CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

sBLA 125057/110

MEDICAL REVIEW(S)

D Cook, MD
12/14/07

CLINICAL REVIEW

Application Type	BLA
Submission Number	125057
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Reviewer Name	Denise Cook, M.D.
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Established Name	Adalimumab
Trade Name	Humira
Therapeutic Class	Anti-TNF-α Inhibitor
Applicant	Abbott Laboratories
Priority Designation	S
Formulation	Injectable solution
Dosing Regimen	80mg loading, then 40 mg eow SQ
Proposed Indication	Moderate to severe chronic plaque psoriasis
Intended Population	Adults who are candidates for systemic therapy or phototherapy

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended from a clinical perspective that HUMIRA (adalimumab) for subcutaneous injection be approved for "the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy *and* when other systemic therapies are medically less appropriate."

There is substantial evidence for effectiveness of HUMIRA to treat patients with chronic moderate to severe psoriasis as demonstrated by 2 adequate and well-controlled trials. The safety of HUMIRA in this population was investigated in both placebo controlled trials and in open-label extension trials, with an adequate population being treated for at least 96 weeks. There were two safety issues, that of fatalities and malignancies, that has resulted in a more restrictive indication than that proposed by the sponsor.

The population for which HUMIRA is being approved, as indicated above, is more restrictive than that proposed by the sponsor. The sponsor's proposed indication was for "the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy." HUMIRA has a boxed warning for severe infection with tuberculosis, invasive fungi, and other opportunistic infections which have lead to fatalities. The label also states, "...the observed rate of lymphomas is ..... approximately 3-fold higher than expected in the general population" and "...the rate (95% confidence interval) of non-melanoma skin cancers was 0.9 (0.57, 1.35)/100 patient-years among HUMIRA-treated patients and 0.3 (0.08, 0.80)/100 patient-years among control patients." In the psoriasis trials, there were 6 fatalities, none of which were due to infection, and although none occurred in the controlled portion of the trials, and a definitive causality cannot be established, it is concerning that all the deaths occurred in subjects on adalimumab. From the data, it may be that HUMIRA may have contributed to the aggressiveness of the cancer found in two of the deaths. However, more patients will need to be studied over a longer period of time in an attempt to elucidate if causality for these fatalities can be linked to HUMIRA. Further, there was a slight increase in the incidence of cutaneous malignancy, primarily basal cell carcinoma in the adalimumab-treated subjects. Psoriasis patients are already at an increased risk for cutaneous malignancy by virtue of exposure to certain types of treatment, i.e. phototherapy. Thus, at this time, for patients who have moderate to severe chronic plaque psoriasis, HUMIRA should be used when other systemic therapies are medically less appropriate.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

1) HUMIRA will have a Medication Guide as part of risk management for patients.

2) As this drug product is an immunosuppressive, a post marketing registry, with at least 5,000 patients, will be conducted over a longer time period, [redacted] to better ascertain the occurrence of rare but serious adverse events. b(4)

1.2.2 Required Phase 4 Commitments

b(4)

The sponsor will conduct a phase 4 registry.

[redacted]

1.2.3 Other Phase 4 Requests

The sponsor should submit the final study report for trial M03-658.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This BLA was submitted in support of HUMIRA (adalimumab) for the proposed indication of treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. To support the indication, the sponsor submitted two pivotal, multicentered phase 3 trials for efficacy, a phase 2 dose ranging trial, and 4 open-label trials (one with a double-blind period) with subjects studied up to 3 years.

Adalimumab was studied in adult patients greater than or equal to 18 years of age. The Placebo Controlled Study Set (which includes subjects from the phase 2 dose-ranging study) consists of 1469 subjects, 966 treated with adalimumab and 503 on placebo. The All Adalimumab Treatment Set consisted of 1696 subjects.

1.3.2 Efficacy

Two phase 3 pivotal trials were conducted to demonstrate efficacy of adalimumab in the treatment of moderate to severe plaque psoriasis: M03-656 and M04-716. Both studies are multicentered trials, the former with multiple centers in the United States and Canada and the latter with multiple centers in Europe and Canada.

Period A of trial M03-656 and trial M04-716 addresses short-term efficacy of adalimumab in the treatment of moderate to severe chronic plaque psoriasis. Twelve hundred and twelve (1212) patients with a baseline PASI $\geq$12 and BSA involvement $\geq$ 10%, were randomized 2:1 to receive adalimumab:placebo for 16 weeks. Efficacy variables used to determine efficacy were proportion of patients with a $\geq$ PASI 75 response rate and patients with a Physician's Global Assessment (PGA) severity score of clear or minimal at 16 weeks. Trial M04-716 also randomized subjects 2:1 to receive adalimumab: placebo. Subjects with a baseline PASI $\geq$12 and BSA involvement $\geq$ 10% were evaluated.

Thus, 99 patients were treated with adalimumab and 48 with placebo. There was an additional arm of 110 patients treated with methotrexate [redacted] b(4)

In trial M03-656, for the efficacy variable ≥ PASI 75 response rate, 578/814 (71.0%) on adalimumab vs. 26/398 (6.5%) achieved this response rate ($p<0.0001$). For a PGA of clear or minimum, 506/814 (62.2%) patients on adalimumab vs. 17/398 (4.3%) were a success ($p<0.0001$). In trial M04-716, for ≥ PASI 75 response rate, 77/99 (77.8%) vs. 9/48 (18.8%) achieved this response ($p<0.0001$). For a PGA of clear or minimum the success was 70/99 (70.7%) vs. 5/48 (10.4%) with a $p<0.0001$.

Periods B and C in trial M03-656 look at the long-term efficacy of adalimumab up to 52 weeks. Patients who attained a ≥ PASI 75 response from period A were entered into Period B at week 16 and continued to receive 40 mg eow of adalimumab up to week 33. Period C is a double-blind placebo-controlled treatment period in which subjects who maintained a ≥ PASI 75 response at week 33 and were originally randomized to active therapy in Period A were re-randomized (1:1) to receive adalimumab or placebo.

The Division investigated in Period C the proportion of subjects losing an adequate response after week 33 and on or before week 52. Loss of adequate response was defined as the following: subjects who did not maintain a ≥PASI 75 response, subjects who did not maintain a PGA score of "clear" or "minimal" and subjects who did not maintain either a ≥PASI 75 response or a PGA score of "clear" or "minimum". Results showed that 52/250 (20.8%) had a loss of adequate response on adalimumab compared to 138/240 (57.5%) on placebo at week 52 ($p<0.0001$) for PASI 75. For PGA, loss of adequate response occurred in 80/250 (32.0%) as compared to 173 /240 (72.1%) on placebo at week 52 ($p<0.0001$). The analysis demonstrates that adalimumab does maintain its efficacy in the long-term (over 52 weeks). This does not drop off over time, as in this analysis at 52 weeks, 68.0% of subjects were able to maintain a success with a PGA of clear or almost clear, which falls between the success in Period A of this trial of 62.2% and trial M04-716 where the success for PGA was 72.2% after 16 weeks of treatment. PASI 75 success was somewhat higher in all analyses. These results were all highly statistically significant. Thus, it has been demonstrated that adalimumab can maintain its efficacy over a period of 52 weeks.

1.3.3 Safety

The evaluation of the safety of adalimumab in patients with moderate to severe chronic plaque psoriasis was obtained from 3 placebo controlled trials and 3 continuation studies. The placebo controlled study set consists of 1469 patients, 966 treated with adalimumab and 503 on placebo. Except for 45 patients in the phase 2 dose ranging study who were treated for 12 weeks, all patients in the adalimumab arms were treated with an initial dose of 80 mg sq followed by 40 mg eow sq for 16 weeks. The second study set is the all adalimumab study set which consists of 1696 subjects.

For the all adalimumab treatment set (1696 subjects), the median and mean durations of treatment were 553.0 days and 542.9 days, respectively, representing an average treatment duration of approximately 1½ years. Treatment duration was more than three years in 6.6% of subjects. Two-thirds of the subjects [1146 subjects (67.6%)] had greater than 60 weeks (15 mo) of exposure. More than half of the subjects [980 (57.8%)] had greater than 72 weeks (18 mo) of exposure and a little more than a quarter of subjects [453 (26.7%)] had greater than 96 weeks (24 mo) of exposure.

The majority of subjects were between the ages of 40-64 years (56.3%) with the median age of 44 years. The next highest group was < 40 years old (37.7%). Two-thirds of the subjects were male with the majority of subjects being Caucasian (91.8%).

In the placebo controlled study set, 86/1469 (5.8%) of subjects discontinued, 50/503 (9.9%) in the placebo arms and 36/966 (3.7%) in the adalimumab arms. The major reason for discontinuation in the placebo arms was "unsatisfactory therapeutic response", 5%, followed by "withdrawal of consent", 3.6%.

The major reason for discontinuation in the adalimumab arms was "adverse event", 1.8% followed by "withdrawal of consent", 1.0%. In the all adalimumab study set, 30.0% (509/1696) of subjects discontinued from the trials. The four leading causes were "unsatisfactory therapeutic effect", 10.8%, "withdrawal of consent", 8.8%, "adverse event", 6.4%, and "lost to follow-up", 4.4%.

The overall incidence of AEs reported in the adalimumab arms (63.6%) was slightly higher than in the placebo arms (59.0%) in the pivotal trials. This difference was not statistically significant. The incidences of AEs at least possibly related to study drug (adalimumab, 22.9%; and placebo 16.9%) and infections (adalimumab, 30.3%; and placebo 23.9%) were statistically significantly higher in adalimumab-treated subjects than in placebo treated subjects. The incidence of serious infections, however, was comparable between the two, 0.5% for adalimumab and 0.8% for placebo.

The most common AEs in descending order of frequency were nasopharyngitis 7.8% in both adalimumab (ADA) and placebo (PBO), upper respiratory tract infection (6.4%ADA; 3.0% PBO), headache (6.1%ADA; 5.6%PBO), arthralgia and injection site reaction (both 2.9%ADA; 1.4%PBO). It should be noted that when one looks at corresponding exposure-adjusted rates (E/100PY), headache occurs more frequently in the placebo group. The incidence of URI was statistically more significant in the adalimumab group than in the placebo group. Arthralgia is a new adverse event for which HUMIRA is not labeled.

The incidence of severe AEs was low in both arms, 27/966 (2.8%) in the adalimumab group and 15/503 (3.0%) in the placebo group as was the incidence of serious AEs, 18/966 (1.9%) in the ADA group and 8/503 (1.6%) in the placebo group. No subjects died in the placebo-controlled study set. Of the 15 AE categories of special interest, no subjects experienced AEs in any of the following categories: lymphoma, demyelinating disorder, opportunistic infection (excluding TB), TB, and lupus-like syndrome. There were 8 (0.8%) malignancies in the ADA group and 2 (0.4%) in the placebo group. The majority of the malignancies were due to non-melanoma skin cancer, the majority of which were BCCs, 5 in the ADA group and 1 in the placebo group. Although slightly higher in the ADA group (0.5% to 0.2%), this was not of statistical significance. The three other cancers that occurred in the adalimumab group were squamous cell carcinoma, malignant melanoma in situ, and breast cancer in patients aged 54, 40, and 71 years, respectively. The other cancer in the placebo group was bladder cancer in a 77 year old.

In the placebo controlled studies, the proportion of patients whose chemistries changed to high was slightly higher in the adalimumab group including ALT (7.8 vs.6.3), AST (4.9 vs. 3.9), bilirubin (2.1 vs. 1.2), cholesterol (21.1 vs. 19.0), CK (8.2 vs. 5.7), and triglycerides (17.7 vs. 14.4). As far as lipid profiles, however, 0.9% of subjects treated with adalimumab reported hypercholesterolemia vs. none in the placebo group. In terms of treatment-emergent AEs per 100 patient-years of exposure, hepatic events are slightly higher in the adalimumab group, 10.2 vs. 9.5 events per 100 patient-years of exposure. Hematologic events were slightly higher in the placebo group, 0.1% vs. 0.2%.

In the All Adalimumab Treatment Set, 85.9% of subjects reported at least one treatment-emergent AE and 35% of subjects reported AEs that were considered by the Investigator to be at least possibly related to adalimumab treatment. Severe AEs were reported in 9.9% of subjects (9.2E/100PY). Serious AEs were reported in 8.2% of subjects (7.3E/100PY). AEs leading to discontinuation occurred in 7.0% of subjects (6.2E/100 PY).

The most common AEs in the All Adalimumab Treatment Set were infections (59.0%, 1000/1696), of which 2.0% were serious infections, injection site reactions, (10.0%, 170/1696), and hepatic events (4.4%, 75/1696). Malignancies occurred in 2.1% of subjects, of which 1.1% were non-melanoma skin cancers and 1.1% were other malignancies. Again, the majority of the non-melanoma skin cancers were BCCs. There were no instances of lymphoma. Four subjects (0.2%) developed opportunistic infections excluding TB and 3 subjects (0.2%) developed TB.

As stated earlier, the All Adalimumab Treatment Set includes the later study phases and subjects had an average duration of treatment of 1½ years and more than 3 years duration of treatment. In this set, the risk of AEs does not appear to increase with chronic adalimumab treatment. The rates of AEs per 100

patient-years of exposure are generally lower in the All Adalimumab Treatment Set compared with the adalimumab arm of the Placebo-Controlled Study Set, particularly for infections (86.0 vs. 134.7/100 PY), injection site reactions (13.1 vs. 29.9 E/100PY), and hepatic events (4.5 vs. 10.2 E/100PY). The exposure-adjusted AE rates for 'any malignancy' and 'nonmelanoma skin cancer' in the All Adalimumab Treatment Set (1.6 and 0.8 E/100PY, respectively) are lower compared with the adalimumab treatment group in the Placebo-Controlled Study Set (2.4 and 1.7 E/100 PY).

There were no severe AEs in the All Adalimumab treatment set that occurred at $\geq 1\%$. The highest incidence of severe AEs was cellulitis which occurred in 6/1696 (0.4%) subjects, followed by coronary artery disease (0.3%). The other severe adverse events occurring at 0.2% were headache, breast cancer, migraine, myocardial infarction, and psoriatic arthropathy.

Six (6) deaths occurred during the open-label portions of the adalimumab trials. None of the deaths were related to known infection. The events occurred from 2 days to 190 days after receiving last treatment of adalimumab. Two were secondary to cardiovascular events, two to cancer, one to suicide, and one post-surgical. It is difficult to unequivocally attribute these deaths solely to adalimumab, as all had confounding factors. However, given that adalimumab is an immunosuppressant and is implicated across other indications with malignancy occurrence, it may have contributed to the 2 deaths associated with malignancy in the psoriasis trials.

1.3.4 Dosing Regimen and Administration

The recommended dosing regimen of HUMIRA for the psoriasis population is 80 mg subcutaneously for the initial dose, followed by 40 mg every other week starting at week one after the initial dose. This dose has been adequately studied in well-controlled trials. Efficacy in the treatment of moderate to severe chronic plaque psoriasis has been demonstrated using this dosing regiment for up to 52 weeks. Safety has been demonstrated in 453 subjects for > 96 weeks of exposure at this dosing regimen.

1.3.5 Drug-Drug Interactions

No new drug-drug interactions were investigated in the conduct of this efficacy supplement for HUMIRA.

Investigations for the development of anti-adalimumab antibodies (AAA) were performed in two of the placebo controlled trials. Results indicate that 77/920 (8.4%) of subjects in the trials developed AAA. While this did decrease efficacy in this subset of patients, it did not increase their risks in terms of safety.

1.3.6 Special Populations

There were not any efficacy or safety findings upon subgroup analyses that would restrict or modify the dosage and administration of HUMIRA within the context of the indication in adult patients with moderate to severe psoriasis.

HUMIRA has not been studied in patients less than 18 years of age. These studies have been deferred.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adalimumab (HUMIRA) is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is comprised of human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin (TNF-β).

TNF-α is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF-α play an important role in pathologic inflammation, including psoriasis (Ps), where TNF-α contributes to proliferative and decreased maturation of keratinocytes and associated vascular changes. Adalimumab binds specifically to TNF-α and neutralizes the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also modulates biologic responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C -reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

HUMIRA is currently approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. Dosage for the first 3 indications is 40 mg sq eow and may be combined with other systemic arthritic medications. As a solo agent, it may be used at a dose of 40 mg every week in RA. In Crohn's disease, the initial dose is 160 mg at week 0, then 80 mg at week 2, followed by 40 mg eow beginning at week 4.

The sponsor seeks with this efficacy supplement an indication for the "treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy." The dosage for patients with psoriasis is an initial dose of 80 mg by subcutaneous (SQ) injection, followed by 40 mg SQ every other week (eow) beginning one week after the initial dose.

2.2 Currently Available Treatment for Indication

There are many drug products on the market for the treatment of moderate to severe chronic plaque psoriasis. These therapies include topical therapies, phototherapy and photochemotherapy, and systemic therapies. However, a perfect treatment for psoriasis does not exist. Treatments to date do not induce a permanent remission and most often must be given in cyclical or continuous fashion in an effort to circumvent unwanted adverse events in a disease that has to be treated over an individual's lifetime.

Topical Corticosteroids

Topical corticosteroids have been the mainstay of treatment of psoriasis since their introduction in 1952. They are often first-line treatment for mild to moderate psoriasis as well as in sites such as the flexures and genitalia. The development of high potency and super potent topical steroids has opened the door for successful treatment of severe psoriasis, as well. The high potency topical steroids include the fluocinonide family (cream, ointment, gel) as well as betamethasone dipropionate cream. The super potent topical steroids include the clobetasol propionate family (cream, ointment, gel, foam, lotion) as well as diflorasone diacetate ointment and betamethasone dipropionate ointment.

The efficacy of these drug products is well established in the treatment of chronic plaque psoriasis. A recent study of clobetasol propionate lotion in the treatment of moderate to severe psoriasis demonstrated efficacy after 4 weeks of twice daily treatment in 36.6% of patients compared to 0% in placebo. Treatment success was achieved in patients who obtained a score of clear or almost clear on the Investigator's Global Assessment Scale, the same scale used to determine success in the oral tazarotene trials.

Side effects associated with the use of topical corticosteroids include skin atrophy, burning and stinging, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This may occur after two weeks of use with certain topical corticosteroids.

Topical Vitamin D_3 Analogues

The prototype of this group of drug products is calcipotriene, approved in the United States. It comes in 3 formulations, cream, ointment, and scalp solution. The former two are approved for plaque psoriasis and the scalp solution is approved for moderately severe psoriasis of the scalp. In clinical trials, patients with at least marked improvement after 8 weeks of twice daily therapy was 50% and 49.6% for the cream and ointment formulations, respectively. Thirty-one percent of patients after 8 weeks of twice daily treatment with scalp solution were clear or almost clear.

Side effects are cutaneous and include burning, stinging, itching, skin irritation, and tingling of the skin.

Topical Retinoids

Topical tazarotene gel is approved in two strengths, 0.05% and 0.1%, for the treatment of stable plaque psoriasis of up to 20% BSA involvement. In clinical trials, patients with at least moderate psoriasis were treated for 12 weeks once daily. The percentage of patient with at least a 75% improvement from baseline was 28% and 18% for the 0.05% concentration in two placebo controlled studies and 38% and 25% for the 0.1% formulation in two placebo controlled studies. The vehicle effect was 12% and 10%.

The most frequent adverse reactions were limited to the skin. These included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain.

Tazarotene gel is a pregnancy category X drug product and as such is contraindicated in women who are or may become pregnant. A negative pregnancy test should be obtained 2

weeks prior to initiation of therapy and therapy should be initiated during a normal menses. Women of childbearing potential should use adequate birth control.

Phototherapy

Phototherapy is usually reserved for moderate to severe psoriasis. Phototherapy involves treatment with UVB alone. Broadband UVB phototherapy has been an effective approach to treatment of moderate to severe psoriasis. In recent years, a shift to narrow band UVB (311-313 nm) has become the most optimal irradiation available today.

Treatment with UVB is time consuming, requiring 2-3 visits/week for treatment for several months and the possibility of experiencing an acute sunburn reaction exists. Cumulative doses over time can also increase the risk of developing cutaneous skin cancer, particularly squamous cell carcinoma and melanoma.

Systemic Therapies

Methotrexate is a folic acid analogue that has been approved to treat severe psoriasis since 1971. It is administered once weekly at a dose up to 30 mg. Alternatively, it can be administered in 3 divided doses 12 hours apart, once a week. Initial improvement is usually seen between 1-7 weeks, with maximal improvement in 8-12 weeks. In one series, >75% improvement was observed in 90% of 248 patients (Bolgnia, et al., 2003, page 142). Major drawbacks of the drug are risk of pancytopenia and hepatic damage with cumulative dose. Patients who remain on the drug long term may have to undergo serial liver biopsies. The drug is also an abortifacient and a teratogen. GI intolerance can be managed with folic acid or using the parental route.

Cyclosporine, a undecapeptide isolated from the fungus *Tolypocladium inflatum* which has immunosuppressant properties, was approved for severe psoriasis in 1997. The dosage for psoriasis is 2.5 – 4.0 mg/kg/day in a bid dosage regimen. Patients generally show some improvement in 2 weeks with satisfactory control and stabilization of disease in 12 – 16 weeks. Although cyclosporine works very well in psoriasis, it is limited by its relatively poor safety profile of renal toxicity, including irreversible renal damage, hepatotoxicity, development of hypertension, and the possibility of the development of neoplasia. The drug is limited to no longer than 1 year of continuous use. Relapse occurs in approximately 6 weeks (50% of subjects) to 16 weeks (75% of subjects).

Soriatane, an oral retinoid was approved in 1990 for the treatment of severe psoriasis. As it is a human teratogen, women of childbearing potential should only be treated with this drug as a last resort. Other major safety risks include hyperlipidemia with its resultant co-morbidities and hepatotoxicity. Soriatane is usually given in a dose of 25 – 50 mg once daily. While it is moderately effective in the treatment of plaque psoriasis, it is highly effective in the treatment of pustular and erythrodermic psoriasis (Bolognia et. al, 2003, page 144).

TNF-α Inhibitors – see sections 2.3 and 2.4

2.3 Availability of Proposed Active Ingredient in the United States

Humira is widely available in the United States, as the drug product is approved for multiple indications. These include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and most recently, Crohn's disease.

Two other TNF-α inhibitors have been approved for treatment of chronic plaque psoriasis. Enbrel was approved in 2004 for the "treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy." Remicade was approved 2006 for "the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate."

2.4 Important Issues With Pharmacologically Related Products

HUMIRA is associated with several warnings and precautions currently in the label. These include risk of serious infection with organisms such as TB, invasive fungi, and other opportunistic organisms. Malignancies are seen more often than in controls and lymphoma is seen more often than in the general population. Anaphylaxis or serious allergic reactions may occur. Hepatitis B virus may be reactivated. Exacerbation or new onset demyelinating disease, and heart failure, worsening or new onset may occur. Cytopenias, including pancytopenia, may occur and lupus-like syndrome may occur.

These associations have also been found with the two other TNF-α inhibitors, Remicade and Enbrel. Remicade has been associated with severe hepatic toxicity in postmarketing reports, some of which have been fatal or necessitated liver transplantation. Elevation of transaminases was not present in all cases. All three TNF-α inhibitors have had associated fatalities from infections.

2.5 Presubmission Regulatory Activity

End-of-phase 2 Meeting with CBER – 2/24/04

- Sponsor advised that 2 adequate and well-controlled studies might be sufficient for demonstrating the short-term efficacy of the product.
- Sponsor advised that for a product intended for chronic therapy, rigorous evidence of long-term (at least 1 year) efficacy will be required.
- A more balanced treatment allocation was recommended (2:1 or preferably 1:1)
- The sponsor should evaluate the development of anti-adalimumab antibodies (AAA) in the psoriasis population
- The proportion of patients achieving a PASI 75 response is acceptable as a primary efficacy variable

- The proportion of patients who achieve a rating of "clear" or "nearly clear" by a validated static Physician's Global Assessment scale should be used as the principle secondary efficacy endpoint or it could be used as the primary endpoint.
- Safety data collected on other populations can not be used in lieu of collecting safety data in the psoriasis population.

Pre-BLA Meeting with CDER – 2/21/07

- For demonstrating efficacy, both the PASI 75 (the primary endpoint in the protocol) and success on the Physician's Global Assessment scale (generally recommended by the Division of Dermatology and Dental Products) will be evaluated.
- The 120 day safety update should include data on subjects through approximately 90 days after the submission of the sBLA.
- It was agreed that the data in the safety update will be non-reconciled and non-queried and will not be reviewed by quality assurance. Key tables from the original sBLA safety summary will be updated.
- The sponsor should await future discussion with the Agency on pediatric studies before their initiation and in the submission should describe the status of the JRA studies.
- The sBLA should include an evaluation on AAA formation and its effect on efficacy and safety.

2.6 Other Relevant Background Information

Through June 2006, adalimumab has been approved for treatment of rheumatoid arthritis (RA) in a total of 66 countries. Indication extensions to include treatment of psoriatic arthritis (PsA) and early RA were granted in the European Union (EU) on 01 Aug 2005 and in the United States (US) on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis (AS) was approved in the EU on 01 Jun 2006 and in the US on 28 Jul 2006.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Gupreet Gill-Sangha, the chemistry reviewer, was asked to comment on the fact that in the psoriasis trials, subjects were treated with pre-filled syringes, yet the sponsor seeks approval of the psoriasis indication with the use of the Humira Pen.

The chemistry review explains that the Humira pen is an auto injector unit for single use, is a disposable drug product in which the functional secondary packaging is integrated with the current adalimumab PFS, which is the primary container closure system for the product.

It goes on the state the following, "The concerns DMA has had with other products (e.g. change in product quality due to new primary container/closure) are not applicable here. CDRH provided a consult for 125057 [redacted] and found the pen in compliance with current standards." b(4)

The conclusion is that there are no product quality issues between the pre-filled syringe and the Humira pen. From a CMC perspective, the application may be approved.

3.2 Animal Pharmacology/Toxicology

There were no new nonclinical studies submitted in support of this indication and none had been required. Dr. Carmen Booker, the pharm/tox reviewer had the following conclusion regarding approvability from a pharm/tox perspective:

"Based on evaluation of previous pharmacology and toxicology reviews, the safety of adalimumab is adequately supported. There are no nonclinical safety issues relevant to the clinical use of adalimumab in patients with psoriasis. No objection is offered to approving this licensing application supplement."

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data used in the review of this drug product for the indication of the treatment of moderate to severe psoriasis in patients 18 years of age or older came entirely from the sponsor's BLA submission. This also includes the 120-day safety update submitted to the BLA on 7/20/07.

4.2 Tables of Clinical Studies

Study ID Number of Study Centers Locations	**Study start Enrollment status, date Total enrollment/ Enrollment goal**	**Design Control Type**	**Study & Ctrl Drugs Dose, Route & Regimen**	**#Subjects by arm entered/ completed**	**Duration**	**Gender M/F Median Age (Range)**	**Diagnosis Inclusion Criteria**	**Primary Endpoints**
Placebo-Controlled Studies								
M02-528 18/ USA Canada	11 Mar 2003 Completed, 25 Sep 2003 147[a]/150	Multicenter, randomized, double-blind, PBO-controlled, dose ranging	ADA 40 mg eow SC + PBO oew SC ADA	ADA eow: 45/43 ADA weekly: 50/47	12 weeks	ADA eow:32M/13F 46 (20-71) ADA weekly: 33 M/17 F	Moderate to severe chronic plaque psoriasis (Ps)	Proportion of subjects achieving a ≥ PASI 7[c] response Week 12

			40 mg weekly SC PBO weekly SC	PBO: 52/50		42 (24-86) PBO: 34M/18F 43 (20-70	(BSA ≥ 5%) Inadequate response to topical therapy	
M03-656 81/ USA Canada	13 Dec 2004 Completed 29 Jun 2006 1212/1200	Multicenter, randomized Period A: 16-week, double-blind, PBO-controlled Period Period B: 17-week, open-label Period Period C: 19-week, double-blind, PBO-controlled Period	Period A: ADA 40 mg eow SC PBO eow SC Period B: ADA 40 mg eow SC Period C: ADA 40 mg eow SC PBO eow SC	Period A: ADA: 814/783 PBO: 398/355 Period B: ADA/ADA 580/550 PBO/ADA: 26/23 Period C: ADA/DA/ ADA: 250/227 ADA/ADA/ PBO: 240/184 PBO/ADA/ ADA: 22/18	52 weeks	Period A: ADA: 546 M/268 F 44 (18-79) PBO 257 M/141 F 46 (18-77) Period B: ADA/ADA: 408 M/172 F 44 (18-77) PBO/ADA: 12 M/14 F 47.5 921-70) Period C: ADA/ADA/ ADA: 176 M/74 F 44 (18-77) ADA/ADA /PBO: 179 M/ 61 F 43 (18-77) PBO/ADA/ ADA: 10 M/ 12 F 48 (26-70)	Moderate to severe chronic plaque Ps (BSA ≥ 10%, PASI ≥ 12, PGA of at least moderate disease)	1. Proportion of subjects achieving a ≥ PASI 75 response at Week 16 & Proportion of subjects with a PGA of clear or almost clear 2.Proportion of subjects losing an adequate response after re-randomiza-tion to placebo at Week 33 and on or before Week52
M04-716 28/Europe Canada	12 Jul 2005 Completed, 17 May 2006 271/250	Multicenter, randomized, double-blind, double-dummy, PBO- and active controlled	ADA 40 mg eow SC + PBO weekly PO MTX 7.5[b] weekly PO + PBO eow SC PBO eow SC and weekly PO	ADA: 108/104 MTX: 110/104 PBO: 53/48	16 weeks	ADA 70 M/ 38F 42 (19-81) MTX: 73 M/ 37 F 41 (19-74) PBO: 35M/ 18F 41 (20-70)	Moderate to severe chronic plaque Ps (BSA ≥ 10%, PASI ≥ 10, PGA of at least moderate disease)	Proportion of subjects achieving a ≥ PASI 74 response at Week 16 & proportion of subjects achieving a PGA of clear or almost clear at Week 16
				Other Study				
02-538	19 Jun 2003	Multicenter,	ADA 40 mg	12-Week	76 weeks	ADA	Moderate to	Time to

16/ USA Canada	Completed 10 Mar 2005 148/145	open-label, double-blind, OPBO-controlled 12-Week Open-lable period 12-Week PBO-controlled period 76-Week follow-up[c]	weekly SC ADA 40 mg eow SC PBO eow	Open-label period ADA weekly: 148/136 12-Week PBO-controlled period ADA eow: 68/51 PBO eow: 68/45		weekly/ADA eow: 38 M/30F 43 (18-64) ADA weekly/PBO eow: 45 M/23F 44 (19-69)	severe chronic plaque Ps (BSA ≥ 5%, PASI ≥ 8)	relapse after Week 12 through Week 24 for subjects who achieved a Week 12 ≥ PASI 50 response relative to Week 0 score
M02-529 18/ USA Canada	11 Mar 2003[d] Completed, 17 Jun 2004 137/148	Multicenter, randomized 12-weekdouble-blind period 36 week open-label period	ADA 40 mg eow SC ADA 40 mg weekly SC ADA 40 mg eow SC Subjects with < PASI 50 any time on or after Week 12x could increase dose to weekly	12-Week Double-blind Period ADA eow: 43/42 ADA weekly: 47/44 PBO/ADA: 47/46 36-Week Open-label Period ADA eow: 42/35 ADA weekly: 44/33 PBO/ADA 40 mg eow SC: 46/38	48 weeks	ADA eow: 30M/13F 46 (20-71) ADA weekly: 33 M/14F 42 (24-86) PBO/ADA 40 mg eow SC: 33 M/14F 44 (20-70)	Moderate to severe chronic plaque Ps Completion of lead-in Study M02-528	Proportion of subjects achieving a ≥ PASI 75 response at Wek 12x (i.e., Week 12 of Stu M02-52
M03-596 14/USA Canada	04 Nov 2003 Completed 02 Sept 2004 32/145	Multicenter, randomized open-label, double-blind, PBO-controlled 12-Week Open-label period	ADA 40 mg weekly SC ADA 40 mg eow SC PBO eow	12 Week-Open-label period ADA weekly: 32/24 12-Week PBO-controlled	24 weeks	20 M/12F 51 (19-66) ADA weekly/PBO: 16M/5 F 49 (19-66) ADA weekly/ADA eow:	Moderate to severe chronic plaque Ps Subjects who were randomized in lead-in Study M02-538 and	Proportion of subjects with clinical response, defined as ≥ PASI 50 response relative to Week 0 PASI sco in lead-in

		12-Week PBO-controlled period		period PBO/ADA eow: 24/15		4M/7F 54 (26-64)	relapsed on or before Week 24	Study M02-538, following 12 weeks of re-treatmetn with open-label adalimumab.
M03-658 104/USA Europe Canada	24 May 2004 Ongoing as of 29 Jun 2006 1456/not applicable[e]	Multicenter, open-lable	ADA 40 mg eow S[f,g]	1456/not applicable (1257 subjects are ongoing as of 29 Jun 2006)	2 years	987 M/469 F 44 (18-81)	Moderate to severe chronic plaque Ps Subjects who participated in Studies M02-529 (continuation of M02-528), M02-538, M03-596 (extension study of Study M02-538), M03-656, or M04-716 and remained eligible.	1. Number and proportion of subjects achieving a ≥ PASI 50/75/90 response every 12 weeks. 2. Number and proportion of subjects achieving a PGA of "Clear or Minimal" every 12 weeks.

ADA = adalimumab; F = female; M = male; PBO = placebo.
a. A total of 148 subjects were randomized in Study M02–528; however, one subject (#005–28) randomized to the adalimumab 40 mg eow arm withdrew consent prior to the performance of Baseline procedures. This subject did not receive study medication.
b. Dose escalation of MTX from 7.5 mg up to 25 mg was allowed.
c. A protocol designed gap of 52 weeks (follow–up period) until relapse or Week 76, whichever came first.
d. First enrolled subject screened in the lead–in study, Study M02–528.
e. The sample size of this study was determined by the number of subjects who were eligible based on the inclusion/exclusion criteria of this study and who participated in Studies M02–529, M02–538, M03–596 and the Phase 3 Ps studies (Study M03–656 and Study M04–716) with adalimumab.
f. Dose escalation of adalimumab from 40 mg eow to 40 mg weekly was allowed.
g. In all studies except Study M03–658, an initial dose of 80 mg adalimumab was administered to adalimumab–treated subjects.
Cross Reference: Study M02–528 CSR (R&D/04/001), Study M02–529 CSR (R&D/04/117), Study M02–538 CSR (R&D/04/118), Study M03–596 CSR (R&D/04/900), Study M03–656 CSR (R&D/05/712), Study M03–658 CSR (R&D/04/921), and Study M04–716 CSR (R&D/05/057).
Source: BLA 125057, ISS, table 1, pages 12-18

4.3 Review Strategy

The pivotal trials, M03-656 and M04-716 were reviewed in detail, as these two trials were the bases for efficacy of adalimumab. The phase 2 trial, M02-528 was also reviewed in detail to assure that appropriate dose ranging had been investigated. All other trials, including the aforementioned trials, were included in the safety analysis, as they were open-label long term

trials. The phase 2 trial, in the safety analysis was included with the phase 3 trials, as these were the placebo controlled trials.

The clinical pharmacology portions of the trials were reviewed by the clinical pharmacologist, Dr. Tien Mien Chen. Efficacy was verified by the biostatistician, Dr. Clara Kim. Their analyses have been incorporated into this review.

Consults were also obtained from the following:

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- SEALD team – [redacted]
- DDRE – On the phase 4 registry protocol & a comparison of the 6 deaths in the adalimumab trials as compared to SMR data in the United States
- OSE – Update on postmarketing safety of HUMIRA
- DDMAC – Label and Medication Guide
- DSRCS (OSE) – Label and Medication Guide
- DSI

4.4 Data Quality and Integrity

DSI was asked to inspect two sites in the pivotal phase 3 trial, M03-656. One site was in [redacted]

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The DSI consult states that inspection of these 2 sites did not identify any regulatory violations. It further stated that overall the data appeared acceptable in support of the respective indication. These conclusions were based on preliminary communications from the field investigators. An addendum will only be generated if conclusions change significantly upon receipt and review of the final EIR.

4.5 Compliance with Good Clinical Practices

At the sites in the United States, the trials were conducted in compliance with the institutional review board regulations in 21 CRF 56. Informed consent was obtained at sites participating in the trials in accordance with 21 CRF 50.

At the sites outside of the United States, the trials were conducted in conformance with the "Declaration of Helsinki" and ICH guidelines for GCP. Informed consent was obtained in accordance with the "Declaration of Helsinki" and ICH guidelines for GCP.

4.6 Financial Disclosures

[redacted] has an equity interest in Abbott common stock of $168,000. [redacted] b(4) b(6)

[redacted] The award was valued at 25,000 Euro. [redacted] b(4) b(6)

The sponsor proposes that the chances of investigator bias in affecting the outcome of the study would be extremely rare, as each site was blinded to the treatment for each subject.

Reviewer's Comment: *In the review of these trials, there was nothing unusual in the efficacy results that warranted a DSI audit.*

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following are excerpts from the biopharmaceutics review by Dr. Tien Mien Chen. It summarizes the pharmacokinetics of adalimumab in the psoriasis population studied in the phase 2 dose ranging study, M02-528 and in the phase 3 trial, M03-656. See biopharmaceutics review for complete details.

For Study M02-528, the mean steady-state adalimumab trough concentrations during 40 mg EOW dosing for 12 weeks was about 6.0 to 7.0 µg/mL (Regimen A) and was about 17.0 to 18.0 µg/mL during 40 mg weekly dosing for 12 weeks (Regimen B). Regimen A was therefore, selected for further clinical development since Regimen A reached similar clinical response rate as Regimen B at a followed-up assessment at Week 24 (an extension study).

For Study M03-656, the mean steady-state serum adalimumab concentrations during 40 mg EOW dosing (up to 52 weeks) were between 5.2 and 6.2 µg/mL. It was within the range of those observed in patients with RA (5 µg/mL), AS (6 to 7 µg/mL), and PsA (6 to 10 µg/mL) during treatment with SC adalimumab 40 mg EOW as monotherapy. PPK results also showed that the mean CL/F and Vd/F of adalimumab in CPP patient population were consistent with those obtained for previous indications.

No significant factors of gender, age, race on the PK of adalimumab were noted from the PPK analyses.

5.2 Pharmacodynamics

No specific pharmacodynamic observations were made on the psoriasis population. Given that the pk in the psoriasis population is similar to the rheumatoid arthritis population, the pharmacodynamics is also most probably similar to that population, as labeled.

5.3 Exposure-Response Relationships

Dr. Tien Mien Chen found in his review the following:

With Study M02-528 and M03-656 combined, the overall rate of anti-adalimumab antibody (AAA) formation in patients with psoriasis (8.4%; 77/920) appears to be in the range of those observed in patients with RA (12%; 54/434), AS (8.6%; 16/185), and PsA (13.5%; 24/178) during adalimumab 40 mg EOW monotherapy. However, they were all higher than that (2.6%; 7/269) observed in patients with CD.

For psoriasis, the development of AAA was associated with significantly reduced adalimumab exposure (i.e., increased clearance of adalimumab) which was also consistent with what was observed in other indications.

Results obtained from Study M03-656 showed that patients who achieved a PASI75 (75% reduction in psoriasis area and severity index) response at Week 16 had mean steady-state concentrations of adalimumab (6.28 μg/mL) almost three fold higher than those in patients who did not achieve PASI75 response (2.24 μg/mL). Further analysis showed that 1) AAA+ patients had a statistically significantly lower PASI75 response rate than AAA– patients at Week 16 (11% vs. 76%; $p < 0.001$) and 2) the 'event' (i.e., loss of adequate response) rate was significantly higher in AAA+ patients than that in AAA- patients (p=0.034; 18% vs. 4%) at Week 52. Consistent results were also obtained from Study M02-528 that all 3 patients tested with AAA+ had lower serum trough adalimumab levels starting Week 8 and none of those AAA+ patients achieved a PASI75 response (n=45 in 40 mg EOW maintenance dosing group).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

HUMIRA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Reviewer's Comment: *This is the sponsor's proposed indication. It may be modified based on the analysis of the safety data in the population studied and the overall safety profile of HUMIRA across all indications.*

6.1.1 Methods

The two pivotal phase 3 trials, M03-656 and M04-716 were reviewed along with the clinical summary of efficacy to support the proposed indication of the sponsor. The phase 2 trial, M02-528 was reviewed to support that adequate dose-ranging had been performed to select the dose, duration, and frequency with the most favorable risk/benefit ratio. These trials were double-bind, placebo controlled, and multicentered. See section 4.1.

6.1.2 General Discussion of Endpoints

There are two primary endpoints, named co-primary endpoints, in the pivotal trials that determined the success of adalimumab in the treatment of moderate to severe psoriasis: the proportion of subjects with a ≥75% reduction in PASI (PASI 75) at week 16 and the proportion of subjects achieving a Physician's Global Assessment (PGA) score of "clear" or "minimal" at week 16 (see PreSubmission Regulatory Activity, Section 2.5).

PASI is an acronym for Psoriasis Area Severity Index and is a scoring system that is calculated based upon the severity of signs of psoriasis for various anatomical locations and an estimated body surface area as described below:

Four anatomic sites - head, upper extremities, trunk, and lower extremities - are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The below table outlines the characteristics of each category.

	Erythema[a]	Desquamation	Induration
0=none	No redness	No scaling	No elevation over normal skin
1=slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2=moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3=marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4=very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10 to <30%
- 3 = 30 to <50%
- 4 = 50 to <70%
- 5 = 70 to <90%
- 6 = 90 to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area,respectively, the PASI score is calculated using the formula

$$PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$$

where *E*, *I*, *D*, and A denote erythema, induration, desquamation, and area, respectively, and *h*, *u*, *t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores

range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

The Physician's Global Assessment score was based on the following scale:

Score	Category	Category Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = ±(hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate definite elevation with rough or sloped edges) Scaling = coarser (coarser scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard or sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most or all of the lesions; rough surface) Erythema = very severe (extreme red coloration, dusky to deep red coloration)

Reviewer's Comment: *This PGA severity scale was accepted by another division. This reviewer would not have accepted a definition of erythema for mild and minimal disease as denoted in the scale above. Most patients, however, who would meet the other parameters for these categories, are not likely to have persistent erythema of "red coloration."*

Study M03-656, Period C included an additional primary efficacy endpoint, the proportion of subjects who experienced "a loss of adequate response (i.e. achieving an event)" after Week 33 and on or before Week 52. An event was defined as a PASI score after Week 33 that results in a less than 50% reduction relative to the Week 0 PASI score (< PASI 50 response) or a 6 point increase in PASI score relative to the Week 33 PASI score, whichever is more stringent (*i.e.* the higher PASI score of the two).

Reviewer's Comment: *Since the sponsor was charged with demonstrating long term efficacy of adalimumab, after discussion with the statistician, it was decided that "loss of adequate response" would be evaluated differently. A subject who did not maintain a response of a PASI 75 reduction or a PGA score of "clear" or "minimal", would be considered as having experienced a loss of adequate response. Conversely, since period C was a double-blind placebo controlled phase of the trial, we would also evaluate the proportion of subjects who maintained a ≥ PASI 75 reduction and a PGA score of "clear" or "minimal" at week 52.*

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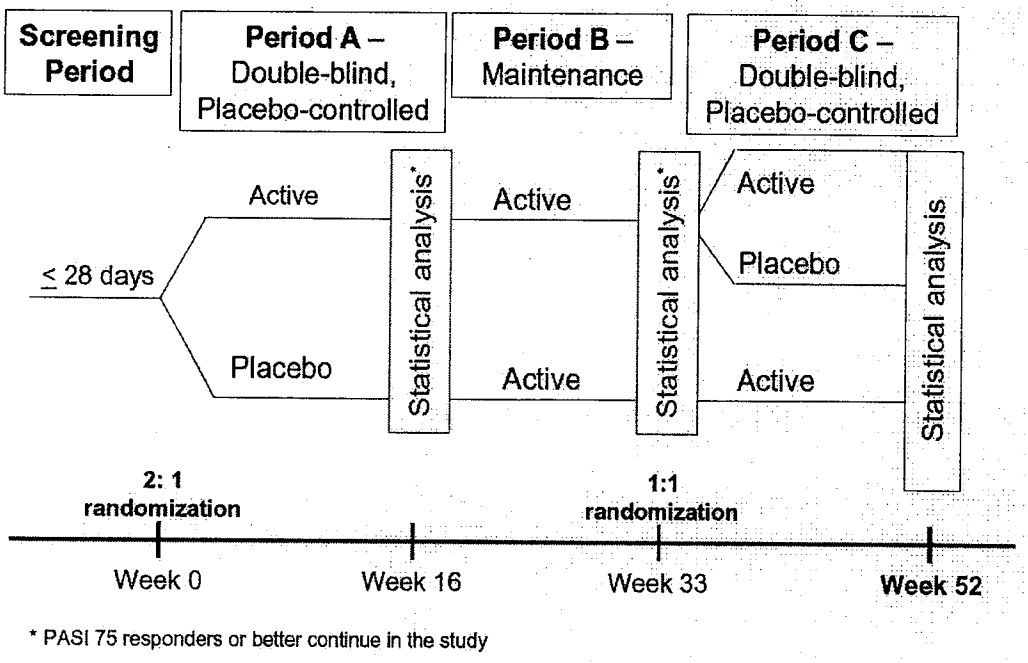
6.1.3 Study Design

Figure 1 shows the study design for pivotal study M03-656:

Figure 1



This trial consisted of 3 phases or study periods, Period A, which is 16 weeks in duration, Period B, which is 17 weeks in duration, and Period C, which is 19 weeks in duration. Subjects with moderate to severe chronic plaque psoriasis (defined at the baseline visit by ≥ 10% BSA involvement, a PASI score of ≥ 12, and a PGA of at least moderate disease) were randomized 2:1 in Period A to receive adalimumab or placebo, respectively. Subjects received 80 mg of adalimumab SC at week 0, followed by 40 mg eow beginning at week 1 until week 16. Those subjects from both arms that achieved a ≥ PASI 75 response then entered Period B and received adalimumab 40 mg eow until week 33. Subjects who maintained a ≥ PASI 75 response and who were on adalimumab in Period A, were re-randomized 1:1 into Period C, where the subject either

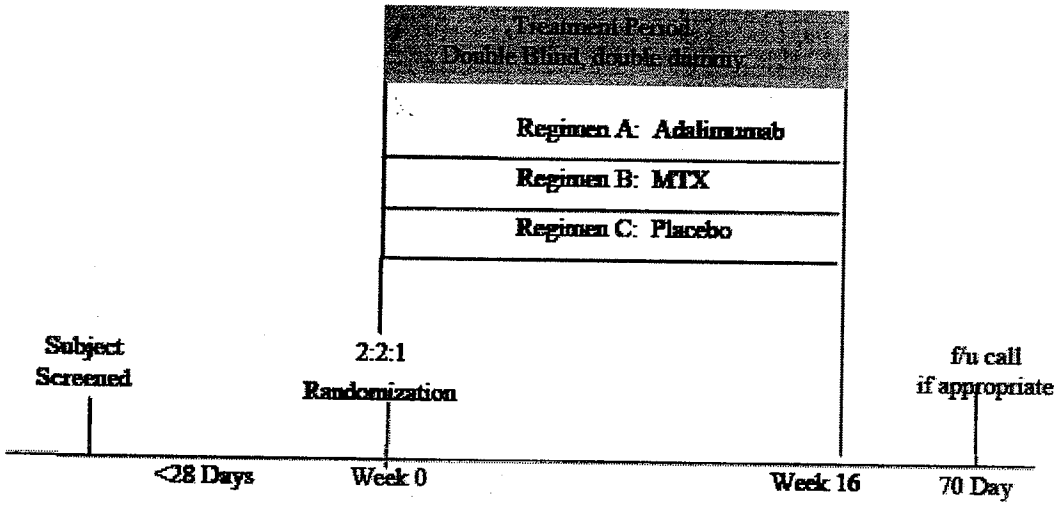
received adalimumab 40 mg eow SC or placebo until time to an "event" (loss of adequate response) or until week 52.

Period A was designed to evaluate the short-term efficacy and safety of adalimumab. Clinical evaluations were performed at Weeks 4, 8, 12 and 16. Period C was designed to evaluate the long term efficacy of adalimumab in subjects who initially responded to adalimumab in Period A and were able to maintain the response in Period B. In Period C, clinical evaluations were done at weeks 33, 36, 40, 44, 48, and 52.

Figure 2 describes the study design for pivotal trial M04-716:

Figure 2

Best Possible Copy



Cross Reference: Module 5, Study M04-716 CSR

This trial is a multicenter, double-blind, double-dummy trial of 16 weeks duration. Subjects with moderate to severe chronic plaque psoriasis (defined at the baseline visit by ≥ 10% BSA involvement and a PASI score of ≥ 10), were randomized 2:2:1 to receive either adalimumab, methotrexate (MTX), or placebo, respectively. The trial was designed to show superiority of adalimumab to placebo for clinical efficacy and non-inferiority to MTX. ⊏ ⊐ b(4)
⊏ ⊐ Clinical evaluations were performed at weeks 1, 2, 4, 8, 12, and 16.

6.1.4 Efficacy Findings

In trial M03-656, 1212 subjects were randomized to receive either adalimumab or placebo in a 2:1 ratio over a 16 week period. Thus, 814 subjects received adalimumab and 398 subjects received placebo. In trial M04-716, 161 subjects were randomized to receive either adalimumab or placebo in a 2:1 ratio over a 16 week period. Table 1 describes the baseline severity of disease for the subjects in the 2 trials.

Table 1
Baseline Severity of Disease
Trials M03-656 and M04-716

	Study M03-656		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108†	Placebo n=53
PGA				
Moderate	417 (51.2%)	220 (55.3%)	52 (48.6%)	20 (37.7%)
Severe	346 (42.5%)	155 (38.9%)	46 (43.0%)	31 (58.5%)
Very Severe	51 (6.2%)	23 (5.8%)	10 (9.3%)	2 (3.8%)
PASI				
Mean (std)	19.0 (7.1)	18.8 (7.1)	20.6 (7.5)	19.2 (6.9)
Median	16.8	16.5	18.7	18.2
Min, Max	(10.8,56.9)	(12.0,55.5)	(10.4,52.9)	(6.5,38.1)
%BSA				
Mean (std)	25.8 (15.5)	25.6 (14.8)	33.7 (19.9)	28.4 (16.1)
Median	20.0	21.0	28.3	25.0
Min, Max	(10.0,92.0)	(10.0,87.7)	(10.0,90.0)	(10.0,90.0)

†Subject ID 16530 withdrew because of a late positive purified protein derivative (PPD) result after randomization, but prior to administration of drug. Therefore, baseline information was not provided for this subject.
‡Subject ID #15601's baseline %BSA was not provided. Therefore, the baseline %BSA calculations for adalimumab were based on n=106 subjects.
Source: M03-656 Clinical Study report, page 239, M04-716 Clinical Study Report, page 140, and statistical review, table 5, page 12.

Reviewer's Comment: *The above baseline severity table includes 14 subjects in trial M04-716 who were enrolled with a baseline PASI score between 10 and 11. These subjects were excluded from the Division's analysis, as for subjects with moderate disease, the PASI score should be greater than or equal to 12, as in pivotal trial M03-656. Table 1a shows the baseline severity of subjects in trial M04-716 whose baseline PASI was ≥ 12.*

Table 1a
Baseline Severity by Treatment Arm
PASI ≥ 12 – Trial M04-716

	Study M04-716	
	Adalimumab n=99‡	Placebo n=48
PGA		
Moderate	43 (43.4%)	17 (35.4%)
Severe	46 (43.0%)	29 (60.4%)
Very Severe	10 (10.1%)	2 (4.2%)
PASI		
Mean (std)	21.4 (7.8)	20.1 (6.5)
Median	20.6	18.6
Min, Max	(12.0,52.9)	(12.3,38.1)
%BSA		
Mean (std)	35.6 (19.8)	30.0 (16.1)
Median	30.6	28.0
Min, Max	(10.4,90.0)	(10.0,90.0)

‡Subject ID #15601 and 16530's baseline %BSA was not provided. Therefore, the Baseline %BSA calculations for adalimumab were based on n=97 subjects
Source: Statistical review, Addendum

Reviewer's Comment: *Baseline severity in the two pivotal trials is fairly evenly distributed between subjects with moderate and severe chronic plaque psoriasis, with almost half of the subjects having at least severe psoriasis (48.7%) in M03-656 (table 1) and more than half having at least severe psoriasis (53.1%) in trial M04-716 (table 1a). Thus, no one level of severity will drive the efficacy results of the trial.*

Efficacy Outcome

As stated before, the parameters that the two co-primary efficacy variables had to achieve for a success of efficacy of adalimumab to treat moderate to severe chronic plaque psoriasis were ≥ PASI 75 response rate and a PGA score of "clear" or "minimum" disease at week 16.

Intent-to-treat (ITT) Analysis

In trial M03-656, for the efficacy variable ≥ PASI 75 response rate, 578/814 (71.0%) on adalimumab vs. 26/398 (6.5%) achieved this response rate ($p<0.001$). For a PGA of clear or minimum, 506/814 (62.2%) patients on adalimumab vs. 17/398 (4.3%) were a success ($p<0.001$). In trial M04-716, for ≥ PASI 75 response rate, 86/108 (79.6%) vs. 10/53 (18.9%) achieved this response ($p<0.001$). For a PGA of clear or minimum the success was 79/108 (73.1%) vs. 6/53 (11.3%) with a $p<0.001$. Table 2 shows the efficacy results for both trials.

Table 2
Pivotal Studies Primary Efficacy Results
Number (%) of Successes on PASI 75 and PGA
At Week 16 (ITT Population)

	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI75				
Number of successes (%)	578 (71.1%)	26 (6.5%)	86 (79.6%)	10 (18.9%)
p-value		<0.0001†		<0.0001‡
PGA				
Number of successes (%)	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (11.3%)
p-value		<0.0001†		<0.0001‡

†P-value is calculated using CMH test, stratified by pooled sites
‡P-value is calculated using CMH test, stratified by country
Source: Statistical review, table 6, page 13

Reviewer's Comment: *The above results include the sponsor's analysis of 14 subjects in trial M04-716 who are not considered to have at least moderate disease by the Division, for their PASI was <12. Table 2a presents the efficacy results of trial M04-716 in all subjects whose baseline PASI was ≥ 12.*

Table 2a
Number (%) of Successes on PASI75
And PGA score at Week 16 (Baseline PASI ≥ 12)
Trial M04-716

	Study M04-716	
	Adalimumab n=99	Placebo n=48
PASI75		
Number of successes (%)	77 (77.8%)	9 (18.8%)
p-value		<0.0001†
PGA		
Number of successes (%)	70 (70.7%)	5 (10.4%)
p-value		<0.0001†

†P-value is calculated using CMH test, stratified by country
All missing values were imputed as failures
Source: Statistical review, Addendum

Reviewer's Comment: *These are highly statistically significant results for both trials and demonstrate clearly adalimumab's ability to treat moderate to severe chronic plaque psoriasis.*

Subgroup Analysis – Severe Population

A primary analysis was conducted in subjects with at least a baseline severity of severe disease. Table 3 presents the results in this population. The results are similar to that of the ITT population in both pivotal trials for both co-primary efficacy variables.

Table 3
Primary Efficacy Results
Number (%) of Successes on PASI75 and PGA Score at Week 16
Severe Population

	Study M03-656a		Study M04-716	
	Adalimumab n=397	Placebo n=178	Adalimumab n=56	Placebo n=33
PASI75				
Number of successes (%)	282 (71.0%)	9 (5.1%)	45 (80.4%)	6 (18.2%)
p-value		<0.0001†		<0.0001†
PGA				
Number of successes (%)	238 (59.9%)	3 (1.7%)	38 (67.9%)	3 (9.1%)
p-value		<0.0001†		<0.0001†

†P-value is calculated using Pearson Chi-Square test.
Source: Biostatistical review, table 22, page 36

Long-term Efficacy

The sponsor was advised at the EOP2 meeting with the Agency that for a drug intended for chronic therapy, "rigorous evidence of long-term (at least 1 year) efficacy will be required". Periods B and C in trial M03-656 look at the long-term efficacy of adalimumab up to 52 weeks. Patients who attained a ≥ PASI 75 response from period A were entered into Period B at week 16 and continued to receive 40 mg eow of adalimumab up to week 33. Only 26 of the 606 patients who entered this period had been on placebo. Period C is a double-blind placebo-controlled treatment period in which subjects who maintained a ≥ PASI 75 response at week 33 and were originally randomized to active therapy in Period A were re-randomized (1:1) to receive adalimumab or placebo. Thus, 490 subjects entered Period C.

The sponsor investigated in Period C the proportion of subjects losing an adequate response after week 33 and on or before week 52. Again, loss of adequate response was defined as a PASI score after week 33 that results in a less than 50% reduction relative to the week 0 PASI score (<

PASI 50 response) or a 6 point increase in PASI score relative to the week 33 PASI score, whichever is more stringent. In the placebo group, 68/240 (28.4%) of subjects lost an adequate response compared to 12/250 (4.9%) of subjects in the adalimumab arm ($p<0.001$).

In this review, as stated earlier, this reviewer and the biostatistician, Dr. Clara Kim, defined and evaluated loss of adequate response using the following definitions: subjects who did not maintain a ≥PASI 75 response, subjects who did not maintain a PGA score of "clear" or "minimal" and subjects who did not maintain either a ≥PASI 75 response or a PGA score of "clear" or "minimum". Since Period C was to investigate long term efficacy of adalimumab, it is more important that the efficacy variables mirror those of Period A. Table 4 presents the analyses of loss of adequate response based on the Division's definitions.

Table 4
Number (%) of Subjects with Loss of Efficacy
Based on PASI 75 and PGA Score
M03-656 – Period C (ITT Population)

	Adalimumab n=250	Placebo n=240
PASI75		
Number of loss of efficacy (%)	52 (20.8%)	138 (57.5%)
p-value		<0.0001†
PGA		
Number of loss of efficacy (%)	80 (32.0%)	173 (72.1%)
p-value		<0.0001†
PASI75 & PGA‡		
Number of loss of efficacy (%)	82 (32.8%)	178 (74.2%)
p-value		<0.0001†

†P-value is calculated using CMH test, stratified by pooled sites.
‡Loss of efficacy was defined s subjects who did not maintain a PASI 75 response or did not maintain a PGA score of clear or minima (composite).
Source: Statistical review, table 7, page 14.

Reviewer's Comment: *The analysis in table 5 is more stringent than the sponsor's analysis and is more reflective of the efficacy of adalimumab that was demonstrated in the short-term, Period A, portion of the trial (see table 2). One would expect that a large percentage of subjects would not maintain efficacy, as defined in Period A, when taken off adalimumab here in Period C. More importantly, the analysis demonstrates that adalimumab does maintain its efficacy in the long-term (over 52 weeks). This does not drop off over time, as in this analysis at 52 weeks, 68.0% of subjects were able to maintain a success with a PGA of clear or almost clear, which*

falls between the success in Period A of this trial of 62.2% and trial M04-716 where the success for PGA was 72.2% after 16 weeks of treatment. PASI 75 success was somewhat higher in all analyses. These results were all highly statistically significant. In this analysis, 28% of subjects, after 33 weeks of adalimumab, were able to maintain efficacy (clear or minimal disease) off adalimumab for at least 19 weeks. This suggests that there could be periods where these patients would not need continued treatment. Thus, two deductions can be made from this analysis: adalimumab can maintain its efficacy over a period of a year and some subjects can maintain efficacy after initial response off adalimumab.

Subgroup Analysis for Severe Population

Table 5 presents the results of "loss of adequate response" based on the PGA score in subjects who had a baseline severity of psoriasis that was severe or very severe. The results are similar to the results from the ITT population. Again, 72.7% of subjects with at least severe disease on adalimumab were able to maintain a success for efficacy at 52 weeks of treatment compared to only 22.9% on placebo. This is highly statistically significant.

Table 5
Severe/Very Severe Population
Number (%) of Subjects with Loss Of
Adequate Response Based on PGA Score (M03-656c)

	Adalimumab n=121	Placebo n=118
PGA		
Number of loss of efficacy (%)	33 (27.3%)	91 (77.1%)
p-value		<0.0001†

†P-value is calculated using Pearson Chi-Square test.
Source: Biostatistical review, table 23, page 36.

Per Protocol Analysis

The per protocol (PP) population included all subjects in the ITT population who did not have major protocol violations. One of the major criteria was that a subject had to have at least 75% compliance with study treatment (i.e. at least 75% compliance with SC injections). A total of 60 (4.4%) subjects were excluded from the PP population in the short term efficacy trials: 37 (4.0%) subjects from the adalimumab arm and 23 (5.1%) subjects from the placebo arm. The efficacy results of the PP population for the short term efficacy is presented in table 6. The results are similar to the ITT population.

Table 6
Primary Efficacy Results – Number (%)
Of Successes Based on PASI75 and PGA
At Week 16 – PP Population

	Study M03-656a		Study M04-716	
	Adalimumab n=792	Placebo n=380	Adalimumab n=93	Placebo n=48
PASI75				
Number of successes (%)	570 (72.0%)	24 (6.3%)	75 (80.1%)	9 (18.8%)
p-value		<0.0001†		<0.0001‡
PGA				
Number of successes (%)	497 (62.8%)	16 (4.2%)	68 (73.1%)	5 (10.4%)
p-value		<0.0001†		<0.0001‡

†P-value is calculated using CMH test, stratified by pooled sites.
‡P-value is calculated using CMH test, stratified by country
Source: Statistical review, table 9, page 16.

Table 7 presents the data results for the PP population for Period C of trial M03-656, the long term efficacy of adalimumab (at 52 week). The results are similar to the ITT population.

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Table 7
Number of Subjects with Loss of Efficacy
Based on PASI 75 and PGA Score
PP population – Period C M03-656

	Adalimumab n=236	Placebo n=225
PASI75		
Number of loss of efficacy (%)	42 (17.8%)	127 (56.4%)
p-value		<0.0001†
PGA		
Number of loss of efficacy (%)	69 (29.3%)	162 (72.0%)
p-value		<0.0001†
PASI75 & PGA‡		
Number of loss of efficacy (%)	71 (30.1%)	166 (73.8%)
p-value		<0.0001†

†P-value is calculated using CMH test, stratified by pooled sites.
‡Loss of efficacy was defined as subjects who did not maintain a PASI75 response or did not maintain PGA score of clear or minimum (composite)
Source: Statistical review, table 10, page 17.

PGA and PASI Response over Time

Table 8 presents the subject response rate over time for the co-primary efficacy variables. Subjects were evaluated at weeks 4, 8, 12, and 16. The table shows that at week 8, approximately half the subjects were a success for PGA in both short-term trials and more than half were a success for PASI 75 at week 8.

Table 8
Number of Subjects (%) Achieving Success
In PGA and PASI 75 at Weeks of Visits

		Study M03-656a		Study M04-716	
		Adalimumab	Placebo	Adalimumab	Placebo
Endpoint	Week	n=814	n=398	n=108	n=53
PGA	4	139 (17.1%)	5 (1.3%)	17 (15.7%)	1 (1.9%)
	8	389 (47.8%)	9 (2.3%)	52 (48.1%)	5 (9.4%)
	12	490 (60.2%)	15 (3.8%)	72 (66.7%)	5 (9.4%)
	16	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (1.3%)
PASI 75	4	154 (18.9%)	5 (1.3%)	25 (23.1%)	2 (3.8%)
	8	440 (54.1%)	12 (3.0%)	67 (62.0%)	7 (13.2%)
	12	551 (67.7%)	19 (4.8%)	83 (76.9%)	8 (15.1%)
	16	578 (71.0%)	26 (6.5%)	86 (79.6%)	10 (19.9%)

Source: Biostatistical review, table 12, page 21.

Subjects in Period C of trial M03-656 were evaluated at weeks 33 (start of Period C), 36, 40, 44, 48, and 52. It should be noted that the criterion for entry in to Period C was that of maintenance of a ≥ PASI 75 response at the end of Period B (the open-label period). It did not take into account the second co-primary, the maintenance of a PGA of clear or minimal. Thus, approximately 18% and 12% of subjects from the adalimumab and placebo arms, respectively were considered to have experienced a loss of adequate response based on the PGA score at the beginning of Period C (week 33). Figure 3 and table 7, from Dr. Clara Kim's review, shows the loss of adequate response over time. The rise in loss of efficacy is much steeper for placebo than for adalimumab subjects.

Figure 3
Loss of Adequate Response Over Time
Period C – M03-656

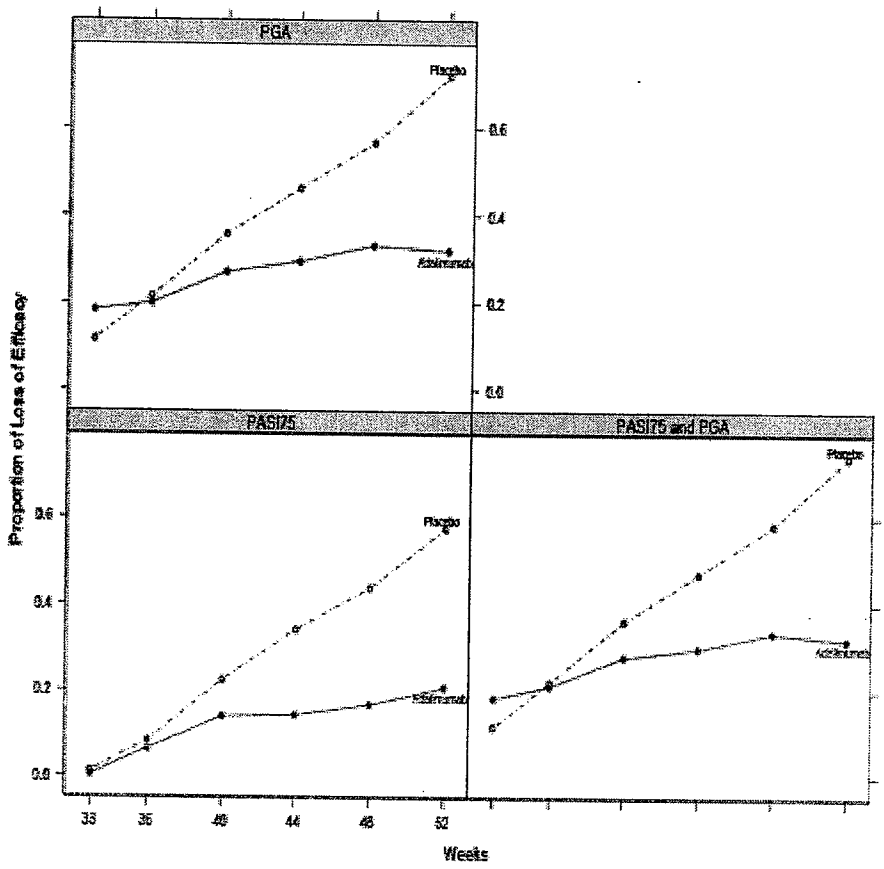

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Table 9
Loss of Adequate Response Over Time
Period C – M03-656

Endpoint	Week	Adalimumab n=250	Placebo n=240
PASI75	33	1 (0%)	3 (1.3%)
	36	16 (6.4%)	20 (8.3%)
	40	35 (14.0%)	54 (22.5%)
	44	36 (14.4%)	82 (34.2%)
	48	42 (16.8%)	105 (43.8%)
	52	52 (20.8%)	138 (57.5%)
PGA	33	46 (18.4%)	28 (11.7%)
	36	50 (20.0%)	52 (21.7%)
	40	68 (27.2%)	86 (35.8%)
	44	74 (29.6%)	111 (46.3%)
	48	83 (33.2%)	136 (56.7%)
	52	80 (32.0%)	173 (72.1%)
PASI75 & PGA†	33	46 (18.4%)	28 (11.7%)
	36	53 (21.2%)	53 (22.1%)
	40	70 (28.0%)	87 (36.3%)
	44	75 (30.0%)	113 (47.1%)
	48	84 (33.6%)	140 (58.3%)
	52	82 (32.8%)	178 (74.2%)

†Loss of adequate response was defined as subjects who did not maintain a PASI 75 response or did not maintain a PGA score of clear or minimal (composite)
Source: Statistical review, table 21, page 34.

Rebound Flare

There were no instances of rebound flare, defined as a PASI ≥ 125% of the baseline value 3 months after the last dose of adalimumab, in the placebo controlled trials. There were no cases of transformation to more serious forms of psoriasis such as erythrodermic or pustular psoriasis.

Subgroup Analyses

Subgroup analyses were performed in the efficacy analysis for success based on gender, race and age in the ITT population. The success rates were consistent across all categories for both PASI 75 and PGA score. The success rates were higher in the adalimumab arm than in the vehicle arm with the exception of the Asian group in study M04-716. However, with only 5 subjects in this group, meaningful conclusions regarding efficacy cannot be ascertained, as also the trials were not powered to draw statistical conclusions about subgroups (see table 10).

Table 10
Number (%) of Successes in PASI 75
And PGA score by Gender, Age, and Race
Pivotal Studies

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		Study M03-656a		Study M04-716	
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
Gender					
	Total	546	257	70	35
Male	PASI75	404 (74.0%)	13 (5.1%)	56 (80.0%)	6 (17.1%)
	PGA	346 (63.4%)	6 (2.3%)	49 (70.0%)	31 (11.4%)
	Total	268	141	38	18
Female	PASI75	174 (64.9%)	13 (9.2%)	30 (78.9%)	4 (22.2%)
	PGA	160 (59.7%)	11 (7.8%)	29 (76.3%)	2 (11.1%)
Age (in years)					
	Total	305	137	49	24
- 39	PASI75	225 (73.8%)	8 (5.8%)	38 (77.6%)	7 (29.2%)
	PGA	197 (64.6%)	8 (5.8%)	33 (67.3%)	5 (20.8%)
	Total	462	237	53	28
40 - 64	PASI75	323 (69.9%)	17 (7.2%)	42 (79.2%)	2 (7.1%)
	PGA	285 (61.7%)	8 (3.4%)	39 (73.6%)	0 (0%)
	Total	47	24	6	1
64 -	PASI75	30 (63.8%)	1 (4.2%)	6 (100%)	1 (100%)
	PGA	24 (51.1%)	1 (4.2%)	6 (100%)	1 (100%)
Race					
	Total	3	1	0	1
American Indian †	PASI75	1 (33.3%)	0 (0%)		1 (100%)
	PGA	1 (33.3%)	0 (0%)		1 (100%)
	Total	21	7	3	2
Asian	PASI75	17 (81.0%)	2 (28.6%)	2 (66.7%)	1 (50.0%)
	PGA	12 (57.4%)	2 (28.6%)	1 (33.3%)	2 (100%)
	Total	28	20	2	1
Black	PASI75	15 (53.6%)	1 (5.0%)	2 (100%)	0 (0%)
	PGA	14 (50.0%)	2 (10.0%)	2 (100%)	0 (0%)
	Total	742	359	103	49
White	PASI75	533 (71.8%)	22 (6.1%)	82 (79.6%)	8 (16.3%)
	PGA	471 (63.5%)	11 (3.1%)	75 (72.8%)	3 (6.1%)
	Total	20	11	0	0
Other	PASI75	12 (30.0%)	1 (9.1%)		
	PGA	8 (40.0%)	2 (18.2%)		

† Also includes Alaska Natives
Source: Statistical Review: table 15, page 28

The subgroup analysis for "loss of adequate response" by gender, race, and age is also similar to the primary analysis. Those on placebo loss efficacy at a much higher rate than those who remained on adalimumab (see table 11).

Table 11
Loss of Adequate Response (Number (%) of Successes)
By Gender, Race, and Age – Study M03-656 –Period C

			Study M03-656c	
			adalimumab n=250	Placebo n=240
Gender	Male	Total	176	179
		Loss of response (%)	47 (26.7%)	133 (74.3%)
	Female	Total	74	61
		Loss of response (%)	35 (47.3%)	45 (73.8%)
Age (in years)	<40	Total	93	95
		Loss of response (%)	34 (36.6%)	72 (75.8%)
	40≤ ≤64	Total	142	134
		Loss of response (%)	44 (31.0%)	100 (74.6%)
	≥64	Total	15	11
		Loss of response (%)	4 (26.7%)	6 (54.5%)
Race	American Indian/ Alaska Native	Total	0	2
		Loss of response (%)	0 (0%)	2 (100%)
	Asian	Total	7	8
		Loss of response (%)	1 (14.3%)	5 (62.5%)
	Black	Total	6	5
		Loss of response (%)	2 (33.3%)	2 (40.0%)
	White	Total	234	222
		Loss of response (%)	79 (33.8%)	167 (75.2%)
	Other	Total	3	3
		Loss of response (%)	0 (0%)	2 (66.7%)

6.1.6 Efficacy Conclusions

The two pivotal trials in this BLA demonstrated that HUMIRA® (adalimumab) is efficacious in the treatment of moderate to severe plaque psoriasis. The data demonstrate that by 16 weeks, in trials M03-656a and M04-716, 62.2% and 70.7% of subjects, respectively, have clearing or almost clearing of their disease. This was highly statistically significant, with a p value less than

0.0001. This efficacy was maintained even in a subgroup analysis of subjects with at least severe disease. This is not unexpected, as subjects with at least severe disease at baseline represented 48.7% of subjects in trial M03-656a and 53.1% in trial M04-716. Long term efficacy was also demonstrated, as only 32.0% of subjects re-randomized to adalimumab compared to 72.1% re-randomized to placebo had a loss of efficacy (adequate response) at 52 weeks ($p<0.0001$). Conversely, 68% vs. 28% of subjects were able to maintain efficacy at 52 weeks. The fact that 28% of subjects re-randomized to placebo, after 33 weeks of treatment with adalimumab, were able to maintain efficacy, has implications for drug free periods until a subject has a relapse. There was no clinically significant difference in the response rate for gender, race, or age. There were no instances of rebound flare or transformation to more life-threatening forms of psoriasis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were 6 deaths in the psoriasis development program for adalimumab. The sponsor reported all of the deaths to the BBIND (BBIND 10811) but only reported 3 initially to the BLA, as only 3 deaths were "treatment emergent" deaths. Treatment emergent adverse events were defined as those adverse events that occurred within 70 days after the last dose of adalimumab. For clarity, the description of these deaths will be divided into those that were "treatment emergent" and those that were "non-treatment emergent", meaning they occurred greater than 70 days after the last dose of adalimumab. There were no deaths in the placebo controlled portions of the trials. However, all of the deaths occurred in patients that were treated with adalimumab.

Treatment emergent deaths

AgeSex SAE report Number Subject number (study) Site	**Day of AE onset** (after 1st dose of Study medication) Length of time (days) on drug (including dosage) or placebo prior to onset of symptoms	**Disease (s) associated with death**	**Cause of death**
45M 03P-028-0243045-0023225 (M02-058, M02-529 Canada	**201 days** (2 days after last treatment) Received adalimumab weekly for 199 days	Migraine, headache, obesity (5'8", 144kg), ex-smoker with 23 year history of cigarette smoking (2 pack/day), HTN	Cerebrovascular accident (Left carotid artery thrombus)
49M 06P-028-0335279-00 Canada	**435 days** (63 days after last treatment) Received adalimumab 40 mg eow for 231 days, followed by placebo for 140 days, followed by 1 injection of adalimumab 40 mg	Depression; on multiple anti-depressant medications at time of entry into study; hx of major depression since 2004.	Suicide
43M 03P-02-0233494-00 2007	**132 days** (25 days after last dose) Received adalimumab 40 mg qweek for 107 days	Symptoms started < 3 months after start of study drug. Progressive weight loss, pyrosis (non-cardiac chest pain), nausea, vomiting. Hx of PUD - 1993	Gastric cancer
Source: \\cbsap58\M\EDR Submissions\2007 BLA\DC600004544\roadmap.pdf section 8 & BBIND 108111 SN152			

Non-treatment emergent deaths

AgeSex SAE report Number Subject number (study) Site	**Day of AE onset** (after 1st dose of Study medication) Length of time (days) on drug (including dosage) or placebo prior to onset of symptoms	**Disease (s) associated with death**	**Cause of death**
68M 06P-028-0353160-00 2855 (M03-0656, M03-658 Canada	**608 days** (117 days after last dose) Received adalimumab 40 mg eow for 413 days, followed by adalimumab weekly for 78 days.	Hypertension, morbid obesity, cardiomegaly, left ventricular hypertrophy, hypercholesterolemia	Myocardial infarction
81M 06P-144-0345192-01	**286 days** (167 days after last treatment)	Within 5 months before death, the following were reported: mild renal insufficiency, cardiac and	Metastatic melanoma; clear

16404 (M04-716, M03-658) Spain	Received adalimumab 40 mg eow for 119 days	respiratory insufficiency and pericardial effusion, suspected (unconfirmed) pulmonary TB), malignant melanoma lymph node metastasis without evidence of a primary tumor	cause of death not known
61M 06P-16300325067-00 450 (M03-656, M03-658 USA	**311 days** (190 days after last treatment) Received adalimumab 40 mg eow for 121 days	Hypertension, hypothyroidiswm, sleep apnea, obesity, ex-smoker (20 years, 1 pack/day) cholescystectomy 35 days before death, with discharge from hospital 29 days before death	Death (cause unknown); CRF states related to surgery
Source: \\cbsap58\M\EDR Submissions\2007 BLA\DC600004544\roadmap.pdf section 8 & BBIND 108111 SN152			

Reviewer's Comment: *It is difficult to unequivocally attribute these deaths solely to adalimumab, as all had confounding factors. In the cases of the treatment-emergent deaths, both the subject who died from a CVA and the subject who committed suicide had co-morbidities that could easily explain their deaths. In the case of the death from gastric cancer, the subject's symptoms began in < 3 months after the start of adalimumab, and he was dead around the 4.7 month mark. Thus, it is unlikely that adalimumab was the initiator of the cancer. However, this subject did receive adalimumab weekly for 107 days. Thus adalimumab, being an immunosuppressant may have contributed to the progression of the disease. The subject who died from the CVA also received adalimumab weekly. It should be noted that adalimumab will not be approved for weekly dosing in psoriatic patients.*

In the cases of the non-treatment emergent deaths, those that occurred beyond the 70 day post adalimumab treatment, again there are confounding factors. The subject, who died of an MI, had many co-morbidities associated with cardiovascular disease. The subject who died 35 days post cholecystectomy may well have died from surgical complications, as this is well within the perioperative period. The actual cause of death of the 81 y/o subject is not known, but he was found to have metastatic melanoma. Melanoma has been observed in other trials in subjects taking adalimumab but the role of adalimumab in the development of malignancies is unknown. In summary, from the available data, adalimumab may have contributed to two of the deaths, the gastric cancer and the melanoma, in terms of progression of the disease.

A consult from Dr. Carolyn McCloskey in the Division of Drug Risk Evaluation was obtained to compare these deaths that occurred in the trials to the standard mortality rate in the United States and in psoriasis populations. She calculated the death rate for these 6 deaths out of 1696 subjects exposed to adalimumab to be 358.8 deaths per 100,000 psoriasis patients on adalimumab. She found this to be below all other death rates found in the US total population, US males, US females, US deaths in 45-62 year olds, US deaths in over 65 year olds, the University of Toronto psoriatic arthritis clinic, and the US multi-center psoriasis patients (see Appendix 10.1).

7.1.2 Other Serious Adverse Events

In the placebo controlled study set, the incidence of serious AEs was low, 18/966 (1.9%) in the ADA group and 8/503 (1.6%) in the placebo group. A total of 20 individual serious adverse events (SAEs) were reported in 18 subjects in the adalimumab treatment group and a total of 8

individual SAEs were reported in 8 subjects in the placebo treatment group. In the adalimumab treatment group, only 2 SAEs were reported in more than one subject: cellulitis in 3 subjects and pancreatitis in 2 subjects. Table 12 lists the serious adverse events for the placebo controlled study set.

Table 12
Serious Adverse Events
Placebo Controlled Study Set

Subject No	Study	Sex/Age	Double-Blind Treatment Group	Rx Onset Day	Rx Resolution Day	Serious Adverse Event Preferred Term
959	M03-656	M/43	PBO	116	192	Perirectal Absecess
2849	M03-656	F/70	PBO	33	37	Myocardial Infarction
3147	M03-656	F/24	PBO	124	140	Pelvic Inflammatory Disease
3168	M03-656	M/49	PBO	58	143	Pleural Effusion
4202	M03-656	F/77	PBO	29	102	Bladder Cancer
4303	M03-656	F/44	PBO	13	21	Subcutaneous Abscess
8961	M03-656	M/49	PBO	106	116	Pneumonia
18007	M04-716	F/20	PBO	5	13	Calculus Ureteric
107	M02-528	M/54	ADA	15	63	Squamous Cell Carcinoma
657	M03-656	M/27	ADA	77	105	Physical Abuse
960	M03-656	F/66	ADA	36 36	92 92	Abscess Limb Cellulitis
1149	M03-656	F/48	ADA	51	83	Thyroid Adenoma
1609	M03-656	M/40	ADA	29	33	Malignant Melanoma *in Situ*
2478	M03-656	M/33	ADA	36	49	Renal Colic
2547	M03-656	M/31	ADA	49	56	Pancreatitis
4306	M03-656	M/71	ADA	33	38	Acute Myocardial Infarction
4407	M03-656	F/49	ADA	54	108	Headache
4616	M03-656	F/59	ADA	78 89	89 108	Streptococcal Infection Cellulitis
5409	M03-656	M/25	ADA	8	20	Ps
6518	M03-656	M/31	ADA	64	100	Pneumonia
7315	M03-656	M/50	ADA	45	50	Ventricular Tachycardia
9402	M03-656	F/51	ADA	103	127	Abscess
9503	M03-656	F/71	ADA	11	36	Breast Cancer
9709	M03-656	F/51	ADA	84	91	Cellulitis
17510	M04-716	M/25	ADA	63	70	Pancreatitis
17715	M040716	F/62	ADA	120	163	Ovarian Cyst

Source: Adapted from table 31, pages 93-94 ISS BLA 125057

In the All Adalimumab Treatment Set, the overall incidence of treatment-emergent SAEs was 5.2%. A total of 17 individual SAEs were reported in ≥ 2 subjects in the All Adalimumab Treatment Set. The most commonly reported individual SAEs were coronary artery disease, cellulitis, myocardial infarction, breast cancer, osteoarthritis, and TB. Of the 6 subjects with coronary artery disease and the four subjects with myocardial infarction, all had one or more of the following risk factors: tobacco use (current or past), hypercholesterolemia, or obesity.

Moreover, in eight of the ten subjects with either coronary artery disease or myocardial infarction, relevant medical history included hypertension, documented coronary disease, and/or diabetes mellitus. Table 13 lists the treatment emergent SAEs that occurred in ≥ 2 subjects both as an incidence and exposure-adjusted rates.

Table 13
Number (%) of Subjects with Treatment-emergent SAEs
Occurring in >= 2 Subjects (All Adalimumab Treatment Set)

Serious Adverse Event[a] Preferred Term	ADA N = 1696 n (%)	ADA N = 1696 PY = 1684.2 E (E/100 PY)
Any SAE	88 (5.2)	111 (6.6)
Coronary Artery Disease	6 (0.4)	6 (0.4)
Cellulitis	5 (0.3)	5 (0.3)
Myocardial Infarction	4 (0.2)	4 (0.2)
Breast Cancer	3 (0.2)	3 (0.2)
Osteoarthritis	3 (0.2)	4 (0.2)
TB[b]	3 (0.2)	3 (0.2)
Atrial Fibrillation	2 (0.1)	2 (0.1)
Calculus Ureteric	2 (0.1)	2 (0.1)
Chest Pain	2 (0.1)	2 (0.1)
Malignant Melanoma	2 (0.1)	2 (0.1)
Nephrolithiasis	2 (0.1)	2 (0.1)
Obesity	2 (0.1)	2 (0.1)
Pancreatitis	2 (0.1)	2 (0.1)
Pneumonia	2 (0.1)	2 (0.1)
Prostate Cancer	2 (0.1)	2 (0.1)
Renal Colic	2 (0.1)	2 (0.1)
Suicidal Ideation	2 (0.1)	2 (0.1)

ADA = adalimumab; E = events; PY = patient-years of exposure.

a. More than one SAE per subject possible.

b. Includes the preferred terms of TB and pulmonary TB.

Cross Reference: Table 2.2__2.1.3.1.1 and Table 2.2__2.1.3.2.1.

Source: ISS, page 96, BLA 125057

Reviewer's Comment: *Although I agree with the sponsor that the subjects that had cardiovascular events in the trials all seemed to have some risk factors and even though the difference in MI occurrence in the placebo controlled trials was not different, it is concerning that there was a cardiovascular death (CVA) in a 43 year old, albeit with risk factors. The current package insert states that cardiovascular events do occur with adalimumab in < 5% of*

subjects on the drug. It would be worthwhile to follow cardiovascular events in the planned phase 4 trial to elucidate further if there is indeed a relationship between cardiovascular events and Humira. The SAEs listed above are not new for this drug product and are labeled, with the exception of pancreatitis. Since one of the instances of pancreatitis was clearly associated with alcohol, an association of pancreatitis with adalimumab cannot be made. The cancers that occurred in this population, breast cancer, prostate cancer, and melanoma have been observed in the clinical trials for other indications (see HUMIRA label). These cancers are common cancers in the United States and from the data one cannot determine the rule of HUMIRA in the development of malignancies. In the psoriasis population, these serious adverse events have not occurred at a rate that is higher than that which is labeled for Humira (see reviewer's comment page 50 re: TB, for example and section 7.3).

Severe Adverse Events

The incidence of severe AEs in the placebo controlled study set was low and comparable in both arms, 27/966 (2.8%) in the adalimumab group and 15/503 (3.0%) in the placebo group. See table 14.

Table 14
Treatment Emergent SAEs and Treatment-Emergent SAEs per 100 Patient-Years of Exposure
Placebo-controlled Study Set

AE Category **Subject with any:**	**PBO** **N=503** **n(%)**	**ADA** **N=966** **n(%)**	**PBO** **N=503** **PY = 147.7** **E (E/100 PY)**	**ADA** **N=966** **PY = 294.0** **E (E/100 PY)**
Severe AE	15 (3.0)	27 (2.8)	17 (11.5)	32 (10.9)
Serious infections	4 (0.8)	5 (0.5)	4 (2.7)	7 (2.4)
Malignancies	2 (0.4)	7 (0.7)	2 (1.4)	7 (2.4)
Non- melanoma skin cancer	1 (0.5)	5 (0.5)	1 (0.7)	5 (1.7)
Other malignancies (excluding non-melanoma skin cancers and lymphomas)	1 (0.2)	2 (0.2)	1 (0.7)	3 (0.7)
Congestive heart failure	0 (0.0)	1 (0.1)	0	1 (0.3)

Adapted from table 15, page 58, ISS, BLA 125057

Reviewer's Comment: *The overall incidence of severe AEs in the adalimumab group is lower than in the placebo group and is born out by the exposure adjusted rates. However, although the incidence of any individual SAE occurred at a rate of less than 1%, as shown in table 14, when adjusted for exposure, there are some SAEs that do occur at a higher than 1% rate as shown, including malignancies and non-melanoma skin cancer. This higher rate was not statistically significant. Although there was virtually no difference in the incidence of serious infections, adalimumab was statistically significantly greater in incidence for all infections (see tables under section 7.1.5.3, Common Adverse Events).*

There were no severe AEs in the All Adalimumab treatment set that occurred at ≥ 1%. The highest incidence of severe AEs was cellulitis which occurred in 6/1696 (0.4%) subjects, followed by coronary artery disease (0.3%). The other severe adverse events occurring at 0.2% were headache, breast cancer, migraine, myocardial infarction, and psoriatic arthropathy (see table 15).

Table 15
Number (%) of Subjects with Treatment-emergent Severe AEs Occurring in > 2 Subjects (All Adalimumab Treatment Set)

Adverse Event[a] Preferred Term	ADA N = 1696 n (%)
Any severe AE	102 (6.0)
Cellulitis	6 (0.4)
Coronary artery disease	5 (0.3)
Headache	4 (0.2)
Breast cancer	3 (0.2)
Migraine	3 (0.2)
Myocardial infarction	3 (0.2)
Psoriatic arthropathy	3 (0.2)

ADA = adalimumab
a. More than 1 AE category per subject possible.
Cross Reference: Table 2.2__2.1.7.
Source: BLA 125057: ISS page 76, table 24

Reviewer's Comment: *The sponsor does not list one of the MIs as a severe adverse event but there were 4 MIs that occurred in the All Adalimumab Treatment set and although that doesn't change the incidence (0.2%), I consider any MI a severe adverse event.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the Placebo-controlled Study Set, fewer subjects prematurely discontinued from the adalimumab treatment group than from the placebo treatment group. The most common reasons for adalimumab treated subjects to discontinue were AEs (1.5%) and withdrawal of consent (1.0%), while placebo treated subjects discontinued most commonly for unsatisfactory therapeutic effect (5.0%) and withdrawal of consent (3.6%). These were also the most common primary reasons for study discontinuation (see table 16).

Table 16
Subject Final Status and Reasons
For Discontinuation
Placebo-Controlled Study Set

	PBO N = 503 n (%)	ADA N = 966 n (%)	Total N=1469 n (%)
Randomized subjects	503	968	1471
Randomized and dosed subjects	503 (100.0)	966 (99.8)	1469 (99.9)
Completed subjects	453 (90.1)	930 (96.1)	1383 (94.0)
Discontinued subjects	50 (9.9)	36 (3.7)	86 (5.8)
Primary reason for premature discontinuation			
AE	6 (1.2)	13 (1.3)	19 (1.3)
Withdrew consent	9 (1.8)	8 (0.8)	17 (1.2)
Lost to follow-up	8 (1.6)	6 (0.6)	14 (1.0)
Unsatisfactory therapeutic effect	22 (4.4)	2 (0.2)	24 (1.6)
Protocol violation	2 (0.4)	2 (0.2)	4 (0.3)
Administrative problems	1 (0.2)	0	1 (0.1)
Death	0	0	0
Other	2 (0.4)	5 (0.5)	7 (0.5)
All reasons for premature discontinuation			
AE	10 (2.0)	15 (1.5)	25 (1.7)
Withdrew consent	18 (3.6)	10 (1.0)	28 (1.9)
Lost to follow-up	9 (1.8)	6 (0.6)	15 (1.0)
Unsatisfactory therapeutic effect	25 (5.0)	3 (0.3)	28 (1.9)
Protocol violation	3 (0.6)	2 (0.2)	5 (0.3)
Administrative problems	1 (0.2)	0	1 (0.1)
Death	0	0	0
Other	6 (1.2)	5 (0.5)	11 (0.7)

ADA = adalimumab; PBO = placebo

Note: Subjects included in the Placebo-Controlled Study Set are from Studies M02-528, M03-656, and M04-716. Subject final status was collected at Week 12 for Study M02-528 and Week 16 for Studies M03-656 and M04-716.

Cross Reference: Table 2.1__1.2.

Source: BLA 125057, ISS page 26

In the All Adalimumab Treatment Set, where 68.7% of subjects had greater than 36 weeks of exposure to adalimumab, a total of 361 subjects (21.3%) prematurely discontinued. The most common of all reasons for adalimumab-treated subjects to discontinue was for unsatisfactory therapeutic effect (7.5%) and withdrawal of consent (6.1%). The most common primary reasons

for discontinuation were unsatisfactory therapeutic effect (6.5%) and AE (4.6%). See table 17 for all reasons for discontinuation in this treatment set.

Table 17
Subject Final Status and Reasons
For Discontinuation
All Adalimumab Treatment Set

	ADA N = 1696 n (%)
Total number of subjects	1696 (100.0)
Discontinued subjects	361 (21.3)
Primary reason for premature discontinuation	
AE	69 (4.1)
Withdrew consent	56 (3.3)
Lost to follow-up	42 (2.5)
Abnormal lab value(s)	1 (0.1)
Abnormal test procedure result(s)	0
Unsatisfactory therapeutic effect	110 (6.5)
Protocol violation	16 (0.9)
Administrative problems	6 (0.4)
Death[a]	3 (0.2)
IVRS required[b]	29 (1.7)
Other	29 (1.7)
All reasons for premature discontinuation	
AE	78 (4.6)
Withdrew consent	104 (6.1)
Lost to follow-up	47 (2.8)
Abnormal lab value(s)	1 (0.1)
Abnormal test procedure result(s)	2 (0.1)
Unsatisfactory therapeutic effect	127 (7.5)
Protocol violation	20 (1.2)
Administrative problems	7 (0.4)
Death[a]	3 (0.2)
IVRS required[b]	17 (1.0)
Other	44 (2.6)

ADA = adalimumab.

a. One fatal AE (Subject 450 in Study M03-658) was not treatment-emergent, since it occurred > 70 days after the subject's last dose of adalimumab. Subject 450 died 190 days after the last documented administration of study drug (Section 2.7.4.2.1.2.2). Therefore, this subject is not included in any AE tables for the All Adalimumab Treatment Set.

b. When a subject's PASI response was < PASI 50 after 8 weeks of dose escalation in Study M02-529, according to the protocol, the IVRS was to instruct the site to discontinue the subject from the study and not to continue the subject into Study M03-658.

Cross Reference: Table 2.1__2.2.

Source: BLA 125057, ISS table 5, page 30.

Reviewer's Comment: *The All Adalimumab Treatment Set also includes a small subset of subjects, "The Dose Escalation Treatment Subset". This subset consisted of 188 subjects who went from eow dosing to weekly dosing. Weekly dosing continued for > 12 weeks in 56.9% of subjects and > 24 weeks for 23.9% of subjects. Only 1.6% (3) of subjects discontinued because of an AE, suggesting that the increased dosing did not lead to more adverse events but 11.2% (21) of subjects discontinued because of unsatisfactory therapeutic effect. This suggests, although not a placebo-controlled trial, that increasing the frequency of dosing in psoriasis patients does not increase efficacy.*

The sponsor only included 3 deaths in the table of discontinuations, as these were considered treatment emergent (occurring within 70 days from the last dose of adalimumab). However, there were 6 total deaths in the psoriasis development program. See discussion under section 7.11.

7.1.3.2 Adverse events associated with dropouts

The overall incidence of treatment-emergent AEs leading to discontinuation of study drug in the placebo-controlled study set was comparable between the adalimumab (1.8%) and the placebo (2.2%) treatment groups. Seventeen (17) subjects reported a total of 21 individual AEs leading to discontinuation in the adalimumab treatment group, and 11 subjects reported a total of 18 individual AEs leading to discontinuation in the placebo treatment group. Table 18 shows the specifics of the discontinuations.

Table 18
Subjects with Treatment-emergent AEs
Leading to Discontinuation
Placebo controlled Study Set

Subject No	Study	Sex/Age	Double-Blind Treatment Group	Rx Onset Day	Rx Resolution Day	Serious Adverse Event Preferred Term
1207	M02-528	M/39	PBO	18	85	Erythrodermic Psoriasis
1156	M03-656	F/51	PBO	1	11	Fatigue
1349	M03-656	M/39	PBO	21 56 56	 56* 56*	Peptic Ulcer ALT Increased AST Increased
3168	M03-656	M/49	PBO	58 80	128* 128*	Renal Mass Liver Scan Abnormal
4143	M03-656	F/68	PBO	21	29	Psoriasis
4202	M03-656	F/77	PBO	24 24	35 35	Lymphadenopathy
4347	M03-656	M/67	PBO	55 62	55 161*	Psoriasis Hepatitis
4404	M03-656	F/55	PBO	18	25	Psoriasis
4639	M03-656	M/44	PBO	3 3	14* 14*	Abdominal Pain Upper Chest Discomfort
5408	M03-656	F/31	PBO	30	228*	Psoriatic Arthropathy
17914	M04-716	M/43	PBO	30	71*@	Hepatic Enzyme Increased

107	M02-528	M/54	ADA	15	63*	Squamous Cell Carcinoma
425	M02-528	M/51	ADA	22	41	Chest Pain
1345	M03-656	M/47	ADA	57	148*	Hepatitis C
1609	M03-656	M/40	ADA	29	33	Malignant Melanoma *In Situ*
1615	M03-656	F/71	ADA	13 78	85* 85*	Xerosis Injection Site Reaction
2547	M03-656	M/31	ADA	49	56	Pancreatitis
2567	M03-656	M/57	ADA	57	127	Hepatitis
3445	M03-656	F/34	ADA	36	87	Drug Eruption
4407	M03-656	F/49	ADA	54	108	Headache
4937	M03-656	M/54	ADA	95	323	Weight Increased
5409	M03-565	M/25	ADA	8	20	Psoriasis
6513	M03-656	F/44	ADA	64	165	Hypoesthesia
7112	M03656	F/43	ADA	8	29	Condition Aggravated
7202	M03-656	F/33	ADA	44 78	44 85*	Anxiety Insomnia
8509	M03-656	M/28	ADA	50 75 75	99* 78 99*	Skin Papilloma Condyloma Acuminatum Molluscum Contagiosum
9503	M03-656	F/71	ADA	11	36*	Breast Cancer
17806	M04-716	M/36	ADA	15	139*	Transaminases Increased

*Ongoing as of this day
@CRF states that by day 70, LFTs were back to normal
Source: BLA 125057, ISS table 35, pages 101-103

Reviewer's Comment: *Two groups of AEs from these discontinuations deserve special mention, those of cancer and the hepatic events. It is difficult to associated adalimumab as definitively responsible for the development of cancer in these patients. According to the CRF, subject 107, who was in the phase 2 dose ranging trial, was discovered to have metastatic squamous cell carcinoma in the neck after 4 weekly injections of adalimumab. Although it is unlikely that adalimumab caused the development of SCC in a month, it is possible that being am immunosuppressant, it may have contributed to the metastasis of the disease. Subject 1609 had malignant melanoma in situ diagnosed on day 29, which would have been after 3 doses of adalimumab. The last cancer patient to discontinue, subject 9503, was diagnosed with breast cancer only 11 days after the start of adalimumab, having received 3 doses. Again, this onset seems too short to be attributable to adalimumab.*

There were 2 subjects on placebo and 3 on adalimumab that discontinued because of hepatic events. For the one subject on adalimumab who was discontinued because of increased transaminases, the event was recorded as mild in his CRF and upon follow-up, repeat tests showed that the liver enzymes were decreasing toward normal. When one looks at the overview of treatment-emergent AEs per 100 patient-years of exposure for this study set, hepatic events occurred at a rate of 9.5 events/100 patient years for placebo and at a rate of 10.2 events/100 patient years for adalimumab, which is not statistically significant.

The overall incidence of treatment–emergent AEs leading to discontinuation of study drug in the All Adalimumab Treatment Set was 5.1%. A total of 19 individual AEs leading to discontinuation of study drug were reported in ≥ 2 subjects in the All Adalimumab Treatment Set. The most commonly reported individual AEs leading to discontinuation of study drug were Ps, breast cancer, psoriatic arthropathy, and TB. The other two most commonly reported AEs

leading to discontinuation of study drug was psoriasis and psoriatic arthropathy (see table 19 for discontinuations).

Table 19
Number (%) of Subjects with Treatment-emergent AEs
Leading to Discontinuation of Study Drug in ≥ 2 Subjects
All Adalimumab Treatment Set

Adverse Event[a] Preferred Term	ADA N = 1696 n (%)	ADA N = 1696 PY = 1684.2 E (E/100 PY)
Any AE leading to discontinuation of study drug	86 (5.1)	115 (6.8)
Ps	4 (0.2)	4 (0.2)
Breast Cancer	3 (0.2)	3 (0.2)
Psoriatic Arthropathy	3 (0.2)	3 (0.2)
TB[b]	3 (0.2)	3 (0.2)
Dizziness	2 (0.1)	2 (0.1)
Hepatic enzyme increased	2 (0.1)	2 (0.1)
Hepatitis C	2 (0.1)	2 (0.1)
Hypoaesthesia	2 (0.1)	2 (0.1)
Injection Site Reaction	2 (0.1)	2 (0.1)
Malignant Melanoma	2 (0.1)	2 (0.1)
Palpitations	2 (0.1)	2 (0.1)
Paraesthesia	2 (0.1)	2 (0.1)
Peripheral Sensory Neuropathy	2 (0.1)	2 (0.1)
Pneumonia	2 (0.1)	2 (0.1)
Prostate Cancer	2 (0.1)	2 (0.1)
Pruritus	2 (0.1)	2 (0.1)
Squamous Cell Carcinoma	2 (0.1)	2 (0.1)
Tuberculin Test Positive	2 (0.1)	2 (0.1)
Urticaria	2 (0.1)	2 (0.1)

ADA = adalimumab; E = events; PY = patient–years of exposure.

a. More than one AE per subject possible.

b. Includes the preferred terms of TB and pulmonary TB.

Cross Reference: Table 2.2__2.1.4.1.1 and Table 2.2__2.1.4.2.1.

Source: BLA 125057, ISS, table 36, page 105.

Reviewer's Comment: *The incidence of tuberculosis is a known risk in using adalimumab and can occur despite screening. Subjects in the trials were screened for latent TB with both CXR and PPD. In the psoriasis population, the data suggests that tuberculosis occurs at a slightly lower rate in the psoriasis population when compared to all populations in which adalimumab is*

indicated (0.17 per 100 patient years vs. 0.26 per 100 patient years[1]). The same can be said for the rate of occurrence of cancer (other than lymphoma and non-melanoma skin cancer). When grouped together the rate for psoriasis patients is 0.5 per 100 patient years vs. 0.6 per 100 patient years in all populations studied[1]. This is compared to a placebo rate of 0.4 per 100 patient years. It is somewhat reassuring that the rate in psoriasis patients is less than in the other populations (i.e. the rheumatoid arthritis population) even though the mean age was higher.

7.1.3.3 Other significant adverse events

Non-Melanoma Skin Cancer

The overall incidence and exposure–adjusted rate of treatment–emergent non–melanoma skin cancers in the Placebo–Controlled Study Set was higher in the adalimumab treatment group (0.5%; 1.7 E/100 PY) than in the placebo (0.2%; 0.7 E/100 PY) treatment group. Three subjects had basal cell carcinoma (BCC) and 2 subjects had SCC. The adalimumab arm accounted for 4 of the cutaneous malignancies and there was 1 cutaneous malignancy (SCC) in the placebo arm. The one subject in the placebo arm was a 55 year old Caucasian female smoker. The duration of exposure for these subjects was between 15 and 109 days.

The overall incidence and exposure–adjusted rate of treatment–emergent non–melanoma skin cancers in the All Adalimumab Treatment Set was 0.7% and 0.9E/100PY. Twelve subjects reported a total of 15 non-melanoma skin cancers, the demographics of which are noted in table 20.

Table 20
Subjects with Treatment-emergent Non-melanoma Skin Cancer
Adalimumab Treatment Set#

Subject No	Initial Study	Initial Treatment Group	Study when AE Occurred	Sex/Age	Rx Onset Day	Rx Resolution Day	Serious Adverse Event Preferred Term
107	M02-528	ADA	M02-528	M/54	15	63*	Squamous Cell Carcinoma
426	M02-528	ADA q wk	M02-529	M/50	1053	1174	Basal Cell Carcinoma
3505	M02-538	ADA	M02-538	M/61	80	99	Basal Cell Carcinoma
					113	171	Squamous Cell Carcinoma
					147	171	Basal Cell Carcinoma
2812	M02-538	ADA	M03-658	F/55	704	NA	Basal Cell Carcinoma
1359	M03-656	ADA/ADA/PBO	M03-656	M/58	293	349	Squamous Cell Carcinoma
2545	M03-656	ADA/ADA/PBO	M03-656	M/41	57	63	Neoplasm Skin
3047	M03-656	ADA	M03-656	F/47	57	80	Basal Cell Carcinoma
5221	M03-656	ADA	M03-656	M/67	91	108	Basal Cell Carcinoma
9602	M03-656	ADA/ADA	M03-658	F/44	291	291	Basal Cell Carcinoma

1 HUMIRA LABEL, Nov. 17, 2007, Section 5.2, page 6.

6207	M03-656	ADA/ADA/PBO	M03-656	M/77	109 221	109 221	Basal Cell Carcinoma Squamous Cell Carcinoma
7707	M03-656	ADA/ADA/PBO	M03-656	M/60	211	211	Squamous Cell Carcinoma
8006	M03-656	ADA	M03-658	M/53	362	406	Basal Cell Carcinoma

#This does not include 6 additional subjects reported in the 120 day safety update, see table 26.
*Ongoing as of this day
Source: Adapted from table 44, BLA125057, ISS page 122.

Reviewer's Comment: *The data suggests that treatment with adalimumab may increase the risk of development of non-melanoma skin cancer as compared to placebo. It is interesting that 9 of the 12 subjects (75%) had an underlying risk factor for the development of skin cancer, either having received PUVA or UVB treatment, or some other immunosuppressant in the treatment of their psoriasis. Only 3 of the 12 (25%) subjects, subject 426, 5221 and 6207, had no underlying risk factors. These 3 subjects all had basal cell carcinomas. At first glance, one might deduce from the data that adalimumab might increase the risk for these subjects who already had risk factors for developing cutaneous malignancy. However, across all indications, according to the HUMIRA label, during the controlled portions of the trials, the rate of nonmelanoma skin cancer was 0.9/100 patient/years in HUMIRA treated subjects and 0.3/100 patient years in placebo treated subjects. There was not that degree of difference in the psoriasis subjects were the rate was 1.7/100 patient/years in HUMIRA treated subjects compared to 0.7/100 patient years in placebo treated subjects. Given this data, treatment with adalimumab does not appear to be additive to other risk factors a subject may have for the development of BCC or SCC.*

It appears from this data, where > 300 patients were exposed to adalimumab for at least 1.8 years of treatment (see table 25, section 7.2.1.3), the risk of development of nonmelanoma skin cancer does not increase with continuing treatment with adalimumab. The rate of occurrence decreased to 0.9E/100PY as compared to the rate in the short-term which was 1.7E/100PY. Indeed, during this duration, the rate approached that of placebo (0.7E/100PY). See also section 7.4.3, Causality Determination.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse event data was collected on a routine basis throughout the development program in all studies. Methods for collection of data included: by query, by observation of the investigator, or through report by the subject. Treatment-emergent AEs were those first occurring or worsening from the first injection of study drug up to 70 days after the last injection of study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The categorization of adverse events with the preferred term did match the investigator's description of the adverse event, particularly for events that led to dropout or were serious for the CRFs that were cross-checked.

7.1.5.3 Common adverse event tables

Number (%) of Subjects with Treatment-emergent AEs Occurring in ≥ 1% of Subjects in Either Treatment Group with Corresponding Exposure-Adjusted Rates Placebo Controlled Study Set

Adverse Event[a] Preferred Term	PBO N=503 n(%)	ADA N=966 n(%)	PBO N=503 PY = 147.7 E (E/100 PY)	ADA N=966 PY = 294.0 E (E/100 PY)
Any AE	297 (59.0)	614 (63.6)	693 (469.1)	1455 (495.0)
AE at least possibly related[#]	85 (16.9)	221 (22.9)**	157 (106.3)	406 (138.1)
Severe AE	15 (3.0)	27 (2.8)	17 (11.5)	32 (10.9)
Serious AE	8 (1.6)	18 (1.9)	8 (5.4)	20 (6.8)
AE leading to discontinuation of study drug	11 (2.2)	17 (1.8)	18 (12.2)	21 (7.1)
Infections	120 (23.9)	293 (30.3)**	146 (98.8)	396 (134.7)
Nasopharyngitis	39 (7.8)	75 (7.8)	41 (27.8)	85 (28.9)
Injection Site Reaction	25 (5.0)	68 (7.0)	39 (26.4)	88 (29.9)
Upper Respiratory Tract Infection	15 (3.0)	62 (6.4)**	16 (10.8)	72 (24.5)
Headache	28 (5.6)	59 (6.1)	44 (29.8)	69 (23.5)
Arthralgia	7 (1.4)	28 (2.9)	8 (5.4)	38 (12.9)
Pruritus	11 (2.2)	24 (2.5)	11 (7.4)	27 (9.2)
Sinusitis	6 (1.2)	24 (2.5)	6 (4.1)	27 (9.2)
Fatigue	11 (2.2)	22 (2.3)	14 (9.5)	25 (8.5)
Hypertension	10 (2.0)	21 (2.2)	10 (6.8)	21 (7.1)
Nausea	10 (2.0)	21 (2.2)	12 (8.1)	22 (7.5)
Diarrhea	9 (1.8)	20 (2.1)	9 (6.1)	29 (9.9)
Hepatic Events	13 (2.6)	17 (1.8)	14 (9.5)	30 (10.2)
Injection site irritation	6 (1.2)	16 (1.7)	6 (1.4)	17 (5.8)
Injection site pain	9 (1.8)	15 (1.6)	18 (12.2)	19 (6.5)
Bronchitis	5 (1.0)	15 (1.6)	5 (3.4)	15 (5.1)
Muscle Strain	2 (0.4)	15 (1.6)	2 (1.4)	17 (5.8)
Myalgia	3 (0.6)	14 (1.4)	4 (2.7)	17 (5.8)
Pharyngolaryngeal pain	9 (1.8)	14 (1.4)	9 (6.1)	16 (5.4)
Back pain	6 (1.2)	12 (1.2)	6 (4.1)	12 (4.1)
Pain in extremity	5 (1.0)	12 (1.2)	6 (4.1)	15 (5.1)
Cough	9 (1.8)	12 (1.2)	9 (6.1)	12 (4.1)
Nasal Congestion	10 (2.0)	12 (1.2)	11 (7.4)	13 (4.4)
Herpes Simplex	3 (0.6)	11 (1.1)	3 (2.0)	12 (4.1)
Influenza	3 (0.6)	11 (1.1)	3 (2.0)	11 (3.7)
Tooth Abscess	3 (0.6)	11 (1.1)	3 (2.0)	11 (3.7)
Urinary tract infection	3 (0.6)	11 (1.1)	3 (2.0)	13 (4.4)
Dizziness	9 (1.8)	11 (1.1)	16 (10.8)	13 (4.4)
Pharyngitis	3 (0.6)	10 (1.0)	3 (2.0)	10 (3.4)
Alanine aminotransferase increased	1 (0.2)	10 (1.0)	1 (0.7)	13 (4.4)
Blood triglycerides increased	4 (0.8)	10 (1.0)	4 (2.7)	11 (3.7)
Muscle spasms	0	10 (1.0)	0	10 (3.4)
Hypercholesterolemia*	1 (0.2)	10 (1.0)	1 (0.7)	10 (3.4)
Psoriasis	10 (2.0)	9 (0.9)	10 (6.8)	9 (3.1)

Edema peripheral	9 (1.8)	8 (0.8)	9 (6.1)	8 (2.7)
Insomnia	7 (1.4)	6 (0.6)	7 (4.7)	6 (2.0)
Lymphadenopathy	8 (1.6)	3 (0.3)	8 (5.4)	3 (1.0)
Pain	5 (1.0)	3 (0.3)	5 (3.4)	3 (1.0)
Rhinitis	7 (1.4)	3 (0.3)	7 (4.7)	3 (1.0)
Psoriatic Arthropathy	10 (2.0)	3 (0.3)**	11 (7.4)	4 (1.4)
Hypoesthesia	5 (1.0)	3 (0.3)	5 (3.4)	4 (1.4)
Erythema	5 (1.0)	3 (0.3)	5 (3.4)	4 (1.4)

a. More than 1 AE category per subject possible
** Statistically significant at the $p \leq 0.01$ level
#According to the investigator
*This category added by the reviewer, as in the line listings, there were 9 subjects recorded with hypercholesterolemia as an AE and 1 subject recorded as high blood cholesterol in the adalimumab arm. One subject was recorded as high blood cholesterol in the placebo arm.
Source: BLA 125057, ISS, adapted from table 19, page 67 and table 15, page 58, and ISS, table 1.1 &1.2 and ISS table 2.2_1.2.1.1, pages 11

Number (%) of Subjects with Treatment-emergent AEs Occurring in ≥ 1% of Subjects with Corresponding Exposure-Adjusted Rates All Adalimumab Treatment Set

Adverse Event Preferred Term	**ADA N=1696 n(%)**	**ADA N=1696 PY = 1684.2 E (E/100 PY)**
Any AE	1300 (76.7)	5351 (317.7)
AE at least possibly related	509 (30.0)	1200 (71.3)
Severe AE	102 (6.0)	138 (8.2)
Serious AE	88 (5.2)	111 (6.6)
AE leading to discontinuation of study drug	86 (5.1)	115 (6.8)
Infections	813 (47.9)	1541 (91.5)
Nasopharyngitis	245 (14.4)	324 (19.2)
Upper Respiratory Tract Infection	212 (12.5)	268 (15.9)
Injection Site Reaction	159 (9.4)	306 (18.2)
Headache	129 (7.6)	165 (9.8)
Sinusitis	95 (5.6)	109 (6.5)
Arthralgia	91 (5.4)	110 (6.5)
Hypertension	78 (4.6)	83 (4.9)
Injection site reaction	76 (4.5)	160 (9.5)
Diarrhea	58 (3.4)	74 (4.4)
Bronchitis	58 (3.4)	66 (3.9)
Back pain	58 (3.4)	65 (3.9)
Hepatic Events	58 (3.4)	83 (4.9)

Cough	56 (3.3)	60 (3.6)
Nausea	54 (3.2)	62 (3.7)
Influenza	54 (3.2)	58 (3.4)
Pruritus	53 (3.1)	59 (3.5)
Fatigue	49 (2.9)	68 (4.0)
Pharyngolaryngeal pain	49 (2.9)	52 (3.1)
Nasal congestion	47 (2.8)	56 (3.3)
Muscle sprain	39 (2.3)	45 (2.7)
Pain in extremity	38 (2.2)	43 (2.6)
Urinary tract infection	35 (2.1)	45 (2.7)
Psoriasis	35 (2.1)	35 (2.1)
Hypercholesterolaemia	34 (2.0)	39 (2.3)
Gastroenteritis	33 (1.9)	36 (2.1)
Herpes simplex	31 (1.8)	34 (2.0)
Psoriatic arthropathy	31 (1.8)	37 (2.2)
Injection site pain	30 (1.8)	50 (3.0)
Dizziness	30 (1.8)	34 (2.0)
Injection site irritation	29 (1.7)	34 (2.0)
Gastroenteritis viral	29 (1.7)	30 (1.8)
Tooth abscess	28)1.7)	30 (1.8)
Blood CPK increased	28 (1.7)	32 (1.9)
Conjunctivitis	27 (1.6)	29 (1.7)
Pharyngitis	27 (1.6)	29 (1.7)
Viral upper respiratory tract infection	27 (1.6)	33 (2.0)
Myalgia	26 (1.5)	31 91.8)
Joint sprain	25 91.5)	26 (1.5)
Blood triglycerides increased	25 (1.5)	33 (2.0)
Edema peripheral	24 (1.4)	26 (1.5)
Anxiety	24 (1.4)	27 (1.6)
Depression	24 (1.4)	26 (1.5)
Sinus congestion	24 (1.4)	27 (1.6)
Dyspepsia	24 (1.4)	27 (1.6)
Skin laceration	23 (1.4)	26 (1.5)
Alanine aminotrasferase increased	23 (1.4)	27 (1.6)
Shoulder pain	23 (1.4)	27 (1.6)
Insomnia	23 (1.4)	27 (1.6)
Vomiting	22 (1.3)	23 (1.4)
Pharyngitis streptococcal	22 (1.3)	23 (1.4)
Viral infection	22 (1.3)	24 (1.4)
Hypertriglyceridemia	22 (1.3)	27 (1.6)
Dermatitis contact	22 (1.3)	26 (1.5)
Malignancies	22 (1.3)	26 (1.5)
Gastroesophageal reflux disease	21 (1.2)	21 (1.2)
Cellulitis	20 (1.2)	24 (1.4)
Dental caries	20 (1.2)	24 (1.4)
Otitis Media	20 (1.2)	21 (1.2)

Skin papilloma	20 (1.2)	20 (1.2)
Paresthesia	20 (1.2)	22 (1.3)
Serious Infections	21 (1.2)	24 (1.4)
Abdominal Pain	19 (1.1)	19 (1.1)
Tooth infection	19 (1.1)	19 (1.1)
Diabetes mellitus	19 (1.1)	19 (1.1)
Muscle spasms	19 (1.1)	21 (1.2)
Toothache	18 (1.1)	20 (1.2)
Chest pain	18 (1.1)	18 (1.1)
Folliculitis	18 (1.1)	20 (1.2)
Contusion	18 (1.1)	18 (1.1)
Neck pain	18 (1.1)	19 (1.1)
Osteoarthritis	18 (1.1)	21 (1.2)
Herpes zoster	17 (1.0)	17 (1.0)
Arthritis	17 (1.0)	19 (1.1)
Migraine	17 (1.0	19 (1.1)
Acne	17 (1.0)	18 (1.1)
Urticaria	17 (1.0)	18 (1.1)
Source: BLA 125057, ISS, adapted from table 16, page 61 and table 22, page 72 And Cross-reference: Table 2.1 and Table 2.2		

Reviewer's Comment: *Within the All Adalimumab Treatment set is the large subset of subjects that only received adalimumab on an every other week basis, the EOW treatment set. This consisted of 1403 subjects. The remainder of the subjects was part of a dose escalation subset of 188 subjects and a q week subset of 105 subjects. For the most part, the EOW treatment set parallels the All Adalimumab Treatment set. It is worth noting, however, that in the case of malignancies, the incidence of the EOW treatment set was 12 (0.9%), which is close to the incidence in adalimumab treated subjects in the placebo controlled trials (0.8%). This is discussed in section 7.1.6, Less Common Adverse Events. Thus, it does not appear that the incidence of malignancies increases over time with treatment of adalimumab.*

7.1.5.4 Identifying common and drug-related adverse events

Number (%) of Subjects with At Least Possibly Related Treatment-emergent AEs Occurring With a Difference of ≥ 1% of Subjects in Either Treatment Group Placebo-Controlled Study Set

Adverse Event [a] Preferred Term	ADA N=966 n(%)	PBO N=503 n(%)
Infections	293 (30.3)	120 (23.9)
Injection Site Reaction	68 (7.0)	25 (5.0)
Upper Respiratory Tract Infection	62 (6.4)	15 (3.0)
Arthralgia	28 (2.9)	7 (1.4)
Sinusitis	24 (2.5)	6 (1.2)
Muscle Strain	15 (1.6)	2 (0.4)
Muscle Spasms	10 (1.0)	0 (0.0)

a. More than 1 AE category per subject possible
Source: BLA 125057, ISS, adapted from table 15, page 58, table 19, page 67,and table 20, page 69

Reviewer's Comment: *These are the common adverse events where there was a difference of at least 1% between placebo and adalimumab.*

7.1.5.5 Additional analyses and explorations

Exposure and Onset of Adverse Events

Overall, most subjects who experienced an AE first did so during the first 90 days of treatment with study drug. Among the five most commonly reported AEs in the All Adalimumab Treatment Set, approximately 40% of those subjects who reported headache (51 of 126 subjects; 40.5%) did so within 30 days of their initial exposure to adalimumab, and nearly two–thirds of those subjects who reported headache (80 of 126 subjects; 63%) did so within the first 90 days of adalimumab exposure. There was also a slight tendency for nasopharyngitis and upper respiratory tract infections to first be reported more commonly during the first 90 days of adalimumab exposure compared with the later exposure intervals. Sinusitis and arthralgia tended to be reported for the first time at comparable incidences across the exposure intervals. Although these events did continue to be reported for the first time at later time intervals, none were reported at a greater frequency than during the first 90 days.

Reviewer's Comment: *Time intervals examined were every 30 days up to day 90 and 90 day intervals beginning at day 1 to greater than 360 days. The data suggests that there is not an increase in these adverse events over time of use of adalimumab.*

Intrinsic and Extrinsic Factors – Effect on Adverse Events

Of the 10 subgroup categories analyzed, eight specifically assessed whether there is any impact of subjects' intrinsic factors (i.e., general demographic characteristics [sex, age, race, weight] or Baseline disease characteristics [Baseline PASI score, Baseline PGA rating, Baseline BSA, and history of PsA]) on the overall safety profile of adalimumab.

With regard to general demographic characteristics in the All Adalimumab Treatment Set, females had higher incidences than males for AEs overall (82.2% vs. 73.9%), AEs at least possibly drug–related (38.3% vs. 25.8%), infections (54.9% vs. 44.4%), and injection site reactions (14.0% vs. 7.1%). There were only approximately half as many females (n=566) than males (n=1130) in the All Adalimumab Treatment Set.

Subjects > 64 years of age had higher incidences than subjects < 40 years of age for AEs overall (81.4% vs. 75.6%), severe AEs, (11.8% vs. 4.7%), SAEs (10.8% vs. 3.3%), and AEs leading to discontinuation of study drug (10.8% vs. 3.6%). Subjects > 64 years of age also had higher incidences than subjects 40–64 years of age for severe AEs (11.8% vs. 6.3%) and AEs leading to discontinuation of study drug (10.8% vs. 5.5%). However, the clinical relevance of these results is difficult to interpret given the fact that there were far fewer subjects > 64 years of age (n=102) relative to subjects < 40 years of age (n=640) and subjects 40–64 years of age (n=954). Furthermore, older subjects are more likely to experience AEs, in general, than younger subjects. However, in subjects > 64 years of age the incidence of infections (43.1%) was not higher than in subjects < 40 years of age (51.1%), which is in contrast to the current HUMIRA® labeling.

Reviewer's Comment: *Agree with the sponsor's assessment that one would expect that older individuals, with more co-morbidities, would have a higher incidence of adverse events. Although this does not seem to be the case for the incidence of infections, given the overall premise, this does not warrant a change in the label for infections based on age category.*

White subjects had a higher incidence of infections (48.9%) than non–White subjects (37.4%); however, this difference is not considered to be clinically relevant. Although there were some notable differences in the incidences of AE categories across weight quartiles (on individual treatment–emergent AEs), there was no consistent pattern to suggest any effect of weight on the safety of adalimumab (e.g., subjects in weight quartile 4 had a higher incidence of AEs overall than subjects in the first three weight quartiles, but subjects in weight quartiles 1 and 4 had higher incidences of AEs at least possibly drug–related than subjects in weight quartile 3).

Similar results across the four demographic characteristics were observed in the remaining subgroup analyses in the All Adalimumab Treatment Set and in all subgroup analyses in the Placebo–Controlled Study Set and EOW Treatment Set.

With regard to the four Baseline disease characteristics, subjects with a Baseline PASI score < 12 had higher incidences than subjects with Baseline PASI scores 12–20 and > 20 for AEs overall (85.2% vs. 76.5% and 74.8%, respectively), AEs at least possibly drug– related (40.6%

vs. 29.7% and 28.1%, respectively), infections (53.1% vs. 48.1% and 46.3%, respectively), and injection site reactions (16.4% vs. 10.3% and 5.8%, respectively). However, the clinical relevance of these results is difficult to interpret given the fact that there were far fewer subjects with a Baseline PASI score < 12 (n=128) relative to subjects with a Baseline PASI score 12–20 (n=1052) or > 20 (n=516).

Reviewer's Comment: *Those subjects in the pivotal trials that had a PASI score of <12 were excluded from the efficacy analysis by our statistician, as they did not meet our criteria for at least moderate psoriasis. Thus, this group of psoriasis patients would not be expected to be treated with adalimumab.*

When other Baseline disease characteristics were analyzed in which there were comparable numbers of subjects for analysis, no trends were observed. Although subjects with a Baseline PGA of severe or very severe had a higher incidence of AEs at least possibly drug–related (29.7%) than subjects with a Baseline PGA of moderate or less (24.3%), this difference is not considered to be clinically relevant; therefore, it is concluded that the AE profile of adalimumab is unaffected by Baseline PGA severity. There were no notable differences in any of the AE categories in the All AdalimumabTreatment Set based on Baseline BSA involvement (< 20% vs. ≥ 20%).

Subjects with a history of PsA had higher incidences than subjects without a history of PsA for AEs overall (83.5% vs. 74.2%) and AEs at least possibly drug–related (36.1% vs. 27.8%). However, only approximately 25% of the subjects in the All Adalimumab Treatment Set (454 of 1696 subjects) had a history of PsA at Baseline. Similar results across the four Baseline disease characteristics were observed in the remaining subgroup analyses in the All Adalimumab Treatment Set and in all subgroup analyses in the Placebo-controlled study set and EOW Treatment set.

There were no notable differences in any of the AE categories in the All Adalimumab Treatment Set based on whether or not subjects had systemic biologic or non–biologic therapy within 12 months of the start of the initial study. Similar results across these two extrinsic factors were observed in the remaining subgroup analyses in the All Adalimumab Treatment Set and in all subgroup analyses in the Placebo–Controlled Study Set and EOW Treatment Set.

Reviewer's Comment: *In summary, the data suggests that of the intrinsic and extrinsic factors that were examined, only subjects >64 years of age, Caucasian subjects, and those with psoriatic arthritis tended to experience more adverse events.*

7.1.6 Less Common Adverse Events

There were 15 categories of adverse events of interest that were followed in the data base because of a known increase in incidence with the use of Humira in other indications. Infections and injection site reactions have already been discussed, as these were common adverse events. No subject experienced an AE in any of the following categories: lymphoma, demyelinating

disorder, opportunistic infection (excluding TB), TB, and lupus-like syndrome in the placebo-controlled study set. There was a slightly higher, though not statistically significant, incidence of non–melanoma skin cancers in the adalimumab treatment group compared with the placebo treatment group, which accounted for the slightly higher incidence of all malignancies in the adalimumab treatment group. Injection site reactions also occurred at a slightly higher incidence in the adalimumab treatment group compared with the placebo treatment group, though this difference was not statistically significant. The incidence of adverse events in most of the AEs of special interest occurred at a rate of < 1% in the psoriasis population as noted in table 21 below.

Table 21
Treatment Emergent AEs and Treatment Emergent AEs
Per 100 Patient-Years of Exposure
AEs of Interest – Placebo Controlled Study Set

Adverse Event Preferred Term	**PBO N=503 n(%)**	**ADA N=966 n(%)**	**PBO N=503 PY = 147.7 E (E/100 PY)**	**ADA N=966 PY = 294.0 E (E/100 PY)**
Infections	120 (23.9)	293 (30.3)	146 (98.8)	396 (134.7)
Serious Infections	4 (0.8)	5 (0.5)	4 (2.7)	7 (2.4)
Malignancies	2 (0.4)	7 (0.7)	2 (1.4)	7 (2.4)
Lymphoma	0	0	0	0
Non-melanoma skin cancers	1 (0.2)	5 (0.5)	1 (0.7)	5 (1.7)
Other malignancies (excluding non-melanoma skin cancers and lymphoma	1 (0.2)	2 (0.2)	1 (0.7)	2 (0.7)
Demyelinating Disorders	0	0	0	0
Congestive Heart Failure	0	1 (0.1)	0	1 (0.3)
Allergic Reactions	0	1 (0.1)	0	1 (0.3)
Injection Site Reaction	25 (5.0)	68 (7.0)	39 (26.4)	88 (29.9)
Opportunistic Infection (excluding TB)	0	0	0	0
TB	0	0	0	0
Lupus-like Syndrome	0	0	0	0
Hematologic Event	1 (0.2)	1 (0.1)	2 (1.4)	1 (0.3)
Hepatic Events	13 (2.6)	17 (1.8)	14 (9.5)	30 (10.2)

Source: BLA 125057, ISS, adapted from table 15, page 58

The All Adalimumab Treatment Set includes the later study phases and subjects had an average duration of treatment of one year and a maximum treatment duration of three years. In this set, at this point in the review, the risk of AEs does not appear to increase with chronic adalimumab treatment. The rates of AEs per 100 patient-years of exposure are generally lower in the All Adalimumab Treatment Set compared with the Placebo-Controlled Study Set, particularly for infections (91.5 vs. 134.7/100 PY), injection site reactions (18.2 vs. 29.9 E/100PY), and hepatic events (4.9 vs. 10.2 E/100PY). The exposure-adjusted AE rates for 'any malignancy' and 'nonmelanoma skin cancer' in the All Adalimumab Treatment Set (1.5 and 0.9 E/100PY, respectively) are lower compared with the adalimumab treatment group in the Placebo-Controlled Study Set (2.4 and 1.7 E/100 PY). Table 22 shows the data of the AE categories of special interest.

Table 22
Treatment Emergent AEs and Treatment Emergent AEs
Per 100 Patient-Years of Exposure
AEs of Interest – All Adalimumab Study Set

Adverse Event Preferred Term	ADA N=1696 n(%)	ADA N=1696 PY = 1684.2 E (E/100 PY)
Infections	813 (47.9)	1541 (91.5)
Serious Infections	21 (1.2)	24 (1.4)
Malignancies	22 (1.3)	26 (1.5)
Lymphoma	0	0
Non-melanoma skin cancers	12 (0.7)	15 (0.9)
Other malignancies (excluding non-melanoma skin cancers and lymphoma	11 (0.6)	11 (0.7)
Demyelinating Disorders	0	0
Congestive Heart Failure	1 (0.1)	1 (0.1)
Allergic Reactions	3 (0.2)	3 (0.2)
Injection Site Reaction	159 (9.4)	306 (18.2)
Opportunistic Infection (excluding TB)	4 (0.2)	4 (0.2)
TB	3 (0.2)	3 (0.2)
Lupus-like Syndrome	1 (0.1)	1 (0.1)
Hematologic Event	3 (0.2)	3 (0.2)
Hepatic Events	58 (3.4)	83 (4.9)

Source: BLA 125057, ISS, adapted from table 16, page 61

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In pivotal study, M03-656, blood and urine samples were obtained for the clinical laboratory tests (hematology, clinical chemistry, and urinalysis). Blood draws were performed after vital sign assessments were completed during a visit. Blood specimens for hematology and chemistry were obtained at Screening, Baseline, Week 4, Week 8, Week 16, Week 24, Week 33, Week 52, and every 20 weeks after Week 52 during Period C or the appropriate Early Termination or Final visit. Blood specimens for triglycerides during Period A were obtained after fasting for 8-12 hours. Blood samples for antinuclear antibody (ANA) and anti-double stranded DNA (dsDNA) antibody test, as well as Rheumatoid Factor (RF), were obtained at Baseline only.

Urine specimens were obtained at Screening, Baseline, Week 16, Week 33, Week 52 and every 20 weeks after Week 52 during Period C or at the appropriate Early Termination or Final visit. The central laboratory performed a macroscopic urinalysis on these specimens. All abnormal macroscopic urinalyses were followed up with a microscopic analysis at the central laboratory.

Blood for pk parameters and anti-adalimumab antibodies (AAA) occurred at baseline (week 0), week 16, week 33, week 52, or early termination before any of those time points.

In the second pivotal study, M04-716, laboratory specimens were obtained at screening, baseline, week 1, 2, 4, 6, 8, 12, 16, early termination, and for any unscheduled visit. Urinalysis and pregnancy testing were obtained at screening, baseline, weeks 4, 8, 12, 16, or early termination.

Any changes in laboratory values were considered to be AEs only if they resulted in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considered them to be AEs.

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Clinical Chemistry

Mean clinical chemistry values at Baseline between the placebo and adalimumab treatment groups were generally comparable except for CK, calcium and chloride, where the differences achieved statistical significance; however, the differences in calcium and chloride are not considered to be clinically relevant. For CK, mean increases from Baseline were observed in the adalimumab treatment group compared with either small mean increases or decreases in the placebo treatment group.

In the adalimumab treatment group, mean ALT, AST and bilirubin were above Baseline values and mean alkaline phosphatase were below Baseline values at all time points; between group differences were statistically significant for alkaline phosphatase and bilirubin at all time points. The maximal mean difference between the adalimumab and placebo treatment groups for bilirubin was 1.1 μmol/L (at the last visit). Between group differences for ALT were statistically significant only at Week 4; no statistically significant between group differences were observed for AST.

For cholesterol and triglycerides, small mean increases from Baseline were observed in the adalimumab treatment group compared with small mean decreases in cholesterol and relatively smaller mean increases in triglycerides in the placebo treatment group. The between group differences were statistically significant for cholesterol at some time points; no statistically significant differences were observed for triglycerides.

Reviewer's Comment: *According to the sponsor, the small mean increases in cholesterol and triglyceride values can be explained by the anti-inflammatory and anti-catabolic effect of TNF-neutralization. Even though this may be the case, as is noted in section 7.1.7.2.2, 0.9% of*

subjects did report hypercholesterolemia as an AE, and thus it should be noted in labeling. The same can be noted for elevations of liver enzymes.

Clinical hematology

Mean hematology values at Baseline between the placebo and adalimumab treatment groups were generally comparable except for eosinophils, where the difference achieved statistical significance (placebo Baseline mean = 0.203 x10^9/L, adalimumab Baseline mean = 0.226x10^9/L, p = 0.006); however, this difference is not considered to be clinically relevant

In the adalimumab treatment group, mean hemoglobin and hematocrit were above Baseline values and mean platelet counts were below Baseline values at all time points; between group differences were statistically significant for mean platelet count and hemoglobin at all time points and for mean hematocrit at most time points. Mean WBC values decreased during treatment with adalimumab at all time points, and WBC differential counts showed small mean decreases from baseline in neutrophil counts and small mean increases from baseline in lymphocyte counts at all time points; between group differences were statistically significant for mean neutrophil and lymphocyte counts at all time points and for mean WBC at all time points except Week 12 (when only approximately one–fifth of the subjects had values recorded compared with other time points). The small although statistically significant mean increases in hemoglobin and hematocrit and mean decreases in platelets and WBC/neutrophil counts in the adalimumab treatment group are compatible with the expected anti–inflammatory effect of adalimumab. Small mean increases in the number of circulating lymphocytes have been observed during treatment with adalimumab in several settings, and appear to be a manifestation of the immune system's response to the TNF–inhibitor.

Reviewer's Comment: *These differences in mean hematologic parameters did not translate into a difference in hematologic AEs reported in subjects on placebo vs. adalimumab.*

Urinalysis

No trends suggesting an effect of treatment were evident based on mean changes from baseline over time for urine pH and specific gravity in the placebo-controlled study set, the all adalimumab, or the EOW treatment sets. In addition, no treatment effects on urine pH or specific gravity were observed based on the number of subjects who shifted from normal value at baseline to abnormal values (above or below normal) at the final visit in any of the three aforementioned treatment sets. No subjects had potentially clinically significant values for urine protein in any of the treatment sets.

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Clinical Chemistry – Placebo-Controlled Study Set

Table 63 below shows the shifts of chemistry values from normal to low or high for subjects from baseline to the final visit. The majority of subjects remained in the normal range for all chemistry parameters evaluated. There are a few parameters where there is more than a 1%

difference in the shift to high between placebo and adalimumab subjects. These parameters are ALT (6.3 vs. 7.8), AST (3.9 vs. 4.9), total cholesterol (19.0 vs. 21.1), CK (5.7 vs. 8.2), and triglycerides (14.4 vs. 17.7). Well over two-thirds of subjects, however, did not shift to higher than 1.5x their own baseline values.

Table 63. Number of Subjects with Clinical Chemistry Values in the Normal Range at Baseline and Low, High, or Normal Values at the Final Visit (Placebo-controlled Study Set)

Clinical Chemistry Parameter (n)[a]	Changed to Low[b] n (%)	Remained Normal[b] n (%)	Changed to High[b] n (%)
Albumin			
PBO (488)	0 (0)	477 (97.7)	11 (2.3)
ADA (945)	0 (0)	922 (97.6)	23 (2.4)
Alkaline phosphatase			
PBO (471)	0 (0)	468 (99.4)	3 (0.6)
ADA (921)	0 (0)	916 (99.5)	5 (0.5)
ALT			
PBO (429)	0 (0)	402 (93.7)	27 (6.3)
ADA (868)	0 (0)	800 (92.2)	68 (7.8)
AST			
PBO (456)	0 (0)	438 (96.1)	18 (3.9)
ADA (911)	0 (0)	866 (95.1)	45 (4.9)
Bilirubin, total			
PBO (481)	1 (0.2)	474 (98.5)	6 (1.2)
ADA (932)	0 (0)	912 (97.9)	20 (2.1)
BUN			
PBO (484)	2 (0.4)	476 (98.3)	6 (1.2)
ADA (943)	3 (0.3)	928 (98.4)	12 (1.3)
Calcium			
PBO (487)	2 (0.4)	485 (99.6)	0 (0)
ADA (949)	5 (0.5)	936 (98.6)	8 (0.8)
Chloride			
PBO (471)	1 (0.2)	430 (91.3)	40 (8.5)
ADA (911)	0 (0)	865 (95.0)	46 (5.0)
Cholesterol, total			
PBO (284)	4 (1.4)	226 (79.6)	54 (19.0)
ADA (487)	4 (0.8)	380 (78.0)	103 (21.1)
CK			
PBO (441)	0 (0)	416 (94.3)	25 (5.7)
ADA (890)	0 (0)	817 (91.8)	73 (8.2)

Clinical Chemistry Parameter (n)[a]	Changed to Low[b] n (%)	Remained Normal[b] n (%)	Changed to High[b] n (%)
Creatinine			
PBO (488)	0 (0)	485 (99.4)	3 (0.6)
ADA (942)	0 (0)	937 (99.5)	5 (0.5)
Glucose			
PBO (427)	6 (1.4)	397 (93.0)	24 (5.6)
ADA (832)	15 (1.8)	772 (92.8)	45 (5.4)
LDH			
PBO (491)	0 (0)	487 (99.2)	4 (0.8)
ADA (954)	0 (0)	942 (98.7)	12 (1.3)
Phosphorus			
PBO (469)	7 (1.5)	450 (95.9)	12 (2.6)
ADA (906)	14 (1.5)	877 (96.8)	15 (1.7)
Potassium			
PBO (485)	1 (0.2)	482 (99.4)	2 (0.4)
ADA (948)	4 (0.4)	940 (99.2)	4 (0.4)
Protein, total			
PBO (491)	0 (0)	489 (99.6)	2 (0.4)
ADA (954)	0 (0)	952 (99.8)	2 (0.2)
Sodium			
PBO (486)	1 (0.2)	481 (99.0)	4 (0.8)
ADA (954)	2 (0.2)	946 (99.2)	6 (0.6)
Triglycerides			
PBO (369)	0 (0)	316 (85.6)	53 (14.4)
ADA (696)	1 (0.1)	572 (82.2)	123 (17.7)
Uric acid			
PBO (447)	1 (0.2)	428 (95.7)	18 (4.0)
ADA (910)	18 (2.0)	864 (94.9)	28 (3.1)

ADA = adalimumab; PBO = placebo.

a. Number of subjects with a normal Baseline value.

b. Number of subjects with low, normal, or high final values who were normal at Baseline (according to the reference range).

Cross Reference: Table 2.2__1.3.2.2.3.

Source: BLA 1125057, ISS table 63, page 185

Reviewer's Comment: *Although the incidence of shifts for hepatic enzymes is higher, the incidence of potentially clinically significant shifts for hepatic enzymes does not show a real difference between placebo and adalimumab (see table 65). Furthermore, as discussed elsewhere in the review, the incidence of hepatic events in the placebo-controlled trials was higher in the placebo arm versus the adalimumab arm (2.6 vs. 1.8). Of the parameters that did show a shift to high of more than 1% difference, only the total cholesterol (3.4 vs. 4.4) and*

triglycerides (4.0 vs. 5.4) remained so as potentially clinically significant. While no subjects in the placebo arm had hypercholesterolemia reported as an adverse event, 0.9% of subjects had hypercholesterolemia reported as an adverse event in the adalimumab arm. However, no subjects in the placebo-controlled trials discontinued because of lipid profile aberrations. It should be noted that lipid profiles for the placebo trials were obtained in the fasting state.

Table 65. Number (%) of Subjects with Potentially Clinically Significant Clinical Chemistry Values (Placebo-controlled Study Set)

Clinical Chemistry Parameter (Unit)	Very Low Criteria	Very High Criteria	PBO N = 503 n/N_Obs[a] (%)	ADA N = 966 n/N_Obs[a]	p-value[b]
Albumin (g/L)	< 30.00		0/494	0/959	—
Alkaline phosphatase (U/L)		> 2.5 x ULN	0/494	0/959	—
ALT (U/L)		> 2.5 x ULN	11/494 (2.2)	23/959 (2.4)	—
AST (U/L)		> 2.5 x ULN	10/494 (2.0)	18/959 (1.9)	—
Bilirubin, total (µmol/L)		> 1.5 x ULN	10/494 (2.0)	14/959 (1.5)	—
Calcium (mmol/L)	< 2.00		1/494 (0.2)	0/959	—
		> 2.90	1/494 (0.2)	0/959	—
Cholesterol, total (mmol/L)		> 7.75	17/494 (3.4)	42/959 (4.4)	—
Creatinine (µmol/L)		> 1.5 x ULN	1/494 (0.2)	2/959 (0.2)	—
Glucose (mmol/L)	< 3.00		3/494 (0.6)	10/959 (1.0)	—
		>8.90	45/494 (9.1)	71/959 (7.4)	—
Phosphorus (mmol/L)	< 0.80		24/494 (4.9)	55/959 (5.7)	—
Potassium (mmol/L)	< 3.00		1/494 (0.2)	0/959	—
		> 5.50	5/494 (1.0)	5/959 (0.5)	—
Sodium (mmol/L)	< 130.00		0/494	1/959 (0.1)	—
		> 150.0	0/494	0/959	—
Triglycerides (mmol/L)		>2.5 x ULN	20/494 (4.0)	52/959 (5.4)	—
Uric acid (µmol/L)		> 590.00	14/494 (2.8)	10/959 (1.0)	0.016*

ADA = adalimumab; PBO = placebo.

***,**,* Statistically significant at the $p \leq 0.001$, ≤ 0.01, and ≤ 0.05 level, respectively.

a. N_Obs = Number of subjects with post-Baseline values.

b. The p-value for comparisons between PBO and ADA using Fisher's Exact Test. Only p-values ≤ 0.100 are presented.

Cross Reference: Table 2.2__1.3.3.2.1.

Source: BLA 125057, ISS , table 65, page 195

Clinical Chemistry – All Adalimumab Treatment Set

The numbers of subjects who changed from normal at Baseline to abnormal values at the final visit were generally small (< 5%) except for shifts to high for ALT (8.4%), chloride (6.1%), cholesterol (21.6%), CK (7.4%), glucose (11.7%), and triglycerides (18.7%). All the values for chemistry parameters are represented in table 67. It should be noted that chemistry values were not obtained in the fasting state.

Table 67. Number of Subjects with Clinical Chemistry Values in the Normal Range at Baseline and Low, High, or Normal Values at the Final Visit (All Adalimumab Treatment Set)

Clinical Chemistry Parameter (n)[a]	Changed to Low[b] n (%)	Remained Normal[b] n (%)	Changed to High[b] n (%)
Albumin (1609)	0 (0)	1596 (99.2)	13 (0.8)
Alkaline phosphatase (1576)	0 (0)	1563 (99.2)	13 (0.8)
ALT (1464)	0 (0)	1341 (91.6)	123 (8.4)
AST (1539)	0 (0)	1464 (95.1)	75 (4.9)
Bilirubin, total (1598)	0 (0)	1571 (98.3)	27 (1.7)
BUN (1604)	7 (0.4)	1575 (98.2)	22 (1.4)
Calcium (1618)	4 (0.2)	1606 (99.3)	8 (0.5)
Chloride (1540)	0 (0)	1446 (93.9)	94 (6.1)
Cholesterol, total (866)	4 (0.5)	675 (77.9)	187 (21.6)
CK (1495)	0 (0)	1384 (92.6)	111 (7.4)
Creatinine (1612)	0 (0)	1600 (99.3)	12 (0.7)
Glucose (1405)	24 (1.7)	1217 (86.6)	164 (11.7)
LDH (1627)	0 (0)	1609 (98.9)	18 (1.1)
Phosphorus (1553)	41 (2.6)	1478 (95.2)	34 (2.2)
Potassium (1620)	7 (0.4)	1602 (98.9)	11 (0.7)
Protein, total (1628)	0 (0)	1623 (99.7)	5 (0.3)
Sodium (1624)	17 (1.0)	1603 (98.7)	4 (0.2)
Triglycerides (1170)	0 (0)	951 (81.3)	219 (18.7)
Uric acid (1524)	31 (2.0)	1437 (94.3)	56 (3.7)

Note: Baseline = last assessment prior to first adalimumab injection.

a. Number of subjects with a normal Baseline value.

b. Number of subjects with low, normal, or high final values who were normal at Baseline (according to the reference range).

Cross Reference: Table 2.2__2.3.2.2.3.

Source: BLA 125057, ISS, table 67, page 202.

Clinical Hematology

Table 55 below shows the shifts of hematology values from normal to low or high for subjects from baseline to the final visit. The majority of subjects remained in the normal range for all hematology parameters evaluated. There are a few parameters where there is more than a 1% difference in the shift to high or low between adalimumab and placebo subjects, where the adalimumab group did the shifting. These parameters are neutrophils (2.4% vs. 0.2% shifted to low, lymphocyte, 2.0% vs. 0.2% shifted to high), and eosinophils (2.4% vs. 1.3% shifted to high. More than 93% of subjects remained normal in the placebo-controlled study set. Only a difference in very low neutrophil counts occurred between adalimumab and placebo for potentially clinically significant hematology values (0.6% vs. 1.7%).

Table 55. Number of Subjects with Hematology Values in the Normal Range at Baseline and Low, High, or Normal Values at the Final Visit (Placebo–controlled Study Set)

Hematology Parameter (n)[a]	Changed to Low[b] n (%)	Remained Normal[b] n (%)	Changed to High[b] n (%)
Hemoglobin			
PBO (464)	13 (2.8)	442 (95.3)	9 (1.9)
ADA (882)	15 (1.7)	849 (96.3)	18 (2.0)
Hematocrit			
PBO (452)	13 (2.9)	412 (91.2)	27 (6.0)
ADA (854)	17 (2.0)	785 (91.9)	52 (6.1)
RBC			
PBO (475)	9 (1.9)	456 (96.0)	10 (2.1)
ADA (921)	18 (2.0)	893 (97.0)	10 (1.1)
WBC			
PBO (460)	2 (0.4)	443 (96.3)	15 (3.3)
ADA (904)	9 (1.0)	872 (96.5)	23 (2.5)
Neutrophils			
PBO (466)	1 (0.2)	450 (96.6)	15 (3.2)
ADA (917)	22 (2.4)	877 (95.6)	18 (2.0)
Lymphocytes			
PBO (481)	4 (0.8)	476 (99.0)	1 (0.2)
ADA (944)	1 (0.1)	924 (97.9)	19 (2.0)
Basophils			
PBO (494)	0 (0)	494 (100.0)	0 (0)
ADA (961)	0 (0)	961 (100.0)	0 (0)
Eosinophils			
PBO (463)	10 (2.2)	447 (96.5)	6 (1.3)
ADA (903)	18 (2.0)	863 (95.6)	22 (2.4)
Monocytes			
PBO (454)	26 (5.7)	428 (94.3)	0 (0)
ADA (901)	54 (6.0)	844 (93.7)	3 (0.3)

Hematology Parameter (n)[a]	Changed to Low[b] n (%)	Remained Normal[b] n (%)	Changed to High[b] n (%)
Platelets			
PBO (475)	0 (0)	471 (99.2)	4 (0.8)
ADA (916)	4 (0.4)	905 (98.8)	7 (0.8)

ADA = adalimumab; PBO = placebo.

a. Number of subjects with a normal Baseline value.

b. Number of subjects with low, normal, or high final values who were normal at Baseline (according to the reference range).

Cross Reference: Table 2.2__1.3.2.1.3.

Source: BLA 125057, table 55, pages 163-164.

Very few subjects had potentially clinically significant aberrations in hematology values in the All Adalimumab Treatment Set. Table 59 denotes these changes.

Table 59. Number (%) of Subjects with Potentially Clinically Significant Hematology Values (All Adalimumab Treatment Set)

Hematology Parameter (Unit)	Very Low Criteria	Very High Criteria	ADA N = 1696 n/N_Obs[a] (%)
Hemoglobin (mmol/L)	< 6.20	—	2/1641 (0.1)
Platelets ($x10^9$/L)	< 75.00	—	2/1639 (0.1)
WBC ($x10^9$/L)	< 3.00	—	8/1641 (0.5)
Lymphocytes ($x10^9$/L)	< 1.00	—	66/1641 (4.0)
Neutrophils ($x10^9$/L)	< 1.50	—	38/1641 (2.3)

ADA = adalimumab.

a. N_Obs = Number of subjects with post-Baseline values.

Cross Reference: Table 2.2__2.3.3.1.1.

Source: BLA 125057, ISS , table 59, page 172

Of the 38 subjects with low neutrophil counts, 28 had either resolution with continued treatment with adalimumab or it was present at baseline. Thus, only 0.6% of subjects had low neutrophil counts that may have been related to study drug and no patient discontinued because of the low neutrophil count or had a hematologic AE reported by the Investigator. Of the 66 subjects with low lymphocyte counts, 58 either had resolution with continued treatment with adalimumab or it was present at baseline. The remaining 8 subjects (0.5%), did not prematurely discontinue or have an hematologic event reported by the Investigator.

Reviewer's Comment: *Upon reviewing some of the CRFs of the subjects whose low counts did not resolve, some had mild infections and some did not. Therefore, a clear correlation between low counts and infection could not be made.*

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

See section 7.1.7.5, Special Assessments

7.1.7.4 Additional analyses and explorations

As stated earlier, the All Adalimumab Treatment Set includes the later study phases where subjects had an average duration of treatment of one year and a maximum treatment duration of three years. In this set, the risk of AEs does not appear to increase with chronic adalimumab treatment. The rates of AEs per 100 patient-years of exposure are generally lower in the All Adalimumab Treatment Set compared with the Placebo-Controlled Study Set, particularly for infections (91.5 vs. 134.7/100 PY), injection site reactions (18.2 vs. 29.9 E/100PY), and hepatic events (4.9 vs. 10.2 E/100PY). The exposure-adjusted AE rates for 'any malignancy' and 'nonmelanoma skin cancer' in the All Adalimumab Treatment Set (1.5 and 0.9 E/100PY, respectively) are lower compared with the adalimumab treatment group in the Placebo-Controlled Study Set (2.4 and 1.7 E/100 PY).

7.1.7.5 Special assessments

The incidence of shifts for hepatic enzymes was higher in the adalimumab group than in the placebo group in the placebo controlled trials: 7.8% vs. 6.3%, respectively for ALT and 4.9% vs. 3.9% , respectively for AST. The incidence of potentially clinically significant shifts for hepatic enzymes, however, does not show a real difference between placebo and adalimumab: ALT >2.5x ULN was 2.4% vs. 2.2%, respectively and AST >2.5x ULN was 1.9 vs. 2.0, respectively. This is supported by the incidence of hepatic events (AEs) reported in the placebo controlled trials where the incidence in the adalimumab group vs. the placebo group was 1.8% vs. 2.6%, respectively. When adjusted for exposure, the result was 10.2% (ADA) vs. 9.5% (placebo), which is not a significant difference.

In the long term treatment with adalimumab, where patients were treated for at least 1 year and up to 3 years, 0.7%(13/1696) subjects had a maximum post-baseline ALT value ≥ 8.0 x ULN (seven ≥5.0 x ULN and six ≥ 8 x ULN). When one considers only the subjects that entered the trial with an ALT <1.5 x ULN, the incidence of the two falls between 0.2-0.3%. For AST, 0.4% (7/1696) subjects had a maximum post-baseline AST value ≥ 8.0 x ULN (two ≥5.0 x ULN and five ≥ 8.0 x ULN).

Hepatic AE(s) were reported by nine subjects, four of whom prematurely discontinued their study as a result of their hepatic AE(s). Alternative etiologies were given by the Investigators for all nine subjects who reported hepatic AEs (concomitant INH for three subjects, alcohol for two subjects, hepatitis for two subjects, a known fatty liver for one subject, and acute pancreatitis/obesity for one subject).

Of the 4 subjects who had increased ALTs that were not reported as hepatic AEs, 2 had ALT values that were >2.5 x ULN at baseline and two had values < 2.5x ULN at baseline. Of the former group, one subject's ALT fell to < 2.5x ULN with continued treatment, suggesting that adalimumab was not the cause. In the latter group, one subject's ALT remained > 2.5x the ULN and one subject's ALT values fell with continued treatment.

From this data, it appears that most subjects with shifts to high on adalimumab were asymptomatic, as only 1.8% of subjects had a reported hepatic event in the placebo controlled portions of the trials. The shifts to high for ALT and AST were observed in 7.8% and 4.9% of subjects, respectively, a much higher rate than actual hepatic events. Some of the abnormalities decreased or resolved with either continuation or discontinuation of adalimumab. It does not appear that adalimumab is a hepatotoxin, either in short term or long term treatment, although in a small subset of subjects, it may cause shifts of the hepatic enzymes to the high range, as observed in the placebo controlled trials. This should be noted in the label, and each case evaluated individually.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were taken at every visit in the clinical trials. Any changes in vital signs were considered to be AEs only if they resulted in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considered them to be AEs.

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies

Mean vital sign values at baseline between the placebo and adalimumab treatment groups were generally comparable. Systolic blood pressure was 126.98 mmHg for placebo and the mean for the adalimumab group was 124.34 mmHg. Diastolic means for placebo and adalimumab subjects were 79.40 mmHg and 78.72 mmHg, respectively. The mean for pulse rate for the placebo controlled study set and the adalimumab study set was 73.37 and 73.42, respectively; for weight 92.81 kg and 91.12 kg, respectively, and for temperature, 36.5°C and 36.53°C.

During treatment, mean changes from baseline in systolic and diastolic blood pressure, pulse rate, weight, and temperature were small and comparable between the two treatment groups.

7.1.8.2.2 Marked outliers and dropouts for vital sign abnormalities

The numbers of subjects with potentially clinically significant values for systolic or diastolic blood pressure or pulse rate were small (see table 75). There were no subjects in the placebo or adalimumab study sets that discontinued for increases or decreases in blood pressure.

Table 75. Number (%) of Subjects with Potentially Clinically Significant Vital Sign Values (Placebo–controlled Study Set)

Vital Sign (Unit)	Very Low Criteria	Very High Criteria	PBO N = 503 n/N_Obs[a] (%)	ADA N = 966 n/N_Obs[a]
Systolic blood pressure (mmHg)		> 180	8/495 (1.6)	10/962 (1.0)
	< 80		2/495 (0.4)	0/962
Diastolic blood pressure (mmHg)		> 110	7/495 (1.4)	7/962 (0.7)
	< 40		0/495	0/962
Pulse rate (bpm)		>110	6/495 (1.2)	6/962 (0.6)
	< 50		7/495 (1.4)	17/962 (1.8)

ADA = adalimumab; PBO = placebo.

a. N_Obs = Number of subjects with post-Baseline values.

Cross Reference: Table 2.2_1.4.2.1.

Source: BLA 125057, ISS, page 224, table 75.

Reviewer's Comment: *As shown in the section of common treatment emergent AEs, the percentage of subjects with an AE of hypertension was not appreciably different between placebo and adalimumab, 2.2 vs. 2.0, respectively.*

7.1.9 Electrocardiograms (ECGs)

ECGs were obtained on subjects at baseline. It was only repeated at week 24, 52, or early termination if the Investigator felt that the development of an AE warranted a repeat. Only a very small number of subjects in the pivotal trials had repeats of their ECGs. These 7 subjects did not have abnormalities that warranted discontinuation from the trials.

7.1.10 Immunogenicity

See biopharmaceutics section (section 5) and section 7.1.12 (Special Safety Studies).

7.1.11 Human Carcinogenicity

The current label of HUMIRA states, "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. The impact of treatment with

HUMIRA on the development and course of malignancies, as well active and/or chronic infections is not fully understood. The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated."

7.1.12 Special Safety Studies

Studies M02-528 and M03-656 evaluated the effect of the development of AAA on the safety of adalimumab in the psoriasis population. As only 3 subjects were AAA+ in study M02-528 and the evaluation was only for 12 weeks, the analysis is on study M03-656, where more subjects were AAA+ and evaluated for 52 weeks.

The overview of number and percentage of subjects with treatment-emergent AEs, stratified by AAA status, is summarized in table 13. The overall percentage of subjects with any AE was lower in the AAA+ subjects (63.0%) than that in the AAA- (78.4%) subjects. There were three serious AEs reported in the AAA+ group. Two of them were considered by the investigator to be not related to study drug (meningioma in the pituitary region and ventricular tachycardia), and the third was considered by the investigator to be probably not related to study drug (deep vein thrombosis). Additionally, there was no suggestion for an underlying mechanism that these events may be caused by AAA. The rate of infections was lower in the AAA+ subjects (27.4%) than that in the AAA- subjects (48.3%), and there was no event of serious infections in any of the AAA+ subjects.

Table 13. Overview of Number and Percentage of Subjects with Treatment–Emergent AEs (All Adalimumab Group in Study M03–656)

	AAA+ (N = 73)	AAA- (N = 750)
	n (%)	n (%)
Subjects with:		
Any AE	46 (63.0)	588 (78.4)
Any AE at least possibly drug-related[$]	14 (19.2)	217 (28.9)
Any severe AE	3 (4.1)	38 (5.1)
Any serious AE	3 (4.1)	25 (3.3)
Any AE leading to discontinuation of study drug	2 (2.7)	27 (3.6)
Any fatal AE	0	0
Infections	20 (27.4)	362 (48.3)
Serious infections	0	10 (1.3)
Malignancies	0	8 (1.1)
Lymphoma	0	0
Non-melanoma skin cancers	0	6 (0.8)
Other malignancies	0	2 (0.3)
Demyelinating disorders	0	0
Congestive heart failure	0	1 (0.1)
Injection site reaction	1 (1.4)	68 (9.1)

$ As assessed by investigator.
Source: BLA 125057, Summary of Clinical Pharmacology, page 26

Table 14 shows the distribution of subjects who reported injection site reactions, stratified by AAA status. The AAA+ subjects had a lower incidence of injection site reactions compared to the AAA- subjects.

Table 14 presents the data for injection site reactions for subjects who were AAA+ compared to those who were AAA-. AAA+ subjects did not experience higher instances of injection site reactions. The only injection site reaction that AAA+ subjects experienced was that of injection site pain and it was comparable to AAA- subjects, 1.4% vs. 1.6%, respectively.

Table 14. Distribution of Subjects Reporting Injection Site Reactions in Study M03-656

	AAA+ (N = 73)	AAA- (N = 750)
	n (%)	n (%)
Injection site bruising	0	8 (1.1)
Injection site erythema	0	5 (0.7)
Injection site haemorrhage	0	5 (0.7)
Injection site induration	0	1 (0.1)
Injection site irritation	0	17 (2.3)
Injection site nodule	0	1 (0.1)
Injection site pain	1 (1.4)	12 (1.6)
Injection site pruritus	0	3 (0.4)
Injection site reaction	0	31 (4.1)
Injection site swelling	0	1 (0.1)
Injection site urticaria	0	1 (0.1)
Injection site vesicles	0	1 (0.1)

Source: BLA 125057, Clinical Pharmacology section, page 27.

Reviewer's Comment: *Adverse event reporting showed that 17/1696 (1%) of subjects reported an AE of urticaria. Upon review of the subjects who were AAA+, none of these subjects reported urticaria as an adverse event. Given all the data, the development of anti-adalimumab antibodies does adversely impact the safety of those subjects who are AAA+ compared to those who are AAA- (see section 5 for impact on efficacy).*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence for and no anticipation of subject abuse of adalimumab. No subject in the clinical trials experienced rebound or deterioration to more severe forms of psoriasis upon discontinuation of the drug product.

7.1.14 Human Reproduction and Pregnancy Data

Female subjects were to have a negative pregnancy test at Screening for all studies included in the Ps clinical development program and were requested to use a reliable method of contraception during the studies and up to 150 days after the last dose of study medication. If a pregnancy occurred, the subject was to have been discontinued from the study.

Seven female subjects treated with adalimumab and the female partner of one male subject treated with adalimumab became pregnant during the Ps clinical development program. Six of the seven subjects delivered healthy babies without complications. One subject had planned to carry her baby to term but had a spontaneous abortion.

Reviewer's Comment: *The current prescribing information for adalimumab does not recommend the use of the drug during pregnancy and lactation. This new information does not inform for a change in the label. Currently, a pregnancy registry is in place for any patients who become pregnant while taking adalimumab to further monitor pregnancy outcomes.*

7.1.15 Overdose Experience

No new information regarding overdose was gained from the psoriasis clinical development program; therefore, no new information is proposed for the adalimumab prescribing information.

7.1.16 Postmarketing Experience

According to a consult prepared by DDRE on May 11, 2006, as of April 1, 2006, the AERS database contained 14,438 adverse event reports for adalimumab (both serious and non-serious). Of these, 628 reports were associated with fatal outcomes. Adalimumab was also used for the treatment of psoriasis and/psoriatic arthritis in 255 of the adverse event reports. The fatalities in the psoriasis/psoriatic arthritis population were 3, two patients died from sepsis and one patient died from a myocardial infarction. They were all male, ages 32, 46, and 65 years. Causality, according to the consult, was difficult to establish given pre-existing medical history and/or co-morbidities.

Since that postmarketing consult to November 2007, the AERS databse contains 17,450 adverse event reports for adalimumab, of which 1024 had an outcome of death. Those adverse events associated with psoriasis/psoriatic arthritis are 487. The total number of fatalities is 14 for the psoriatic arthritis population. This includes the 3 fatalities described above. Seven of the deaths are US, six are foreign, and one is definitely not related to adalimumab, as the patient died from a subdural hematoma as the result of a fall. Six of the 14 deaths were due to infection, 3 to a cardiovascular event (MI x 2 and CVA), and one to promyelocytic leukemia. One patient died of peritonitis as the result of a perforated diverticulum and in another case the cause of death is unknown. Finally, in the last death reported, the subject complained of epigastric pain, chest pain, and lethargy after 1 dose of adalimumab and was found dead 1 month later.

For the infection-related deaths, HUMIRA may have been a contributing factor. The label has a black-box warning that states that infection can result in fatality. For the other non-infection-related deaths, causality cannot be definitively established, as there did not appear to be a particular trend that could be discerned and some cases did not provide enough information and/or had co-morbidities. A phase 4 long-term trial will try to elucidate some of these issues. Finally, a review of all the adverse events reported does not raise any new safety issues with HUMIRA.