Adalimumab

HUMIRA® 20 mg/0.2 mL

Solution for Injection in pre-filled syringe
Subcutaneous use

FORMULATION

Each 0.2mL pre-filled syringe contains:
Adalimumab 20mg

DESCRIPTION

Humira (adalimumab) is a recombinant human immunoglobulin (IgG_1) monoclonal antibody containing only human peptide sequences. Humira was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human tumor necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. Humira binds with high affinity and specificity to soluble tumor necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). 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.

Humira is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use 1 mL pre-filled glass syringe, 1 mL single-use glass vial or as a single-use pre-filled Pen (Humira Pen). Enclosed within the Pen is a single-use, 1 mL pre-filled glass syringe. The solution of Humira is clear and colorless, with a pH of about 5.2.

Inactive ingredients for Humira 40 mg per 0.8 mL (50 mg/mL) include: 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, sodium hydroxide, as needed (for pH adjustment) and water for injection.

Inactive ingredients for Humira 20 mg per 0.2 mL (100 mg/mL) include: 8.4 mg mannitol, 0.2 mg polysorbate 80, and water for injection.

Inactive ingredients for Humira 40 mg per 0.4 mL (100 mg/mL) include: 16.8 mg mannitol, 0.4 mg polysorbate 80, and water for injection.

Inactive ingredients for Humira 80 mg per 0.8 mL (100 mg/mL) include: 33.6 mg mannitol, 0.8 mg polysorbate 80, and water for injection.

INDICATIONS

Pediatrics

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

Humira is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients, 2 years of age and older. Humira can be used alone or in combination with methotrexate.

Enthesitis-Related Arthritis

Humira is indicated for the treatment of enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Pediatric Crohn's Disease

Humira is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients, 6 years of age and older, with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

Pediatric Plaque Psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Pediatric Uveitis

Humira is indicated for the treatment of chronic non-infectious uveitis in pediatric patients 2 years of age and older.

DOSAGE AND ADMINISTRATION

Pediatrics

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

[Note: The clinical study to support the indication was done using a dose by body surface area throughout the controlled phase. In the open label part of the study, the dosing was changed to a fixed dose according to a body weight cut-off.]

The recommended dose of Humira for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 1). MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with Humira. Humira may be available in different strengths and/or presentations.

Table 1. Humira Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Humira has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of Humira in children aged <2 years in this indication.

Enthesitis-Related Arthritis

The recommended dose of Humira for patients from 6 years of age with enthesitis-related arthritis is based on body weight (Table 2). Humira may be available in different strengths and/or presentations.

Table 2. Humira Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Pediatric Crohn's Disease

The recommended dose of Humira for patients from 6 to 17 years of age with Crohn’s disease is based on body weight (Table 3). Humira is administered via subcutaneous injection. Humira may be available in different strengths and/or presentations.

Table 3. Humira Dose for Pediatric Patients with Crohn’s disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	20 mg every other week
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	40 mg every other week

Some patients may benefit from increasing the dosage if a disease flare or an inadequate response is experienced during maintenance dosing;

- < 40 kg: 20 mg every week
- ≥ 40 kg: 40 mg every week or 80 mg every other week

Humira has not been studied in children with Crohn's disease aged less than 6 years.

Pediatric Plaque Psoriasis

The recommended Humira dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 4). Humira is administered via subcutaneous injection. Humira may be available in different strengths and/or presentations.

Table 4. Humira Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.

There is no relevant use of Humira in children aged less than 4 years in this indication.

Pediatric Uveitis

The recommended dose of Humira for pediatric patients 2 years of age and older with chronic non-infectious uveitis is based on body weight (Table 5). Humira is administered via subcutaneous injection. Humira may be available in different strengths and/or presentations. Humira may be used in combination with methotrexate or other non-biologic immunomodulatory agents based on clinical judgment.

Table 5. Humira Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

When Humira is initiated, a loading dose of 40 mg for patients <30 kg or 80 mg for patients ≥30 kg may be administered one week prior to the start of maintenance therapy.

There is no relevant use of Humira in children aged less than 2 years in this indication.

Preparation of Humira

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

Sites for self-injection include thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Humira should not be mixed in the same syringe or vial with any other medicine.

Any unused product or waste material should be disposed of in accordance with local requirements.

Pediatric Use

Humira has not been studied in children less than 2 years of age.

The safety and efficacy of Humira in pediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), pediatric Crohn's disease, pediatric plaque psoriasis, and adolescent hidradenitis suppurativa have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of Humira, 9.4% were 65 years and over while approximately 2.0% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. No dose adjustment is needed for this population.

CONTRAINDICATIONS

Humira should not be administered to patients with known hypersensitivity to Humira or any of its excipients.

WARNINGS AND PRECAUTIONS

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis) viral, parasitic, or other opportunistic infections have been reported in patients receiving TNF-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, Legionellosis and pneumocystis have also been reported with the use of TNF-antagonists, including Humira. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Many of the serious infections

have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections.

Treatment with Humira should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have traveled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy (see **Opportunistic Infections**).

As with other TNF-antagonists, patients should be monitored closely for infections, including tuberculosis before, during and after treatment with Humira.

Patients who develop a new infection while undergoing treatment with Humira, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until infections are controlled.

Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions, which may predispose patients to infections.

Tuberculosis

Tuberculosis including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated).

Before initiation of therapy with Humira, all patients should be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (e.g., chest x-ray and tuberculin skin test) should be performed in accordance with local recommendations. Treatment of latent tuberculosis infections should be initiated prior to therapy with Humira. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG)$^{+}$.

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.

If active tuberculosis is diagnosed, Humira therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of Humira and in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of Humira in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If

necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with Humira. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Also, active tuberculosis has developed in patients receiving Humira whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with TNF blocking agents.

Patients receiving Humira should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Humira.

[+]as permitted by local regulations.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving Humira. These infections are not consistently recognized in patients taking TNF-blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Reactivation

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system,

which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurologic Events

TNF antagonists, including Humira, have been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and optic neuritis, and peripheral demyelinating disease, including Guillain Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Humira should be considered if any of these disorders develop.

There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Humira therapy to assess for pre-existing central demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open label trials with Humira, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. The malignancies occurred after a median of 30 months of therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Very rare postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of

the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6–mercaptopurine and Humira should be carefully considered. The causal association of HSTCL with adalimumab is not clear.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving Humira. Thus additional caution should be exercised in considering Humira treatment of these patients.

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Humira.

Cases of acute and chronic leukemia have been reported in association with postmarketing TNF blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukemia, even in the absence of TNF-blocking therapy.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Allergic

Serious allergic reactions associated with Humira were rare during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

Hematologic Events

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

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy,

similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended.

Concomitant administration of adalimumab with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF antagonists is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Immunosuppression

In a study of 64 patients with RA that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils.

Vaccinations

In a randomized, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with Humira, antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86% of patients in the Humira group compared to 82% in the placebo group. A total of 37% of Humira-treated subjects and 40% of placebo-treated subjects achieved at least a 2-fold increase in at least 3 out of 5 pneumococcal antigens. In the same study 98% of patients in the Humira group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of Humira-treated subjects and 63% of placebo-treated subjects achieved at least a 4-fold increase in at least 2 out of 3 influenza antigens.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Humira therapy.

Patients on Humira may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving Humira.

Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother’s last adalimumab injection during pregnancy.

Congestive Heart Failure

Humira has not been formally studied in patients with congestive heart failure (CHF), however, in clinical studies with another TNF antagonist, a higher rate of serious CHF-related adverse events including worsening CHF and new onset CHF have been reported. Cases of worsening CHF have also been reported in patients receiving Humira. Physicians should exercise caution when using Humira in patients who have heart failure and monitor them carefully.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies.

The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown.

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira, treatment should be discontinued (see **ADVERSE REACTIONS - Autoantibodies**).

Geriatric Use

The frequency of serious infection among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Of the total number of subjects in clinical studies of Humira, 9.4% were 65 years and over, while approximately 2.0% were 75 and over. Because there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

DRUG INTERACTIONS

When Humira was administered to 21 RA patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29% and 44% respectively**.** The data do not suggest the need for dose adjustment of either Humira or MTX.

Interactions between Humira and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when Humira was administered with commonly used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

Drug/Laboratory Test Interaction

There is no known interference between Humira and laboratory tests.

PREGNANCY AND LACTATION

Pregnancy

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (373 times human AUC when given 40 mg SC) and has revealed no evidence of harm to the fetuses due to adalimumab.

In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled.

There were no significant differences in the overall rates for the primary endpoint of major birth defects (adjusted Odds Ratio 0.84, 95% Confidence Interval (CI) 0.34, 2.05) as well as the secondary endpoints which included minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections. No stillbirths or malignancies were reported.

Although the registry has methodological limitations, including small sample size and non-randomized study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not

treated with adalimumab. In addition, data from post-marketing surveillance does not establish the presence of a drug-associated risk.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Labor and Delivery

There are no known effects of Humira on labor or delivery.

Nursing Mothers

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally ingested immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability, systemic effects of adalimumab in a breast fed infant are unlikely. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects on the breastfed child from adalimumab or from the underlying maternal condition.

ADVERSE REACTIONS

Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis), Psoriatic Arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis), Crohn's Disease, Ulcerative Colitis, Psoriasis, Hidradenitis Suppurativa and Uveitis Clinical Trials

Humira was studied in 9506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long-term disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients.

The controlled pivotal studies involved 6089 patients receiving Humira and 3801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

Approximately 13% of patients can be expected to experience injection site reactions, based on one of the most common adverse events with adalimumab in controlled clinical studies.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥ 1/10,000 to <1/1000) in Table 6 below. The highest

frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections Contraindications, Warnings and Precautions and Adverse Reactions.

Table 6: Adverse Reactions in Clinical Studies

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very Common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections,
Neoplasms benign, malignant and unspecified (including cysts and polyps) *	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	lymphoma**, solid organ neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm) melanoma**
Blood and the lymphatic system disorders*	Very Common	leucopenia (including neutropenia and agranulocytosis), anemia
	Common	thrombocytopenia, leucocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia

System Organ Class	Frequency	Adverse Reaction
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very Common	lipids increased
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycemia, hypophosphotemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very Common	headache
	Common	paraesthesias (including hypoasthesia), migraine, nerve root compression
	Uncommon	tremor, neuropathy
	Rare	multiple sclerosis
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	hypertension, flushing, haematoma
	Uncommon	vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	cough, asthma, dyspnoea

System Organ Class	Frequency	Adverse Reaction
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very Common	abdominal pain, nausea and vomiting
	Common	GI hemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face edema
Hepato-biliary disorders*	Very Common	liver enzymes elevated
	Uncommon	cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash),
	Common	pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis
	Uncommon	night sweats, scar
Musculoskeletal and connective tissue disorders	Very Common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis systemic lupus erythematosus
Renal and urinary disorders	Common	haematuria, renal impairment
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common	injection site reaction (including injection site erythema)

System Organ Class	Frequency	Adverse Reaction
	Common Uncommon	chest pain, edema inflammation
Investigations	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody tests positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning, and procedural complications	Common	impaired healing

* Further information found elsewhere in Contraindications, Warnings & Precautions and Adverse Reactions
** Includes open label extension studies

Uveitis

The safety profile for patients with non-infectious uveitis treated with Humira was consistent with the known safety profile of Humira.

Pediatric Population

In general, the adverse reactions in pediatric patients were similar in frequency and type to those seen in adult patients.

Injection Site Reactions

In the pivotal controlled trials in adults and children, 12.9% treated with Humira developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7.2% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient-year in the Humira treated patients and 1.46 per patient year in the control-treated patients. The incidence of serious infections was 0.04 per patient-year in Humira treated patients and 0.03 per patient-year in control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infections, and sinusitis. Most patients continued on Humira after the infection resolved.

In the controlled and open label adult and pediatric studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) and invasive opportunistic infections (e.g., disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis).

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 pediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 pediatric patients with an exposure of 498.1 patient years during a Humira trial in pediatric patients with Crohn's disease.

No malignancies were observed in 77 pediatric patients with an exposure of 80.0 patient years during a Humira trial in pediatric patients with plaque psoriasis.

No malignancies were observed in 60 pediatric patients with an exposure of 58.4 patient years during a Humira trial in pediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1000 patient-years among 5291 Humira treated patients versus a rate of 6.3 (3.4, 11.8) per 1000 patient-years among 3444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients.

The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1000 patient-years among Humira-treated patients and 3.2 (1.3, 7.6) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1000 patient-years in the controlled portion of clinical trials and in ongoing and completed open label extension studies. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1000 patient-years, and the observed rate of lymphomas is approximately 1.3 per 1000 patient-years. The median duration of these studies is approximately 3.3 years and included 6427 patients who were on Humira for at least 1 year or who developed a malignancy within a year of starting therapy, representing 26439.6 patient-years of therapy.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in RA Studies I − V. In these adequate and well-controlled trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control-treated patients that had negative baseline anti-nuclear antibody titers reported positive titers at week 24.

Two patients out of 3989 treated with Humira in all RA, PsA and AS studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system

symptoms. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown.

Psoriasis: New-onset and Worsening

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF blockers, including Humira. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of Humira should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations

In controlled Phase 3 trials of Humira (40 mg SC every other week), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between Humira and the liver enzyme elevations is not clear. In controlled Phase 3 trials of Humira (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in patients with Crohn's disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of Humira-treated patients and 0.9% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In the Phase 3 trial of Humira in patients with pediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 X ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled trials of Humira (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in Humira-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of Humira in pediatric patients with plaque psoriasis.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare postmarketing reports of severe hepatic reactions including liver failure in patients

receiving TNF blockers, including adalimumab. The causal relationship to adalimumab treatment remains unclear.

Concurrent treatment with azathioprine/6–mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6–mercaptopurine compared with Humira alone.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

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

Table 7: Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

System Organ Class	Adverse Reaction
Infections and infestations	diverticulitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)*	hepatosplenic T-cell lymphoma, leukemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)
Immune system disorders*	anaphylaxis, sarcoidosis
Nervous system disorders*	demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident.
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, pleural effusion, pulmonary fibrosis
Gastrointestinal disorders*	intestinal perforation
Hepatobiliary disorders*	reactivation of hepatitis B, liver failure, hepatitis
Skin and subcutaneous tissue disorders	cutaneous vasculitis, Stevens Johnson Syndrome, angioedema, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis) erythema multiforme, alopecia, lichenoid skin reaction**
Musculoskeletal and connective tissue disorders	lupus-like syndrome
Cardiac disorders	myocardial infarction
General disorders and administration site conditions	pyrexia
* further information is found elsewhere in Contraindications, Warnings & Precautions and Adverse Reactions. ** occurring in patients receiving a TNF-antagonist including Humira	

OVERDOSAGE

The maximum tolerated dose of Humira has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with Humira. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

CLINICAL PHARMACOLOGY

General

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with Humira may reduce the epidermal thickness and infiltration of inflammatory cells. Increased levels of TNF are also found in hidradenitis suppurativa (HS) lesions. The relationship between these pharmacodynamic activities and the mechanism(s) by which Humira exerts its clinical effects is unknown.

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

Pharmacodynamics

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and serum cytokines (IL-6)) was observed compared to baseline in patients with RA. A decrease in CRP levels was also observed in patients with JIA, Crohn's disease, ulcerative colitis and hidradenitis suppurativa as well as a significant reduction in the expression of TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after Humira administration. Patients with RA, PsA and AS often experience mild to moderate anemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with Humira usually experienced improvement in these hematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown below:

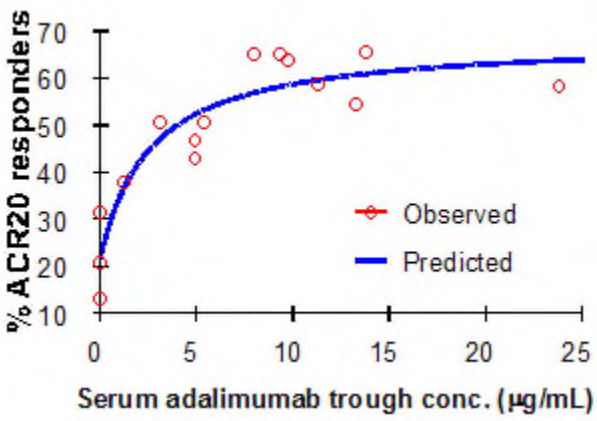


Figure 1: Concentration-Efficacy Relationship

EC_{50} estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic/ pharmacodynamic modeling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.

Pharmacokinetics

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was slow, with mean peak serum concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%.

Distribution and Elimination

The single dose pharmacokinetics of adalimumab were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 mcg/mL (without concomitant methotrexate (MTX) and 8 to 9 mcg/mL (with concomitant MTX), respectively. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg every other

week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with psoriasis, the mean steady-state trough concentration was 5 mcg/mL during adalimumab 40 mg eow without concomitant methotrexate treatment.
In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 mcg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/mL during adalimumab 40 mg every week treatment.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 mcg/mL.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS, and pediatric patients ≥ 40 kg with CD).

Population pharmacokinetic analyses with data from over 1200 patients revealed that coadministration of MTX had an intrinsic effect on adalimumab apparent clearance (CL/F) (see **DRUG INTERACTIONS).** As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult non-radiographic axial spondyloarthritis patients, the mean (±SD) trough steady-state concentration at Week 68 was 8.0 ± 4.6 μg/ml.

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

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 mcg/mL during the induction period. Mean steady-state trough levels of approximately 8 mcg/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

In Japanese patients with intestinal Behcet's disease, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 13 mcg/mL during the induction period. Mean steady-state trough levels of approximately 9 mcg/mL were observed in Japanese intestinal Behcet's disease patients who received a maintenance dose of 40 mg adalimumab every other week.

Special Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Geriatrics

Age appeared to have a minimal effect on adalimumab apparent clearance. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n=850) and ≥65 years (n=287) were 0.33 and 0.30 mL/h/kg, respectively.

Pediatrics

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/mL (102 % CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/mL (47.7% CV) with concomitant methotrexate. The mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.6 µg/mL and 8.1 µg/mL, respectively. In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/m^2, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/mL (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 µg/mL (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/mL with concomitant methotrexate.

In pediatric patients with moderately to severely active Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomized 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7±6.6 µg/mL for patients ≥ 40 kg (160/80 mg) and 10.6±6.1 µg/mL for patients < 40 kg (80/40 mg).

For patients who stayed on their randomized therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5±5.6 µg/mL for the Standard Dose group and 3.5±2.2 µg/mL for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3±11.4 µg/mL (40/20 mg, weekly) and 6.7±3.5 µg/mL (20/10 mg, weekly).

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to pediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/mL (79% CV).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of 40 mg every other week is predicted to provide serum adalimumab exposure similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.

Gender

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Race

No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and Renal Insufficiency

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

Disease States

Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

PRE-CLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

No clastogenic or mutagenic effects of adalimumab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

DESCRIPTION OF CLINICAL STUDIES

Adults

RHEUMATOID ARTHRITIS CLINICAL STUDIES

Humira was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of Humira were assessed in five randomized, double-blind and well-

controlled studies. Some patients were treated for greater than 60 months duration. Some patients were treated for up to 120 months duration. Injection site pain of Humira 40 mg/0.4 mL compared to Humira 40 mg/0.8 mL was assessed in two randomized, active control, single-blind, two-period crossover studies.

RA Study I (DE009) evaluated 271 patients with moderately to severely active RA who were ≥18 years old, had failed therapy with at least one but no more than four disease-modifying anti-rheumatic drugs (DMARDs) (e.g., hydroxychloroquine, oral or injectable gold, azathioprine, D-penicillamine, sulfasalazine), and had insufficient efficacy with MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained constant at 10 to 25 mg every week. Patients had ≥6 swollen joints and ≥9 tender joints and RA diagnosed according to ACR criteria. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

RA Study II (DE011) evaluated 544 patients with moderately to severely active RA who were ≥18 years old and had failed therapy with at least one DMARD (e.g., MTX, sulfasalazine, hydroxychloroquine, oral or injectable gold, D-penicillamine, azathioprine). Patients had ≥10 swollen joints and ≥12 tender joints and were also diagnosed according to ACR criteria. Doses of 20 or 40 mg of Humira were given by SC injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration.

RA Study III (DE019) evaluated 619 patients with moderately to severely active RA who were ≥18 years old, had insufficient efficacy to MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained constant at 12.5 to 25 mg every week. Unlike RA Study I, patients in RA Study III were not required to have failed therapy with any DMARDs other than MTX. Patients had ≥6 swollen joints and ≥9 tender joints and RA diagnosed according to ACR criteria. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of Humira/MTX was administered every other week up to 60 months. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of Humira/MTX was administered every other week up to 10 years.

RA Study IV (DE031) assessed 636 patients with moderately to severely active RA who were ≥18 years old. These patients met the ACR criteria for diagnosis of RA for at least three months and had at least 6 swollen joints and 9 tender joints. Patients were permitted to be either DMARD-I or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of Humira or placebo every other week for 24 weeks.

RA Study V (DE013) evaluated 799 methotrexate-naïve, adult patients with moderately to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Humira 40 mg every other week/methotrexate combination therapy, Humira 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms of RA and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 10 years.

RA Studies VI and VII each evaluated 60 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Enrolled patients were either current users of Humira 40 mg/0.8 mL and rated their average injection site pain as at least 3 cm (on a 0-10 cm VAS) or were biologic-naïve subjects who were starting Humira 40 mg/0.8 mL. Patients were randomized to receive a single dose of Humira 40 mg/0.8 mL or Humira 40 mg/0.4 mL, followed by a single injection of the opposite treatment at their next dose.

Results of RA Study I-V were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary end point in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA Study V was the percent of patients who achieved an ACR 50 response at Week 52. RA Study III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by x-ray results). RA Study III also had a primary endpoint of changes in quality of life. The primary endpoint in RA studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

Clinical Response

Studies I, II and III

The percent of Humira treated patients achieving ACR 20, 50 and 70 responses was consistent across all three trials. The results of the three trials are summarized in Table 8.

Table 8: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a*]		RA Study II[a*]		RA Study III[a*]	
	Placebo/ MTX n=60	Humira[b]/ MTX n=63	Placebo n=110	Humira[b] *n=113	Placebo/ MTX n=200	Humira[b]/ MTX n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] RA Study I at 24 weeks, RA Study II at 26 weeks, and RA Study III at 24 and 52 weeks
[b] 40 mg Humira administered every other week
* p<0.01, Humira *vs.* placebo at all timepoints for ACR 20, 50, 70

Patients receiving Humira 40 mg every week in RA Study II also achieved statistically significant ACR 20, 50 and 70 response rates of 53.4%, 35.0% and 18.4%, respectively, at six months.

The results of the components of the ACR response criteria for RA Study III are shown in Table 9. The results depicted below are generally representative of each trial conducted.

ACR response rates and improvement in all ACR response criteria were maintained to week 104. Over the 2 years in RA Study III, 24% of Humira patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 60 months with continuous Humira treatment in the open-label portion of RA study III.

In the open-label extension for RA Study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomized to Humira 40 mg every other week, 114 patients continued on Humira 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on Humira 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

Table 9: Components of ACR Response in RA Study III

	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Parameter (median)	Placebo/MTX (N=200)			Humira [a]/MTX (N=207)		
Number of tender joints (0-68)	26.0	15.0	15.0	24.0	8.0*	6.0*
Number of swollen joints (0-66)	17.0	11.0	11.0	18.0	5.0*	4.0*
Physician global assessment disease activity[b]	63.0	35.0	38.0	65.0	20.0*	16.0*
Patient global assessment disease activity[b]	53.5	39.0	43.0	52.0	20.0*	18.0*
Pain[b]	59.5	38.0	46.0	58.0	21.0*	19.0*
Disability index (HAQ)[c]	1.50	1.25	1.25	1.50	0.75*	0.75*
CRP (mg/ L)	10.0	9.0	9.0	10.0	4.0*	4.0*

[a] 40 mg Humira administered every other week

[b] Visual analogue scale; 0 = best, 100 = worst

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

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

In RA Study III, 84.7% of patients with ACR 20 responses at Week 24 maintained the response at 52 weeks. The following figures illustrate the durability of ACR 20 responses to Humira in Studies III and II.

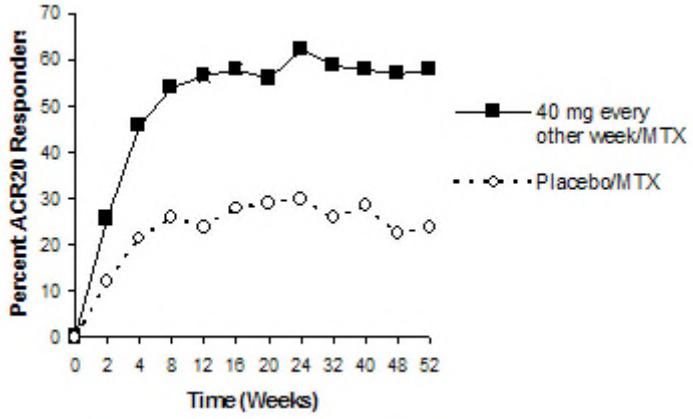


Figure 2: RA Study III ACR 20 Responses over 52 Weeks

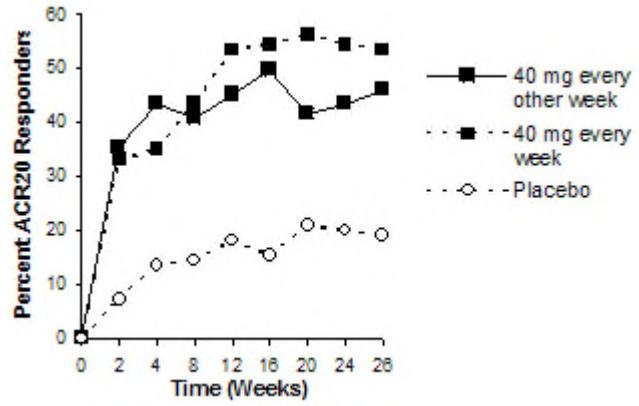


Figure 3: RA Study II ACR 20 Responses over 26 Weeks

RA Study IV

The ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of Humira and other DMARDs were observed.

In RA Studies I-IV, Humira treated patients achieved ACR 20, 50 and 70 responses faster and more often than placebo-treated patients. In RA Study I, there was a statistically significant difference in ACR 20 responses at week one (first study visit) between patients treated with Humira (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in RA Studies II, III and IV at week two (first study visit) between patients treated with Humira (36.4%, 29.1% and 33.7%, respectively) and placebo (7.3%, 13.0% and 8.6%, respectively). A similar pattern of the time to first ACR 50 and 70 responses was noted in all four studies.

Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of Humira to 40 mg every week. This was confirmed in a long-term open label

study where patients with an incomplete response increased their dosing frequency from 40 mg every other week to 40 mg weekly.

RA Study V

In RA Study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Humira monotherapy at Week 52 and responses were sustained through Week 104 (see Table 10).

At Week 52 all individual components of the ACR response criteria improved with Humira/methotrexate therapy and improvements were maintained to Week 104.

Over the two-year study, 48.5 % patients who received Humira/methotrexate combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ($p<0.001$) and 24.5% of patients who received Humira monotherapy ($p<0.001$).

Table 10: ACR Response in RA Study V (Percent of Patients)

Response	MTX[b] N=257	Humira[c] N=274	Humira/MTX N=268
ACR 20			
Week 52	62.6%	54.4%	72.8%
Week 104	56.0%	49.3%	69.4%
ACR 50			
Week 52	45.9%	41.2%	61.6%
Week 104	42.8%	36.9%	59.0%
ACR 70			
Week 52	27.2%	25.9%	45.5%
Week 104	28.4%	28.1%	46.6%
Major Clinical Response[a]			
Week 104	27.2%	24.5%	48.5%

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

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

c $p<0.001$, Humira/MTX *vs.* Humira

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomized to Humira 40 mg every other week, 170 patients continued on Humira 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At week 52, 42.9% of patients who received Humira/methotrexate combination therapy achieved clinical remission (Disease Activity Score (DAS28)-CRP <2.6) compared to 20.6% of patients

receiving methotrexate monotherapy and 23.4% of patients receiving Humira monotherapy. Humira/methotrexate combination therapy was statistically and clinically superior to methotrexate ($p<0.001$) and Humira monotherapy ($p<0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis (see Table 11). Of 342 subjects originally randomized to Humira monotherapy or Humira/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of Humira treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Table 11: DAS28 Responses in RA Study V

DAS28 Response	MTX N=257	Humira N=274	Humira/MTX N=268
Week 52			
Baseline (Mean)	6.3	6.4	6.3
Mean Change from Baseline (Mean ± SD)	-2.8 ± 1.4[a]	-2.8 ± 1.5[b]	-3.6 ± 1.3
Percent of Patients in Remission (DAS28<2.6)	20.6%[a]	23.4%[b]	42.9%
Week 104			
Baseline (Mean)	6.3	6.3	6.3
Mean Change from Baseline (Mean ± SD)	-3.1 ± 1.4[a]	-3.2 ± 1.4[b]	-3.8 ± 1.3

a p<0.001, Humira/methotrexate *vs.* Methotrexate
b p<0.001, Humira/methotrexate *vs.* Humira

Radiographic Response

In RA Study III, where Humira treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and forefeet were read at baseline, 6 months and 12 months. The 12-month results are shown in Table 12. A statistically significant difference for change in modified total Sharp score (TSS) and the erosion score was observed at 6 months and maintained at 12 months. Humira/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 12: Radiographic Change Over 12 Months in RA Study III With Background MTX

	Placebo N=200	**Humira[a] N=207**	**Difference Between Humira[a] and Placebo**	**p-value**
Change in Modified Total Sharp Score (mean)	2.7	0.1	-2.6	≤ 0.001[b]
Change in Erosions (mean)	1.6	0.0	-1.6	≤ 0.001
No New Erosions (% of Patients)	46.2	62.9	16.7	≤ 0.001
Change in JSN Score (mean)	1.0	0.1	-0.9	0.002

a 40 mg administered every other week
b Based on analysis of ranked ANCOVA

In the open-label extension of RA Study III, 77% of the original patients treated with any dose of Humira were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS; fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with Humira 40 mg every other week were evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with Humira 40 mg every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with Humira 40 mg every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

In RA Study V, structural joint damage was assessed as in RA Study III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN, was observed in the Humira/methotrexate combination group as compared to either methotrexate or Humira monotherapy group at Week 52 as well as at Week 104 (see Table 13).

Table 13: Radiographic Mean Changes at Week 52 in RA Study V

	MTX[a] N=257 (95% confidence interval)	Humira[b] N=274 (95% confidence interval)	Humira/MTX N=268 (95% confidence interval)
Total Sharp score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)

a $p<0.001$ Humira/MTX *vs.* MTX at 52 and 104 weeks
b $p<0.01$ for Humira/MTX *vs.* Humira at 52 weeks and
$p<0.001$ for Humira/MTX *vs.* Humira at 104 weeks

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified total Sharp score ≤ 0.5) was significantly higher with Humira/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p<0.001$) and Humira monotherapy (50.7%, $p<0.002$ and 44.5%, $p<0.001$ respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of Life and Physical Function

Health-related quality of life was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in all five adequate and well-controlled trials, and was a pre-specified primary endpoint at Week 52 in RA Study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo. In RA Study III, the mean (CI) improvement in HAQ from baseline at week 52 was -0.60 (-0.65, -0.55) for the Humira/MTX patients and -0.25 (-0.33, -0.17) for placebo/MTX ($p<0.001$) patients. Sixty-three percent of Humira/MTX-treated patients achieved a 0.5 or greater improvement in HAQ at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open label treatment. Most subjects who achieved improvement in physical function and continued treatment maintained improvement through week 520 (10 years) of open-label treatment.

The Short Form Health Survey (SF 36) was also used to assess general health-related quality of life in all four adequate and well-controlled trials. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in SF 36 physical component summary scores from baseline to Month 6 compared to placebo, and this was maintained at Week 52 in RA Study III. Mean improvement in the SF-36 was also maintained through the end of measurement at week 156 (36 months). The SF 36 mental component summary scores in Studies II and IV were also statistically significantly greater at Month 6 for Humira *vs.* placebo. The pain and vitality domain scores of the SF 36 showed statistically significantly greater improvement from baseline to Month 6 in all four studies for the 40 mg every other week dose of Humira compared to placebo. These findings were supported by functional assessment of chronic illness therapy (FACIT) scores that showed a statistically significant decrease in fatigue at Month 6 in all three studies analyzed that was maintained at Week 52 in RA Study III.

In RA Study V the improvement in the HAQ disability index and the physical component of the SF 36 was greater for the Humira/methotrexate combination therapy group versus both methotrexate and Humira monotherapy groups ($p<0.001$) at Week 52; this improvement was maintained through Week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Injection site pain

For the pooled crossover RA studies VI and VII, a statistically significant difference for injection site pain immediately after dosing was observed between Humira 40 mg/0.8 mL and Humira 40 mg/0.4 mL (mean VAS of 3.7 cm versus 1.2 cm, scale of 0-10 cm, $P < 0.001$). This represented an 84% median reduction in injection site pain.

ADULT CROHN'S DISEASE CLINICAL STUDIES

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

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In CD Study I (M02-403), 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg Humira at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, CD Study II (M04-691), 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg Humira at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in CD Study III (M02-404). In this study, 854 patients with active disease received open-label Humira, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg Humira every other week, 40 mg Humira every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (CR-70=decrease in CDAI ≥70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg Humira achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD Study I), or had lost response to or were intolerant to infliximab (CD Study II) (see Table 23).

Table 23: Induction of Clinical Remission in CD Study I and CD Study II (Percent of Patients)

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

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

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

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

Maintenance of Clinical Remission

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the Humira 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 24). The group that received Humira therapy every week did not demonstrate significantly higher remission rates compared to the group that received Humira every other week.

Table 24: Maintenance of Clinical Remission in CD Study III (Percent of Patients)

	Placebo N=170	40 mg Humira every other week N=172	40 mg Humira every week N=157
Week 26			
Clinical remission	17%	40%*	47%*
Clinical response	28%	54%*	56%*
Week 56			
Clinical remission	12%	36%*	41%*
Clinical response	18%	43%*	49%*

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.
*p<0.001 for Humira *vs.* placebo pairwise comparisons of proportions

Of those in response at Week 4 who attained remission during the study, patients in the Humira every other week group maintained remission for a longer time than patients in the placebo maintenance group. Disease-related hospitalizations and surgeries were statistically significantly reduced with Humira compared with placebo at Week 56.

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label Humira therapy. 88 (75.2%) and 189 (69.5%) patients, respectively, continued to be in clinical remission. Clinical response (CR-70) was maintained in 107 (91.5%) and 248 (91.2%) patients, respectively.

117/854 patients (from CD study III) had draining fistulas both at screening and at baseline. For the assessment of fistula healing, the data for both doses of adalimumab used in the study were pooled. The proportion of subjects with fistula healing at Week 26 was statistically significantly greater in patients treated with adalimumab [21/70 (30.0%)] compared to placebo [6/47 (12.8%)]. Complete fistula healing was maintained through Week 56 in 23/70 (32.9%) and 6/47 (12.8%) patients in the adalimumab and placebo groups, respectively.

An endoscopy study (M05-769), which enrolled 135 patients, indicated an effect of Humira on mucosal healing. 27.4% of patients treated with Humira had mucosal healing at Week 12 compared to 13.1% of patients given placebo (p=0.056), and 24.2% of patients treated with Humira had mucosal healing at Week 52 compared to 0% of patients given placebo (p<0.001).

Quality of Life
In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomized to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

PLAQUE PSORIASIS CLINICAL STUDIES

The safety and efficacy of Humira were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomized, double-blind studies. 73% of

patients enrolled in Psoriasis Studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of Humira were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomized double-blind study (Psoriasis Study III).

Psoriasis Study I (M03-656) evaluated 1212 patients within three treatment periods. In period A, patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg Humira every other week. Patients who maintained ≥PASI 75 response at week 33 and were originally randomized to active therapy in Period A, were re-randomized in period C to receive 40 mg Humira every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis Study II (M04-716) compared the efficacy and safety of Humira versus methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to week 12, with a maximum dose of 25 mg or an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing Humira and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enroll into an open-label extension trial (M03-658), where Humira was given for at least an additional 108 weeks.

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at week 16 (see Tables 26 and 27).

Table 26: Ps Study I (REVEAL) Efficacy Results at 16 Weeks

	Placebo N=398 n (%)	Humira 40 mg eow N=814 n (%)
≥PASI 75[a]	26 (6.5)	578 (70.9)[b]
PASI 100	3 (0.8)	163 (20.0)[b]
PGA: Clear/minimal	17 (4.3)	506 (62.2)[b]

[a] Percent of patients achieving PASI 75 response was calculated as center-adjusted rate
[b] p<0.001, Humira *vs.* placebo

Table 27: Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

	Placebo N=53 n (%)	MTX N=110 n (%)	Humira 40 mg eow N=108 n (%)
≥PASI 75	10 (18.9)	39 (35.5)	86 (79.6) [a, b]
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) [c, d]
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) [a, b]

[a] p<0.001 Humira *vs.* placebo
[b] p<0.001 Humira *vs.* methotrexate
[c] p<0.01 Humira *vs.* placebo
[d] p<0.05 Humira *vs.* methotrexate

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomized to placebo at week 33 compared to 5% continuing on Humira, p<0.001, experienced "loss of adequate response" (PASI score after week 33 and on or before week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to week 33). Of the patients who lost adequate response after re-randomization to placebo who then enrolled into the open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I, and continued Humira in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 94 patients were randomized to Humira therapy in Psoriasis Study II, and continued Humira in the open label extension trial. PASI 75 and PGA clear or minimal response rates in these patients were 58.1% and 46.2%, respectively, after an additional 108 weeks of open-label therapy (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1% [123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively).

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of Humira *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one

week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared the efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis was assessed using the Modified Nail Psoriasis Severity Index (mNAPSI) and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A statistically significantly higher proportion of patients randomized to Humira achieved at least a 75% improvement in mNAPSI (mNAPSI 75) at Week 26, as compared with patients randomized to placebo (see Table 28). The percent improvement in NAPSI was statistically significantly greater in Humira patients compared with placebo at Week 16 (44.2% vs 7.8%) and at Week 26 (56.2% vs 11.5%).

A statistically significant higher proportion of patients in the Humira group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo. In this study, Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% and BSA<10% and ≥5%) and a statistically significant improvement in scalp psoriasis compared with placebo.

Table 28: Efficacy Results at 26 Weeks

Endpoint	Placebo N=108	Humira 40 mg eow N=109
≥ mNAPSI 75 (%)	3.4	46.6[a]
PGA-F clear/minimal and ≥2-grade improvement (%)	6.9	48.9[a]
Percent Change in Total Fingernail NAPSI (%)	-11.5	-56.2[a]
mNAPSI = 0 (%)	0	6.6[b]
Change in Nail Pain Numeric Rating Scale	-1.1	-3.7[a]
Change in Nail Psoriasis Physical Functioning Severity score	-0.8	-3.7[a]
B-SNIPI 50 Scalp (%)	N=12 0.4	N=18 58.3[b]

[a] p<0.001, Humira *vs.* placebo
[b] p<0.05, Humira *vs.* placebo
B-SNIPI 50: At least a 50% reduction in scalp component of Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis index (B-SNIPI) among subjects with Baseline scalp score of 6 or greater).

Of those who continued to receive Humira treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response.

Humira treated patients showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI (Dermatology Life Quality Index). The mean decrease (improvement) from baseline at Week 26 was 8.0 in the Humira group (N=94) and 1.9 in the placebo group (N=93).

UVEITIS CLINICAL STUDIES

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis (also known as “non-infectious uveitis affecting the posterior segment”), excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (UV Study I (M10-877) and UV Study II (M10-880)). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of non-biologic immunosuppressants were permitted. The primary efficacy endpoint in both studies was ´time to treatment failure´. Following initial control of disease, a prolongation in time to treatment failure will result in reduced risk of disease flares, inflammation and vision loss.

Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

UV Study I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

UV Study II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

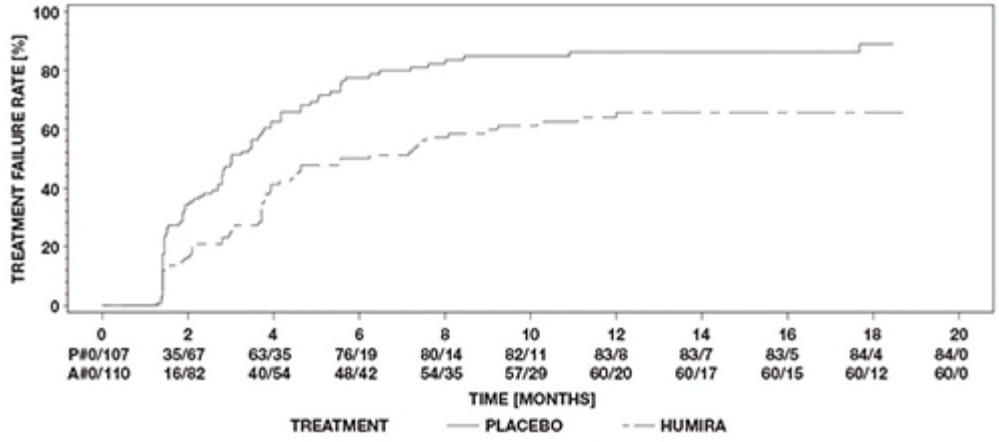
Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with HUMIRA versus patients receiving placebo (See Table 30). Both studies demonstrated an early and sustained effect of HUMIRA on the treatment failure rate versus placebo (see Figure 6).

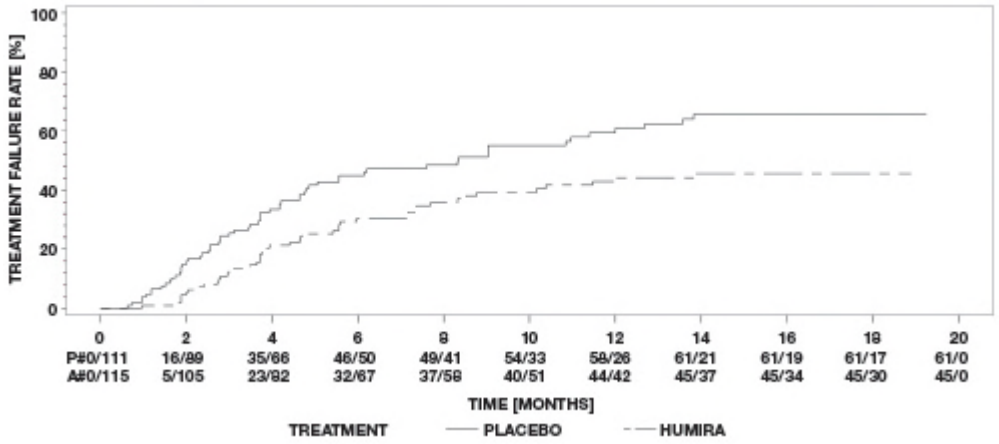
Table 30: Time to Treatment Failure in UV Studies I and II

Analysis Treatment	**N**	**Failure N (%)**	**Median Time to Failure (months)**	**HR[a]**	**CI 95% for HR[a]**	***P* Value[b]**
Time to Treatment Failure At or After Week 6 in UV Study I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in UV Study II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.
a. HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.
b. 2-sided *P* Value from log rank test.
c. NE = not estimable. Fewer than half of at-risk subjects had an event.



Study UV I



Study UV II

Figure 6: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (UV Study I) or Week 2 (UV Study II)

In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between Humira and placebo groups (Table 31).

Table 31: Treatment Failure Components in UV Studies I and II

	UV I	UV II

Component of Time-to-Treatment Failure	**HR[a]**	**CI 95%**	***p* Value[b]**	**HR[a]**	**CI 95%**	***p* Value[b]**
New Active Inflammatory Lesions	0.38	(0.21-0.69)	*0.001*	0.55	(0.26-1.15)	*0.105*
Anterior Chamber Cells Grade	0.51	(0.30-0.86)	*0.01*	0.7	(0.42-1.18)	*0.18*
Vitreous Haze Grade	0.32	(0.18-0.58)	*<0.001*	0.79	(0.34-1.81)	*0.569*
Best Corrected Visual Acuity	0.56	(0.32-0.98)	*0.04*	0.33	(0.16-0.70)	*0.002*
Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out. a. HR of adalimumab vs placebo from proportional hazards regression with treatment as factor. b. 2-sided *P* value from log rank test.						

Additionally, in UV Study I, statistically significant differences in favor of adalimumab versus placebo were observed for changes in AC cell grade, vitreous haze grade, and logMAR BCVA (mean change from best state prior to Week 6 to the final visit; *P* Values: 0.011, <0.001 and 0.003, respectively).

Of the 417 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 46 subjects were regarded ineligible (e.g. developed complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 371 remaining patients, 276 evaluable patients reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 222 (80.4%) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 184 (66.7 %) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.4% of the eyes at week 78. Among the patients who discontinued the study prior to week 78, 11% discontinued due to adverse events, and 5% due to insufficient response to adalimumab treatment.

Quality of Life

In UV Study 1, treatment with Humira resulted in maintenance of vision-related functioning and health-related quality of life, as measured by the NEI VFQ-25.

Pediatrics

JUVENILE IDIOPATHIC ARTHRITIS CLINICAL STUDIES

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS (pJIA)

The safety and efficacy of Humira was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of Humira were assessed in a multicenter, randomized, double-blind, parallel-group study in 171 children (4 to 17 years old) with polyarticular juvenile idiopathic arthritis (JIA). In the open-label lead in phase (OL LI), patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase, all patients received 24 mg/m^2 up to a maximum of 40 mg of Humira every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presenting in Table 32.

Table 32: Distribution of patients by age and Humira dose received during the OL LI phase

Age Group	Number of patients at Baseline n (%)	Minimum, median and maximum dose
4 to 7 years	31 (18.1)	10, 20 and 25 mg
8 to 12 years	71 (41.5)	20, 25 and 40 mg
13 to 17 years	69 (40.4)	25, 40 and 40 mg

Patients demonstrating a Pediatric ACR 30 response at week 16 were eligible to be randomized into the double blind (DB) phase and received either Humira 24 mg/m^2 up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enroll into the open label extension phase.

Table 33: Ped ACR 30 Responses in the JIA study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 week				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Double Blind	Humira (n = 38)	Placebo (n = 37)	Humira (n = 30)	Placebo (n = 28)
Disease flares at the end of 32 weeks[a] (n/N)	36.8% (14/38)	64.9% (24/37)[b]	43.3% (13/30)	71.4% (20/28)[c]
Median time to disease flare	>32 weeks	20 weeks	>32 weeks	14 weeks

[a] Ped ACR 30/50/70 responses week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Among those who responded at week 16 (n=144), the Pediatric ACR 30/50/90 responses were maintained for up to six years in the OLE phase in patients who received Humira throughout the study. Overall, 19 subjects were treated 6 years or longer, 11 of the 19 were in baseline age group 4 to 12 and 8 of the 19 were in baseline age group 13 to 17 years.

Overall responses were generally better and fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone. Taking these results into consideration, Humira is recommended for use in combination with MTX and for use as monotherapy in patients for who MTX use is not appropriate.

pJIA II

The safety and efficacy of Humira was assessed in an open-label, multicenter study in 32 children (2 to <4 years old or aged 4 and above weighing <15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At Week 12 and Week 24, Pediatric ACR 30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with Pediatric ACR 50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received Humira throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

ENTHESITIS-RELATED ARTHRITIS

The safety and efficacy of Humira were assessed in a multicenter, randomized, double-blind study in 46 pediatric patients (6 to 17 years old) with enthesitis-related arthritis. Patients were randomized to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved (p=0.039) with mean percent decrease of -62.6% in patients in the Humira group compared to -11.6% in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the open label period through Week 156. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 30 response, Pediatric ACR 50 response, and Pediatric ACR 70 response and maintained these improvements during the open label period through Week 156 of the study.

PEDIATRIC CROHN'S DISEASE CLINICAL STUDY

Humira was assessed in a multicenter, randomized, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 pediatric subjects between the ages of 6 and 17

(inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomized 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 34.

Table 34: Maintenance Regimen

Patient Weight	Low Dose	Standard Dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy Results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 35. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 36.

Table 35: Pediatric CD Study
PCDAI Clinical Remission and Response

	Standard Dose 40/20 mg eow N = 93	**Low Dose 20/10 mg eow N = 95**	**P value***
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038
* p value for Standard Dose *versus* Low Dose comparison.			

Table 36: Pediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission

	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N=33**	**N=38**	

Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups. Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

Patients from the Pediatric CD Study had the option to continue in an open-label long-term extension study. Following 5 years of Humira therapy, 74% (37/50) of patients continued to be in clinical remission and 92% (46/50) of patients continued to be in clinical response per PCDAI.

PEDIATRIC PLAQUE PSORIASIS CLINICAL STUDY

The efficacy of Humira was assessed in a randomized, double-blind, controlled study of 114 pediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or PASI ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received Humira 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomized to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomized to MTX.

Table 37: Pediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	**Humira 0.8 mg/kg eow N=38**
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)

a MTX = methotrexate
b P=0.027, Humira 0.8 mg/kg versus MTX
c P=0.083, Humira 0.8 mg/kg versus MTX

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (loss of PGA response). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and responses observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

PEDIATRIC UVEITIS CLINICAL STUDY

The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 pediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was ‘time to treatment failure.’ The criteria determining treatment failure were worsening, or sustained non-improvement in ocular inflammation, or partial improvement with development of sustained ocular co-morbidities, or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 7, P < 0.0001 from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

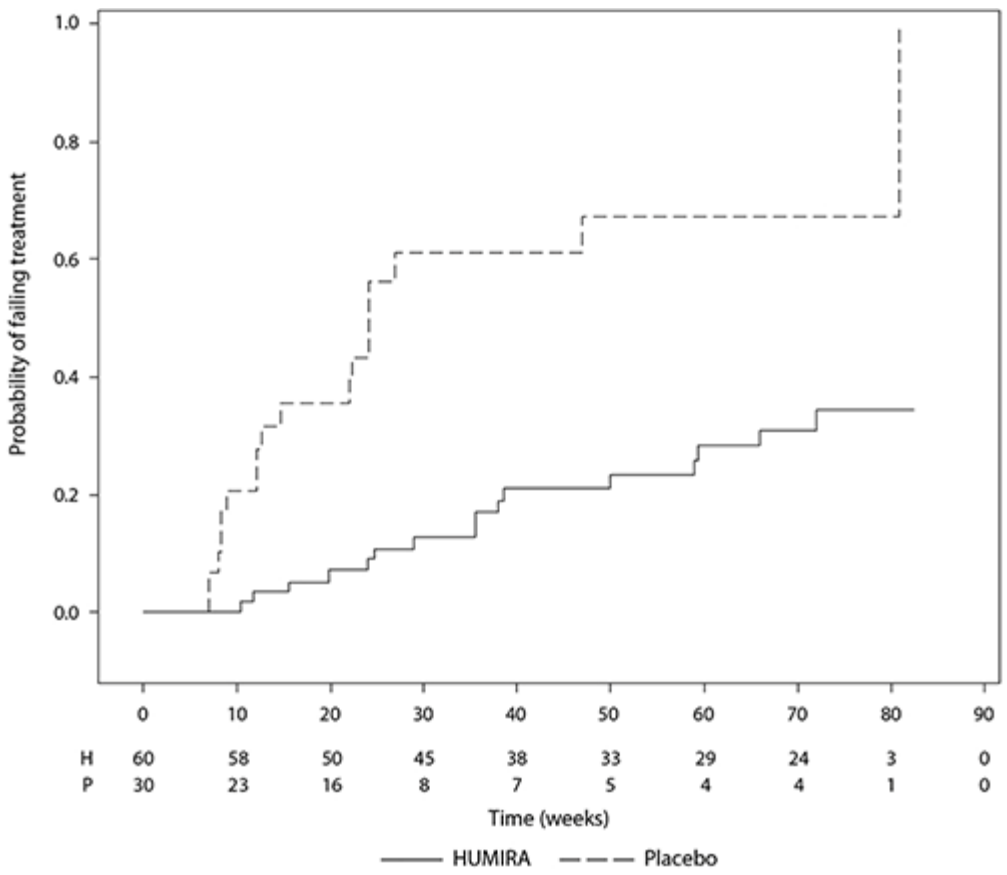


Figure 7: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Pediatric UV Study

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Adults

Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4% compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with Crohn’s disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab.

In patients with psoriasis, anti-adalimumab antibodies were identified in 8.4% (77/920) of patients treated with adalimumab without concomitant methotrexate. In plaque psoriasis patients

on long term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was 2.3%, and was similar to the rate observed prior to withdrawal 1.9%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

Pediatrics

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 16% of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 26%, compared to 6% when adalimumab was used as add-on to methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years old or aged 4 and above weighing <15 kg, anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 11% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 14% (3/22), compared to 8% (2/24) when adalimumab was used as add-on to methotrexate.

In patients with moderately to severely active pediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

In patients with pediatric psoriasis, anti-adalimumab antibodies were identified in 13% (5/38) of subjects treated with 0.8 mg/kg adalimumab monotherapy.

STORAGE

Store at 2° C to 8° C (36° F to 46° F) (in a refrigerator) and store the syringe, pen or vial in the outer carton in order to protect from light. Do not freeze.

A Humira pre-filled syringe or Pen may be stored at temperatures up to a maximum of 25°C (77°F) for a single period of up to 14 days. The syringe or Pen must be protected from light, and discarded if not used within the 14-day period.

Do not use beyond the expiration date.

HOW SUPPLIED

Humira 20 mg per 0.2 mL for injection in a single-use pre-filled syringe:

- Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled syringe.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction (ADR), report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of adverse drug reaction (ADR)

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