 (61.9%)	150 (58.4%)	
Immunosuppressants					0.1672
Yes	399 (46.7%)	133 (51.0%)	111 (42.7%)	121 (47.1%)	
No	455 (53.3%)	128 (49.0%)	149 (57.3%)	136 (52.9%)	
Oral Aminosalicylates					0.1550
Yes	324 (39.1%)	114 (43.7%)	96 (36.9%)	93 (36.2%)	
No3	520 (60.9%)	147 (56.3%)	164 (63.1%)	164 (63.8%)	
Previous Anti-TNT					0.9914
Yes	424 (49.6%)	133 (51.0%)	133 (51.2%)	130 (50.6%)	
No	430 (50.4%)	128 (49.0%)	127 (48.8%)	127 (49.4%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 13 Summary of Demographic and Baseline Characteristics --- mITT Population --- Protocol M02-404

Characteristics	Placebo (N=170)	Adalimumab eow (N=172)	Adalimumab ew (N=157)	p-value
Sex				0.7405
Male	65 (38.2%)	61 (35.5%)	62 (39.5%)	
Female	105 (61.8%)	111 (64.5%)	95 (60.5%)	
Race				0.5941
White	161 (94.7%)	159 (92.4%)	140 (89.2%)	
Black	4 (2.4%)	5 (2.9%)	9 (5.7%)	
Hispanic	0 (0.0%)	1 (0.6%)	2 (1.3%)	
Asian	2 (1.2%)	4 (2.3%)	4 (2.5%)	
Other Races	3 (1.8%)	3 (1.7%)	2 (1.3%)	
Age (months)				0.9578
Mean (SD)	36.9 (11.9)	36.4 (11.1)	36.8 (11.8)	
Age				0.7418
< 40 years	105 (61.8%)	106 (61.6%)	93 (59.2%)	
40 - 64 years	61 (35.9%)	65 (37.8%)	61 (38.9%)	
65-74 years	3 (1.8%)	1 (0.6%)	3 (1.9%)	
≥ 75	1 (0.6%)	0 (0.0%)		
Height (cm)				0.9534
Mean (SD)	169.0 (9.9)	169.1 (9.6)	168.7 (9.4)	
Weight (kg)				0.9287
Mean (SD)	70.4 (18.8)	70.4 (17.3)	69.8 (17.4)	
Weight				0.5982
≤ 70 kg	102 (60.0%)	95 (55.2%)	94 (59.1%)	
>70 kg	68 (40.0%)	77 (44.8%)	63 (40.1%)	
Tobacco use				0.1702
Never used	64 (37.7%)	77 (44.8%)	58 (36.9%)	
Current user	63 (37.1%)	62 (36.1%)	51 (32.5%)	
Ex-user	43 (25.3%)	33 (19.2%)	48 (30.6%)	
Alcohol use				0.9110
Non-drinker	72 (42.4%)	68 (39.5%)	64 (41.0%)	
Drinker	90 (52.9%)	98 (57.0%)	84 (53.9%)	
Ex-drinker	8 (4.7%)	6 (3.5%)	8 (5.1%)	
Unkown		2 (0.8%)		

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 13 Summary of Demographic and Baseline Characteristics --- mITT Population--- Protocol M02-404(Continued)

Characteristics	Placebo (N=170)	Adalimumab eow (N=172)	Adalimumab ew (N=157)	p-value
Crohn's disease location				
Leum	180 (69.0%)	196 (75.4%)	195 (75.9%)	
Colon	200 (76.6%)	192 (73.8%)	189 (73.5%)	
Gastroduodenum	8 (12.0%)	19 (7.3%)	13 (5.1%)	
Other	40 (15.3%)	36 (13.8%)	36 (14.0%)	
CDAI score at baseline				0.6216
Mean (SD)	321.1 (67.1)	315.7 (61.5)	312.6 (58.3)	
Baseline CDAI scores				0.1511
<220			1 (0.6%)	
220-270 points	41 (24.1%)	47 (27.3%)	44 (28.0%)	
271-330 points	63 (37.1%)	57 (33.1%)	61 (38.9%)	
331-390 points	32 (18/8%)	46 (26.7%)	30 (19.1%)	
391-450 points	31 (18.2%)	22 (12.8%)	21 (13.4%)	
≥ 451	3 (1.8%)			
IBDQ				0.3235
Mean (SD)	122.7 (29.5)	126.4 (28.3)	122.0 (26.6)	
CRP Level at baseline				0.5861
N	170	171	157	
<1 mg/L	85 (50.0%)	95 (55.6%)	82 (52.2%)	
≥1 mg/L	85 (50.0%)	76 (44.4%)	75 (47.8%)	
Corticosteroids				0.0440
Yes	66 (38.8%)	58 (33.7%)	74 (47.1%)	
No	104 (61.2%)	114 (66.3%)	83 (52.9%)	
Immunosuppressants				0.5763
Yes	83 (48.8%)	77 (44.8%)	79 (50.3%)	
No	87 (51.2%)	95 (55.2%)	78 (49.7%)	
Oral Aminosalicylates				0.2919
Yes	78 (45.9%)	66 (38.4%)	61 (38.9%)	
No	92 (54.1%)	106 (61.6%)	96 (61.2%)	
Previous Anti-TNT				0.9214
Yes	83 (48.8%)	86 (50.0%)	75 (47.8%)	
No	87 (51.2%)	86 (50.0%)	82 (52.2%)	

Compiled by this reviewer. Wilcoxon test for continuous variables chi-square test for categorical variables.

Table 14 Summary of Treatment Differences from Placebo in IBDQ Variable at Week 56 (mITT Dataset)

Summary of Treatment Differences from Placebo in IBDQ Variables at Week 56 mITT Dataset Protocol M02-404

Variable	Placebo	Adalimumab eow	Adalimumab ew
Total Score	N=32	N=77	N=81
Baseline Mean (SD)	127.4 (26.78)	128.0 (30.26)	126.7 (28.02)
Mean Change (SD)	45.9 (31.90)	59.8 (29.64)	59.7 (32.27)
Domain Score (Social Function)	N=32	N=77	N=80
Baseline Mean (SD)	22.8 (6.71)	22.0 (7.66)	22.4 (7.62)
Mean Change (SD)	6.8 (6.39)	10.7 (7.36)	9.9 (6.68)
Domain Score (Systemic Function)	N=32	N=77	N=81
Baseline Mean (SD)	15.4 (4.37)	17.1 (5.32)	16.3 (4.98)
Mean Change (SD)	8.8 (6.40)	9.6 (5.89)	9.2 (7.23)
Domain Score (Emotional Function)	N=32	N=77	N=81
Baseline Mean (SD)	49.2 (13.06)	49.3 (12.97)	49.0 (12.90)
Mean Change (SD)	15.8 (12.73)	21.2 (12.53)	20.2 (13.44)
Domain Score (Bowel Symptoms)	N=32	N=77	N=81
Baseline Mean (SD)	40.2 (7.95)	39.6 (7.94)	39.1 (8.88)
Mean Change (SD)	14.6 (10.80)	18.3 (9.05)	20.3 (11.36)

Variable	Treatment Comparison	Difference in Means	95% CI	p-value[a]
Total Score	Adalimumab 40 mg eow *vs.* placebo	14.36	(4.20, 24.52)	0.006
	Adalimumab 40 mg ew *vs.* placebo	13.26	(3.17, 23.35)	0.010
Social Function	Adalimumab 40 mg eow *vs.* placebo	3.36	(1.65, 5.07)	< 0.001
	Adalimumab 40 mg ew *vs.* placebo	2.86	(1.16, 4.56)	0.001
Systemic Function	Adalimumab 40 mg eow *vs.* placebo	2.08	(-0.20, 4.37)	0.074
	Adalimumab 40 mg ew *vs.* placebo	1.13	(-1.13, 3.39)	0.326
Emotional Function	Adalimumab 40 mg eow *vs.* placebo	5.49	(1.30, 9.69)	0.011
	Adalimumab 40 mg ew *vs.* placebo	4.24	(0.07, 8.41)	0.046
Bowel Symptoms	Adalimumab 40 mg eow *vs.* placebo	3.35	(-0.07, 6.77)	0.055
	Adalimumab 40 mg ew *vs.* placebo	4.95	(1.55, 8.34)	0.005

eow = every other week; ew = weekly; CI = confidence interval

a. Mean, confidence intervals, and p-values are from ANCOVA model with factors for treatment, Baseline value, previous anti-TNF use, and Week 4 responder status.

Note: Evaluations after discontinuation of DB study drug were excluded from analysis. Week 56 data include subjects receiving DB treatment.

Cross Reference: Section 14, Table 14.2__9.2.1 and Table 14.2__9.2.2.

Table 15 Summary of Demographic and Baseline Characteristics --- Randomized Population --- Protocol M02-433

Demographic Characteristic	Randomized Analysis Set					Open-label Analysis Set[a]		
	Placebo N = 18	Adalimumab 40 mg eow N = 19	Adalimumab 40 mg ew N = 18	Total N = 55	p-value[b]	Adalimumab 40 mg eow N = 115	Adalimumab 40 mg ew N = 89	Total N = 204
Sex, n (%)					0.615			
Female	12 (66.7)	12 (63.2)	9 (50.0)	33 (60.0)		57 (49.6)	47 (52.8)	104 (51.0)
Male	6 (33.3)	7 (36.8)	9 (50.0)	22 (40.0)		58 (50.4)	42 (47.2)	100 (49.0)
Race, n (%)					0.429			
White	17 (94.4)	17 (89.5)	15 (83.3)	49 (89.1)		105 (91.3)	77 (86.5)	182 (89.2)
Black	1 (5.6)	0	1 (5.6)	2 (3.6)		5 (4.3)	3 (3.4)	8 (3.9)
Hispanic	0	0	1 (5.6)	1 (1.8)		3 (2.6)	5 (5.6)	8 (3.9)
Asian	0	2 (10.5)	0	2 (3.6)		1 (0.9)	0	1 (0.5)
Other	0	0	1 (5.6)	1 (1.8)		1 (0.9)	4 (4.5)	5 (2.5)
Age, years					0.434			
Mean ± SD	35.7 ± 12.9	34.2 ± 11.5	38.1 ± 9.8	36.0 ± 11.4		40.4 ± 13.1	38.9 ± 11.7	39.8 ± 12.5
Median (range)	32.0 (20–68)	31.0 (20-58)	37.5 (23–60)	34.0 (20-68)		38.0 (18-74)	38.0 (19-73)	38.0 (18-74)
Age, n (%)					1.000			
< 40 years	12 (66.7)	13 (68.4)	12 (66.7)	37 (67.3)		60 (52.2)	47 (52.8)	107 (52.5)
40–64 years	5 (27.8)	6 (31.6)	6 (33.3)	17 (30.9)		49 (42.6)	40 (44.9)	89 (43.6)
65–74 years	1 (5.6)	0	0	1 (1.8)		6 (5.2)	2 (2.2)	8 (3.9)
Weight, kg					0.868			
Mean ± SD	69.6 ± 12.5	69.1 ± 18.8	72.1 ± 19.9	70.2 ± 17.1		77.7 ± 18.8	75.2 ± 17.6	76.6 ± 18.3
Median (range)	68.5 (50-95)	68.0 (45-109)	67.0 (52-134)	68.0 (45-134)		76.0 (41-128)	71.0 (44-125)	74.0 (41-128)

eow = every other week; ew = every week

a. Subjects who had dosing at or after Week 4.

b. The p-value is from the Fisher's Exact test for comparison across the three treatment groups.

Cross Reference: Section 14, Table 14.1__5.1, Table 14.1__5.2, Table 14.1__6.1, and Table 14.1__6.2

Table 15 Summary of Demographic and Baseline Characteristics --- Randomized Population (continued) --- Protocol M02-433

	Randomized Analysis Set					Open-label Analysis Set[a]		
Baseline Disease Characteristic	Placebo N = 18	Adalimumab 40 mg eow N = 19	Adalimumab 40 mg ew N = 18	Total N = 55	p-value[b]	Adalimumab 40 mg eow N = 115	Adalimumab 40 mg ew N = 89	Total N = 204
Number of Draining Fistulas					0.041			
Mean ± SD	0.17 ± 0.38	0	0	0.05 ± 0.23		0.13 ± 0.45	0.12 ± 0.39	0.13 ± 0.43
Median (range)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-1)		0 (0-2)	0 (0-2)	0 (0-2)
CDAI Score					0.589			
Mean ± SD	167.2 ± 62.4	106.1 ± 33.2	87.6 ± 50.3	100.4 ± 49.7		237.3 ± 59.3	255.4 ± 86.8	245.2 ± 73.0
Median (range)	95 (20-322)	110 (34-163)	94.5 (0-149)	102 (0-322)		224.0 (117-402)	267 (30-492)	237.5 (30-492)
IBDQ Score[c]					0.412			
Mean ± SD	187.2 ± 22.1	180.6 ± 27.7	191.5 ± 22.2	186.4 ± 24.2		151.4 ± 31.9	139.9 ± 34.7	146.3 ± 33.6
Median (range)	191 (138-224)	188 (128-213)	200 (138-216)	193.5 (128-224)		155 (68-209)	143 (58-216)	149 (58-216)
Baseline Corticosteroid Use, n (%)	10 (55.6)	9 (47.4)	9 (50.0)	28 (50.9)	NA	NA	NA	74 (36.3)
Baseline Immunosuppressant Use, n (%)	3 (16.7)	4 (21.1)	5 (27.8)	12 (21.8)	NA	NA	NA	67 (32.8)
Baseline Aminosalicylate Use, n (%)	8 (44.4)	14 (73.7)	12 (66.7)	34 (61.8)	NA	NA	NA	110 (53.9)

eow = every other week; ew = every week

a. Subjects who had dosing at or after Week 4.

b. The p-value is from the Fisher's Exact test for comparison across the three treatment groups.

c. N = 16 for placebo, N = 109 for adalimumab 40 mg eow, and N = 85 for adalimumab 40 mg ew.

Cross References: Section 14, Table 14.1__7.1, Table 14.1__7.2, and Table 14.1__9.

Table 16 Number of Subjects in Clinical Remission at Week 56 (Randomized Analysis Set Up to Week 56) – LOCF Analysis

Number of Subjects in Clinical Remission at Week 56
Randomized Analysis Set Up to Week 56
Imputed Analysis
Protocol M02-433

	CLINICAL REMISSION	PLACEBO (N=18) n (%)	40 MG EOW (N=19) n (%)	40 MG WKLY (N=18) n (%)	OVERALL P-VALUES[a]
WEEK 56_EXT LOCF	YES	8 (44.4)	15 (78.9)	15 (83.3)	0.029
	NO	10 (55.6)	4 (21.1)	3 (16.7)	

CLINICAL REMISSION IS DEFINED AS A CDAI SCORE < 150 POINTS.
FOR SUBJECTS WHO SWITCHED TO OPEN LABEL, 'NO' IS ASSIGNED TO REMISSION STATUS AFTER THE SWITCH.
LOCF REMISSION STATUS IS BASED ON LAST OBSERVED NON-MISSING CDAI SCORE BEFORE SUBJECT SWITCHED TO OPEN LABEL.
[a] P-VALUE IS FROM FISHER'S EXACT TEST ACROSS THREE TREATMENT GROUPS (PLACEBO, 40 MG EOW AND 40 MG WKLY).
PERCENTAGE IS CALCULATED BASED ON NON-MISSING DATA.
LOCF - LAST OBSERVATION CARRIED FORWARD. MISSING CDAI IS COUNTED AS 'NO' TO REMISSION, EXCEPT FOR LOCF.

Table 17 Change in IBDQ Scores from M02-403 Baseline (Week 0) to Week 24 and Week 56 (Randomized Analysis Set Up to Week 56)

Number of Subjects in Clinical Remission at Week 56
Randomized Analysis Set Up to Week 56
Observed Analysis
Protocol M02-433

	Randomized Analysis Set		
	Placebo N=18	Adalimumab 40 mg eow N=19	Adalimumab 40 mg ew N=18
M02-403 Baseline (Week 0)			
N	16	18	18
Mean (95% CI)	137.7 (118.8, 156.6)	133.1 (113.8, 152.4)	140.3 (120.7, 160.0)
Median (range)	136.5 (53 – 189)	135.5 (72 – 200)	146.5 (76 – 218)
M02-433 Baseline			
N	16	18	18
Mean (95% CI)	187.2 (175.4, 199.0)	180.6 (166.8, 194.4)	191.5 (180.5, 202.5)
Median (range)	191.0 (138 – 224)	188.0 (128 – 213)	200.0 (138 – 216)
Week 24			
N	9	13	17
Mean (95% CI)	34.9 (2.4, 67.4)	47.2 (30.5, 64.0)	53.4 (31.2, 75.7)
Median (range)	31.0 (-2 - 123)	43.0 (-2 – 96)	55.0 (-34 – 125)
Week 56			
N	6	11	15
Mean (95% CI)	42.2 (-22.6, 106.9)	49.2 (25.4, 73.0)	38.7 (16.2, 61.1)
Median (range)	19.5 (-16 - 151)	40.0 (11 - 129)	33.0 (-30 - 109)

eow = every other week; ew = every week

Note: For subjects who switched to OL adalimumab, IBDQ scores were classified as missing.

Cross Reference: Section 14, Table 14.2__15.1.1 and Table 14.2__15.2.1

Table 18 Number of Subjects in Clinical Remission at Week 24 Week 56 (Open-label Analysis Set [by Last Administered Treatment Up to Week 56])

Number of Subjects in Clinical Remission at Week 24 and Week 56
Open-label Analysis Set [by Last Administered Treatment Up to Week 56])
Protocol M02-433

	Open-label Analysis Set (By Last Administered Treatment Up to Week 56)		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Subjects in Clinical Remission at Week 24	46 (40.0)	28 (31.5)	74 (36.3)
Subjects in Clinical Remission at Week 56	46 (40.0)	28 (31.5)	74 (36.3)

eow = every other week; ew = every week

Cross Reference: Section 14, Table 14.2__3.2

Table 19 Clinical Responses CR-70 and CR-100 at Week 24 and Week 56 (Open-label Analysis Set [by Last Administered Treatment Up to Week 56])

Clinical Response CR-70 at Week 24 and Week 56
Open-label Analysis Set [by Last Administered Treatment Up to Week 56])
Protocol M02-433

	Open-label Analysis Set (By Last Administered Treatment Up to Week 56)		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Imputed Analysis			
Week 24	69 (60.0)	54 (60.7)	123 (60.3)
Week 56	62 (53.9)	48 (53.9)	110 (53.9)

eow = every other week; ew = every week

Cross Reference: Section 14, Table 14.2__12.1.2

Clinical Response CR-100 at Week 24 and Week 56
Open-label Analysis Set [by Last Administered Treatment Up to Week 56])

	Open-label Analysis Set (By Last Administered Treatment Up to Week 56)		
	Adalimumab 40 mg eow N=115	Adalimumab 40 mg ew N=89	Total N=204
	n (%)		
Imputed Analysis			
Week 24	62 (53.9)	48 (53.9)	110 (53.9)
Week 56	58 (50.4)	43 (48.3)	101 (49.5)

eow = every other week; ew = every week

Cross Reference: Section 14, Table 14.2__13.1.2

Table 20 Change in IBDQ Scores from M02-403 Baseline (Week 0) to Week 24 and Week 56 (Open-label Analysis Set [by Last Administered Treatment Up to Week 56])

Number of Subjects in Clinical Remission at Week 56
Open-Label Analysis Set Up to Week 56
Protocol M02-433

	Open – label Analysis Set		
	Adalimumab 40 mg eow N = 115	Adalimumab 40 mg ew N = 89	Total N = 204
M02-403 Baseline (Week 0)			
N	112	88	200
Mean (95% CI)	126.5 (121.4, 131.7)	124.4 (118.7, 130.2)	125.6 (121.8, 129.4)
Median (range)	127.0 (57 – 181)	125.0 (52 – 185)	126.5 (52 – 185)
Week 24			
N	78	73	151
Mean (95% CI)	44.5 (38.3, 50.7)	34.3 (27.7, 41.0)	39.6 (35.0, 44.2)
Median (range)	50.0 (-27 – 115)	37.0 (-17 – 103)	41.0 (-27 – 115)
Week 56			
N	65	58	123
Mean (95% CI)	49.0 (39.9, 58.2)	39.4 (32.2, 46.5)	44.5 (38.6, 50.3)
Median (range)	52.0 (-71 – 129)	38.0 (-29 – 116)	45.0 (-71 – 129)

eow = every other week; ew = every week

Note: For subjects who switched to OL adalimumab, IBDQ scores were classified as missing.

Cross Reference: Section 14, Table 14.2__15.1.2 and Table 14.2__15.2.2

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA:	125057/89
Brand Name:	Humira
Generic Name:	Adalimumab
Dosage form and Strength:	Injectable solution and a single-use, 1 mL pre-filled glass syringe or a single-use, pre-filled pen (Humira Pen), providing 40 mg (0.8 mL)
Route of administration:	Subcutaneous Injection
Indication:	Crohn's Disease
Sponsor:	Abbott
Type of submission:	Efficacy Supplement (089)
Clinical Division:	Gastrointestinal Drug Division (HFD-180)
OCPB Division:	DCP III
Priority:	6-Month Priority
Submission date:	08/25/06
OCPB Consult date:	09/25/06
PDUFA Goal date:	02/28/07
Reviewer:	Tien-Mien Chen, Ph.D.
Acting Team leader:	Tapash Ghosh, Ph.D.
Pharmacometrics Reviewer:	Chistoffer Tornoe, Ph.D.

I. Executive Summary

Abbott's Humira (adalimumab) for subcutaneous (SC) injection was approved by the Agency in 2002 for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) and later for patients with active psoriatic arthritis and for patients with active ankylosing spondylitis. The approved dosing regimen is 40 mg given every other week (EOW) for induction and maintenance therapies.

On 08/25/06, Abbott submitted an efficacy supplement under BLA 125057/89. The proposed new indication seeking approval is for Crohn's disease (CD), both in subjects who have had an inadequate response to conventional therapy and in subjects who have lost response to or do not tolerate infliximab (Remicade) therapy. This efficacy supplement was granted for a 6-month priority review.

The proposed SC dosing regimen for CD is 160 mg given on Day 1 of Week 0 and 80 mg given on Day 1 of Week 2 (induction therapy) and then 40 mg given EOW as maintenance therapy. Some patients with active CD may derive additional benefit by increasing the frequency of maintenance dosing to 40 mg every week (EW).

Submitted under BLA125057/89, were five clinical trials, i.e., two double-blind randomized studies and two long-term randomized studies for the maintenance of clinical remission plus an extension study for a long-term safety and efficacy study. For all these studies, the currently marketed Humira SC formulation was used. Pharmacokinetic (PK) data was obtained from 3 clinical studies. A population PK (PPK) approach was also employed for PK analyses and PK/PD (pharmacodynamic) assessments.

Mean serum trough adalimumab levels obtained from a dose-ranging study for induction therapy (160/80 mg, 80/40 mg, and 40/20 mg plus a placebo) appeared dose-proportional (at Week 1, 2, and 4). There was a trend for an increase response with an increase in serum trough adalimumab levels at Week 4. Only the highest induction dosing regimen (160/80 mg) was chosen for further clinical development since it provided significant benefit against placebo ($p < 0.05$).

Immunogenicity of adalimumab in patients with CD showed that the % of CD patients who developed anti-adalimumab antibody (AAA) is considered low and seemingly the incidence is not proportional to the dose administered. Overall, the immunogenicity of adalimumab in subjects with CD who developed AAA was 1.6%.

In general, concomitant medications as permitted per study design seemingly had only minor effect on clearance (CL/F) of adalimumab in CD patients. For subjects in the induction study who had lost response to infliximab or were intolerant to infliximab, concomitant use of any of the three immunosuppressants (6-MP, AZA or MTX) increased adalimumab concentrations by 18% ($p = 0.0296$), but may not be considered clinically significant.

Mean steady-state serum trough adalimumab levels obtained during the maintenance study were about 7 μg/mL for those who remained on the open-label trial of 40 mg EOW and around 12 μg/mL for those who remained on the open-label trial of 40 mg EW for 52 weeks. The above steady-state PK data supports the labeling statement, "for some patients with CD may derive benefit by increasing maintenance dosing frequency from 40 mg EOW to 40 mg EW".

Serum trough adalimumab levels were obtained at Week 0 and 4 in patients with moderate to severe CD who have lost response to or were intolerant to infliximab. Subgroup analyses showed that mean serum trough adalimumab levels were similar (1) between patients who lost response to (Yes/No) and (2) between patients who do not tolerate infliximab (Yes/No). The overall mean serum trough adalimumab level (12.63 μg/mL) at Week 4 was consistent with that (12.61 μg/mL) obtained from infliximab-naïve patients with CD.

No clinical or PK data was submitted to support the alternative induction dosing regimen, splitting the induction dose of 160 mg into two 80 mg doses administered over two days, Day 1 and 2 at Week 0. Based on PPK analyses, the PK profiles of the proposed and the alternative induction dosing regimens after SC administration of adalimumab are comparable or nearly superimposable. There is a convenience advantage in splitting the induction dose administered over two days.

The analytical methodology and validation of the assays used for this submission are found acceptable. Due to recent in-house report on problematic — analytical sites in —— Office of Clinical pharmacology (OCP) made a request for an audit at the ——— analytical site in ——— or the two (out of three) PK studies. However, the above audit request was unable to be executed due to DSI being in short of budget. OCP would presume that the analytical work done at the —— ——— s acceptable. Nevertheless, if further information on ——— indicates problematic, the Agency should audit the ——— subsequently. b(4)

A. Recommendations

BLA125057/89 for Humira SC Injection for the indication of treating patient with moderate to severe CD has been reviewed by OCP and the submission is considered acceptable from OCP perspective provided that the recommended labeling changes are incorporated into the package insert. The labeling comments (p. 19) need to be conveyed to the sponsor.

B. Phase IV Commitments: None

07/15/07

Tien-Mien Chen

01/22/07

Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Acting Team Leader

Tapash Ghosh, Ph.D. 01/26/07

II. Table of Contents

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Submitted under BLA125057/89, were two double-blind randomized studies (M02-403 and M04-691) provide comparative evidence of the efficacy of adalimumab vs. placebo for the induction of clinical remission, and two long-term randomized studies (M02-433 and M02-404) provide comparative evidence of the efficacy of adalimumab vs. placebo for the maintenance of clinical remission plus an extension study for a long-term safety and efficacy study (M04-690). For all these studies, a currently marketed Humira SC formulation was used. PK data was obtained from Study 02-403, 02-433, and 04-691 for serum trough adalimumab levels. A PPK approach was also employed for PK analyses and for PK/PD assessments.

In a phase 2/3 dose-ranging trial (M02-403), three dosing regimens for induction therapy were employed, 160/80 mg, 80/40 mg, and 40/20 mg plus a placebo arm, to explore the optimal dose(s) for patients with moderate to severe CD. The mean serum trough adalimumab levels appeared to be dose-proportional to dose (at Week 1, 2, and 4). There was a trend for an increase response with an increase in serum trough adalimumab levels at Week 4. However, only the highest induction dosing regimen (160/80 mg) was chosen for further clinical development since it provided significant benefit against placebo ($p < 0.05$).

Serum level of AAA was also measured in Study M02-403. The results show that the % of CD patients who developed AAA is very low (around 1%) and seemingly the incidence is not proportional to the dose administered. Immunogenicity of adalimumab in patients with CD was also assessed in the other two PK studies. Overall, the immunogenicity of adalimumab in subjects with CD was low at 1.6% (7 of 436 subjects).

The effects of commonly co-administered immunosuppressants on the PK of adalimumab in patients with CD in terms of CL/F were examined using PPK approach. The results show that in general, concomitant medications as permitted per study design seemingly had only minor effect on CL/F of adalimumab in CD patients. For subjects in the induction study who had lost response to infliximab or were intolerant to infliximab (Study M04-691), concomitant use of any of the three immunosuppressants (6-MP, AZA

or MTX) increased adalimumab concentrations by 18% ($p = 0.0296$), but may be considered less clinically significant.

Mean steady-state serum trough adalimumab levels obtained during the maintenance study (Study M02-433) were about 7 μg/mL for those who remained on the open-label trial of 40 mg EOW and around 12 μg/mL for those who remained on the open-label trial of 40 mg EW for 52 weeks. The above steady-state PK data (serum trough adalimumab levels), therefore, supports the labeling statement, "for some patients with CD may derive benefit by increasing maintenance dosing frequency from 40 mg EOW to 40 mg EW".

PK samples were obtained for serum trough adalimumab levels at Week 0 and 4 from study M04-691, a Phase 3, multicenter, randomized, double-blind, placebo-control, 2-arm induction study of clinical remission in patients with moderate to severe CD who have lost response to or were intolerant to infliximab. Based on the subgroup analyses, mean serum trough adalimumab levels were similar (1) between patients who lost response to (Yes/No) and (2) between patients who do not tolerate infliximab (Yes/No). The overall mean serum trough adalimumab level (12.63 μg/mL) at Week 4 was consistent with that (12.61 μg/mL) obtained from infliximab-naïve patients with CD in study M02-403.

No clinical or PK data was submitted to support the alternative induction dosing regimen, splitting the induction dose of 160 mg into two 80 mg doses administered over two days, Day 1 and 2 at Week 0. From a scientific point of view [for a drug with a very long terminal half-life ($T_{1/2}$) of 2 weeks] and based on PPK analyses, the PK profiles of the proposed and the alternative induction dosing regimens after SC administration of adalimumab are comparable or nearly superimposable. From a patient perspective, there is a convenience advantage in splitting the induction dose administered as 4 injections over two days. Nevertheless, in the pre-NDA meeting on 05/11/06, the Agency did encourage the sponsor to investigate the alternative induction dosing regimen of splitting the dose of 160 mg over two days in a clinical equivalence study.

[

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IV. Question Based Review

A. General Attributes

Adalimumab is a recombinant full length human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilo-Daltons. Adalimumab is compromised of fully human heavy and light chain variable regions, which confer specificity to human TNF (tumor necrosis factor), and human IgG1 heavy chain and kappa light chain sequences. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and is recognized as an important contributor in the pathogenesis of CD. Elevated levels of TNF play an important role in pathologic inflammation.

Adalimumab binds specifically to and neutralizes the biological function of human TNF by blocking its interaction with the p55 and p75 cell surfaces TNF receptors. It also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration. Adalimumab binds with high affinity and specificity to soluble TNF-α but not lymphotoxin (TNF-ß).

Abbott's adalimumab (Humira) was first approved for treatment of RA on 12/31/02 in the US under BLA125057/0. Indication extension to include treatment of patients with active psoriatic arthritis was granted in the US on 10/03/05 and later to include patients with ankylosing spondylitis. The approved dosing regimen is 40 mg given every other week EOW for induction and maintenance therapies.

B. General Clinical Pharmacology

On 08/25/06, Abbott submitted an efficacy supplement to BLA125057/89 for the treatment of moderately to severely active CD both in subjects who have had an inadequate response to conventional therapy and in subjects who have lost response to or do not tolerate infliximab (Remicade) therapy. This efficacy supplement was granted a 6-month priority review.

The proposed SC dosing regimen is 160 mg given on Day 1 of Week 0 and 80 mg given on Day 1 of Week 2 (induction therapy) and then 40 mg given EOW as maintenance therapy. Some patients with active CD may derive additional benefit by increasing the frequency of maintenance dosing to 40 mg EW.

Crohn's disease is an immunologically-mediated disease. It is an idiopathic incurable chronic inflammatory disorder of the gastrointestinal tract and it can involve any section of the gastrointestinal tract from the mouth to the anus, but most commonly affects the small intestine and/or the colon. CD is defined by a baseline Crohn's Disease Activity Index (CDAI) score between 220 and 450 points, moderately active CD being baseline CDAI $\leq$300 and severely active CD being baseline CDAI >300. Successful treatment of CD is regarded as induction of remission (primary endpoint being CDAI <150), followed

by long-term maintenance of remission. A flare is defined as a recurrence of a very active disease (CDAI being above 220), i.e., an increase of CDAI of 70 or more points when compared to their previous value of CDAI of 150.

Under BLA125057/89, two double-blind randomized studies (M02-403 and M04-691), provide comparative evidence of the efficacy of adalimumab vs. placebo for the induction of clinical remission. Two long-term randomized studies (M02-404 and M02-433) provide comparative evidence of the efficacy of adalimumab vs. placebo for the maintenance of clinical remission plus an extension study from M02-404 and M02-433 for a long-term safety and efficacy study (M04-690) as shown below in Table 1:

Table 1. Study submitted under BLA125057/89 for Crohn's Disease

Study No.	No. Patients Enrolled	Location/ Number of Sites	Study Design	Primary Objective	Status
M02-403	299	Europe, United States, Canada/ 55	4-week, randomized, double-blind, placebo-controlled, multicenter, dose ranging study in anti-TNF naïve subjects with moderate to severe CD	Assess efficacy, safety, and pharmacokinetics of adalimumab for the induction of clinical remission	Study completed
M04-691	325	United States, Canada, Belgium, France/ 52	Randomized, double blind, placebo-controlled, multicenter study in patients with moderate to severe CD who had lost response to or were intolerant to infliximab	Assess efficacy, safety, and pharmacokinetics of adalimumab for the induction of clinical remission	Study completed
M02-404	854	Europe, United States, Canada, Australia, and South Africa/ 92	Randomized, double-blind, placebo-controlled, multicenter study in patients with moderate to severe CD	Assess efficacy and safety of adalimumab for the maintenance of clinical remission	Study completed
M02-433	276	Europe, United States, Canada/ 53	Multicenter extension study of M02-403 Randomized, double-blind, placebo-controlled phase and concurrent open-label phase	Assess efficacy, safety, and pharmacokinetics of adalimumab for the maintenance of clinical remission	Study ongoing
M04-690	777	Europe, United States, Canada, Australia, and South Africa/ 114	Multicenter extension study of M02-404 and M04-691	Assess efficacy and safety of long-term use of adalimumab as maintenance therapy	Study ongoing

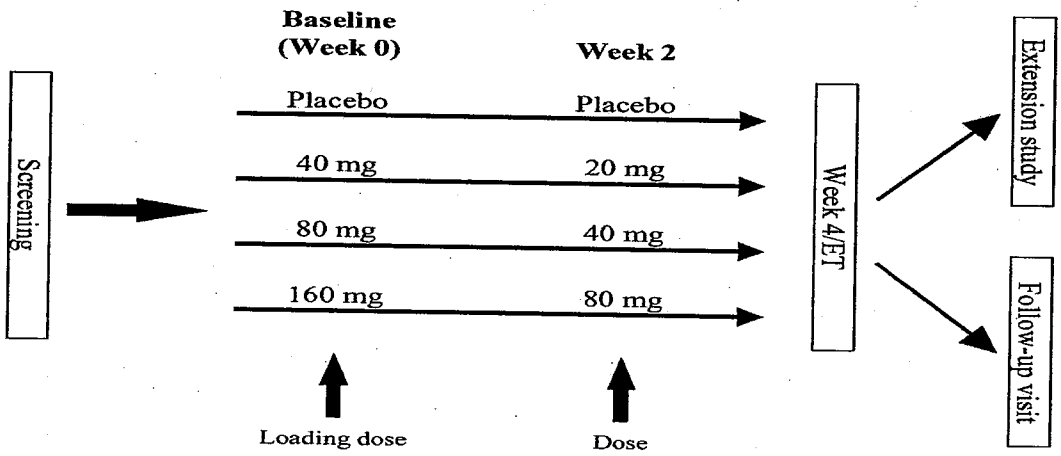
PK data was obtained from Study M20-403, M02-433, and M04-691. A PPK approach was also employed for PK analyses and PK/PD (pharmacodynamic) assessments.

Q1: Was an appropriate dose selected for the Phase 3 clinical trial?

A1: Yes, a Phase 2/3 dose-ranging study (M02-403) was conducted to explore the optimal dose(s) for patients with moderate to severe CD. Three dosing regimens for induction therapy were explored, 160/80 mg, 80/40 mg, and 40/20 mg and mean serum trough adalimumab levels appeared dose-proportional (at Week 1, 2, and 4). The highest induction dosing regimen (160/80 mg) was chosen for further clinical development because only the highest induction dosing regimen provided significant benefit against placebo ($p < 0.05$). However, there was a trend for an increase response (larger difference in CDAI at Week 4 from baseline) with an increase in serum trough adalimumab levels at Week 4.

Study M02-403 was a randomized, double-blind, placebo controlled, multicenter, Phase 2/3 dose-ranging, efficacy, safety, and PK study. PK and dose proportionality of three dose regimens for induction therapy was assessed in terms of serum trough adalimumab levels (Scheme 1).

Scheme 1: Study Design of Study M02-403



ET = Early Termination

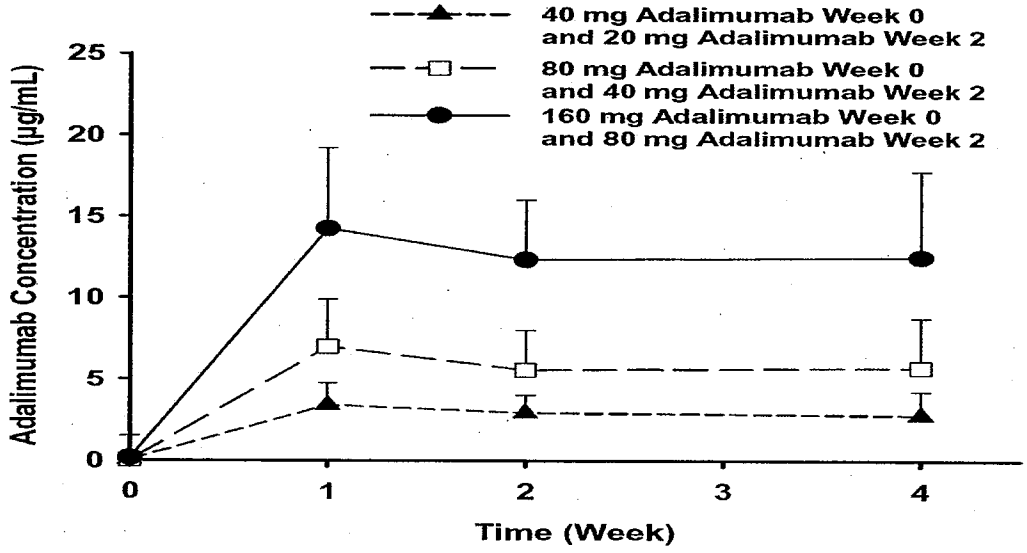
Blood samples at baseline and the end of Week 1, 2, and 4 were obtained for determining serum trough adalimumab levels using an enzyme-linked immunosorbent assay (ELISA) method. The results of the dose-ranging PK study showed that the mean serum trough adalimumab levels appeared dose-proportional as shown below in Table 2 and Figure 1:

Table 2. Summary of Mean ± SD Serum Trough Adalimumab Levels (µg/mL) obtained from Study M02-403

	Mean ± SD (n_{nmiss}) Adalimumab Concentrations in µg/mL			
	Week			
Treatment	0	1	2	4
40 mg adalimumab at Week 0 and 20 mg adalimumab at Week 2	0.06 ± 0.44 (62)	3.42 ± 1.37 (64)	2.95 ± 1.08 (69)	2.79 ± 1.48 (66)
80 mg adalimumab at Week 0 and 40 mg adalimumab at Week 2	0.03 ± 0.25 (66)	7.00 ± 2.89 (68)	5.57 ± 2.42(68)	5.65 ± 3.06 (65)
160 mg adalimumab at Week 0 and 80 mg adalimumab at Week 2	0.17 ± 1.34 (66)	14.26 ± 4.92 (66)	12.34 ± 3.68 (68)	12.61 ± 5.25 (67)

*. Number in parentheses (n_{nmiss}) indicates the number of non-missing observations.

Figure 1. Mean ± SD Serum Trough Adalimumab Levels (µg/mL) At Week 0, 1, 2, and 4



Q2: Is AAA developed considerably after adalimumab administration which may decrease efficacy of adalimumab treatment?

A2: No, overall, the percentage (%) of CD patients enrolled developed positive AAA is considered low (< 2%) and seemingly the incidence is not proportional to the dose administered.

Serum level of AAA was also measured in Study M02-403 using an ELISA assay method. Since serum adalimumab level interferes with the ELISA for serum AAA level determination, only those samples where serum adalimumab levels were < 2 μg/mL upon sample collection were chosen and analyzed, i.e., 528 (out of 1080) samples collected were analyzed for serum AAA levels.

The results show that the % of CD patients who developed AAA is considered low (around 1%) and seemingly the incidence is not proportional to the dose administered as shown in Table 3:

Table 3. Positive Serum AAA Levels obtained from Study M02-403

AAA Levels*	Placebo Group (n=70)	Treatment Total (n=211)	40/20 mg Group (n=69)	80/40 mg Group (n=71)	160/80 mg Group (n=71)
Positive (%)	n= 1 (1.4%)	n=1 (0.5%)	-----	n=1 (1.4%)	-----

*. Analyzed only when serum adalimumab levels were < 2 μg/mL (528 out of 1080 blood samples collected).

However, an assumption was made, i.e., if the lapse time is long enough since the last adalimumab SC injection (week 2 in this study) to allow serum adalimumab level to decline to < 2 μg/mL, the rest of 552 samples would show the same % in positive AAA results.

Immunogenicity of adalimumab in patients with CD was also assessed in the other induction study, a 4-week duration study (Study M04-691), and a maintenance study, a 52-week duration (Study M02-433). For subjects who had lost response or were intolerant to infliximab (Study M04-691), the AAA-positive rate was 0% (0 of 156 subjects) during the induction phase. For subjects who were on longer durations of therapy, up to 56 weeks in Study M02-433, the immunogenicity rate was also low at 2.6% (7 of 269 subjects).

Q3: Would concomitant medication [Methotrexate (MTX), Azathioprine (AZA), or 6-Mercaptopurine (6-MP)] as permitted per study design affect the PK of adalimumab which warranted dose adjustment?

A3: No, based on PPK analysis, only minor changes to the estimated clearance (CL/F) were found as shown in Table 4 (Study M02-403) and less than 10% decrease was found from Study M02-433 (Table 5). For Study M04-691, overall, a 18% decrease in adalimumab CL/F (p = 0.0296) was found for the co-medication, MTX, AZA, or 6-MP.

The sponsor indicated that the number of subjects on MTX was too small to make conclusions regarding its effects on serum trough adalimumab levels (or CL/F). Dose adjustment for adalimumab SC dosing seemingly may not be needed when patients are on the concomitant medication of MTX, AZA, or 6-MP. However, detailed information on the dose, frequency, and/or timing of co-medication of MTX, AZA, or 6-MP was not available for PPK analysis and review.

Table 4. Summary Statistics for the Effect of Concomitant Medication on Adalimumab Estimated Clearance (CL/F, mL/hr) Using PPK Approach (Study No. M02-403)

Co-Medication	Category	N	Mean CL/F* (mL/hr)	Std	Geo. Mean	Median	Min.	Max.	% CV
MTX	No	149	14.29	5.68	13.34			48.20	39.77
	Yes	7	12.52 (12% ↓)	1.40	12.45			15.01	11.17
AZA	No	149	14.29	5.68	13.34			48.20	39.77
	Yes	33	13.97 (2 % ↓)	8.61	12.36			44.46	58.42
6-MP	No	149	14.29	5.68	13.34			48.20	39.77
	Yes	21	14.82 (4 % ↑)	7.01	13.55			34.79	47.30

*. Mean of estimated individual CL/F values.

The effects of commonly co-administered immunosuppressants on the PK of adalimumab in patients with CD in terms of CL/F were examined in Study M02-403 using PPK approach. The results show that in general, CD patients with concomitant medications as permitted per study design seemingly had only minor effect (slightly changed CL/F).

The effects of co-medication were also analyzed for a long-term study (M02-433) and results show that MTX, AZA, and 6-MP had slight effects on adalimumab CL/F (Table 5).

Table 5. Summary Statistics for the Effect of Concurrent Medications (MTX, AZA, 6-MP) on Adalimumab Estimated Clearance (CL/F, mL/hr) Using PPK Approach (Study No. M02-433)

Co-Medication	Category	N	Mean CL/F* (mL/hr)	Std	Geo. Mean	Median	Min.	Max.	% CV
MTX	No	154	17.06	7.08	15.71	15.49			41.51
	Yes	6	15.50 (9% ↓)	4.31	14.97	15.61			27.80
AZA	No	154	17.06	7.08	15.71	15.49			41.51
	Yes	36	16.90 (1% ↓)	8.40	15.16	13.87			49.67
6-MP	No	154	17.06	7.08	15.71	15.49			41.51
	Yes	23	15.28 (10% ↓)	6.72	14.06	12.73			43.98

*. Mean of estimated individual CL/F values.

For subjects in the induction study who had lost response to infliximab or were intolerant to infliximab (Study M04-691), concomitant use of any of the three immunosuppressants (6-MP, AZA or MTX) increased adalimumab concentrations overall by 18% (n=73; p = 0.0296), but may be of less clinical significance. The sponsor indicated that the number of subjects on MTX was too small to make conclusions regarding its effects on serum trough adalimumab levels (or CL/F) when patients are on concomitant medication, MTX (n=15, p=0.0796), AZA (n=33; p=0.4736), or 6-MP (n= 25; p=0.0668). Dose adjustment for adalimumab SC dosing seemingly may not be needed. However, detailed information on dose, frequency, and timing of co-medication of MTX, AZA, or 6-MP was not available for PPK analysis and review.

Q4: Is there PK data of adalimumab to support a maintenance therapy of 40 mg EOW and 40 mg EW dosing as proposed in labeling?

A4: Yes, steady-state serum trough adalimumab levels during maintenance therapy were monitored up to 56 weeks in Study M022-433. Mean steady-state serum trough adalimumab levels were about 7 µg/mL for those who remained on the open-label trial of 40 mg EOW and around 12 µg/mL for those who remained on the open-label trial of 40 mg EW for 52 weeks as shown in Table 6.

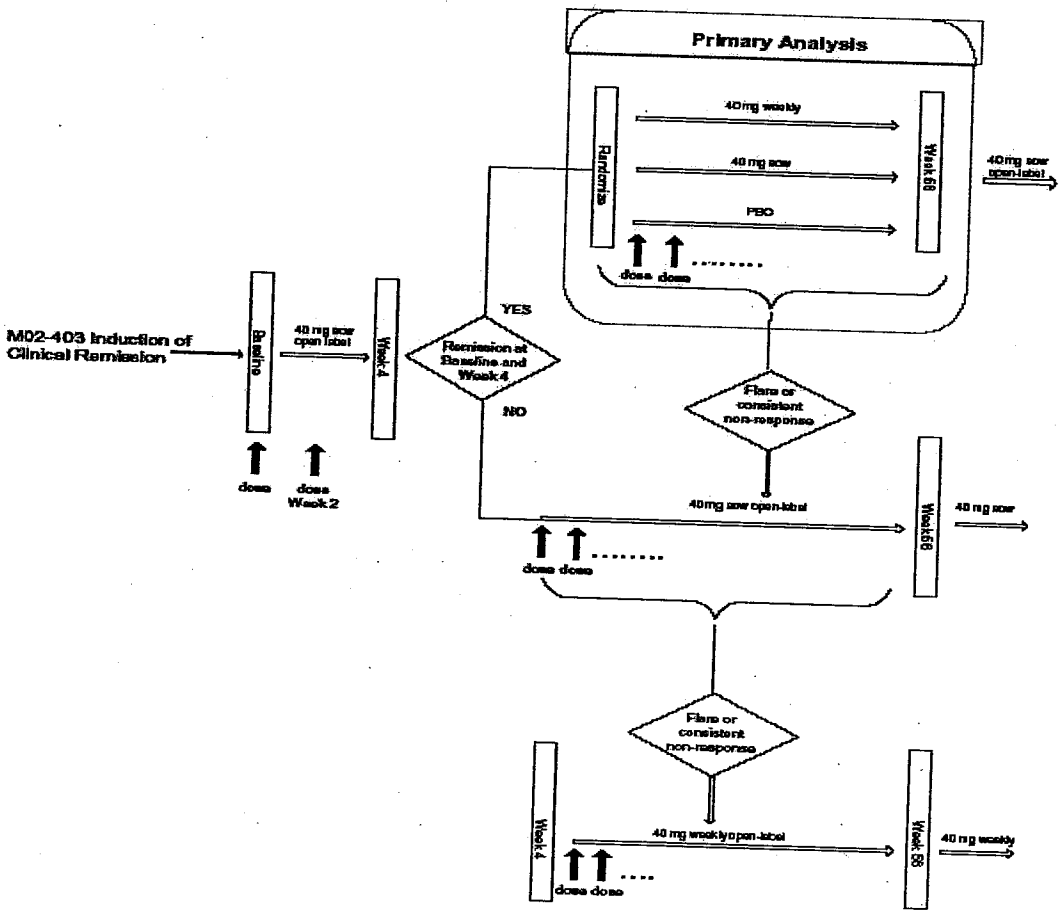
Table 6. Mean (± SD) Steady-State Serum Trough Adalimumab Levels (µg/mL) obtained from Study M02-433

Treatment	Week			
	4	24	56	Early Termination
DB Placebo (n=18)	7.84 (± 4.20) (n=8)	2.55 (± 5.84) (n=6)	0.00 (± 0.00) (n=6)	0.06 (± 0.08) (n=5)
DB 40 mg EOW (n=18)	6.91 (± 3.61) (n=12)	8.20 (± 4.69) (n=10)	10.92 (± 6.57) (n=10)	0.00 (n=1)
DB 40 mg Weekly (n=18)	8.83 (± 7.07) (n=17)	17.04 (± 11.86) (n=16)	15.03 (± 8.72) (n=14)	10.67 (± 7.17) (n=2)
OL 40 mg EOW (n=128)	5.60 (± 3.37) (n=112)	6.64 (± 4.28) (n=82)	7.22 (± 4.58) (n=71)	4.55 (± 4.32) (n=50)
OL 40 mg Weekly (n=88)	5.02 (± 3.68) (n=86)	9.92 (± 6.65) (n=70)	12.03 (± 7.53) (n=57)	10.19 (± 9.70) (n=21)

DB: Double-blind
OL: Open-label

Study M02-433 was a continuation of Study M02-403. Subjects who completed induction study M02-403 at week 4 could rollover into Study M02-433 as baseline (Week 0) as shown in scheme 2 below:

Scheme 2: Study Design of Study M02-433



All subjects received SC 40 mg of adalimumab at Baseline (Week 0) and Week 2 (open-label). Subjects were randomized at Week 4 in the double-blind M02-433 trial based upon their clinical remission status at Baseline and Week 4. The first cohort was comprised of subjects who achieved clinical remission at the end of Study M02-403 (baseline for Study M02-433), and remained in clinical remission at Week 4 of Study M02-433. These subjects were randomized to receive SC injections of either 40 mg adalimumab EW, 40 mg adalimumab EOW, or placebo for a primary analysis in this double-blind trial. If subjects in this randomized portion of Study M02-433 developed a disease flare, they were switched to the open-label portion of the study. Subjects who developed a flare of CD while receiving 40 mg EOW of adalimumab at open-label portion, were to have their dose frequency increased to open-label 40 mg EW.

The PK results showed that during the maintenance phase (Study M02-433), the mean steady-state serum trough adalimumab level was about 7 μg/mL for those who remained on the open-label trial of 40 mg EOW and was around 12 μg/mL for those who remained on the open-label trial of 40 mg EW for 52 weeks (Table 5).

Q5: **Are there differences in steady-state serum trough adalimumab levels for those patients with CD who have lost response to or do not tolerate infliximab (Remicade) therapy (M04-691)?**

A5: **No, seemingly, there are no differences in mean serum trough adalimumab levels for the subgroup analyses, between patients who lost response to (Yes vs. No; p= 0.741) or between patients who do not tolerate infliximab (Yes vs. No; p=0.148) as shown below in Table 7. The overall mean serum trough adalimumab level (12.63 µg/mL) at Week 4 was consistent with that (12.61 µg/mL) obtained from infliximab-naïve patients with CD in study M02-403.**

Table 7. Mean (± SD) Serum Trough Adalimumab Levels (µg/mL) obtained from Study M04-691 for Patients Who Lost Response to or Who Were Intolerant to Infliximab

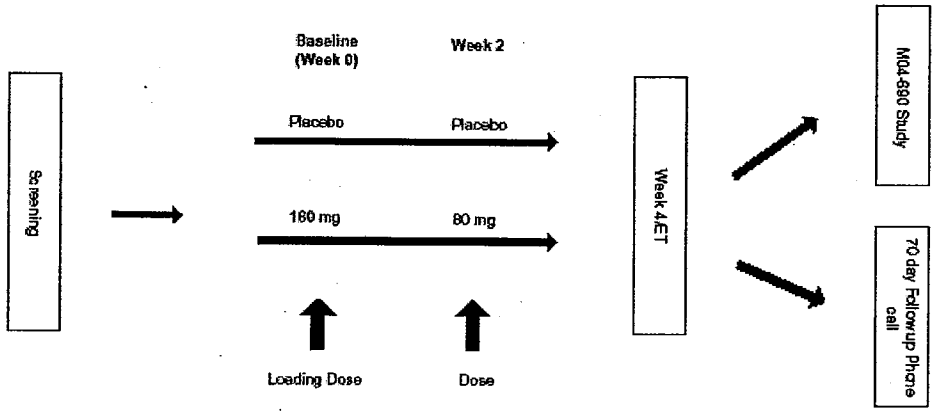
	Adalimumab Treatment Group (N=159)							
	Loss of Response to Infliximab				Intolerance to Infliximab			
	Yes (n=77)		No (n=82)		Yes (n=96)		No (n=63)	
	Week							
Mean (± SD) Serum Trough Adalimumab Levels	0 (n=68)	4 (n=72)	0 (n=72)	4 (n=77)	0 (n=88)	4 (n=90)	0 (n=55)	4 (n=59)
	0.276[1] (1.748)	**12.553 (6.496)**	**0.024[1] (0.119)**	**12.697 (5.614)**	**0.017[1] (0.104)**	**11.961 (5.768)**	**0.347[1] (1.941)**	**13.644 (6.339)**

1. Non-zero serum adalimumab levels due to possible interference of serum infliximab levels to the ELISA method used

*. Patients' serum AAA levels were all below LOQ

Study M04-691 was a Phase 3, multicenter, randomized, double-blind, placebo-control, 2-arm induction study of clinical remission in 325 patients with moderate to severe CD who have lost response to or were intolerant to infliximab as shown in the following scheme 3.

Scheme 3. Study Design of Study M04-691



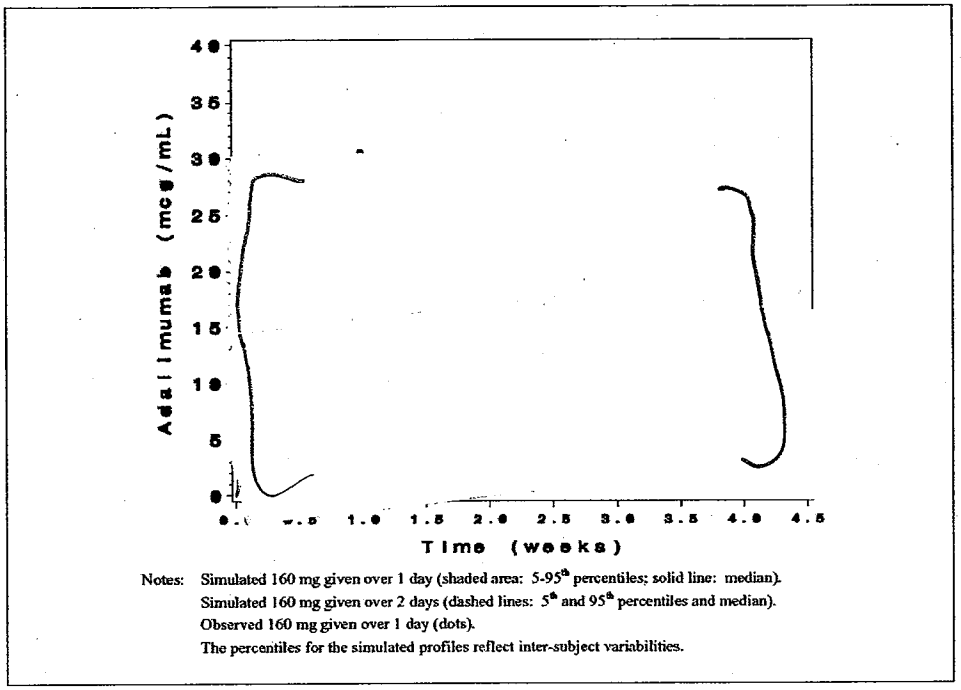
Serum samples were also obtained from this study for trough adalimumab levels at Week 0 and 4. The results show that based on the subgroup analyses, mean serum trough adalimumab levels were similar in terms of serum trough adalimumab levels (1) between patients who lost response to (Yes/No) or (2) between patients who do not tolerate infliximab (Yes/No). Their overall mean serum trough adalimumab level (12.63 μg/mL) at Week 4 was consistent with that (12.61 μg/mL) obtained from infliximab-naïve patients with CD in study M02-403.

Q6: Does the population PK/PD analysis support the proposed alternative induction dosing regimen, splitting the induction dose of 160 mg into two 80 mg doses administered over two days, Day 1 and 2 at Week 0?

A6: No clinical or PK data was submitted to support the alternative induction dosing regimen. From a scientific point of view [for a drug with a very long terminal half-life ($T_{1/2}$) of 2 weeks] and based on PPK analyses, splitting the induction dose of 160 mg into two 80 mg doses administered over two days will not result in any meaningful differences in the pharmacokinetics of adalimumab (see Figure 2 below) where the predicted PK exposures from the two induction dosing regimens are superimposable.

From a patient perspective, there is a convenience advantage in splitting the induction dose administered as 4 injections over two days. However, this advantage is not derived post phase III analysis and should preferably have been identified before embarking on these induction studies so that it could have been prospectively studied. In a pre-NDA meeting on 05/11/06, the Agency did encourage the sponsor to investigate the alternative induction dosing regimen of splitting the dose of 160 mg over two days in a clinical equivalence trial after the induction studies were finalized. (Please see PM review for details)

Figure 2. PK profile comparisons between the proposed and the alternative induction dosing regimens



Notes: Simulated 160 mg given over 1 day (shaded area: 5-95th percentiles; solid line: median).
Simulated 160 mg given over 2 days (dashed lines: 5th and 95th percentiles and median).
Observed 160 mg given over 1 day (dots).
The percentiles for the simulated profiles reflect inter-subject variabilities.

b(4)

Q7: Is there evidence of exposure-response at week 4 and week 56?

A7: Base on PPK analyses, 1) the probability of clinical remission (defined as CDAI < 150) in the induction studies is clearly dependent upon serum trough adalimumab levels and 2) however, there is no clear evidence of exposure-response for clinical remission in the maintenance studies. However, the percentage patients responding in the active treatment groups in maintenance studies M02-433 and M02-404 are clearly separated from the placebo group. The efficacy is comparable between the 40 mg maintenance dosing EOW and EW. (Please see PK review in Appendix 4 for details.)

C. Intrinsic Factors:

No significant factors of gender, age, race on the PK of adalimumab were noted from the PPK analyses.

D. Extrinsic Factors:

Upon request, the sponsor updated the labeling on the Drug Interaction section based on the co-administration of medications allowed in the trials. For MTX, AZA, and 6-MP, less than 20 % changes to adalimumab PK was detected. However, no dose adjustment seemed necessary.

E. General Biopharmaceutics:

The currently approved formulation of Humira, a single-use 1-mL prefilled glass syringe (40 mg/0.8 mL) was employed in the studies.

F. Analytical Section

Q8: Are the analytical methods employed for determinations of serum adalimumab and AAA levels and their validation reports acceptable?

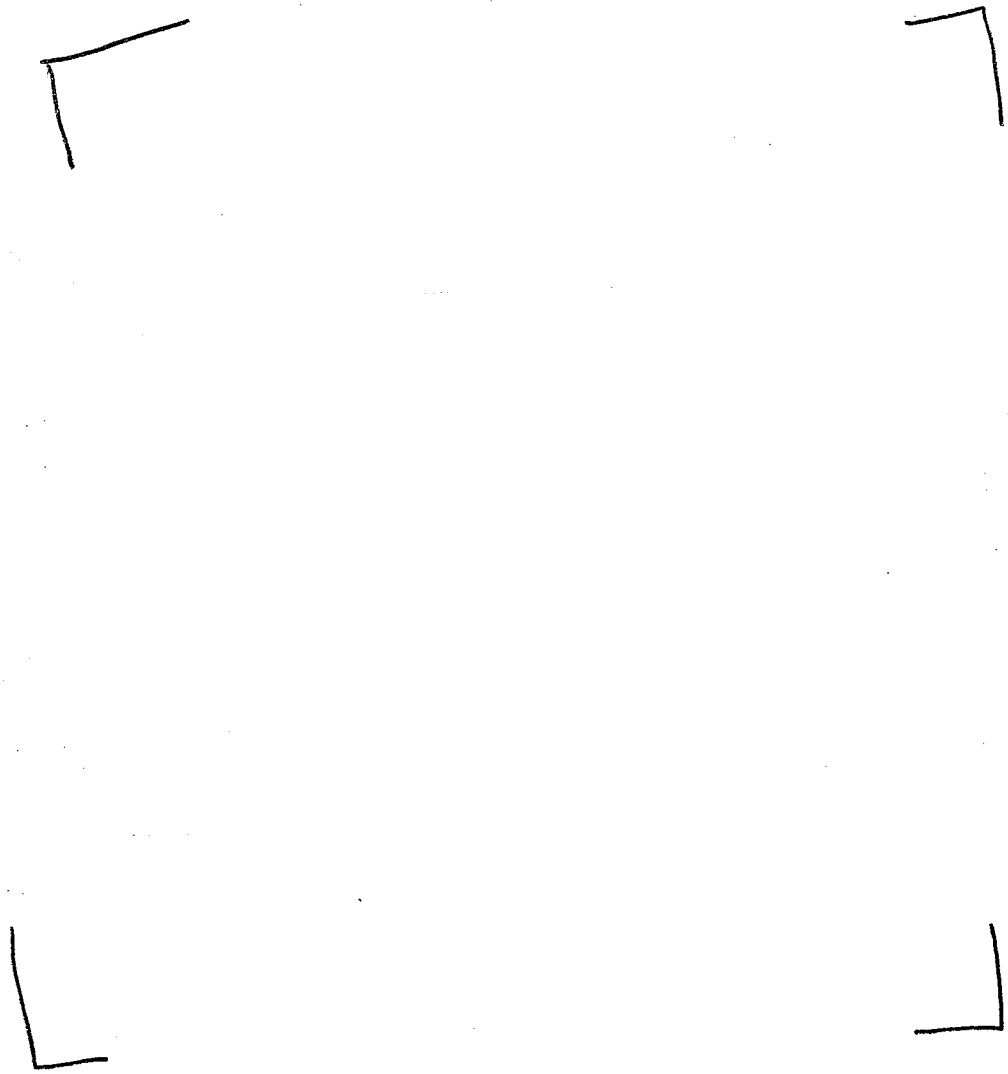
A8: [redacted]

Reviewer's comments:

The analytical methods were found satisfactory.

For Adalimumab Assay:

Blood samples (5 ml each) were obtained at baseline, Week 1, 2, and 4, and follow-up visits. Blood sample was allowed to clot for 30 min at room temperature prior to centrifugation Samples were analyzed for serum adalimumab levels using an ELISA [redacted]

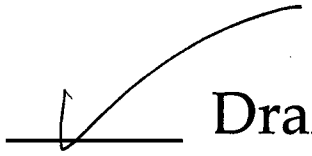


For AAA Assay:

Serum samples were analyzed for AAA using a validated double antigen immunoassay ELISA assay at Abbott GmbH & Co KG, [redacted] The assay detects antibodies directed against epitopes on the entire adalimumab molecule. The LOQ for AAA was established at [redacted] g/mL in diluted serum or [redacted] g/mL in undiluted serum. In-study QC samples, supplemented with concentrations of [redacted] ng/mL of rabbit anti-idiotypic anti-adalimumab antibodies, were analyzed with the unknowns. The % CV values were $\leq 11.01\%$, and the mean analytical recoveries ranged between [redacted] of their theoretical values.

5C Page(s) Withheld

_____ Trade Secret / Confidential (b4)



_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio-_____

PHARMACOMETRIC REVIEW

BLA:	125057
Drug name:	Humira (adalimumab)
Indication:	Moderate to Severe Crohn's Disease
Proposed Regimen (Sponsor):	160/80 mg (Induction) 40 mg eow (Maintenance)
Applicant:	Abbott Lab
OCP Reviewer	Tien-Mien Chen, Ph.D.
PM Reviewer:	Christoffer W. Tornoe, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	BLA
Submission Date:	August 25, 2006
PDUFA Date:	February 28, 2007

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Executive Summary

Humira (Adalimumab) is a recombinant human IgG1 monoclonal antibody that contains exclusively human sequences. Adalimumab has been approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS),

This supplemental BLA is to support an indication for treatment of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy and/or patients who have lost response to or are intolerant to infliximab.

The application included two 4-week induction studies (study m02-403 and m04-691) and two 52-week maintenance studies (study m02-433 and m02-404) in patients with Crohn's disease to demonstrate the effectiveness of adalimumab.

The primary endpoint of proportion of subjects in clinical remission (CDAI<150) at week 4 was met in both induction studies m0-2403 and m0-4691 and a clear exposure-response relationship was identified for clinical remission and clinical response (decrease in CDAI score ≥ 100).

The co-primary endpoints of proportion of subjects in clinical remission at week 26 and 56 with at least a decrease in CDAI score ≥ 70 at week 4 was met in maintenance study m02-404. The primary endpoint in maintenance study m02-433 was not met mainly due to very few patients (N=55) being randomized.

An exposure-response relationship could not be identified for the maintenance phase at week 56. However, the percentage patients responding in the active treatment groups in maintenance studies m02-433 and m0-2404 were clearly separated from the placebo group. Comparable efficacy was observed between 40 mg every other week and 40 mg every week dosing.

The pharmacokinetics of adalimumab were evaluated in 211 and 276 infliximab-naïve patients following a 4-week induction phase (study m02-403) and a 52-week maintenance phase (study m02-433), respectively, and in a 4-week induction study (m04-691) in 159 patients who had previously not responded to infliximab.

For the proposed induction dose regimen of 160 mg/80 mg, the 160 mg dose requires four injections on a single day. Because this regimen may be inconvenient for some patients, an analysis was conducted using population PK and PK/PD modeling and simulation to support the administration of the 160 mg dose as two 80 mg doses given on two consecutive days.

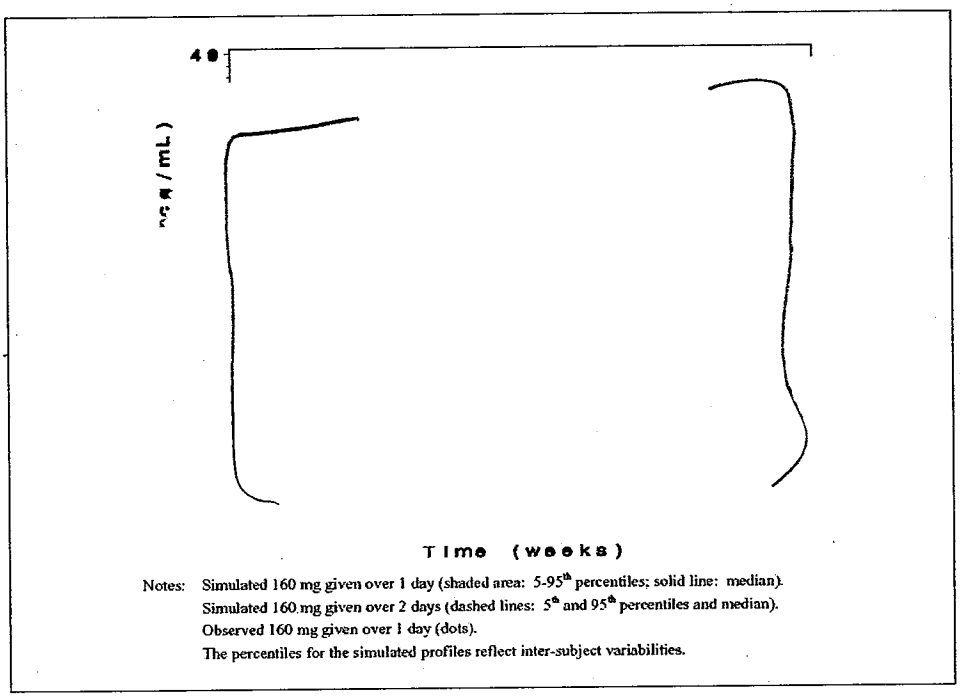
The predicted exposure at week 1 when splitting the induction dose of 160 mg into two 80 mg doses administered over two days is superposable to that of 160 mg given as 4 injections on day 0. From a pharmacokinetic point of view, the two dosing regimens are therefore similar.

Question Based Review

Does the population PK/PD analysis support splitting the induction dose of 160 mg into two 80 mg doses administered over two days?

From a patient perspective, there is a convenience advantage in splitting the induction dose administered as 4 injections over two days. However, this advantage is not derived post phase III analysis and should preferably have been identified before embarking on these induction studies so that it could have been prospectively studied. The agency did encourage the sponsor to investigate the alternative dosing regimen of splitting the dose of 160 mg over two days in a clinical equivalence study on May 11, 2006 after the induction studies were finalized.

From a scientific point of view, splitting the induction dose of 160 mg into two 80 mg doses administered over two days will not result in any meaningful differences in the pharmacokinetics of adalimumab (see figure below) where the predicted exposures from the two dosing regimens are superposable.

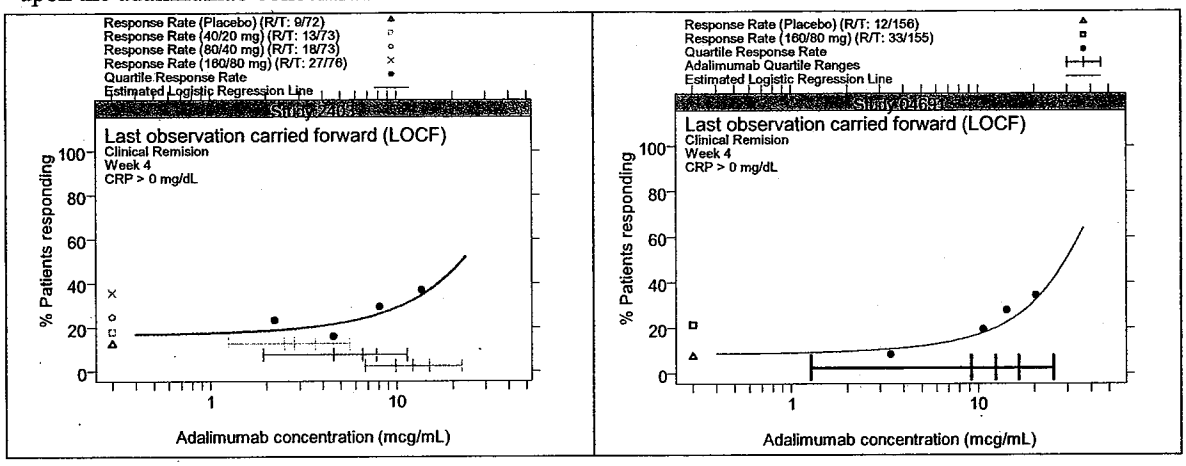


Notes: Simulated 160 mg given over 1 day (shaded area: 5-95th percentiles; solid line: median).
Simulated 160 mg given over 2 days (dashed lines: 5th and 95th percentiles and median).
Observed 160 mg given over 1 day (dots).
The percentiles for the simulated profiles reflect inter-subject variabilities.

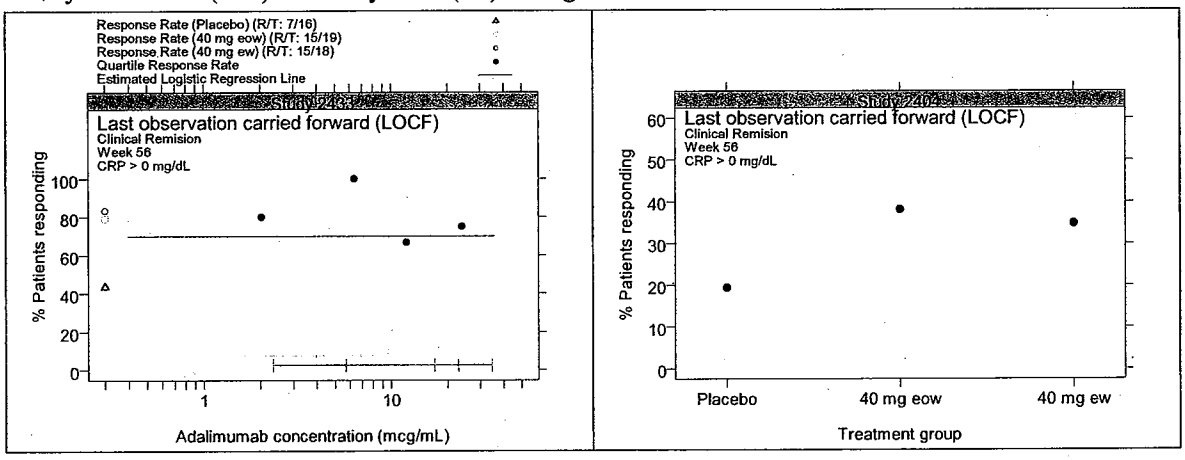
b(4)

Is there evidence of exposure-response at week 4 and week 56?

The probability of clinical remission (defined as CDAI < 150) in the induction studies is clearly dependent upon the adalimumab concentration.

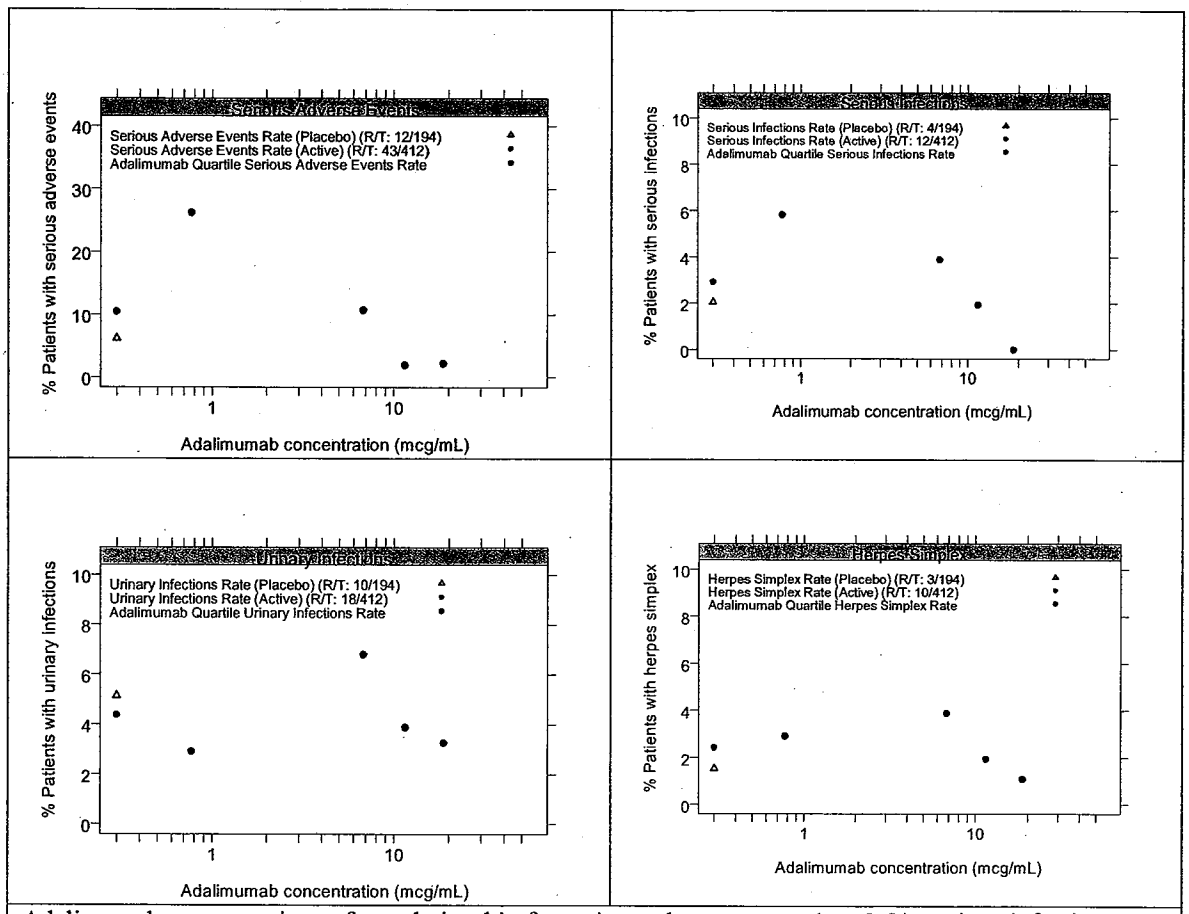


There is no clear evidence of exposure-response for clinical remission in the maintenance studies (see figures below). However, the percentage patients responding in the active treatment groups in maintenance studies 2433 and 2404 are clearly separated from the placebo group. The efficacy is comparable between every other week (eow) and every week (ew) dosing.



Is there evidence of adequate safety data?

There does not seem to be a relationship between adalimumab concentration and the serious adverse events, serious infections, urinary infection rates, and herpes simplex infections rate (see figures below).



Adalimumab concentration-safety relationship for serious adverse events (**top left**), serious infections (**top right**), urinary infections (**bottom left**), and herpes simplex (**bottom right**).

Recommendations

The Office of Clinical Pharmacology finds that the BLA is acceptable.

Splitting the induction dose over two days for patient convenience is acceptable and will not lead to any meaningful differences in the pharmacokinetics of adalimumab.

Introduction

Background

Humira (Adalimumab) is a recombinant human IgG1 monoclonal antibody that contains exclusively human sequences. Adalimumab has been approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS),

This supplemental BLA is to support an indication for treatment of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy and/or patients who have lost response to or are intolerant to infliximab.

The application included two 4-week induction studies (study m02-403 and m04-691) and two 52-week maintenance studies (study m02-433 and m02-404) in patients with Crohn's disease to demonstrate the effectiveness of adalimumab.

Aims of Analysis

The overall aim of this analysis is to investigate the exposure-response and exposure-safety relationships and to evaluate the pharmacokinetic/pharmacodynamic effect of splitting the clinically tested induction dose of 160 mg on day 0 into two 80 mg doses administered over two days.

Sponsor' s Analysis

Background

For the induction dose regimen of 160 mg/80 mg, the 160 mg dose requires four injections on a single day. Because this regimen may be inconvenient for some patients, an analysis was conducted using population PK and PK/PD modeling and simulation to support the administration of the 160 mg dose as two 80 mg doses given on two consecutive days.

Studies

Study M02-403 was a randomized, double-blind, placebo-controlled, multi-center, efficacy, safety and pharmacokinetic study designed to demonstrate the effectiveness of adalimumab in the treatment of infliximab-naïve subjects with moderately to severely active Crohn's disease. The pharmacokinetics and immunogenicity of adalimumab were also assessed. Subjects were randomized to receive one of three adalimumab induction regimens (40/20 mg, 80/40 mg, or 160/80 mg adalimumab at week 0/2) or matching placebo during a 4-week placebo-controlled period. A total of 299 subjects were randomized in the study; 211 subjects received adalimumab. The design of study M02-403 is schematically shown in Figure 3.

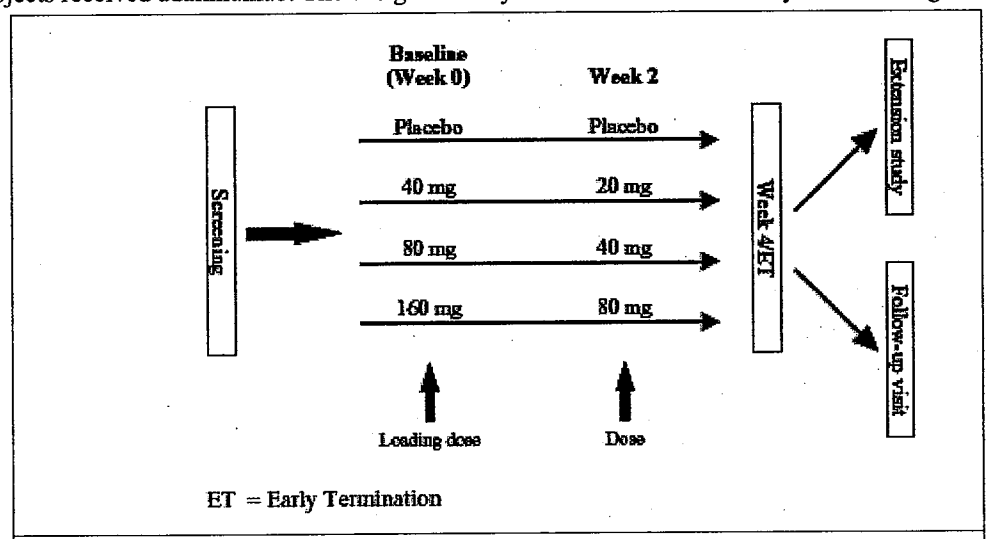


Figure 3 M02-403 Schematic study design.

Methods

Population PK/PD models were built with NONMEM software (double precision, Version V, Level 1.1) and a NMTRAN pre-processor. Models were run using the Compaq Visual Fortran Compiler (Version 6.6) on a Dual Processor Workstation (DELL Precision 530) under the Windows 2000 (service pack 4) operating system.

PK Analysis

Non-linear mixed effects modeling was applied to the pharmacokinetic data from the induction study M02-403 to construct a population pharmacokinetic model.

The general approach to the population pharmacokinetic analysis was to first estimate the population pharmacokinetic parameters for the base pharmacokinetic model and to subsequently investigate covariate-parameter relationships in the population pharmacokinetic model.

Because sampling in the Crohn's disease program was mainly performed just before dosing, the initial assumption was that the pharmacokinetic profile of adalimumab follows a one-compartment model with first-order absorption from a dose depot compartment, and first-order elimination from central compartment. The initial model utilized the adalimumab absorption rate observed in earlier studies in subjects with RA with subcutaneous dosing.

PD Analysis

Crohn's Disease Activity Index (CDAI) is a continuous variable with a higher score reflecting more severe disease. A CDAI score evaluates eight Crohn's-related variables during a one-week assessment period, yielding a composite score ranging from zero to approximately 600.

An indirect response model was chosen to describe CDAI response. This model was chosen because it was found to be appropriate in describing PD response for adalimumab in other indications, such as ankylosing spondylitis.

The assumptions for this model are listed as follows:

- CDAI response resides in a third compartment with a zero-order 'synthesis' rate constant (Kin) and a first-order 'elimination' rate constant (Kout);
- Kin is reduced by adalimumab treatment.

The model has the following general structure

$$\frac{dR}{dt} = K_{in} \bullet \left(1 - \frac{I_{max} \bullet C_p}{IC_{50} + C_p}\right) - K_{out} \bullet R \qquad \textbf{Equation 1}$$

$$\textbf{CDAI} = \textbf{R} \bullet \textbf{BL\_CDAI} \qquad \textbf{Equation 2}$$

where R is the ratio of CDAI score to the observed baseline value (BL_CDAI); Kin is the zero-order 'synthesis' rate constant and Kout is the first-order 'elimination' rate constant for CDAI response. Because the CDAI score at time 0 is equal to BL_CDAI (*i.e.*, R = 1), and the CDAI score is assumed to be constant when adalimumab concentration is zero (*i.e.*, dR/dt = 0), Kout should equal to Kin; Imax is the maximum inhibitory effect and IC50 is the concentration at which 50% of the maximum inhibitory effect is obtained; Cp is the predicted adalimumab concentration; and CDAI is the predicted CDAI score.

PK parameters (individual post-hoc estimates for CL/F and V/F, and population mean for Ka) from the population PK analysis were fixed in the population PK/PD analysis. The post-hoc individual PD parameters for the base PK/PD model were estimated and covariate-parameter relationships were investigated.

PK/PD Simulations

Simulations were carried out using the final population PK/PD model to identify an alternative dosing regimen that would achieve adalimumab exposure and efficacy similar to the 160/80 mg regimen. The following regimens were simulated: (1) 160 mg on Day 0 and 80 mg on Day 14; and (2) 80 mg on Day 0, 80 mg on Day 1 and 80 mg on Day 14.

Simulations were conducted using Trial Simulator software, Version 2.2. A total of 2,500 subjects were simulated for each regimen; 100% compliance was assumed. The model structure and population PK/PD parameter estimates from the final PK/PD model were used for the simulations. The distributions of relevant covariates were based upon observed values from Study M02-403.

No residual error term was included in the simulations to prevent introduction of random noise into the simulated adalimumab concentration-time and CDAI score-time profiles.

Results

PK Analysis

The final population pharmacokinetic model was a one-compartment model with first-order absorption from a depot compartment and first-order elimination from a central compartment. The effect of covariates (body weight, age, body surface area, treatment group, and sex) was tested in a stepwise procedure by adding each covariate separately to the base model.

The final model included body weight as a covariate on apparent volume of distribution (V/F), two exponential inter-individual error terms (one each on V/F and apparent clearance [CL/F]) and a proportional residual error term. The absorption rate constant Ka was fixed because the data did not contain sufficient information to estimate the parameter. The fixed value, 0.648/day, came from the population pharmacokinetic analysis of adalimumab in subjects with rheumatoid arthritis.

The population pharmacokinetic parameter estimates are presented in Table 1.

Table 1 Parameter estimates for the final adalimumab population PK model.

Parameter	Estimate	SE	%RSE	95% CI
Ka (1/day)	0.648#	--	--	--
CL/F (mL/h)	12.7	0.539	4.24	[11.6, 13.8]
Intersubject variance (ω^2 for η) for CL/F	0.227	0.0418	18.4	[0.145, 0.309]
V/F (L)	9.39	0.305	3.25	[8.79, 9.99]
	+ 0.126 • (WT – 72)	0.0193	15.3	[0.088, 0.164]
Intersubject variance (ω^2 for η) for V/F	0.123	0.0243	19.8	[0.075, 0.171]

\# Fixed in the model fitting process.
Ka = first-order absorption rate constant.
%RSE = 100 • SE / Estimate.
WT = Body weight (kg).
CI = Confidence Interval; 95% CI = Estimate ± 1.96 • SE.
η = the difference between the true value for individual i and the typical value for the population.
ω^2 = variance.

Goodness-of-fit plots of the individual predicted adalimumab concentrations versus the observed concentrations and the weighted residuals versus time are shown in Figure 4. These plots indicate that the model was adequate since the observed and predicted adalimumab concentrations were randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) and the plot of weighted residuals revealed no systematic trends over time.

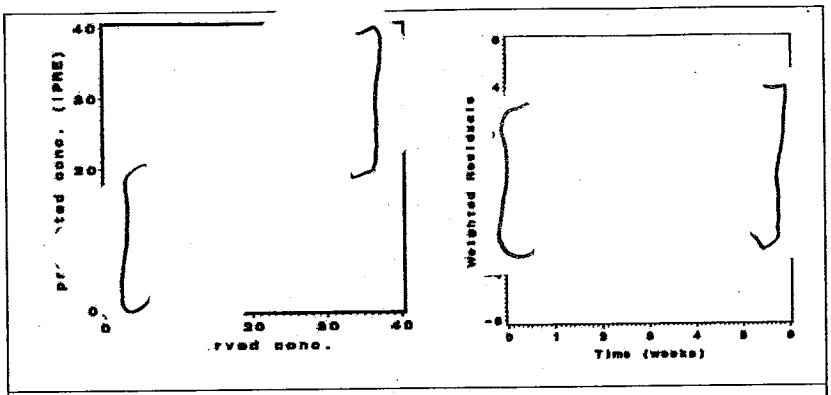


Figure 4 Goodness of fit plots for population PK model.

PD Analysis

An indirect response model with an inhibitory Emax function on Kin yielded an OFV of 5739.595 (run1.mod). Including a delay compartment to allow hysteresis between adalimumab serum concentrations and CDAI response (run4.mod), did not significantly lower the OFV. Models with an additional η on the parameter Kin did not converge; therefore, only one exponential inter-individual error term on parameter IC50 was allowed in the model. The estimate of parameter Imax was not significantly different from 1. The OFV of the model with Imax fixed to 1 (run7.mod, OFV = 5739.619) was very similar to that with Imax unfixed (run1.mod, OFV = 5739.595). Therefore, an indirect response model with Imax fixed to 1, an exponential inter-individual error term on IC50 and an additive residual error term (run7.mod) was used as the base model for covariate identification.

Of all the covariates included in the analysis (weight, age, sex, baseline CRP concentration, presence of AAA, concomitant MTX, 6-MP or AZA, and baseline CDAI score), only log-transformed CRP reached statistical significance for both forward selection and backward deletion (run17.mod, OFV = 5731.391, p = 0.0041). Therefore, an indirect response model with Imax fixed to 1, an exponential inter-individual error term on IC50 and the effect of log-transformed CRP on IC50, and an additive residual error term was used as final model (run17.mod). Table 2 summarizes the parameter estimates for the population PD model of adalimumab on CDAI score. The relative standard errors (%RSE) for all parameters were less than 24%.

Table 2 Parameter estimates for the final adalimumab population PD model.

Parameter	Estimate	SE	%RSE	95% CI
K_{in} (1/day)	0.175	0.017	9.8	[0.14, 0.21]
IC_{50} (μg/mL)	45.6	6.74	14.8	[32.39, 58.81]
	-5.74 • (Ln CRP + 3.82)	1.34	23.3	[-8.37, -3.11]
Intersubject variance (ω^2 for η) for IC_{50}	2.29	0.386	16.9	[1.53, 3.05]
I_{max}	1#	--	--	--

Fixed in the model fitting process.
K_{in} = zero-order 'synthesis' rate constant.
%RSE = 100% • SE / Estimate.
CI = Confidence Interval; 95% CI = Estimate ± 1.96 • SE.
η = the difference between the true value for individual i and the typical value for the population.
ω^2 = variance.

The calculated median IC50 for CDAI score was 21.9 µg/mL (5% to 95% percentiles ranged from 2.4 to 126.0 µg/mL). The IC50 values were estimated under the assumption that the CDAI score of each subject could theoretically decline to zero (*i.e.*, Imax = 1). The very large IC50 values in some subjects treated with adalimumab suggest that those subjects will likely not respond to anti-TNF treatment. It has been shown that 61% of patients with Crohn's disease did not achieve remission (CDAI score < 150) following a 30-week treatment of 5 mg/kg infliximab (administered at Weeks 0, 2 and 6 and then every eight weeks). For subjects who did achieve remission with adalimumab treatment, the median IC50 value was approximately 4.5 µg/mL for the two lower dose groups, and 10.8 µg/mL for the 160 mg/80 mg dose group.

Goodness-of-fit plots for the final CDAI model are presented in Figure 5. The observed and predicted CDAI scores were randomly distributed across the line of unity, and there were no systematic trends in weighted residuals over time and over different covariates. Generally, the final indirect response model adequately described the observed CDAI response in this population.

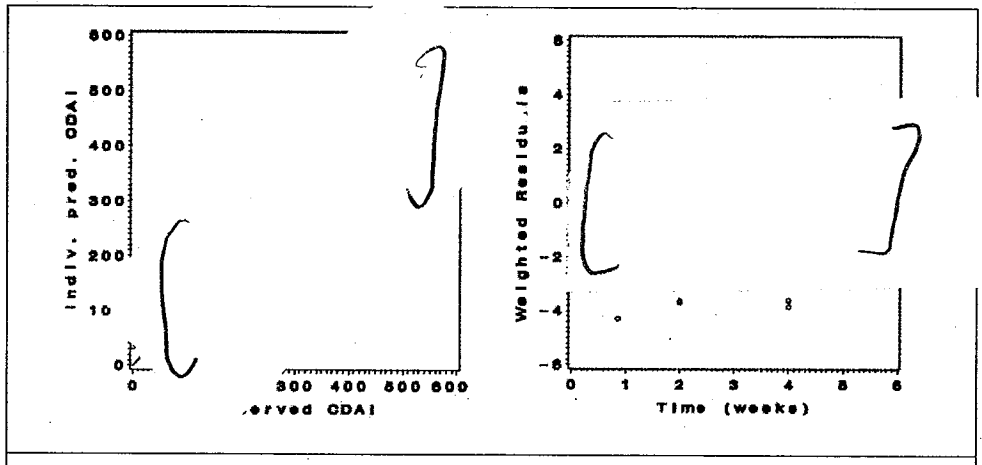


Figure 5 Goodness of fit plots for population PD model.

PK/PD Simulations

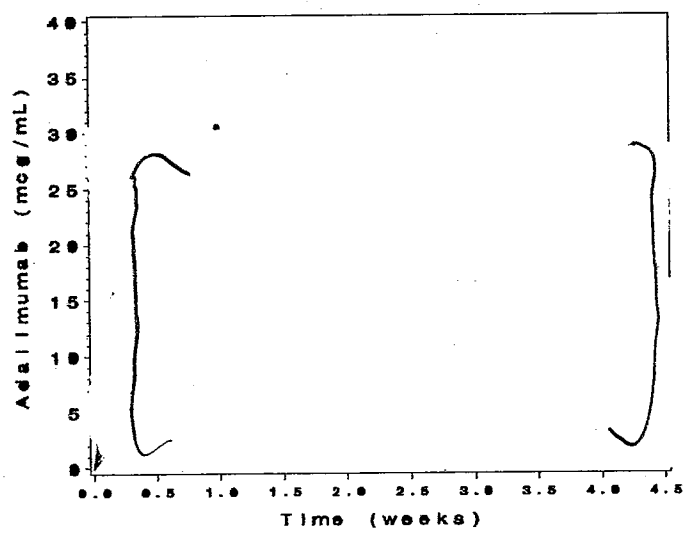
The following regimens were simulated: (1) 160 mg on Day 0 and 80 mg on Day 14; and (2) 80 mg on Day 0, 80 mg on Day 1 and 80 mg on Day 14. To simulate adalimumab concentrations and CDAI scores over time, the model structure and the parameter estimates from the final population PK/PD model were used. All three η's were assumed to follow normal distributions with a mean equal to zero and a standard deviation (std) equal to ω. The range of each η was set to equal to –3std to +3std, which covers more than 99% of the area under the probability distribution curve for a normal distribution. Histograms of the observed body weight, baseline CRP concentrations and baseline CDAI scores from Study M02-403 were plotted, and log-normal distributions were found to be appropriate to describe their distributions. Therefore, the observed mean, std, min and max of log-transformed covariate values were used in the simulations (see Table 3).

Table 3 Distributions of parameters and covariates used in the simulations.

	Distribution	Mean	Std	Min	Max
Parameters					
η for CL/F	Normal	0	0.476		
η for V/F	Normal	0	0.351		
η for IC_{50}	Normal	0	1.513		
Covariates					
LNWT	Normal	4.295	0.233		
LNCRP	Normal	-0.278	1.418		
LNBL_CDAI	Normal	5.683	0.184		

η = the difference between the true value for individual i and the typical value for the population.
LNWT = log-transformed weight.
LNCRP = log-transformed baseline CRP concentration.
LNBL_CDAI = log-transformed baseline CDAI score.

Figure 6 shows the simulated serum adalimumab concentrations for the 4-week induction periods following 160 mg adalimumab given over 1 or 2 days, along with the observed adalimumab concentrations following 160 mg adalimumab given over 1 day in Study M02-403; 80 mg adalimumab was given on 1 day at Week 2 for all regimens.



Notes: Simulated 160 mg given over 1 day (shaded area: 5-95th percentiles; solid line: median).
Simulated 160 mg given over 2 days (dashed lines: 5th and 95th percentiles and median).
Observed 160 mg given over 1 day (dots).
The percentiles for the simulated profiles reflect inter-subject variabilities.

Figure 6 Serum adalimumab concentrations for 160 mg adalimumab given over 1 or 2 days at week 0, followed by 80 mg adalimumab on day 1 at week 2.

The results indicate that by Week 1, the serum adalimumab concentrations expected following administration of the two regimens during the induction period almost completely overlay.

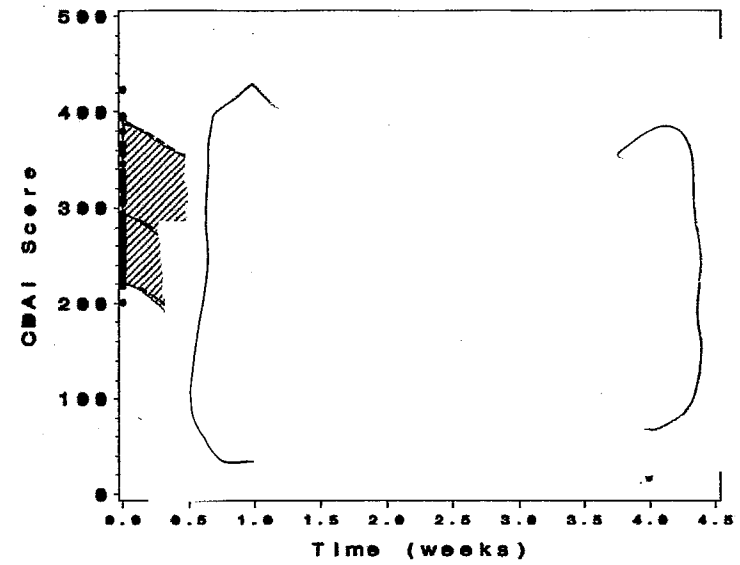
Simulated serum adalimumab concentrations at Weeks 1, 2 and 4 during the induction periods following a 160 mg/80 mg induction regimen with the 160 mg dose given over 1 or 2 days as well as the observed concentrations from the 160 mg/80 mg regimen from Study M02-403 are shown in Table 4. The results demonstrate that by Week 1 serum adalimumab concentrations are similar whether 160 mg adalimumab is given over 1 or 2 days.

Table 4 Summary statistics for observed (160 mg on a single day) and simulated (160 mg over one or two days) serum adalimumab concentrations at weeks 1, 2, and 4.

Regimen*	Mean	Std	Median	p5	p25	p75	p95
Week 1							
Observed 160 mg over 1 day	14.26	4.92	13.65	8.00	10.60	16.60	23.40
Simulated 160 mg over 1 day	14.28	4.71	13.63	7.71	10.81	17.10	23.01
Simulated 160 mg over 2 days	14.53	5.08	13.76	7.80	10.91	17.17	24.27
Week 2							
Observed 160 mg over 1 day	12.34	3.68	12.10	7.30	10.00	14.80	20.60
Simulated 160 mg over 1 day	11.05	3.53	10.61	6.14	8.51	13.11	17.52
Simulated 160 mg over 2 days	11.15	3.61	10.62	6.47	8.56	13.08	18.06
Week 4							
Observed 160 mg over 1 day	12.61	5.25	12.20	4.60	9.10	16.80	21.50
Simulated 160 mg over 1 day	12.40	4.42	11.98	5.96	9.38	14.97	20.43
Simulated 160 mg over 2 days	12.23	4.35	11.71	5.88	9.20	14.60	20.35

* All regimens are given at Week 0, followed by 80 mg on a single day at Week 2.

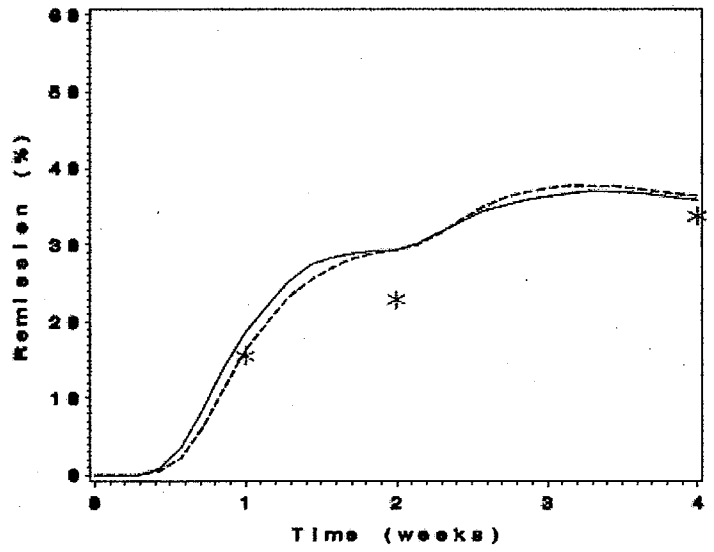
Figure 7 shows the simulated CDAI scores for the 4-week induction periods following 160 mg adalimumab given over 1 or 2 days, along with the observed CDAI scores following 160 mg adalimumab given over 1 day in Study M02-403; 80 mg adalimumab was given on 1 day at Week 2 for all regimens. The results indicate that the median and 5th and 95th percentiles of CDAI scores for the two induction regimens completely overlay, and the two regimens are expected to produce similar efficacy.



Notes: Simulated 160 mg given over 1 day (shaded area: 5-95th percentiles; solid line: median).
Simulated 160 mg given over 2 days (dashed lines: 5th and 95th percentiles and median).
Observed 160 mg given over 1 day (dots).
The percentiles for the simulated profiles reflect inter-subject variabilities.

Figure 7 CDAI scores for 160 mg adalimumab given over 1 or 2 days at week 0, followed by 80 mg adalimumab on day 1 at week 2.

Simulations of the percent of subjects who achieved remission (CDAI score < 150) for the two induction regimens show similar results, indicating that splitting the 160 mg induction dose over 2 days is not expected to alter efficacy (Figure 8, along with the observed remission rate from Study M02-403).



Note: Simulated 160 mg given over 1 day: solid line.
Simulated 160 mg given over 2 days: dashed line.
Observed 160 mg given over 1 day: stars.

Figure 8 Percent remission for 160 mg adalimumab given over 1 or

2 days at week 0, followed by 80 mg on day 1 at week 2.

Sponsor's Conclusions

- For subjects who achieved remission after 4-week treatment of adalimumab, the median IC50 value was approximately 4.5 µg/mL for the 40 mg/20 mg and 80 mg/40 mg dose groups, and 10.8 µg/mL for the 160 mg/80 mg dose group. The IC50 values were estimated under the assumption that the CDAI score of each subject could theoretically decline to zero (*i.e.*, Imax = 1).

- The results of the population PK and PK/PD analyses predict that splitting the 160 mg induction dose given over one day into two 80 mg doses administered over two days will have minimal impact on the pharmacokinetic profile of adalimumab and should not alter the efficacy in patients with Crohn's disease compared to administering the 160 mg induction dose on a single day.

Reviewer's Comments on Sponsor Analysis

- The population PK/PD analysis of the induction study m02403 was adequately performed using non-linear mixed-effects analysis.

- Since no PK samples in the absorption phase were available, the absorption rate constant Ka was fixed to 0.648/day obtained from the population pharmacokinetic analysis of adalimumab in subjects with rheumatoid arthritis.

- The sponsor concluded from the covariate PK model building that body weight influences the volume of distribution V/F with an increase of 1.34% per kg change in body weight. The unexplained inter-individual variability of V/F was reduced from 50 CV% to 35 CV% when including body weight as a covariate. Dose adjustments are not necessary based on body weight.

- The predicted exposure at week 1 when splitting the induction dose of 160 mg into two 80 mg doses administered over two days is superposable to that of 160 mg given as 4 injections on day 0. From a pharmacokinetic point of view, the two dosing regimens are therefore similar.

- An indirect response model was used to describe the CDAI response over time. The CDAI score is a continuous variable with a higher score reflecting more severe disease. A CDAI score evaluates eight Crohn's-related variables during a one-week assessment period, yielding a composite score ranging from zero to approximately 600.

- The sponsor assumes that the production of CDAI response is inhibited by adalimumab serum concentration through an inhibitory E_{max} model thereby assuming that the serum concentration is a surrogate for the concentration in the GI tract.

- The maximal inhibitory effect was fixed to 1 since it could not be estimated with the available data. The median IC_{50} (the concentration associated with 50% of maximum inhibitory effect) was estimated to be 21.9 mcg/mL. Less than 1% of the measured serum adalimumab concentrations in study m2403 exceed 21.9 mcg/mL. The IC_{50} estimate is therefore highly questionable since the data does not contain much information about the parameter.

- The application of such PK/PD analysis for determining clinical equivalence of effectiveness between alternative dosing regimens is therefore unclear due to uncertainties whether the assumptions made are valid.

Reviewer's ANALYSIS

Studies

Study M02-403: See Section 0.

Study M04-691: Study M04-691 was a randomized, double-blind, placebo-controlled, multi-center, efficacy, safety and pharmacokinetic study designed to demonstrate the effectiveness of adalimumab in the treatment of subjects with moderately to severely active Crohn's disease who either had initially responded to administration of infliximab but stopped responding or were intolerant to infliximab. A total of 325 subjects were randomized in the study; 159 subjects received adalimumab.

Study M02-433: Study M02-433 was an extension of Study M02-403. Week 4 of Study M02-403 was the Baseline visit (Week 0) for Study M02-433. In Study M02-433, all subjects received adalimumab 40 mg subcutaneous (*sc)* at Weeks 0 and 2. Subjects in remission at both Weeks 0 and 4 were randomized to receive adalimumab 40 mg *sc* every other week (eow), adalimumab 40 mg weekly, or placebo for up to one year. Subjects who developed flare or had no response were allowed to switch to open-label adalimumab 40 mg eow. Subjects not in remission at both Weeks 0 and 4 received open-label adalimumab 40 mg *sc* eow. Subjects receiving open-label adalimumab 40 mg eow who developed flare or persistently had no response were allowed to switch to open-label adalimumab 40 mg weekly. Trough serum samples for adalimumab and anti-adalimumab antibodies (AAA) assays were obtained at Weeks 4, 24, and 56. A total of 276 subjects were enrolled in this study but only 37 subjects were randomized.

Study M02-404: Study M02-404 was a multi-center, randomized, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn's disease. The objective of this study was to assess the efficacy and safety of 40 mg weekly (ew) or 40 mg every other week (eow) subcutaneous (sc) doses of adalimumab. A total of 778 subjects were randomized in the study; 517 subjects received adalimumab.

Data

The sponsor was requested to submit a pooled dataset with longitudinal PK, CDAI scores, and safety information from studies 2403, 2404, 2433, and 04691 for this analysis.

Methods

When considerable data are missing, especially mostly due to symptom worsening, it is important to analyze the data in multiple ways to arrive at sound inferences about effectiveness.

Last observation carried forward (LOCF) for missing data can be an inappropriate imputation technique for these types of data when the dropouts are not missing completely at random (MCAR) but rather due to lack of effectiveness.

Two alternative methods have therefore been investigated, i.e. longitudinal modeling and mixed-model repeated measures (MMRM) analyses which are briefly described in the following.

Longitudinal Model of Change in CDAI Score

A longitudinal model was developed to explore the change in CDAI score over time and to investigate the impact of patient covariates using non-linear mixed-effects modeling.

Mixed-Model Repeated Measures Analysis

Mixed-model repeated measures analysis is similar to the longitudinal model with the exemption that time is handled as a discrete and not continuous variable.

The MMRM analysis was implemented via PROC MIXED in SAS 9.1 by fitting all the data collected during the open-label and double blind phases (no imputation). The model was fitted to baseline corrected CDAI score as a dependent variable and baseline, treatment, visit and treatment-by-visit interaction. An unstructured (co)variance matrix was used to model the within subject errors. Parameters were estimated using maximum likelihood method.

Exposure-Response Analysis

The model predictions from the longitudinal model were used to substitute the missing data and use observed data when available. The adalimumab concentration in placebo patients was set to 0 mcg/mL to be used in the logistic regression estimation. The adalimumab concentration was only added as a covariate for the logistic regression when the p-value was 0.05 or below.

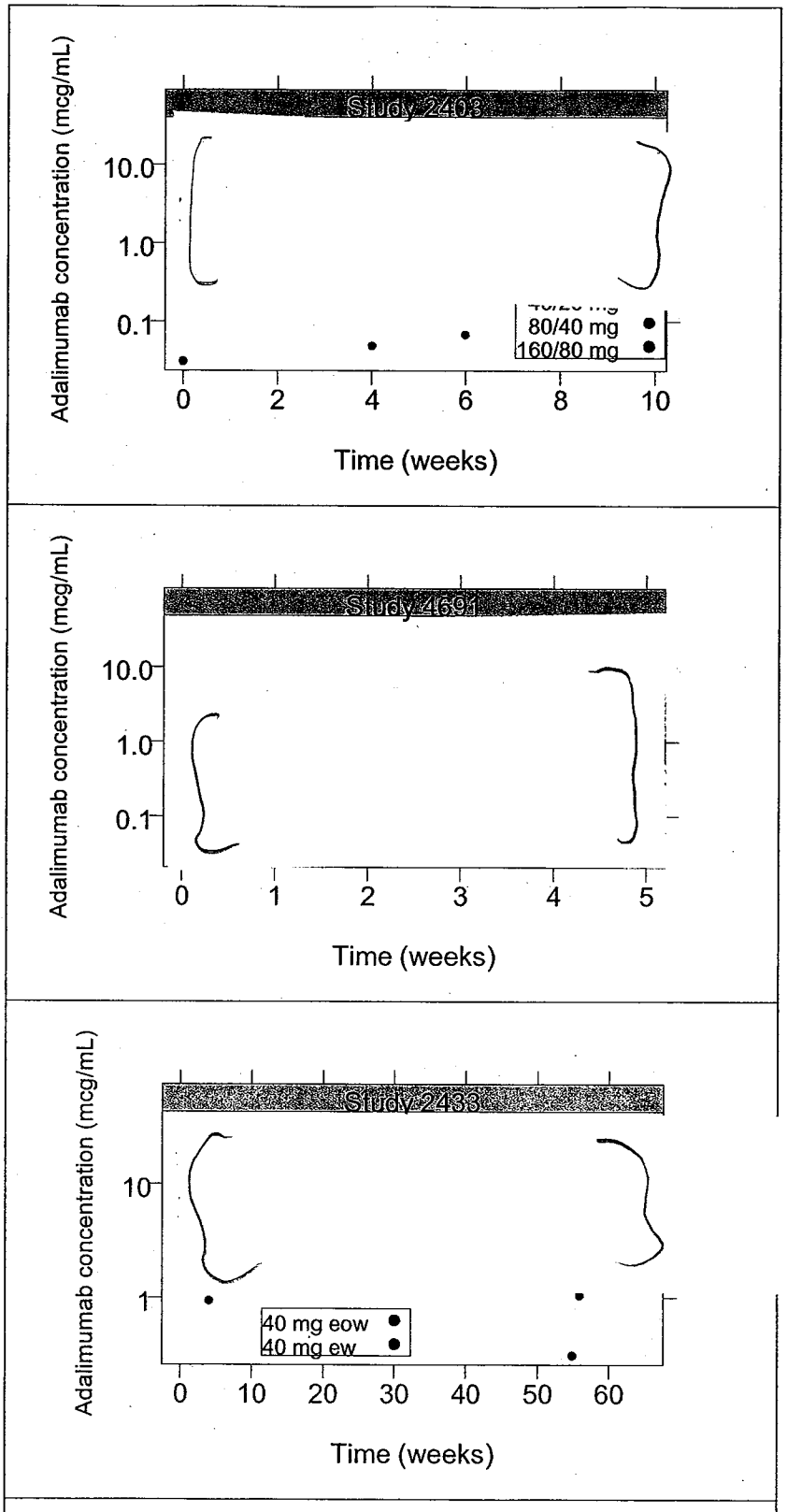
Results and Discussion

Adalimumab Exposure Analysis

The pharmacokinetics of adalimumab were evaluated in 211 and 276 infliximab-naïve patients following a 4-week induction phase (study m02-403) and a 52-week maintenance phase (study m02-433), respectively, and in a 4-week induction study (m04-691) in 159 patients who had previously not responded to infliximab.

The adalimumab trough concentrations were consistent between week 2 and 4 with a mean of 2.8, 5.7, and 12.6 mcg/mL for the induction doses of 40/20, 80/40, and 160/80 mg, respectively (see Figure 9).

The mean adalimumab trough concentration during the maintenance phase were 17 and 15 mcg/mL at weeks 24 and 56 for the 40 mg weekly dosing and 8.2 and 10.92 mcg/mL at weeks 24 and 56 for the 40 mg every other week dosing regimen (see Figure 9).



b(4)

b(4)

b(4)

Figure 9 Adalimumab PK concentration-time profiles in study 2403 (top), 4691 (middle), and 2433 (bottom).

Distribution of Baseline Corrected CDAI Score at Final Visit

The cumulative distribution plot of change in CDAI score from baseline at final visit is shown in Figure 10 for induction studies 2403 and 04691 (top) and maintenance studies 2433 and 2404 (bottom). All treatment groups are separated to the left of placebo indicating a treatment benefit.

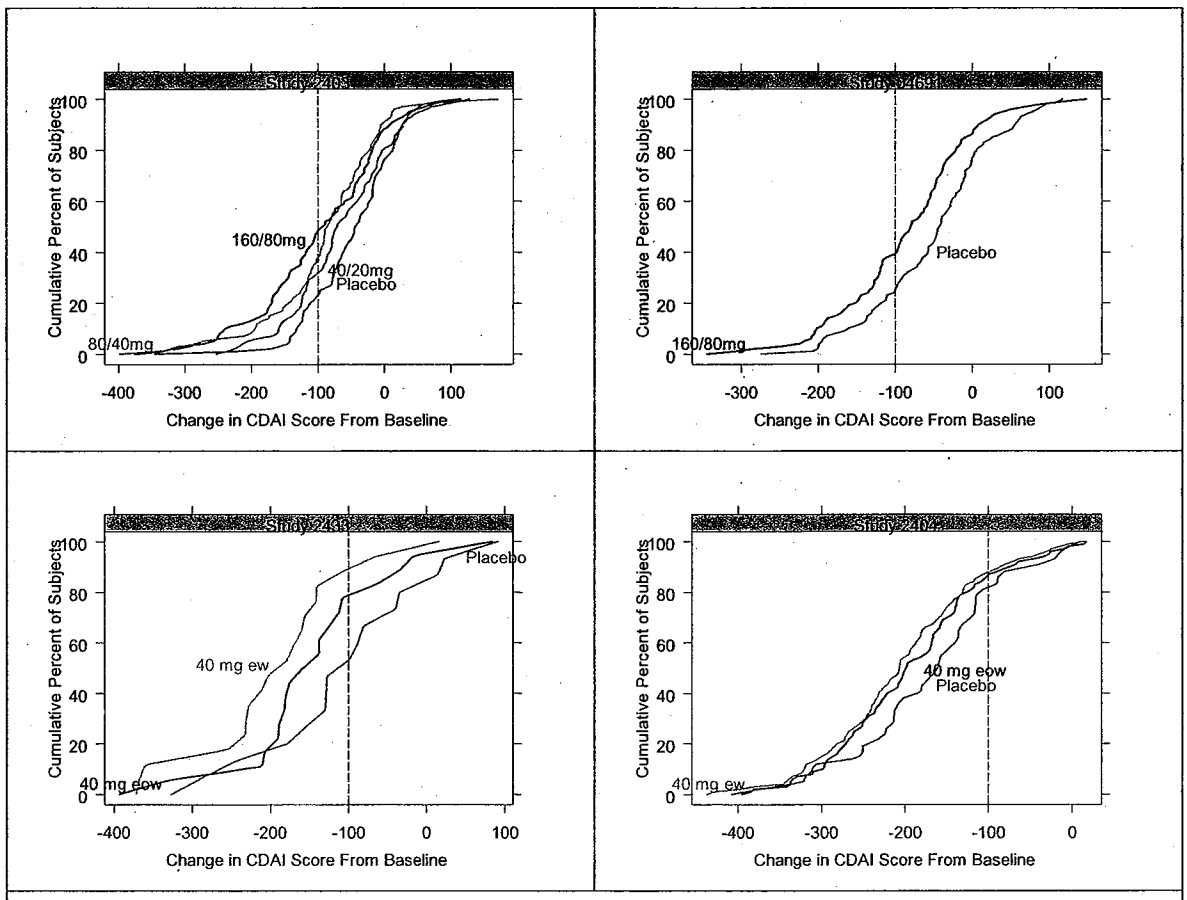


Figure 10 Cumulative distribution plot of change in CDAI score from baseline at final visit. A curve shifted to the left indicates a better response. The dashed vertical line shows the clinical response criteria of -100.

Dropout Analysis

The dropout rate in the induction studies is low and as expected for a 4-week trial in Crohn's disease population (see Figure 11).

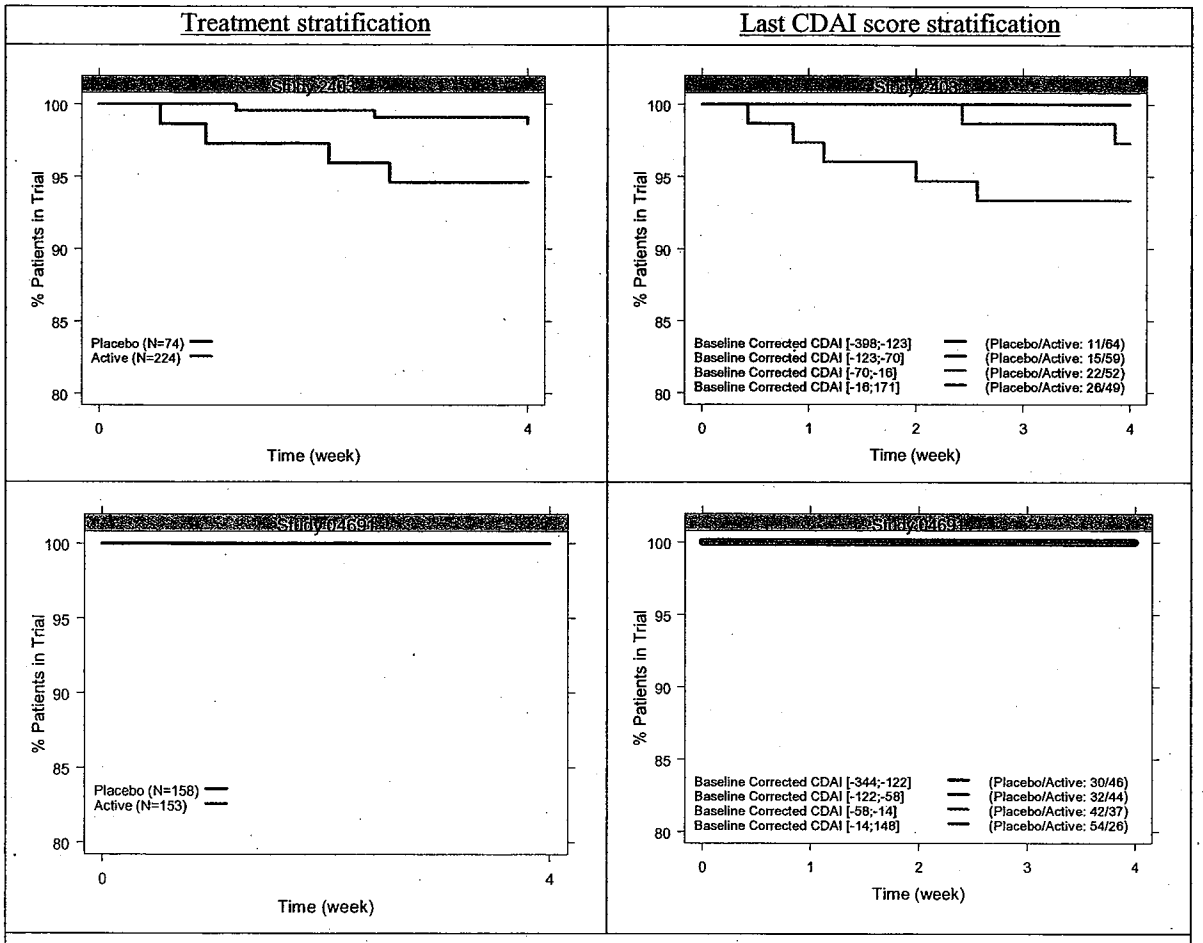


Figure 11 Dropouts in induction studies stratified on treatment (left) and last CDAI score (right) for study 2403 (top) and 04691 (bottom).

Analysis of the baseline corrected CDAI score in the maintenance studies (2433 and 2404) is complicated by a significant dropout due to the lack of effectiveness, i.e. see Figure 12, where the percentage of patients remaining in the trial is plotted against time stratified on treatment (left) and the baseline corrected CDAI score at final visit (right).

Patients seem to be dropping out of study 2404 due to worsening of symptoms. The overall dropout rate is about 40%, and the dropouts are not missing completely at random (MCAR), rather they are correlated with the ΔCDAI score. In particular, 50% of patients with ΔCDAI score > 3 drop out by Week 52 in study 2404, whereas only 20% of those patients with ΔCDAI score < -169 drop out of the study by Week 56.

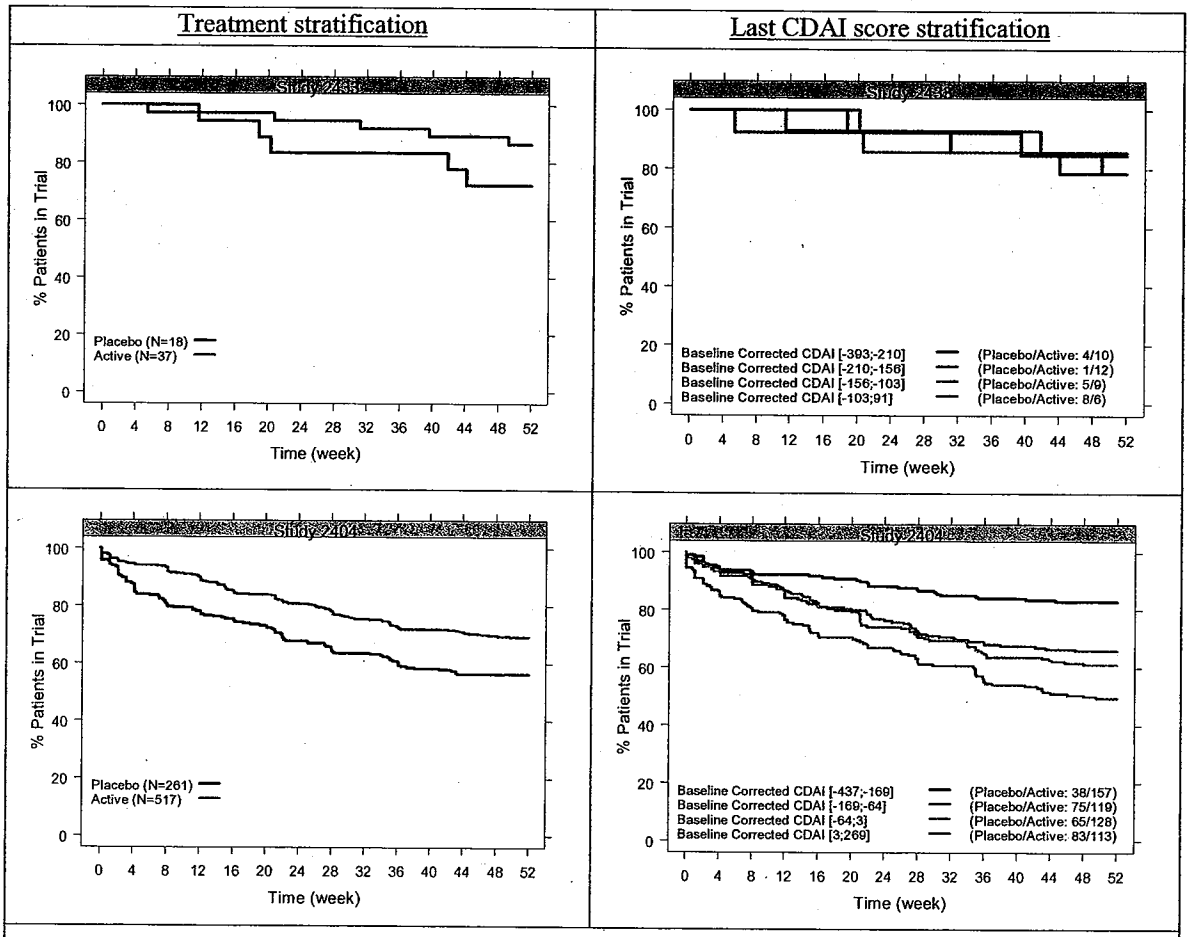


Figure 12 Dropouts in maintenance studies stratified on treatment (left) and last CDAI score (right) for study 2433 (top) and 2404 (bottom).

Longitudinal Model of Change in CDAI Score

The developed longitudinal model for the change in baseline corrected CDAI score (ΔCDAI) over time is described by the equation below:

$$\Delta CDAI(t) = CDAI_{max,i} * (1 - \exp(-k_i*t)) + \varepsilon_{ij}$$

where

$$CDAI_{max,i} = CDAI_{max,Slope}*BSL_i + \eta_{CDAImax,i}$$
$$k_i = k*\exp(\eta_{k,i})$$

with BSL_i being the observed baseline CDAI score for subject i which was identified as the only significant covariate.

By this model, the baseline corrected CDAI score can increase or decrease over the time to reach the maximal effect, $CDAI_{max}$. The rate constant k is the first-order rate constant of baseline corrected CDAI score change over time. The inter-individual variability (IIV) for maximal CDAI effect ($CDAI_{max}$) and the residual variability were assumed to be normally distributed, whereas for rate of CDAI score changes from baseline (k) a log-normal distribution was assumed. Missing data were not imputed using last observation carry forward (LOCF) for estimation. The data was modeled by NONMEM VI using the FOCE method (see section 0 for NONMEM control stream). The estimated parameters are presented in **Table 5** .

Table 5 Longitudinal model parameters to describe CDAI score change from baseline over time.

		Population Mean		Inter-Individual Variability	
Parameter	**Unit**	**Estimate**	**RSE (%)**	**Estimate**	**RSE(%)**
$CDAI_{max,Slope}$	[-]	-0.362	2.54	85.3 (SD)	4.32
k	[$Week^{-1}$]	0.453	5.21	91.4 (CV%)	8.08
Residual error (SD)	[-]	46.3	1.91	-	-

The maximum CDAI score ($CDAI_{max}$) is estimated to decrease by -0.362 by an increase of 1 in baseline CDAI score. The model thereby suggests that patients with high CDAI scores are more likely to get better than subjects with low CDAI scores. The time to reach the maximal effect is about 6 weeks, i.e. $4*t_{1/2}=4*\log(2)/0.453\ week^{-1}= 6.1$ weeks.

The goodness-of-fit plots in Appendix 0 (**Figure 21**) suggest that the model has a slight tendency to over predict the higher baseline corrected CDAI scores.

The estimated relationship between $CDAI_{max}$ and baseline CDAI score is shown in Figure 13.

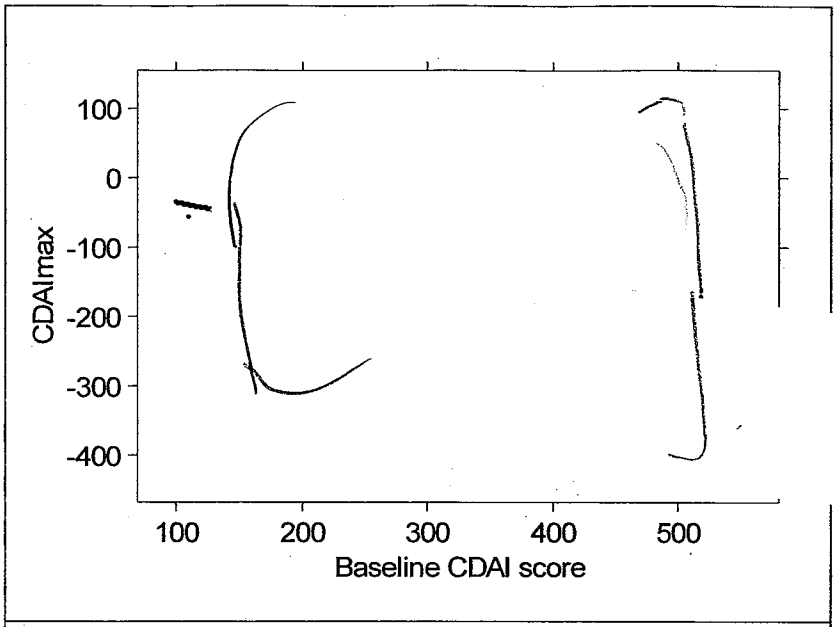


Figure 13 Estimated $CDAI_{max}$ (blue dots) and model predicted relationship between $CDAI_{max}$ and baseline CDAI score (solid red line).

Mixed Model Repeated Measures (MMRM) Analysis

The developed mixed-model repeated measures (MMRM) model is described by:

$$\Delta CDAI = \beta_0 + \beta_1 Visit + \beta_2 Treatment + \beta_3 Base\ CDAI + \beta_4 Visit*Treatment$$

where β_0, β_1, β_2, β_3, β_4 refer to the intercept, slope in placebo group, symptomatic effect, baseline CDAI covariate effect, and slope differences between the treatment and placebo groups.

The mean observed baseline corrected CDAI scores (top) and least-squares (LS) mean predicted baseline corrected CDAI scores (bottom) are shown in Figure 14 for induction studies 02403 (left) and 04691 (right).

Since the dropout rate is low in the induction studies, the mean and LS mean predicted curves are similar in the figure below. The mean baseline corrected CDAI score at week 4 for the induction dose groups of 80/40 and 160/80 mg are clearly separated from that of the placebo group.

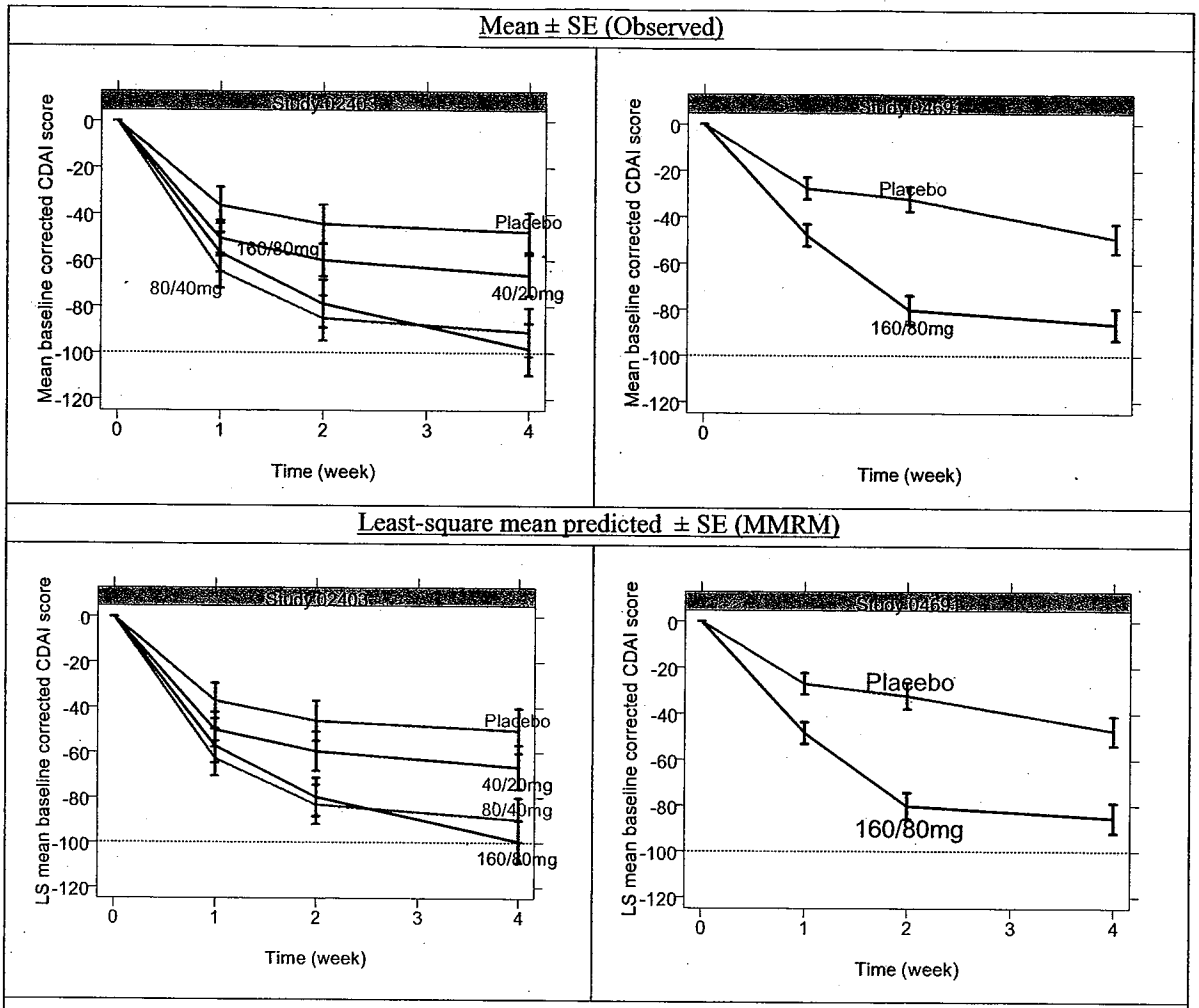


Figure 14 Mean observed (top) and least squares mean predicted (±SE) (bottom) baseline corrected CDAI score for study 2403 (left) and 04691 (right).

The mean observed baseline corrected CDAI scores (top), mean LOCF imputed baseline corrected CDAI scores (middle), and least-squares mean predicted baseline corrected CDAI scores (bottom) are shown in Figure 15 for maintenance studies 2433 (left) and 2404 (right).

The time course of the mean observed, LOCF imputed, and least-squares predicted baseline corrected CDAI scores are very different due to dropouts are not missing completely at random (MCAR) but are correlated with the underlying disease (see Section 0).

The active treatment groups are clearly separated from the placebo group in study 2404 at week 56 but there does not seem to be a significant difference between 40 mg eow and ew. In study 02433, the placebo and treatment groups are similar which might be due to the very low number of subjects (N=37).

Mean ± SE (Observed)

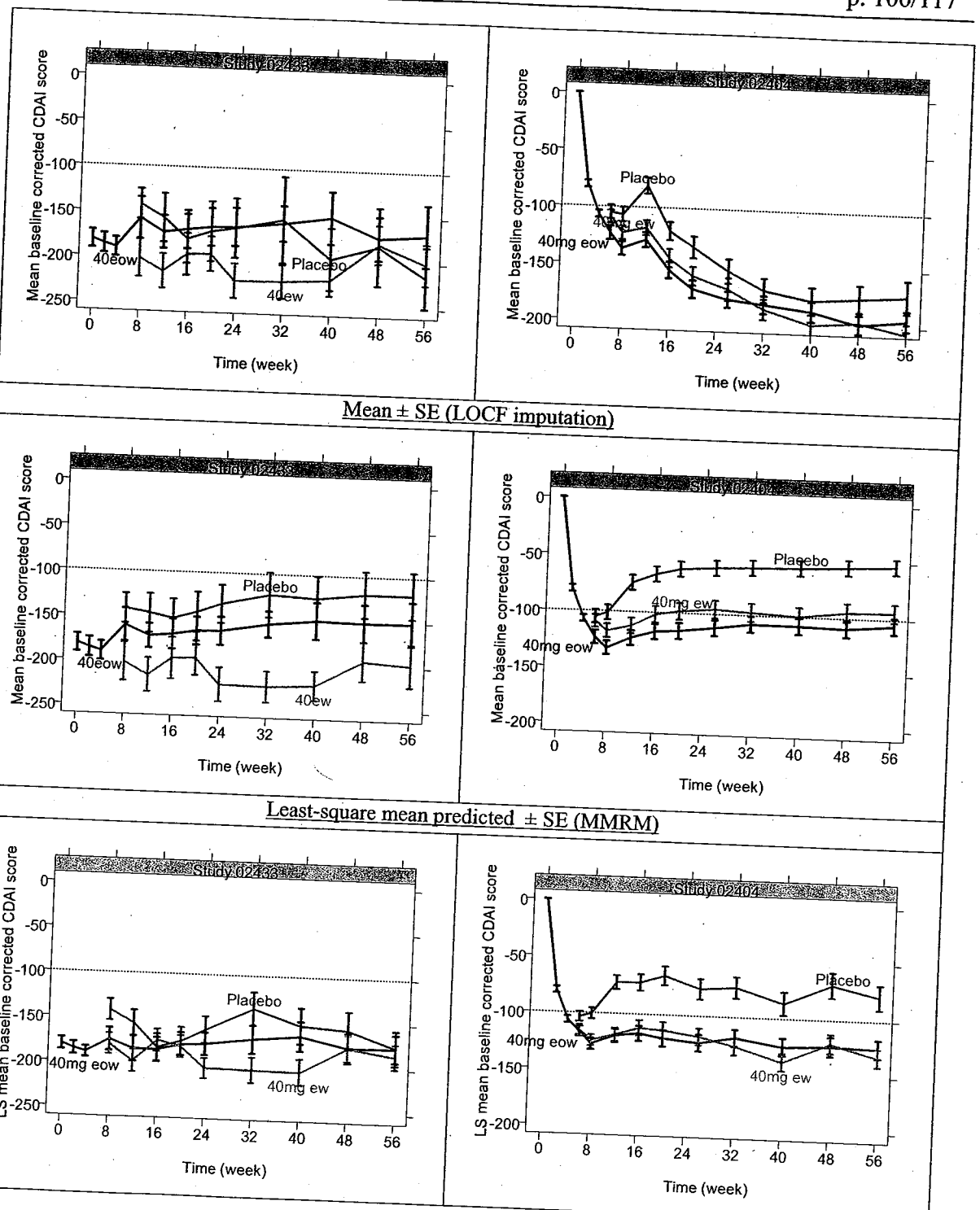


Figure 15 Mean observed (top), mean LOCF imputed (middle), and least-squares mean predicted (±SE) (bottom) baseline corrected CDAI score for study 2403 (left) and 04691 (right).

Exposure-Response Analysis

The probability of clinical remission (defined as CDAI < 150) and clinical response (defined as baseline corrected CDAI ≤ -100) in the induction studies is clearly dependent upon the adalimumab concentration. Patients having lower concentrations (e.g., less than 5 mcg/mL) exhibit lower response rates (see Figure 16 and Figure 17).

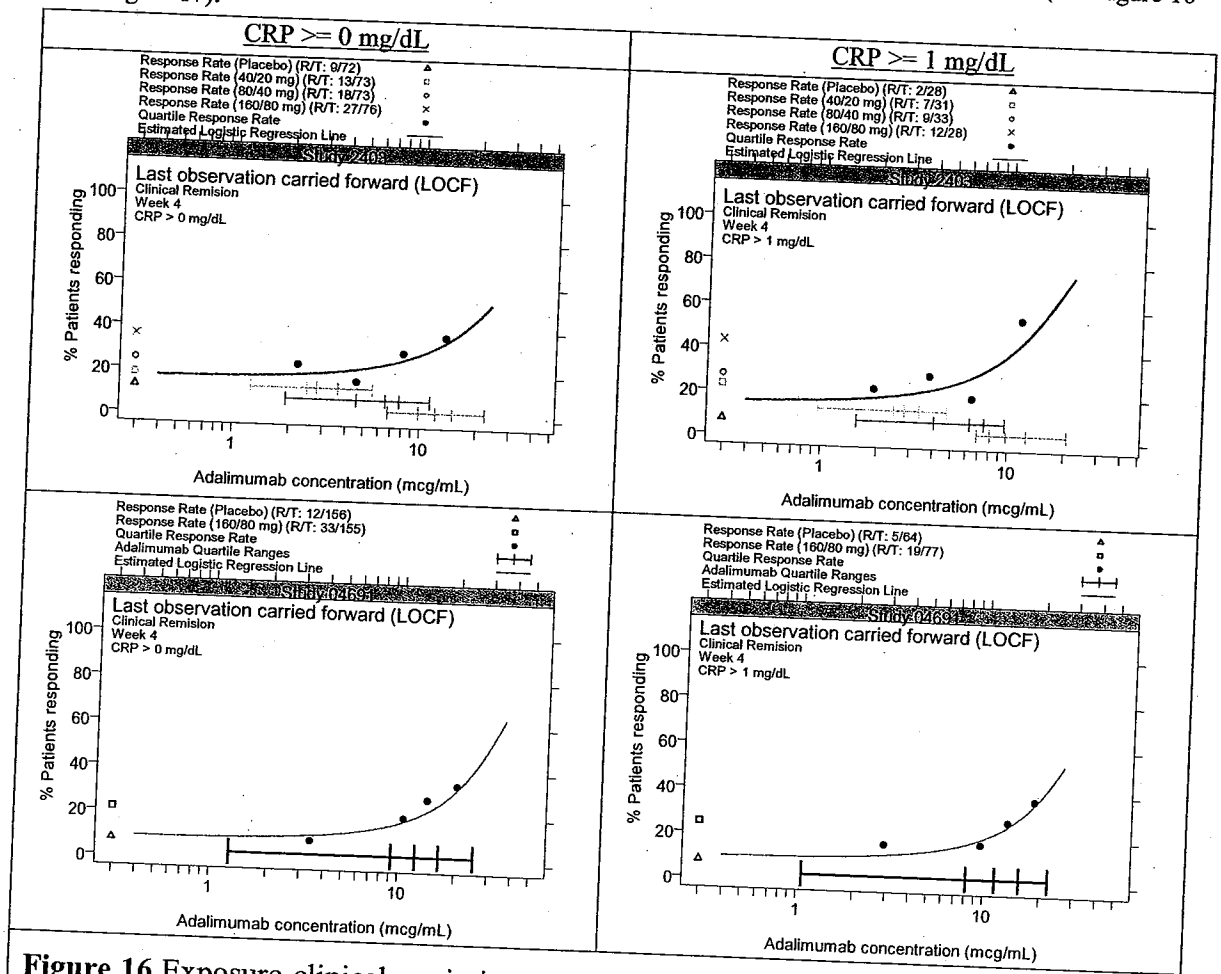


Figure 16 Exposure-clinical remission analysis for induction study 2403 (top) and 04691 (bottom) stratified on baseline CRP≥0 mg/dL (left) and baseline CRP≥1 mg/dL (right).

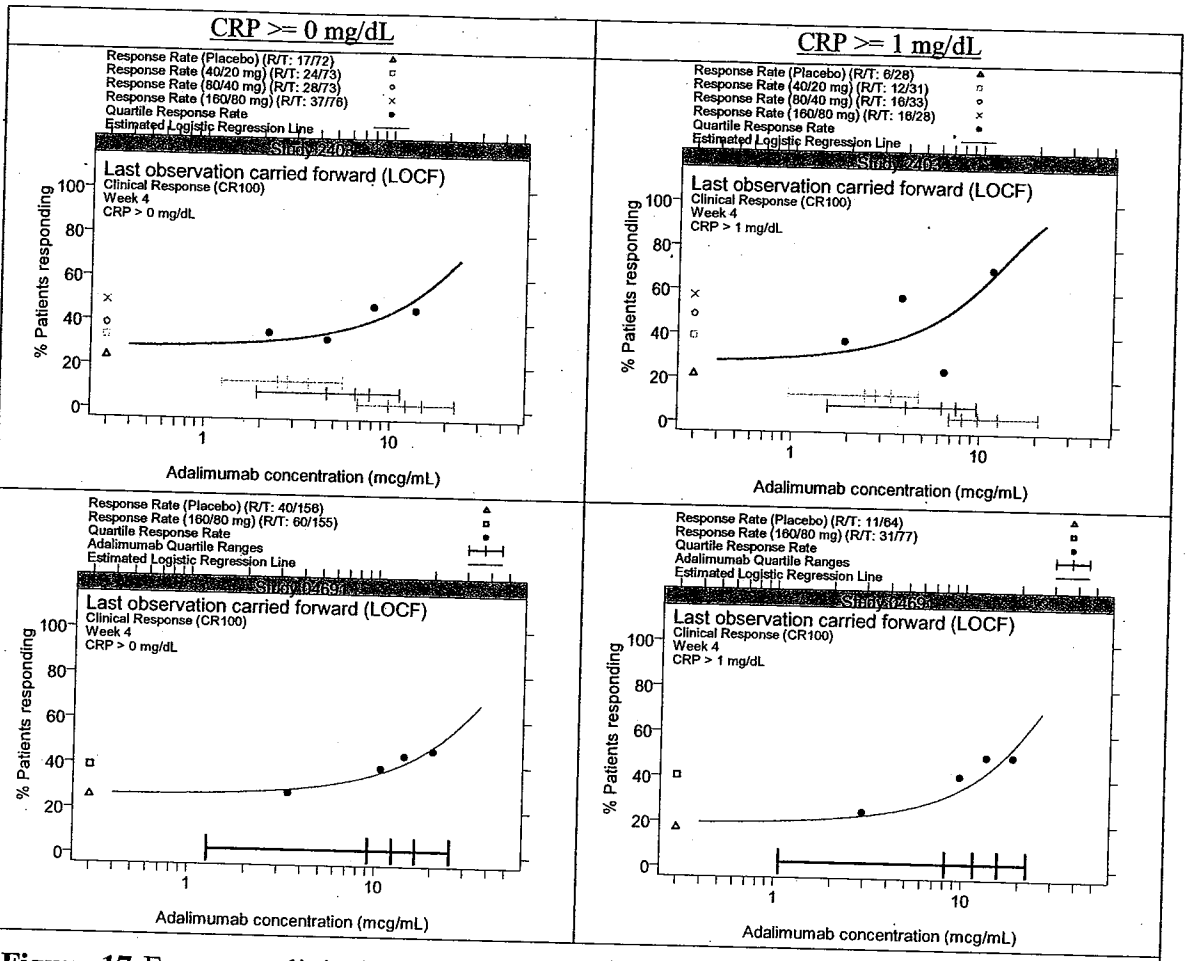


Figure 17 Exposure-clinical response analysis for induction study 2403 (top) and 04691 (bottom) stratified on baseline CRP≥0 mg/dL (left) and baseline CRP≥1 mg/dL (right).

There is no clear evidence of exposure-response in the maintenance studies. However, the percentage patients responding in the active treatment groups in maintenance studies 2433 and 2404 are clearly separated from the placebo group while the efficacy is comparable between every other week (eow) and every week (ew) dosing (see Figure 18 and Figure 19). The baseline CRP stratification of 1 mg/dL reduces the placebo response rate from 40% to around 20% while the active treatment response rate stays at 80%.

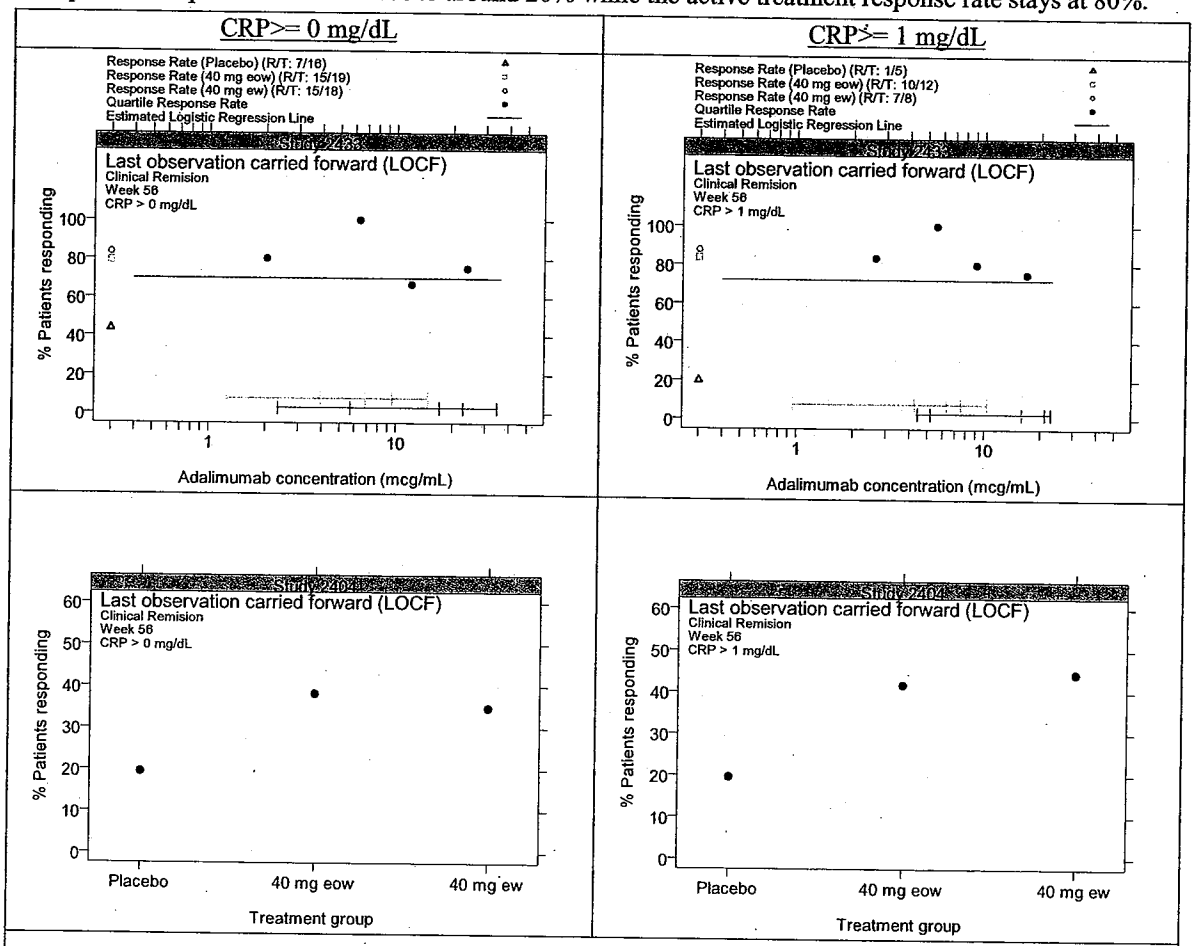


Figure 18 Exposure-clinical remission analysis for maintenance study 2433 (top) and 2404 (bottom) stratified on baseline CRP≥0 mg/dL (left) and baseline CRP≥1 mg/dL (right).

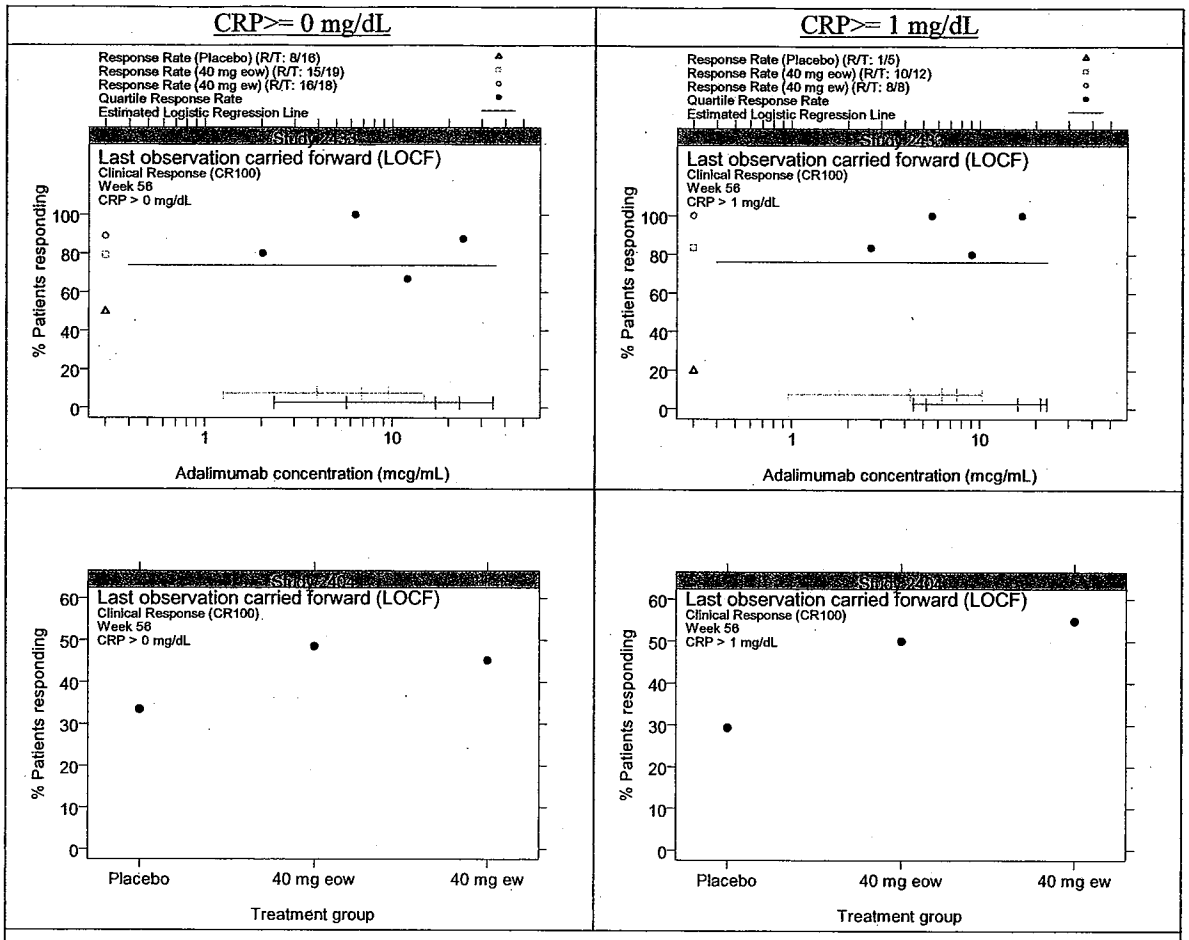


Figure 19 Exposure-clinical response analysis for maintenance study 2433 (top) and 2404 (bottom) stratified on baseline CRP≥0 mg/dL (left) and baseline CRP≥1 mg/dL (right).

Exposure-Safety Analysis

There does not seem to be a relationship between adalimumab concentrations and the serious adverse events, serious infections, urinary infection rates, and herpes simplex infections rate (see figures below).

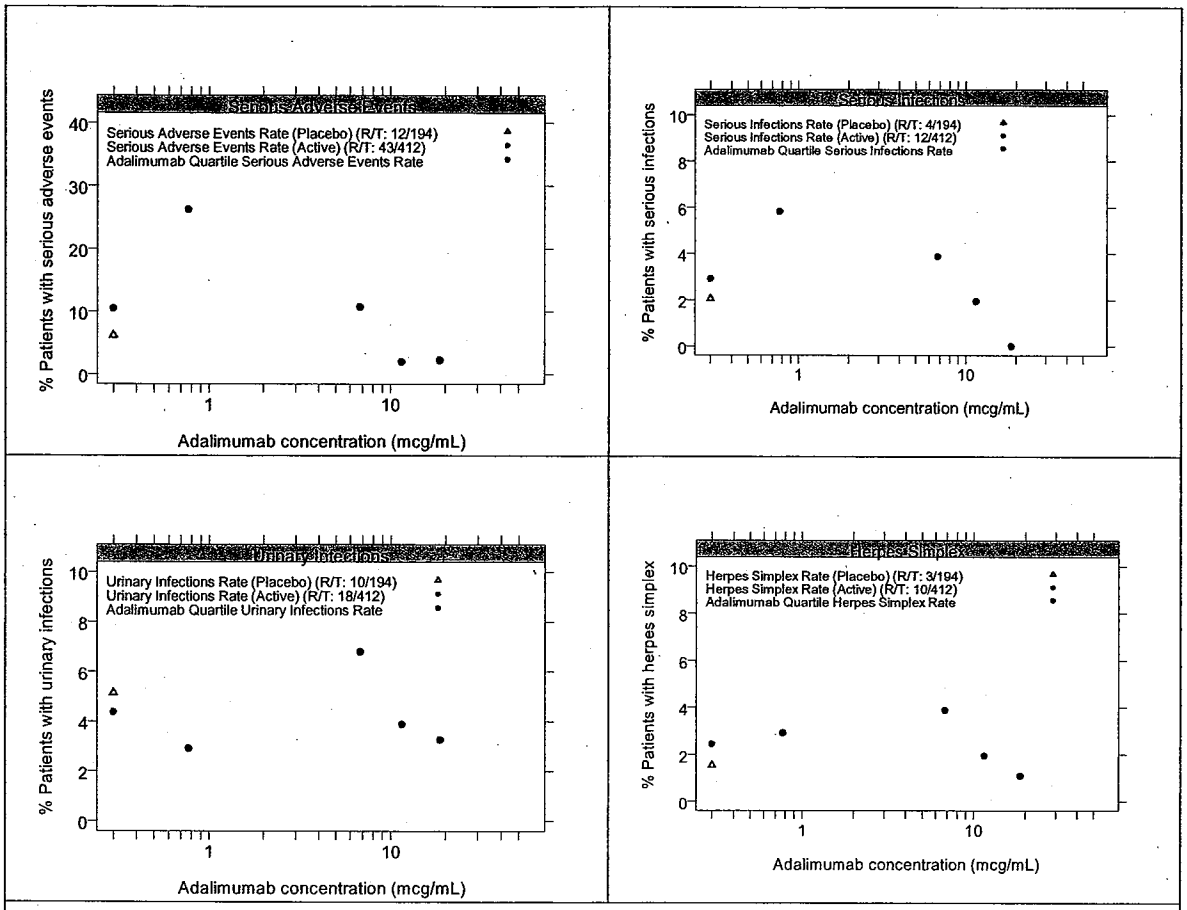


Figure 20 Adalimumab concentration-safety relationship for serious adverse events (top left), serious infections (top right), urinary infections (bottom left), and herpes simplex (bottom right).

Pharmacometric Review Conclusions

The overall conclusions for the Pharmacometric review are:

- The primary endpoint of proportion of subjects in clinical remission (CDAI<150) at week 4 was met in both induction studies and a clear exposure-response relationship was identified for clinical remission and clinical response (decrease in CDAI score ≥ 100).

- The co-primary endpoints of proportion of subjects in clinical remission at week 26 and 56 with at least a decrease in CDAI score ≥ 70 at week 4 was met in maintenance study m02-404. The primary endpoint in maintenance study m02-433 was not met mainly due to very few patients (N=55) being randomized.

- An exposure-response relationship could not be identified for the maintenance phase at week 56. However, the percentage patients responding in the active treatment groups in maintenance studies 2433 and 2404 were clearly separated from the placebo group. Comparable efficacy was observed between 40 mg every other week and 40 mg every week dosing.

- Population PK predictions of the exposures at week 1 when splitting the induction dose of 160 mg into two 80 mg doses administered over two days is superposable to that of 160 mg given as 4 injections on day 0. From a pharmacokinetic point of view, the two dosing regimens are therefore similar.

- The application of population PK/PD analysis for determining clinical equivalence of effectiveness between alternative dosing regimens is unclear due to uncertainties whether the assumptions made are valid.

Appendices

Longitudinal Model NONMEM Control Stream

```
;*****************************************************************
$PROB  HUMIRA, BLA 125057
; Studies 2403, 2433, 2404, 4691
; Programmed by Christoffer W. Tornoe, OCP, CDER, FDA
; Date:12/21/2006
;*****************************************************************
$INPUT  ID STUD GRP=DROP DOSE CP AAA APOS TIME CRP CORT
        IFLX CDAI DV RESP AE SAE SINF UINF HERP LOCS BSL
;*****************************************************************
$DATA ../Data/Derived/longitudinalv2.dta IGNORE=@

$PRED
 TVCMX = THETA(1)
 MXCDAI = TVCMX*BSL + ETA(1)
 K    = THETA(2)*EXP(ETA(2))
 DCDAI = MXCDAI*(1-EXP(-K*TIME))

 IPRED = DCDAI
 IRES  = DV-IPRED
 W     = THETA(3)
 IWRES = IRES/W
 Y     = IPRED + W*EPS(1)

$THETA (-1)   ; MAXIMUM CDAI SCORE
$THETA (0,0.4)  ; K (week^-1)
$THETA (0,51)   ; ADDITIVE RES ERROR

$OMEGA 7500 ; CDAIMAX
$OMEGA 0.5 ; K

$SIGMA 1 FIX

$EST MAXEVAL=9999 METHOD=1 PRINT=1 NOABORT MSFO=run2.msf
$COV

$TABLE ID TIME IPRED IWRES CP STUD CRP DOSE BSL
    ONEHEADER NOPRINT FILE=sdtab2
$TABLE ID ETA1 ETA2 MXCDAI K
    ONEHEADER NOPRINT FILE=patab2
$TABLE ID BSL CRP DOSE
    ONEHEADER NOPRINT FILE=cotab2
$TABLE ID APOS IFLX AE SAE SINF UINF HERP LOCS
    ONEHEADER NOPRINT FILE=catab2
```

Longitudinal Model Goodness-of-Fit Graphs

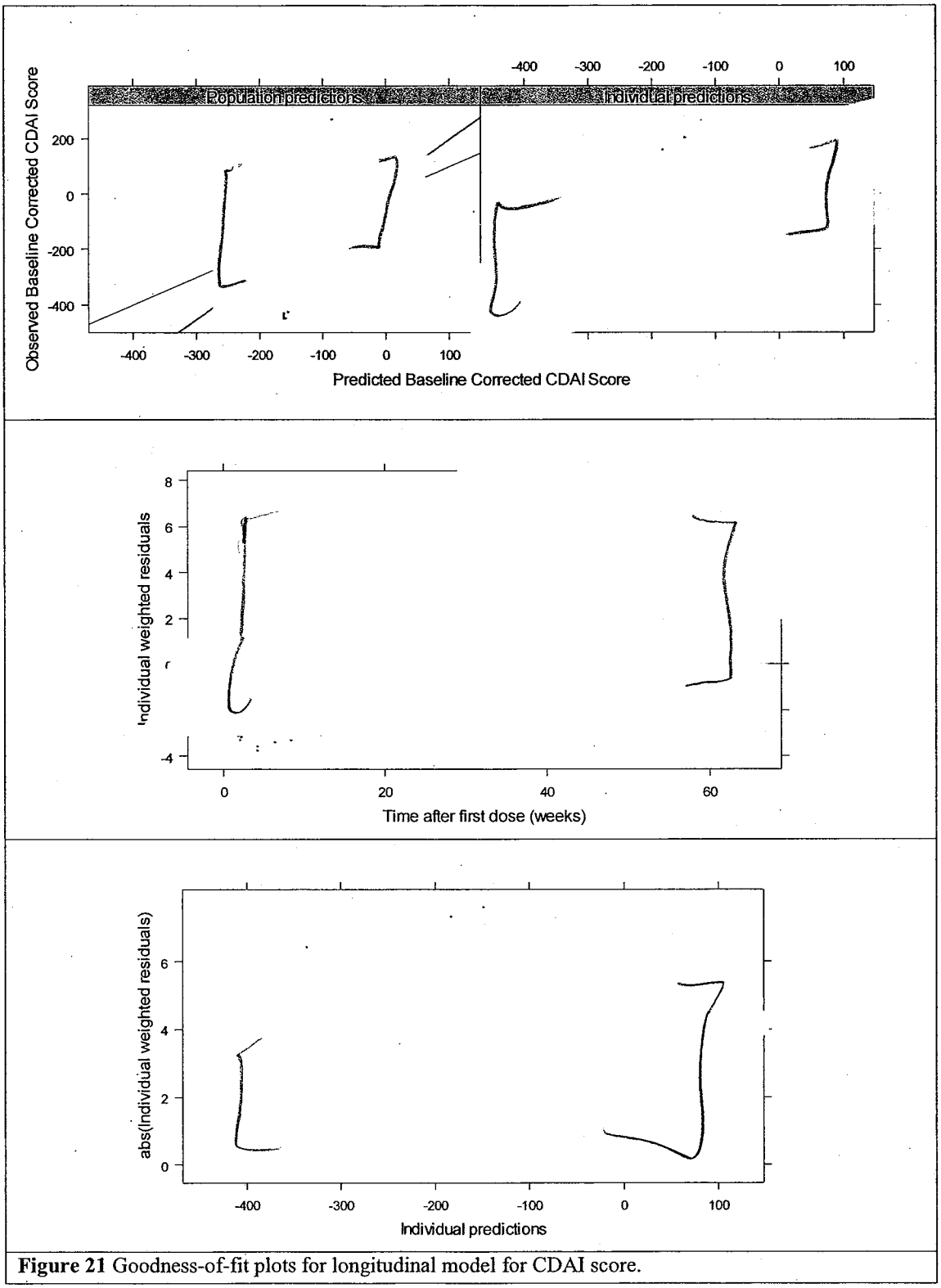


Figure 21 Goodness-of-fit plots for longitudinal model for CDAI score.

b(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057 / S-0089

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA # : 125057 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** 89
Stamp Date: 8/28/2006 **PDUFA Goal Date:** 2/27/2007
HFD 180 **Trade and generic names/dosage form:** Humira (adalimumab) injector pen
Applicant: Abbott Pharmaceuticals **Therapeutic Class:** TNF-alpha Inhibitor

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X Yes. Please proceed to the next question.
No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only):

Rheumatoid Arthritis (RA) (1.1)

- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Psoriatic Arthritis (1.2)

- Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Ankylosing Spondylitis (1.3)

- Reducing signs and symptoms in patients with active disease.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: _____

Crohn's Disease (1.4)

- Reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (including infliximab).

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.
X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.
X No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0__
Max_____ kg_____ mo._____ yr.__6__
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☒ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo._____ yr.__greater than or equal to 6__
Max_____ kg_____ mo._____ yr.__less than or equal to 17__

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): ____December 31, 2009_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

2/1/2007

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

REQUEST FOR PARTIAL WAIVER OF PEDIATRIC STUDIES

Product Name:	Adalimumab
IND No.:	BB-IND 10,425
Sponsor:	Abbott Laboratories
Indication:	Crohn's Disease

1. What age ranges are included in your waiver request?

The Sponsor requests a partial waiver for pediatric patients 0 up to 6 years of age.

2. Reasons for waiving pediatric studies:

(a) Studies are impossible or highly impractical because the number of patients is so small, geographically dispersed, and the disease may be difficult to accurately diagnose.

3. Justification for waiver:

Crohn's disease has been reported at all ages but is rare in early childhood. In one study of patients with Crohn's disease 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6[1]. In a second study of patients diagnosed with Crohn's disease before the age of 15, 7.5% of the patients were under the age of 5[2]. Finally, results from the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry show that less than 2% of the 664 children enrolled at 20 sites since January, 2002 were 5 years of age or less[3]. Setting an age cut-off at 6 years of age or older is a reasonable approach to allowing data collection in the largest group of children that are likely to be enrolled by investigators.

Furthermore, the ability to firmly established the diagnosis of Crohn's Disease as opposed to indeterminate colitis or ulcerative colitis is diminished in children in younger age groups. In one study 20% of the children under the age of 5 diagnosed with inflammatory bowel disease had indeterminate colitis[4].

In addition, some of the children diagnosed with Crohn's in that age group later proved to have chronic granulomatous disease[5] as has been previously described[6]. Thus, establishing a firm diagnosis of Crohn's disease in this age group may be difficult.

Based on these considerations, the Sponsor requests a partial waiver for pediatric patients 0 up to 6 years of age.

References

1. Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr 2005;146(1):35-40.

2. Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984-1995. Journal of Pediatric Gastroenterology and Nutrition 2000;30(3):259-64.

3. Hyams, J. Personal communication.

4. Mamula P, Telega GW, Markowitz JE, Brown KA, Russo PA, Piccoli DA, Baldassano RN. Inflammatory bowel disease in children 5 years of age and younger. Am J Gastroenterol. 2002 Aug;97(8):2005-10.

5. Baldassano, personal communication.

6. Isaacs D, Wright VM, Shaw DG, Raafat F, Walker-Smith JA. Chronic granulomatous disease mimicking Crohn's disease. J Pediatr Gastroenterol Nutr. 1985 Jun;4(3):498-501

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

Product:	Adalimumab
IND No.:	BB-IND 10,425
Sponsor:	Abbott Laboratories
Indication:	Crohn's Disease

(a) **Is the indication for a life-threatening condition that occurs in the pediatric population?**
No.

(b) **If yes, are there approved therapies labeled for use in the pediatric population?**
Yes.

(c) **If yes, list the approved therapies and labeled pediatric age group(s) of approval.**
Remicade® (infliximab) is approved for pediatric use. The indication reads, "REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy." As noted in the PRECAUTIONS section of the package insert, Remicade has not been studied in children with Crohn's disease < 6 years of age.

1. **What ages are included in your deferral request?**
6-17 years

Reason for not including the entire pediatric population in the studies or in the deferral request?
Requesting a partial waiver for pediatric patients 0 up to 6 years of age.

2. **Reason(s) for deferring pediatric studies:**
(a) The adult studies are completed and ready for approval: Awaiting the completion of pediatric studies would delay the availability of the product to adults. This deferral was verbally agreed upon at the adult Crohn's disease pre-sBLA meeting held May 11, 2006.

3. Have pediatric drug development plans been submitted to the Agency?

Yes.

If yes, date submitted: A formal pre-phase 3 meeting with the Agency was held June 1, 2006 during which the pediatric development program proposed as part of the briefing book submitted on May 1, 2006 was discussed.

4. Suggested deferred date for submission of studies:

Phase III pediatric Crohn's disease revised draft protocol submitted for FDA review	August, 2006
Final protocol to be submitted to IND	September, 2006
Enrollment to begin	November, 2006
Enrollment to be complete	November, 2007

27 February 2007

Brian Harvey, MD, PhD, Director
Division of Gastroenterology Products
CDER Therapeutic Biological Products Document Room
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: Adalimumab (D2E7)
BLA 125057/89.5

Amendment to Pending Application

Dear Dr. Harvey,

The sponsor, Abbott Laboratories, submits the following information under the provisions of section 351 of the Public Health Service Act and 21 CFR 601.2.

The purpose of this submission is to provide revised labeling as agreed in a teleconference with the Agency held 26 February 2007. This version of the label contains the same text as provided to Abbott via email by Mr. Thomas Moreno, FDA Project Manager on 26 February 2007 following the teleconference.

Additionally, the following post-marketing commitments, proposed by Abbott via email to Mr. Moreno on 23 February 2007 and revised by the Agency on 23 February 2007 via email, were accepted by Abbott during the 26 February 2007 teleconference:

- To conduct study protocol P06-134, a 5-year, 5000 patient, multi-center, uncontrolled, observational study of adult patients with Crohn's disease treated in a routine clinical setting with adalimumab. The final protocol will be submitted by 30 April 2007 for concurrence, the study will be initiated by 31 August 2007, and enrollment will be complete by 31 August 2009. The study will be complete by 31 August 2014. Abbott will submit interim safety analyses of the study by 28 February 2009, 28 February 2011, and 28 February 2013, and will submit a final clinical study report by 31 May 2015.

- To complete and submit data from study protocol M06-806, a one-year, multi-center, randomized, double-blind study designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in the induction and maintenance of clinical remission in pediatric subjects 6 to 17 years of age with moderate to severe Crohn's disease. The study will include collection of baseline data on prior loss of response to or intolerance to infliximab, using definitions similar to those used in protocol M04-691. The final study protocol was submitted to Abbott's IND on 24 January 2007. Enrollment of 186 patients will begin by 31 March 2007 and will be complete by 31 March 2008. The study will be complete by 31 March 2009, and the final clinical study report will be submitted by 31 December 2009.

This submission is being provided electronically. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format -General Considerations, IT2 (January 1999), and Providing Regulatory Submissions to CBER in Electronic Format - Biologics Marketing Applications (November 1999). The submission is comprised of less than 5 megabytes of space. The content of the submission was checked for viruses using McAfee VirusScan Enterprise 8.0i and determined to be virus free.

Should you have any questions concerning this submission, please contact me at the number provided below. Thank you for your consideration in this matter.

Sincerely,

ABBOTT LABORATORIES

Meg Drew, MPH
Associate Director, Immunology Development
Global Pharmaceutical Regulatory Affairs
TEL: 847/938-8472
FAX: 847/887-8251
email: meg.drew@abbott.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125057/89

SEP 27 2006

Abbot Laboratories
Attention: Meg Drew, MPH
Associate Director, Immunology Development
Dept RA72
Bldg. AP34-3
200 Abbot Park Rd.
Abbot Park, IL 60064-6188

Dear Ms. Drew,

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	**Name of Biological Product**
BL 125057/89	Humira (Adalimumab)

Reason for the submission: New indication for the treatment of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy, and who have lost response to or are intolerant to infliximab.

Review Priority Classification: Standard (S)

Date of Supplement: August 25, 2006

Date of Receipt: August 28, 2006

Action Due Date: June 28, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver and deferral of pediatric studies for this application. Once the application has been filed we will notify you whether we have partially waived and/or deferred the pediatric study requirement for this application.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Thomas Moreno, at (301) 796-2247.

Sincerely,

Thomas Moreno, M.S.
Consumer Safety Officer
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: February 28, 2007

APPLICATION NUMBER: BLA 125057/89

BETWEEN:

Name: Meg Drew, Associate Director, Regulatory Affairs
Phone: 847-938-8472
Representing: Abbott Laboratories

AND

Name: Dr. John Hyde, Medical Team Leader
Tom Moreno, RPM
Division of Gastroenterology Products, HFD-180

SUBJECT: Changes Being Effected (CBE) for Humira PI

BLA 125057 Supplement 89, Humira for Crohn's Disease was approved February 27, 2007 and Abbott was required to send Final Printed Labeling (FPL) that matches the labeling sent with the Approval Letter. However, Abbott discovered 3 errors in the label that was sent with the Approval Letter. The purpose of this teleconference was to discuss how to address the following errors:

1. T
   d
2. T
3. '

b(4)

The Division recommended that Abbot make the changes and submit a combined FPL and CBE. The CBE should refer to error 3 minimally because errors 1 and 2 could be reported with the Annual Report. Alternatively, all three could be referred to in the CBE/FPL submission.

2/28/07

Thomas Moreno, M.S.
Consumer Safety Officer
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 10425

Abbott Laboratories
Attention: Lee M. Muroaka, BSPharm, MS
Regulatory Affairs Manager
Global Pharmaceutical Regulatory Affairs
DRA76, AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Dear Mr. Muroaka:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Adalimumab (HUMIRA) DOSAGE FORM AND STRENGTH(S).

We also refer to the meeting between representatives of your firm and the FDA on May 11, 2006. The purpose of the meeting was to describe the information that will be submitted, discuss preliminary efficacy/safety results and appropriate methods for final statistical analysis and identify the studies that they will rely upon.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Marlène G. Swider, Regulatory Project Manager, at (301) 796-2104.

Sincerely,

{See appended electronic signature page}

Marlène G. Swider
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 11, 2006
TIME:	11:00 A.M. – Noon
LOCATION:	Room 1421, Bldg. 22 at White Oak, FDA
APPLICATION:	IND 10425
DRUG NAME:	Adalimumab (HUMIRA)
TYPE OF MEETING:	Type B Meeting

MEETING CHAIR: John E. Hyde, M.D.

MEETING RECORDER: Marlène G. Swider, M.H.S.A.

FDA ATTENDEES:

Division of Gastroenterology Products

Brian E. Harvey, M.D.	Director, DGP
John E. Hyde, M.D.	Medical Team Leader
Li Liang, M.D.	Clinical Reviewer
Laurie Burke, M.P.H.	Director, Study Endpoints and Labeling (SEALD)
Marlene G. Swider, MHSA	Regulatory Project Manager
Edward D. Bashaw, Ph.D.	Clinical Pharmacology Team Lea
Stella Grosser, Ph.D.	Biometrics Team Leader
Shewit Bezabeh, M.D.	Clinical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

M. Shamsul Alam, PhD	Director of Scientific Data, Immunology
Meg Drew, MPH	Associate Director, Global Development RA, Immunology
Thomas Harris, RPh	Senior Director, Global Development RA, Immunology
Lauren Hetrick	Senior Director, Regulatory Intelligence
Rebecca Hoffman, MD	Divisional Vice President, Immunology Development Center
David Morris, PhD	Consultant, Biostatistician
Lee Muraoka, BSPharm, MS	Manager, US Area Regulatory Affairs, Immunology
Paul Pollack, MD	Global Medical Director, Immunology Development Center
Cheryl Renz, MD	Global Project Head, Immunology Development Center
Susan Paulson, PhD	Director of Clinical Pharmacokinetics - Immunosciences
Rich Shikiar	Consultant, Health Economics and Outcomes Research

BACKGROUND:
Abbott Laboratories is requesting a face-to-face Type B meeting to discuss the planned supplemental BLA submission for Adalimumab for the treatment of Crohn's Disease (BB IND 10425). Abbott would like to describe the information that will be submitted, discuss preliminary efficacy/safety results and appropriate methods for final statistical analysis and identify the studies that they will rely upon.

DISCUSSION POINTS:
The following questions are those received from Abbott Laboratories, Inc., in their April 10, 2006, Meeting Background Package. Following each question are responses (in **bolded** text) sent to the firm from the Divisions via e-mail on May 9, 2006. Where needed there are discussion points (in ***bolded italicized*** text) that occurred at the May 11, 2006, meeting.

Clinical

1. Abbott believes that the scope of the clinical program is sufficient to support the planned sBLA for the proposed indication. We believe that the trial designs and statistical methodology are in compliance with current Food and Drug Administration (FDA) requirements and are adequate to demonstrate safety and efficacy of adalimumab for the treatment of CD. Does the Agency agree?

Response:
The scope of the clinical program is sufficient to support the planned submission of the sBLA for the proposed indication though the actual wording of the indication would have to be discussed after review of the submitted data. The trial designs and statistical methodology are in compliance with current FDA requirements.

2. Abbott believes that the number of subjects in the clinical program and the length of time for subject follow-up to be included in the planned sBLA (clinical database cut-off of 14 February 2006) will provide adequate characterization of the safety of adalimumab in CD, particularly in view of the large safety database in rheumatoid arthritis (RA) patients treated with adalimumab. Does the Agency agree?

Response:
The number of subjects in the Crohn's disease clinical program and length of time for subject follow-up to be included in the planned submission appears adequate. Please submit an integrated safety summary of adalimumab for all approved indications and include this with the sBLA submission for CD. Please also include a safety summary of AE's seen in the postmarketing safety database for adalimumab and the current safety update to the long-term CD extension studies. Case report forms for all serious adverse events (SAE's) should be included in the application at the time of submission. Please provide complete safety information in the same manner as described in 21 CFR 314.50(d)(5). Please include a safety analysis using the MedDRA search strategy for the terms of "Anaphylactic Responses" (HTL) and "Type I Hypersensitivity" (PT).

Discussion at Meeting:
FDA requests that all serious adverse events be reported in as timely a manner as possible, including the ones identified after the dates given in the timeline included in Abbott's slides. The safety summary should be as complete as possible at the time of the Crohn's disease supplement submission.

3. There is currently no marketed drug that has been proven to be safe and effective

in inducing clinical remission of CD in patients who no longer respond to or are intolerant to infliximab, and hence there is an urgent unmet medical need in this population. The Agency has previously acknowledged this unmet need by granting Fast Track status for the development of adalimumab in this population on 16 September 2004 (BB IND 10425). Abbott believes that this need will still exist at the time of our planned filing (August 2006). Therefore, based on preliminary positive results from Study M04-691, which evaluated adalimumab in this patient population, Abbott intends to request priority review status for our marketing application for adalimumab in CD. Does the Agency agree a priority review request is appropriate and, in principle, should be granted pending review of the application?

Response:
A priority review request appears reasonable and would be considered if the application supports the unmet medical need aspect in this CD population. Review priority will be determined at the time of filing of the supplement.

Discussion at Meeting:
Please include your best argument for priority review at the time of the supplement submission.

4. Abbott plans to propose a recommended induction dose of 160 mg at Week 0 and 80 mg at Week 2. The proposed induction dose is supported by the statistically significant results from Study M02-403 in infliximab-naive subjects and Study M04-691 in infliximab "failure" subjects. Does the Agency agree with the proposed induction dose?

Response:
The recommended 160/80 mg induction dose appears to be a reasonable induction dose, but this will be subject to the review process.

5. The initial induction dose of 160 mg requires [redacted] a single day. This regimen may be inconvenient for some patients. Abbott intends to provide data from pharmacokinetic modeling and simulation to support the administration of the 160 mg dose over an interval of 2-4 days. Would the Agency consider data from pharmacokinetic modeling and simulation to be adequate to support this alternative regimen for product labeling?

Response:
No. A clinical equivalence study should be done to evaluate clinical efficacy with this alternative dosing regimen.

Discussion at Meeting:
Abbott proposes that splitting the 160 mg regimen to be given as 80 mg on two consecutive days should be an acceptable alternative due to the slow absorption of the product and Abbott plans to submit PK modeling and simulations to support this. FDA would want to see very

robust data to justify the use of this approach. The modeling data can be submitted for review, but FDA's current best advice is that clinical data would be needed.

1. [redacted]

Response:
As in the answer to Question #4, the optimum maintenance dosing regimen will be evaluated at the time of review and will be balanced between efficacy and safety findings.

7. Abbott proposes that the 120-day safety update will contain safety data from subjects with cumulative exposure to adalimumab from 14 February 2006 through 14 August 2006. Does the Agency agree with the proposed period for the 120-day safety update?

Response:
The period of February to August 2006 appears reasonable. Please also provide case report forms for all SAEs so that they are as current as possible at the time of submission and at the update. These data should also be presented within the integrated safety summary report.

Discussion at Meeting:
FDA's response is based on a 10 month review clock. FDA asked Abbott to provide a comprehensive safety summary at the time of submission. Abbott agreed on integrating the Post Market information with the reports submitted to FDA.

Regulatory /Labeling:

8. Abbott considers that the proposed clinical information from Studies M02-403, M02-404, M02-433 (1st year), and M04-691, supported by safety results from M02-433 (extension) and M04-690, will provide adequate evidence of safety and efficacy for the following proposed indication:

[redacted]

infliximab.

Does the Agency agree with the proposed indication for use?

Response:
The data submitted in the pre-sBLA package support a submission to address the ideas expressed in the indication proposed above. Wording of an actual indication statement would be discussed if the data in the submission support the proposed indications.

9. To meet FDA requirements for the Integrated Summary of Efficacy, Common Technical Document (CTD) Module 2.7.3 format will be used; and for the Integrated Summary of Safety, CTD Module 2.7.4 format will be used with additional safety tables provided, where appropriate, in the Summary of Clinical Safety. Abbott believes that the planned structure and content of these documents, in accordance with the International Conference on Harmonisation (ICH) M4E CTD Guidance, should provide reviewers with complete analyses of key safety parameters, and a thorough evaluation of any identified safety issues, as well as the protocol-driven primary efficacy endpoints. Does the Agency agree?

Response:
The above format appears acceptable. Please make sure safety information is complete and also see response to Question #2 above.

10. Abbott proposes to summarize new safety findings that resulted in labeling changes identified from spontaneous reports and other available post-marketing sources since approval of HUMIRA in the US on 31 December 2002 in the CSS (Section 2.7.4.6, Module 2, CTD-format). Does the Agency agree?

Response:
Yes. Please summarize new safety findings from spontaneous reports and other available post-marketing sources since Humira's approval in an integrated safety summary, and also by separate indications. See response to Question #2.

11. Abbott will be requesting a partial waiver for the evaluation of adalimumab use in pediatric CD patients given the low prevalence of disease in pediatric patients less than 6 years of age and a deferral for patients 6 to 17 years of age (inclusive). Abbott intends to seek Agency advice on the design of the pediatric development program via a separate meeting request in second quarter 2006. Does the Agency agree with Abbott's plans to address pediatric CD?

Response:
This appears to be a reasonable proposal. Your request for partial waiver or deferral will be considered based upon review of your plan and proposed timeline to study pediatric CD.

Discussion at Meeting:

FDA advised Abbott to add details and be specific about the type of dosage methods. Abbott stated that they plan to begin the pediatric CD program in the fourth quarter of 2006. During the June 1, 2006, Type B meeting Abbott would be addressing these details. Abbott noted that they plan to use vials for the pediatric study, but would then plan to market smaller prefilled syringes.

12. Does the Agency agree that the proposed format and content for the planned sBLA as presented in Appendix A is adequate and appropriate?

Response:
The proposed format as outlined in Appendix A is adequate.

13. For the planned sBLA, Abbott plans to provide CTD-formatted documents mapped to an electronic Biologics License Application (eBLA) structure. The planned sBLA will conform to the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations (January 1999, IT2) and FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format-New Drug Applications (NDAs) (January 1999). Does the Agency agree with the proposed format and structure for the planned sBLA?

Response:
This is acceptable.

14. Draft labeling will be submitted in accordance with the final rule amending labeling format and content requirements (21 CFR 201.56 and 201.57). Abbott understands that the reformatted existing labeling will be reviewed by the Division of Analgesics, Anesthetics and Rheumatology Products (DAARP), which has responsibility for the original BLA (BLA 125057). Abbott is seeking confirmation that the cross-divisional reviews of labeling will be planned and coordinated in a manner that will not impact completion of the supplement review by the user fee goal date. In addition, per 21 CFR 201.58, Abbott intends to submit a waiver with the sBLA to allow the Highlights section of the labeling to extend beyond the one-half page requirement due to the multiple indications and warnings to be included. Does the Agency have a preliminary response or recommendations regarding this request?

Response:
Draft labeling and the reformatting of existing labeling will be cross-reviewed by DGP and DAARP in a manner that will not impact completion of the supplement review. The Highlights section will have to be further discussed as the Agency gains experience with the new labeling format.

Discussion at Meeting:
Abbott intends to keep the content of the labeling as it is currently as much as possible, integrating changes to reflect the Crohn's disease indication. Future changes are to be expected based on supplements currently being reviewed by FDA.

15. Abbott intends to analyze effect of adalimumab on the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short Form 36 Physical Component Summary (SF-36 PCS) as described in the Study M02-404 statistical analysis plan submitted to FDA on 22 December 2005 (Serial No. 161). However, Abbott recognizes the February 2006 Federal Register publication of the draft FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Abbott believes that the previously agreed-upon analysis methods are still sufficient to include patient reported outcome results in labeling, provided that the analyses are positive according to the statistical analysis plan. Does the Agency agree?

Response:
The End-of-Phase-2 meeting in June 2004 did not include agreements regarding patient-reported outcomes. The proposal to include patient-reported outcome results in labeling will be considered during the course of the review in accordance with current guidelines and practices. Please refer to the draft FDA Guidance for recommendations as to what information you should plan to provide in order to support the validation of the measures you have chosen.

Discussion at Meeting:
FDA advised Abbott to look at the current draft guidances and provide comments if applicable. FDA is interested in understanding Abbott's definition of measurements and how these are accomplished. The results need to be expressed in a way that is meaningful to clinicians.

ADDED NOTE:
After the meeting, the FDA's Office of Drug Safety provided the following additional comments to be conveyed to Abbott:

- **If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e., package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**

- **For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**

  Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

  Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>

  Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: http://www.fda.gov/cder/guidance/6359OCC.htm

- **If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.**

ATTACHMENTS/HANDOUTS:

Abbott' slides for the May 11, 2006, Type B Meeting

HUMIRA Crohn's Disease Adult Pre-sBLA Meeting

FDA Meeting

11 May 2006

Questions Considered Resolved

- Question 1: Scope of Program
- Question 3: Priority Review
- Question 4: Loading Dose
- Question 6: Maintenance Dose and Dose Escalation
- Question 8: Indication
- Question 9: ISE/ISS Format
- Question 11: Pediatric Waiver
  - Type B FDA Meeting Scheduled June 1, 2006
  - Study scheduled to start in 4Q 2006
- Question 12: sBLA format
- Question 13: eBLA mapping

Questions for Further Discussion

- Questions 2, 7 and 10: Clinical Summary of Safety and 120-day Safety Update
- Question 5: Pharmacokinetic Modeling for Induction Dosing
- Question 14: Physician's Labeling Rule
- Question 15: Patient Reported Outcomes

Questions 2, 7 and 10: Clinical Summary of Safety and 120-day Safety Update

- Provide the planned contents of the CSS for CD
- Review the planned cut-off dates for the submission of the sBLA and 120-day Safety Update, including CRFs for SAEs
- Discuss the Agency's request for an Integrated Summary of Safety for all approved indications, including post-marketing safety data

Clinical Summary of Safety

- Populations for analysis
  - Induction Pooling
    - M02-403 double-blind induction
    - M04-691 double-blind induction
    - M02-404 open induction
  - Maintenance Pooling
    - M02-404
    - M02-433
  - All Studies

CSS: Analysis Details

- Adverse events (categorized by MedDRA)
  - Review of infection, malignancy, drug hypersensitivity ("Anaphylactic responses", "Type I Hypersensitivity"), demyelinating disease, congestive heart failure, and injection site reaction
  - Subgroup analyses based on ICH suggested intrinsic factors and on typical Crohn's medications and tobacco use as extrinsic factors
- Clinical laboratory values
  - Mean change
  - Shift tables based based on CTC Grade ≥3
  - Additional transaminase criteria

Review Planned Cut-off Dates for sBLA and 120-day Safety Update

- Original sBLA: August 2006
  - Safety data cut-off for all studies, including extension studies: Up to February 14, 2006
  - Includes CRFs for SAEs thru cut-off date
- 120-day Safety Update: December 2006
  - Safety data cut-off for all studies, including extension studies: Up to August 14, 2006
  - Includes additional CRFs for SAEs between February 15-August 14

Integrated Summary of Safety Request

- Request for Information from DAARP/ODS dated May 3, 2006
- Analysis requested by May 31, 2006
- Requested comprehensive integrated summary of safety for all indications:
  - Clinical trials
  - Registry
  - Post-marketing safety data (domestic)

Integrated Summary of Safety Request

- Clinical trials and registry analysis:
  - Deaths, including cause of death
  - Hospitalization
  - Serious infection, including TB and OIs
  - Analysis rates by:
    - Dose
    - Study treatment vs. control
    - Indication

Post-marketing Analysis

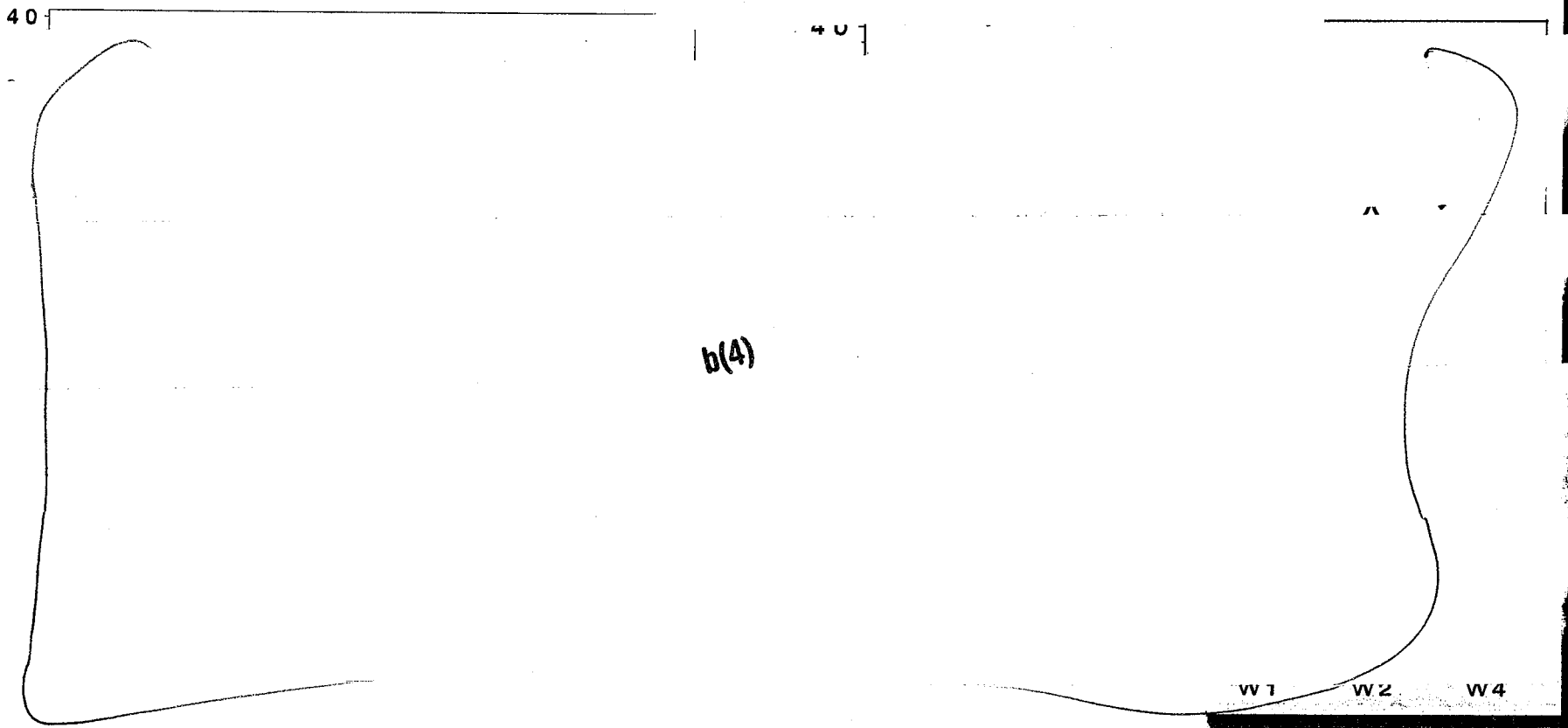
- Death
  - Reporting rates for death
  - Tabular summaries for each case
- TB
  - Failures due to lack of screening
  - Failures due to false negative PPD test
  - Cases where INH was initiated
- Descriptive Review of Interstitial lung disease cases

Question 5: PK Modeling for Induction Dosing

b(4)

Serum Adalimumab Concentrations

160 mg over



b(4)

Question 14: Draft Labeling

- Current approach to PLR
  - Minimize content changes to FDA previously agreed text
  - Integrate CD content
  - Ongoing AS and Humira Pen supplements will be integrated if approved by July 31, 2006
  - Waiver anticipated on Highlights section due to number of indications and warnings

Question 14: Draft Labeling and PLR Review

- Would DGP be interested in the following to facilitate PLR review:
  - Advanced unofficial copy of PLR reformat prior to sBLA submission?
  - Simultaneous submission to DAARP of PLR text at time of CD sBLA?
  - Informal telecon before or after submission with DGP, DAARP and Abbott to discuss process?

Question 15: PROs

- PRO selection and analyses are consistent with the draft FDA guidance
- FDA Guidance may change based on public comments
- Is compliance with the current FDA guidance sufficient?

Linked Applications	Sponsor Name	Drug Name
IND 10425	ABBOTT LABS PHARMACE	Adalimumab [Human Monoclonal Antibody (LU200134; D2E7)(BASF Pharma)] to Tumor Necrosis Factor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARLENE SWIDER
06/09/2006

PRE BLA

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 4, 2007

TO: Brian Harvey, M.D., Ph.D., Director
Division of Gastroenterology Products

VIA: Thomas Moreno, Regulatory Project Manager
Division of Gastroenterology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Humira (adalimumab) solution for subcutaneous injection, BLA 125057/89

Background and Summary

The sponsor submitted an Efficacy Supplement on August 28, 2006, for Humira (adalimumab) solution for subcutaneous injection, BLA 125057/89, for an additional indication (the treatment of Crohn's disease). The sponsor revised the existing prescribing information (PI) and patient package insert (PPI) to include information of the proposed indication.

Comments and Recommendations:

1. See the attached document for our suggested revisions to the Humira PPI. We have simplified the wording where possible, made it consistent with the PI, removed unnecessary information, and revised the sections to be consistent with the other TNF blocker PPIs we have reviewed. Our revisions have lowered the reading level from a 7.8 grade level to a 6.6 grade level (Flesch-Kincaid Grade Level).

2. The Patient Counseling section (section 17) of the PI should be expanded to include information necessary for patients to use the product safely and effectively (see 201.57(18). The patient labeling does not replace this section. This section is written for prescribers and should contain the necessary counseling information for prescribers to pass on to their patients.

3. Patient Information should always be consistent with the prescribing information. All future

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Administrative-*_____

Study Endpoints and Label Development (SEALD) Team
Review of Product Labeling in the Physician Labeling Rule Format

Application Number: BL 125057/89

Applicant: Abbott Laboratories

Drug Names: Humira (adalimumab)

Receipt Date: August 4, 2006
SEALD Review Date: February 16, 2007

Project Manager: Thomas Moreno, MS
Review Division: Division of Gastroenterology Products

SEALD Reviewer(s): Jeanne M. Delasko; Iris Masucci
Concurrence(s): Laurie B. Burke, Director, SEALD

EXECUTIVE SUMMARY

This memo provides a list of revisions for the proposed labeling (FDA version dated 2-11-07). These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

GENERAL COMMENTS

- Any text in the Full Prescribing Information (FPI) that corresponds to a "Recent Major Change" as listed in Highlights must have a vertical left margin mark next to the new text. An older version of the draft label contained these, but the version dated 2-11-07 did not. They must be reinserted.

- The Highlights section is currently a bit too long. Highlights must fit on ½ page, with extra allowance for the length of the boxed warning. The revisions proposed below will delete some text; we can assist in paring it down further if necessary.

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, "*[see Clinical Pharmacology (12.3)]*," not "*[See Pharmacokinetics (17.3)]*." Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please fix all cross-references throughout the labeling. [See Implementation Guidance]

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative-_____

Moreno, Thomas

m: Brony, Michael
t: Friday, February 09, 2007 12:32 PM
To: Moreno, Thomas
Subject: Humira proposed PLR 4 Aug 06.doc

Follow Up Flag: Follow up
Flag Status: Red

Attachments: Humira proposed PLR 4 Aug 06.doc

DDMAC Review

Hi Tom,

I had one small tiny comment/question on page 14....

Iris will be sending other comments as well.

Thanks

Michael

Humira proposed PLR 4 Aug 06.d...

Date: October 20, 2006

From: Jeanne M. Delasko, RN, MS
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Thomas Moreno, MS
Consumer Safety Officer, DGP

Subject: Proposed Labeling Format Review
BL 125057/89
Humira (adalimumab)

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant in the 74-day letter. Please contact me at 796-0146 with questions or concerns.

Comments to convey to the applicant:

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Highlights:

- The Highlights and Contents must each be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]

- Regarding the highlights limitation statement, insert the name of the drug product (i.e., Humira) and not the entire phrase "Humira (adalimumab) solution for subcutaneous injection." [See 21 CFR 201.57(a)(1)]

- For recent major changes, the date will be the month/year that the supplement is approved.

- Under Dosage and Administration, do not use the asterisk (*) to footnote information in tables in Highlights since this symbol is used in the Table of Contents (i.e., *Sections or subsections omitted from the full prescribing information are not listed). Use a different symbol. Also, there appears to be extra white space after the Dosage and Administration heading. Please delete.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative-_____

Review Memo

Ref:	**STN 125057/69, Carton label review**
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology; Director, DMA
RPM:	Thomas Moreno
Sponsor:	Abbott
Product:	Humira (adalimumab)
Date of submission:	Feb 22, 2006
Date of Review:	Feb 25, 2007

Background

Humira is a human derived (phage display library) IgG1:κ monoclonal antibody specific for human TNF-α. Its presumed mechanism of action is to bind and eliminate soluble TNF-α. It may also function by mediating the complement dependent lysis of mTNF+ cells, such as activated T cells.

- Humira drug substance is manufactured using standard bioprocess technology at the licensed, GMP compliant Abbott BioSciences facility in Worchester, MA, and at a licensed, GMP compliant facility in
- Humira drug product is manufactured at a licensed, GMP compliant filling site under contract by b(4)
- Labeling and packaging of syringes occurs at Abbott Lake County (Abbott Park, IL).
- DP testing occurs at Abbott GmbH and Abbott Lake County (labeled and packaged syringes, Abbott Park, IL). Sterility testing occurs at
- Humira is supplied as a liquid sterile dosage form in pre-filled syringes. Each syringe contains 40 mg of D2E7 (Humira) antibody in 800 µl of buffer with USP grade excipients.

b(4)

STN 125057/69 contains information supporting a new indication for Humira, Crohn's disease. Abbott intends to market a "starter package" specific for the Crohn's disease population. The package will contain additional labeling directed to Crohn's disease patients. The new starter packages will have a revised carton for a six dose tray package. Copies of new cartons were submitted to CDER for review on Feb 23, 2007.

The carton complies with the following drug labeling requirements.

- Name and place of business of manufacturer (Abbott labs, North Chicago, IL; FFDCA § 502(b)(1), 21 CFR 201.1)
- Quantity of contents in terms of weight, and numerical count. (800 µl in six or two dose trays; FFDCA § 502(b)(2), 21 CFR 201.51)
- Established drug name. (Humira; FFDCA 502(e)(1)(A)(i), 21 CFR 201.50)
- Established name and quantity (or proportion) of active ingredient(s) in the product. (adalimumab, 40 mg; FFDCA 502(e)(1)(A)(ii), 21 CFR 201.10, 21 CFR 201.100(b))
- The symbol "Rx only" is on the front of the carton (FFDCA 503(b)(4)(A), 21 CFR 201.100(b))
- Expiration date on outer package, if any (21 CFR 201.17). **Note:** *This information was e-mailed to FDA on Feb 26, 2007 (see attachment). The lot number and expiration date are printed during packaging operations on the bottom panel; "Lot" will be followed by a 9-character alphanumeric code and "Exp" will be followed by month and year as follows: FEB2007.*
- Humira doesn't contain FD&C Yellow #5 or #6, so 21 CFR 201.20 is not applicable.
- Bar code is on the side of the box (21 CFR 201.26)
- The recommended or usual dosage is on the side of the box (21 CFR 201.100(b))
- Lot number should be reflected on each immediate container and outer package, if any (21 CFR 201.18, 21 CFR 201.100(b), 21 CFR 211.130). **Note:** *This information was e-mailed to FDA on Feb 26, 2007 (see attachment). The lot number and expiration date are printed during packaging on the bottom panel; "Lot" will be followed by a 9-character alphanumeric code and "Exp" will be followed by month and year as follows: FEB2007.*
- There is no Medication Guide; instead there is a patient administration instruction booklet. The carton instructs users to read the administration instruction booklet (21 CFR 208.24).

The cartons also comply with the following Biologics Label Requirements

- 21 CFR 610.61 Package label
  - The proper name of the product;
  - The name, address, and license number of manufacturer (#0043);
  - The lot number or other lot identification;
  - The expiration date;

- The words "no preservative";
- The number of pen-injection devices;
- The amount of product in the container expressed as the number of doses, volume, weight.
- The recommended storage temperature;
- The words "Do not Freeze";
- The recommended individual dose (two and six);
- The route of administration recommended (sc injection), and reference to such directions in an enclosed circular;
- The inactive ingredients;
- The words "No U.S. standard of potency."
- The statement: "'Rx only'" for prescription biologicals.

- The following elements of 21 CFR 610.61 are not applicable:
  - The source of the product is not a factor in safe administration;
  - Microorganisms are not used in manufacture;
  - Humira does not contain known sensitizing substances, adjuvants or antibiotics added during manufacture;

The following additional biologics regulations are not applicable to Humira:

- Humira, a monoclonal antibody, is a "specified" biological products listed in 21 CFR 601.2(a). Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a). These requirements specify the position and prominence of the proper name of the product (adalimumab) relative to the trade name (Humira). Nevertheless, the carton is in "legible type", i.e. a size and character which can be read with ease when held in a good light and with normal vision.
- Abbott both manufactures and distributes Humira, and Abbott's name and address is on the carton. There is no distributor identification beyond this (21 CFR 610.64).

Recommendation: The six tray pack Humira Pen starter kit cartons comply with relevant drug and biologics labeling regulations.

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125057/89 Product: Humira (Adalimumab) Applicant: Abbot Laboratories

Final Review Designation (circle one): Standard (Priority)

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date Oct 12 2006 Committee Recommendation (circle one): (File) RTF

RPM: _____
(signature/date)

Attachments:

Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

1 Part A – RPM
1 Part B – Product/CMC/Facility Reviewer(s):
Kurt Brorson
NA Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): None

3 Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical)
Reviewers Li Liang, Tien Mien Chen, Stats TBA

Memo of Filing Meeting

Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y
legible	Y
English (or translated into English)	Y
compatible file formats	Y
navigable hyper-links	Y
interpretable data tabulations (line listings) & graphical displays	Y
summary reports reference the location of individual data and records	Y
protocols for clinical trials present	Y
all electronic submission components usable (e.g. conforms to published guidance)	Y
companion application received if a shared or divided manufacturing arrangement	NA
if CMC supplement:	
description and results of studies performed to evaluate the change	NA
relevant validation protocols	
list of relevant SOPs	
if clinical supplement:	
changes in labeling clearly highlighted	Y
data to support all label changes	Y
all required electronic components, including electronic datasets (e.g. SAS)	Y
if electronic submission:	
required paper documents (e.g. forms and certifications) submitted	Y

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Part B – Product/CMC/Facility Reviewer(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum of Filing Review

STN:	125057/89
Applicant:	Abbott
Product:	Humira
Short Summary:	Crohn's disease indication
Reviewer:	Kurt Brorson
Office/Division:	OTRR/DMA

I have conducted a filing review of the above referenced BLA supplement to determine whether it is sufficiently complete to permit a complete review.

Brief description of the change:
Addition of new clinical indication (Crohn's disease)- CMC information not required for filing

The following was submitted in support of the change (check all that apply):

✓	A detailed description of the proposed change
✓	Identification of the product(s) involved
	A description of the manufacturing site(s) or area(s) affected
	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
	The data derived from such studies
	Relevant validation protocols and data
	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

Recommendation:

✓	I recommend that this supplement be filed.
	I recommend that this supplement be refused for filing for the reasons stated above.

Reviewer: Kurt Brorson 10/11/06 Type (circle one): Product (Chair) Facility (DMPQ)
(signature / date)

Concurrence:
Branch/Lab Chief: [signature] 10/12/06 Division Director: Kathleen A. Clouse 10/12/06
(signature / date) (signature / date)

Recommendation (circle one): File RTF

Pharm/Tox reviewer: _____
(signature/ date)

Branch Chief concurrence: _____
(signature/ date)

Division. Director concurrence: _____
(signature/ date)

~~Part D – Clinical~~ (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
Biopharmaceutics and associated analytical methods	Y	N	
Clinical pharmacology [includes immunogenicity]			
Clinical Efficacy [for each indication]	(Y)	N	
Clinical Safety			
Synopses of individual studies 2 ~	(Y)	N	
	Y	N	
	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	

statement for each clinical investigation:		
conducted in compliance with IRB requirements	Y	N
conducted in compliance with requirements for informed consent	Y	N
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y)	N
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N
drug interaction studies communicated as during IND review as necessary are included	Y	N
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N
comprehensive analysis of safety data from all current world-wide knowledge of product	Y	N
data supporting the proposed dose and dose interval	Y	N

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: _____ Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

10/23/06

Recommendation (circle one): File RTF

Pharm/Tox reviewer: _____
(signature/ date)

Branch Chief concurrence: _____
(signature/ date)

Division. Director concurrence: _____
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
Biopharmaceutics and associated analytical methods	(Y)	N	
Clinical pharmacology [includes immunogenicity]	(Y)		
Clinical Efficacy [for each indication]	Y	N	
Clinical Safety			
Synopses of individual studies	(Y)	N	
	Y	N	
	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	

statement for each clinical investigation:			
conducted in compliance with IRB requirements	Y	N	
conducted in compliance with requirements for informed consent	Y	N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N	
drug interaction studies communicated as during IND review as necessary are included	Y	(N)	IR to be sent: Labeling update for DDI sections 7 & 12.K
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y	N	
data supporting the proposed dose and dose interval	(Y)	N	Review issue → population PK-PD modeling/simulation

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: Jian Mei Chen Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date) 10/17/06

Concurrence:
Acting TL
Branch Chief: [signature] 10/16/06
(signature/ date)

Concurrence limited to OCP issues
Division. Director: Ed Roth 10/17/06
(signature/ date)

Recommendation (circle one): File RTF

Pharm/Tox reviewer: _____
(signature/ date)

Branch Chief concurrence: _____
(signature/ date)

Division. Director concurrence: _____
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
Biopharmaceutics and associated analytical methods	(Y)	N	
Clinical pharmacology [includes immunogenicity]			
Clinical Efficacy [for each indication]	(Y)	N	
Clinical Safety			
Synopses of individual studies	(Y)	N	
	Y	N	
	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	

Study Reports and related information [5.3]	Y	N
Biopharmaceutic		
Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N
Pharmacokinetics (PK)	Y	N
Pharmacodynamic (PD)		
Efficacy and Safety	Y	N
Postmarketing experience	Y	N
Case report forms	Y	N
Individual patient listings (indexed by study)	Y	N
o electronic datasets (e.g. SAS)	Y	N
	Y	N
	Y	N
Literature references and copies [5.4]	Y	N

Examples of Filing Issues	**Yes?**		**If not, action & status**
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
legible	Y	N	
English (or certified translation into English)	Y	N	
compatible file formats			
navigable hyper-links	Y	N	
interpretable data tabulations (line listings) & graphical displays	Y	N	
	Y	N	
summary reports reference the location of individual data and records	Y	N	
protocols for clinical trials present			
all electronic submission components usable	Y	N	
	Y	N	

statement for each clinical investigation:
conducted in compliance with IRB requirements (Y) N
conducted in compliance with requirements for informed consent (Y) N

adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy) (Y) N

adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication (Y) N

study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim (Y) N

study(ies) assess the contribution of each component of a combination product [21 CFR 610.17] Y N (N/A)

total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents) (Y) N

adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy (Y) N

drug interaction studies communicated as during IND review as necessary are included Y N

assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review (Y) N

comprehensive analysis of safety data from all current world-wide knowledge of product (Y) N

data supporting the proposed dose and dose interval (Y) N

appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data (Y) N

adequate characterization of product specificity or mode of action (Y) N

data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred (Y) N

inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations (Y) N

all information reasonably known to the applicant and relevant to the safety and efficacy described? (Y) N

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?	
M02-403	(Y) N	(Y)	N	NR	(Y)	N	Y NR	N
M02-433	(Y) N	(Y)	N	NR	(Y)	N	Y NR	N
M02-404	(Y) N	(Y)	N	NR	(Y)	N	Y NR	N
M04-690	(Y) N	(Y)	N	NR	(Y)	N	Y NR	N
M04-691	(Y) N	(Y)	N	NR	(Y)	N	Y NR	N
	Y N	Y	N	NR	Y	N	Y NR	N
	Y N	Y	N	NR	Y	N	Y NR	N
	Y N	Y	N	NR	Y	N	Y NR	N
	Y N	Y	N	NR	Y	N	Y NR	N
	Y N	Y	N	NR	Y	N	Y NR	N

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

yes

Is an Advisory Committee needed?

no

Recommendation (circle one): File RTF

Reviewer: _____ 10/12/06 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Team Leader ~~Branch Chief~~: _____ 10-12-06 Division. Director: _____
(signature/ date) (signature/ date)

10/12/06

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	October 12, 2006 3:30 PM
Meeting Type:	Internal
Meeting Category:	BLA supplement filing meeting
Meeting Location:	White Oak 5266
Application Number:	BLA 125057/89
Product Name:	Humira (Adalimumab)
Received Briefing Package	Application 8/28/2006
Sponsor Name:	Abbot Laboratories
Meeting Requestor:	NA
Meeting Chair:	Brian Harvey
Meeting Recorder:	Tom Moreno

Meeting Attendees:

FDA Attendees

Hyde, John E; Liang, Li; Brorson, Kurt; Grosser, Stella C; Lee, Sue Chih H; Strongin, Brian K; Barraco, Ryan; Stark, Cristi L; Harvey, Brian; Korvick, Joyce A; Chen, Tien Mien (Albert); Adebowale, Abimbola O; Phillips, Chantal; Tornoe, Christoffer

External Attendees

Not applicable

2 BACKGROUND

Filing Meeting for sBLA

STN: 125057/89, Efficacy Supplement for Crohn's Disease
Product: _Humira (Adalimumab) Applicant: Abbot Laboratories

- Receipt date August 28; Filing goal date October 27, 2006
- Label is in PLR format
- Need for priority vs standard decision
- Need to decide if application is fileable

3 DISCUSSION

3.1 Clinical Background on Product: Li Liang

Discussion:

Dr. Liang gave a brief background.

3.2 Clinical summary of issues and deficiencies—collect review

Discussion:

Clinical stated that the supplement is fileable and turned in a signed filing worksheet. They will be choosing some clinical sites for DSI inspection later.

3.3 Statistics summary of issues and deficiencies—collect review

Discussion:

Statistics stated that they have not been able to complete their filing review because the data was not easily accessible. However, they think that this should be quickly resolved by speaking with Abbot and anticipate declaring the application filable. RPM will set up a meeting with Abbot and collect a completed filing worksheet from Statistics.

3.4 Clinical Pharmacology summary of issues and deficiencies—collect review

Discussion:

Clinical Pharmacology stated that the supplement is fileable and will turn in a signed filing worksheet next week. They also stated a concern about the dosing regimen for a particular study requiring a discussion with Pharmacology/Toxicology. An information request for Abbot will be forthcoming. Clinical Pharmacology requested a consult from Pharmacometrics that was represented by Christoffer Tornoe.

3.5 OBP Product summary of issues and deficiencies—collect review

Discussion:

OBP stated that the supplement is fileable and turned in a signed filing worksheet.

3.6 RPM summary of issues and deficiencies

Discussion:

Project Management found application fileable with one concern. One registration number was not listed by the sponsor. Abbot will be queried.

3.7 Decision on Priority and File-ability

Discussion:

The division director granted priority review and the team found the application to be fileable pending the filing review from Statistics.

3.8 Consults:

Discussion:

The following consults will be required.

- 2.1 DDMAC
- 2.2 DSI
- 2.3 OSE- combined consult
  - 2.3.1 DDRE
  - 2.3.2 DSRCS
- 2.4 SEALD—combined consult
  - 2.4.1 End Point—Dr. Liang to help write consult
  - 2.4.2 PLR
- 2.5 Div. of Anesthesia, Analgesia, and Rheumatology
- 2.6 Advisory committee—not needed.

3.9 Schedule for team meetings: Priority = monthly Std = every other month

Discussion:

Team Meetings to be scheduled

4 ISSUES REQUIRING FURTHER DISCUSSION

See action items

5 ACTION ITEMS

Action Item/Description
Tom Moreno will set up teleconference with Abbot and Statistics.
Statistics will complete filing worksheet after speaking with Abbot.
60 day letter is due by October 27, 2006 (Tom Moreno).
Clinical Pharmacology will turn in a signed filing worksheet next week.
Christoffer Tornoe will submit an information request to Tom Moreno.
Team Meetings to be scheduled by Tom Moreno. Mid cycle mid December 1 ½ hours.

6 ATTACHMENTS AND HANDOUTS

None.