NEW ZEALAND DATA SHEET

1. HUMIRA® ADALIMUMAB (RCH) SOLUTION FOR INJECTION.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HUMIRA 20 mg: each 0.4 mL single-use pre-filled syringe contains 20 mg of adalimumab.

HUMIRA 20 mg: each 0.2 mL single-use pre-filled syringe contains 20 mg of adalimumab.

HUMIRA 40 mg: each 0.8 mL single-use pre-filled syringe or pen contains 40 mg of adalimumab.

HUMIRA 40mg: each 0.4mL single-use pre-filled syringe or pen contains 40mg of adalimumab.

HUMIRA 80 mg: each 0.8 mL single use pre-filled syringe or pen contains 80mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

Adalimumab is a recombinant human immunoglobulin (IgG1) 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 tumour necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. Humira binds with high affinity and specificity to soluble tumour 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.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Humira is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The solution of Humira is clear and colourless with a pH of 5.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis

Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Humira can be used alone or in combination with methotrexate.

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 years of age and older. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

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 to, conventional therapy.

Psoriatic Arthritis

Humira is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

Ankylosing Spondylitis (AS)

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

Non-radiographic Axial Spondyloarthritis (axial spondyloarthritis without radiographic evidence of AS)

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs.

Crohn's Disease in Adults and Children (≥ 6 years)

Humira is indicated for the treatment of moderate to severe Crohn's disease to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients:

- who have had an inadequate response to conventional therapies, or,
- who have lost response to or are intolerant to infliximab.

Ulcerative Colitis

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6- mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Psoriasis in Adults and Children (≥ 4 years)

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

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

Hidradenitis Suppurativa in Adults and Adolescents (from 12 years of age)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients with an inadequate response to conventional systemic HS therapy.

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis (≥ 2 years)

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

4.2 Dose and method of administration

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 discolouration prior to administration, whenever solution and container permit.

Humira should not be mixed in the same syringe with any other medicine. Any unused product or waste material should be disposed of in accordance with local requirements.

Humira contains no antimicrobial agent. Discard any residue.

Dose

Rheumatoid Arthritis

The recommended dose of Humira for adult patients with rheumatoid arthritis is 40 mg administered fortnightly as a single dose. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics may be continued during treatment with Humira.

Some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosage of Humira to 40 mg every week or 80 mg fortnightly.

Psoriatic Arthritis

The recommended dose of Humira for patients with psoriatic arthritis is 40 mg adalimumab administered fortnightly as a single dose.

Glucocorticoids, salicylates, nonsteroidal anti−inflammatory drugs, analgesics or disease-modifying anti-rheumatic drugs can be continued during treatment with Humira.

Ankylosing Spondylitis

The recommended dose of Humira for patients with ankylosing spondylitis is 40 mg adalimumab administered every fortnight as a single dose.

Glucocorticoids, salicylates, nonsteroidal anti−inflammatory drugs, analgesics or disease-modifying anti-rheumatic drugs can be continued during treatment with Humira.

Non-radiographic Axial Spondyloarthritis

The recommended dose of Humira for patients with non-radiographic axial spondyloarthritis is 40 mg adalimumab administered fortnightly as a single dose via subcutaneous injection.

Glucocorticoids, salicylates, nonsteroidal anti−inflammatory drugs, analgesics or disease-modifying anti-rheumatic drugs can be continued during treatment with Humira.

Available data suggest that the 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.

Crohn's Disease

	Dose	**Frequency**
Induction	160 mg	Initial Dose (Day 0) as two 80 mg injections in one day OR as one 80 mg injection per day for two consecutive days OR as four 40 mg injections in one day OR as two 40 mg injections per day for two consecutive days.
	80 mg	Second Dose (Day 14) as one 80 mg injection OR two 40 mg injections
Maintenance	40 mg	Starting Day 28 and continuing fortnightly

Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with Humira.

Patients usually respond within the induction phase. However, if a patient does not show any response, available data do not sufficiently support further Humira treatment.

Some patients may benefit from increasing the dosage of Humira to 40 mg every week or 80 mg fortnightly if a disease flare or an inadequate response is experienced during maintenance dosing.

Ulcerative Colitis

The recommended Humira dose regimen for adult patients with moderate to severe ulcerative colitis is:

	Dose	**Frequency**
Induction	160 mg	Initial Dose (Day 0) can be administered as two 80 mg injections in one day OR as one 80 mg injection per day for two consecutive days OR as

		four 40 mg injections in one day OR as two 40 mg injections per day for two consecutive days.
	80 mg	Second Dose (Day 14) as one 80 mg injection OR two 40 mg injections
Maintenance	40 mg	Starting Day 28 and continuing fortnightly

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience a decrease in their response may benefit from increasing the dosage to 40 mg Humira every week or 80 mg fortnightly.

Available data suggest that clinical response is usually achieved within 2 to 8 weeks of treatment. Humira should only be continued in patients who have responded during the first 8 weeks of therapy.

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg (given as one 80 mg injection or two 40 mg injections), followed by 40 mg fortnightly, starting one week after the initial dose.

Patients with inadequate response after 16 weeks may benefit from increasing the dosage to 40 mg every week or 80 mg fortnightly.

The benefits and risks of continued weekly Humira therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency. If adequate response is achieved with an increased dosage, the dose may subsequently be reduced to 40 mg fortnightly.

Uveitis

The recommended dose of Humira for adult patients with uveitis is an initial dose of 80 mg (given as one 80 mg injection OR two 40 mg injections), followed by 40 mg fortnightly, starting one week after the initial dose.

Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents.

Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Humira. There is limited experience in the initiation of treatment with Humira alone. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Hidradenitis Suppurativa

The recommended Humira dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as two 80 mg injections in one day OR as one 80 mg injection per day for two consecutive days OR as four 40 mg injections in one day OR as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as one 80 mg injection OR two 40

mg injections). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg fortnightly. Antibiotics may be continued during treatment with Humira if necessary.

Should treatment need to be interrupted, Humira may be re-introduced.

In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1 - Clinical efficacy and safety).

Adolescent Hidradenitis Suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended Humira dose is 80 mg at Week 0 (given as one 80 mg injection OR two 40 mg injections), followed by 40 mg fortnightly, starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Humira 40 mg fortnightly, increasing the dosage to 40 mg every week or 80 mg fortnightly may be considered.

Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period (see section 5.1 Clinical efficacy and safety).

Should treatment be interrupted, Humira may be re-introduced as appropriate. The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1 Clinical efficacy and safety).

There is no relevant use of Humira in children aged less than 12 years of age with HS.

Elderly

No dose adjustment is needed for this population (see section 4.4 - Elderly).

Renal Impairment and Hepatic Impairment

Humira has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Juvenile Idiopathic Arthritis

The recommended dose of Humira for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis or patients 6 years of age and older with enthesitis-related arthritis are based on weight as shown in the table below. Methotrexate, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with Humira.

Patients (2 years of age and older)	**Dose**
10 kg to < 30 kg	20 mg fortnightly (20 mg Pre-filled Syringe)
≥ 30 kg	40 mg fortnightly (Humira 40mg Pen or 40 mg Pre-filled Syringe)

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. Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years of age. The safety and efficacy of Humira has not been established in systemic juvenile idiopathic arthritis or oligoarticular juvenile idiopathic arthritis.

Paediatric Crohn's Disease (≥ 6 years)

Patients < 40 kg body weight		
	Moderate to Severe CD	**Frequency**
Induction	80 mg	Initial Dose (Day 0) as one 80 mg injection OR two 40 mg injections
	40 mg	Second Dose (Day 14) as one 40 mg injection or two 20 mg injections
Maintenance	20 mg	Starting Day 28 and continuing fortnightly

Patients ≥ 40 kg body weight		
	Moderate to Severe CD	**Frequency**
Induction	160 mg	Initial Dose (Day 0) as two 80 mg injections in one day OR as one 80 mg injection per day for two consecutive days OR as four 40 mg injections in one day OR as two 40 mg injections per day for two consecutive days
	80 mg	Second Dose (Day 14) as one 80 mg injection OR two 40 mg injections
Maintenance	40 mg	Starting Day 28 and continuing fortnightly

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: 40mg every week or 80mg fortnightly.

Continued therapy should be carefully considered in a subject not responding by Week 12.

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

Paediatric Plaque Psoriasis (≥ 4 years)

The recommended dose of Humira is based on body weight as shown in the table below. Doses are administered subcutaneously weekly for the first two doses and fortnightly thereafter. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

Patients (4 years of age and older)	Dose
< 30 kg	20 mg fortnightly (20 mg Pre-filled Syringe)
≥ 30 kg	40 mg fortnightly (Humira 40 mg Pen or 40 mg Pre-filled Syringe)

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 with chronic plaque psoriasis aged less than 4 years of age. The safety and efficacy of Humira has not been studied in children with paediatric psoriasis weighing < 15 kg.

Paediatric Uveitis (≥ 2 years)

The recommended dose of Humira for paediatric patients with uveitis from 2 years of age is based on body weight as shown below. Humira is administered via subcutaneous injection. Humira may be available in different strengths and/or presentations depending on the individual treatment needs.

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with methotrexate.

Patients (2 years of age and older)	Dose
< 30 kg	20 mg fortnightly in combination with methotrexate
≥ 30 kg	40 mg fortnightly in combination with methotrexate

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. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

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

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Paediatric Hidradenitis Suppurativa (2 to less than 12 years)

There is no relevant use of Humira in children aged less than 12 years of age for this indication.

Paediatric Ulcerative Colitis (4 to 17 years)

The safety and efficacy of Humira in children aged 4 to 17 years of age have not yet been established for ulcerative colitis. No data are available. There is no relevant use of Humira in children aged less than 4 years of age for this indication.

Psoriatic Arthritis and Axial Spondyloarthritis including Ankylosing Spondylitis

There is no relevant use of Humira in children for these indications.

Method of administration

Humira is administered by subcutaneous injection.

This product is for one dose in one patient only.

4.3 Contraindications

Humira should not be administered to patients with known hypersensitivity to adalimumab or any of the excipients listed in section 6.1.

Humira is contraindicated in severe infections including sepsis, active tuberculosis and opportunistic infections (see section 4.4).

Concurrent administration of Humira and anakinra (interleukin-1 receptor antagonist) is contraindicated (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV).

4.4 Special warnings and precautions for use

Infections

Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving TNF-blocking agents, including Humira. Sepsis, rare cases of tuberculosis and candidiasis 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 septicaemia. Hospitalisation 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 localised infections until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have travelled 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 section 4.4 - Other Opportunistic Infections).

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.

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.

Hepatitis B Virus

Use of TNF blockers, including Humira, 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 evidence of prior 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.

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 and 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 5mm 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 travelled 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 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. The benefit/risk balance of therapy with Humira should be very carefully considered.

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) occur during or after therapy with Humira.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving Humira. These infections are not consistently recognised 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, dyspnoea, 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.

Neurologic Events

Humira has 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 pre-existing 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 and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Hypersensitivity Reactions

Serious allergic reactions associated with Humira were rare during clinical trials. Allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed-drug reaction, non-specific drug reaction, urticaria) have been observed in approximately 1% of patients. 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.

Haematologic Events

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF blocking agents. Adverse events of the haematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with Humira (see section 4.8). The causal relationship of these reports to Humira remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Immunosuppression

The possibility exists for TNF blocking agents, including Humira, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with Humira on the development and course of malignancies, as well as active and/or chronic infections is not fully understood. The safety and efficacy of Humira in patients with immunosuppression have not been evaluated. (See section 4.4 - Infections and section 4.8 - Infections and Malignancies).

Vaccinations

In a randomised, 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.
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 Humira in utero is not recommended for 5 months following the mother's last Humira injection during pregnancy
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

Congestive Heart Failure

In a clinical trial with another TNF antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate or severe heart failure. Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

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, including Humira, compared with control patients (see section 4.8 - Malignancies). However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active inflammatory disease, which complicates the risk estimation.
Very rare post-marketing 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.
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 post-marketing reports.

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 for these patients.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk for malignancy due to heavy smoking.

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 leukaemia have been reported in association with post-marketing 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 leukaemia, 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.

Autoimmune Processes

Treatment with Humira may result in the formation of autoantibodies and rarely in the development of a lupus-like syndrome. The impact of long-term treatment with Humira on the development of autoimmune disease is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira, treatment should be discontinued (see section 4.8 - Autoantibodies).

Concurrent Administration of biologic DMARDS or TNF-antagonists

Concurrent administration of etanercept and anakinra has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. 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, combination of adalimumab and anakinra is contraindicated.

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

Use in Psoriasis

The safety and efficacy of adalimumab in combination with other systemic agents used in psoriasis or with phototherapy have not been studied. Adalimumab should not be used in combination with such agents.

Surgery

There is limited safety experience of surgical procedures in patients treated with Humira. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Humira.

Paediatric Population

See Vaccinations above.
The long-term effects of Humira on the growth and development of children have not been studied.

Elderly

Of the total number of subjects in clinical studies of Humira 10.2% were 65 years and over, while approximately 2.2% were 75 and over. A total of 519 RA patients 65 years of age and older, including 107 patients 75 years and older, received Humira in clinical RA studies I-IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among Humira-treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly. Two patients older than 65 years of age received Humira in the clinical non-radiographic axial spondyloarthritis study (see section 4.2).

Renal Impairment and Hepatic Impairment

Humira has not been studied in these patient populations. No dose recommendations can be made.

4.5 Interaction with other medicines and other forms of interaction

Humira has been studied in RA patients taking concomitant methotrexate (see section 5.1 - Clinical efficacy and safety and section 5.2 - Steady State). The data do not suggest the need for dose adjustment of either Humira or methotrexate. Interactions between Humira and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. Concurrent administration of TNF-alpha inhibitors with anakinra or abatacept has been associated with an increased risk of serious infections (see section 4.4 above).
There is no known interference between Humira and laboratory tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category C)

Results obtained with a very high intravenous adalimumab dose (100 mg/kg/week) in an embryofoetal toxicity study in cynomolgus monkeys were inconclusive. No developmental toxicity was observed with an intravenous dose of 30 mg/kg/week, which resulted in a serum drug concentration greater than 100-fold higher than the maximum value expected during therapy during 40 mg fortnightly. Parturition was unaffected by both doses.

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-randomised 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.

The long half-life of Humira should also be considered when discontinuing therapy.

Lactation

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.

The long half-life of Humira should also be considered when discontinuing therapy.

Fertility

The effect of adalimumab on fertility has not been investigated.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

Humira was studied in 9506 patients in controlled and open label trials.

These trials included rheumatoid arthritis patients with short term and long-standing 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 pivotal controlled 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 across all indications was 5.9% for patients taking Humira and 5.4% for control treated patients. The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of RA Studies I, II, III and IV was 6.6% for patients taking Humira and 4.2% for placebo-treated patients.

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

Tabulated summary of adverse reactions

Adverse events at least possibly causally-related to adalimumab for clinical studies, 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); and rare ≥ 1/10000 to < 1/1000 in Table 1 below.

The highest frequency seen among the various indications has been included.

Table 1: Adverse Drug Reactions in Clinical Studies

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
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 neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), Melanoma**
Blood and the lymphatic system disorders*	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	thrombocytopenia, leucocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
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, hyperglycaemia, hypophosphatemia, dehydration

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoaesthesia), 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
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
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 (e.g. nail disorders), 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

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

* Further information found in section 4.3, 4.4 and 4.8

** Includes open label extension studies

a) MedDRA

Table 1 contains adverse drug reactions (ADRs), which in some cases represent groups of related Preferred Terms to represent a medical concept. The ADRs presented in the table were included based on criteria including statistical significance, doubling in rate in adalimumab treated patients compared to placebo treated patients, a rate greater than 1% for adalimumab treated patients and medical importance assessment.

Table 2 contains adverse reactions reported in at least 1% of RA patients with higher incidence (≥ 1%) in patients treated with adalimumab compared to control in 4 placebo-controlled RA trials (RA study I to IV). In general, the adverse reactions across all indications were similar to those seen in RA patients.

Table 2: Adverse Reactions reported by Patients Treated with Humira during Placebo-Controlled Period of Rheumatoid Arthritis Studies

System Organ Class[a)]	Adverse Reaction[a)]	Adalimumab (N = 1380) (%)	Control (N = 690) (%)
Infections and infestations	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)	39	33
	oral infections (including herpes simplex, oral herpes and tooth infections)	7	5
	reproductive tract infections (including vulvovaginal mycotic infection)	3	1
Blood and the lymphatic system disorders	anaemia	13	8
	leukopaenia (including neutropenia and agranulocytosis)	14	8
	leucocystosis	1	0
	thrombocytopenia	1	0
Metabolism and nutrition disorders	lipids increased	17	8
	uric acid increased	6	3
	blood sodium abnormal	10	3
	hypokalaemia	3	2
	hypophosphatemia	2	1
	blood potassium increased	3	1
Nervous system disorders	headache	14	8
Vascular disorders	hypertension	6	3
	flushing	2	1
Respiratory, thoracic and mediastinal disorders	cough	7	6
Gastrointestinal disorders	nausea and vomiting	12	11
	abdominal pain	10	6

System Organ Class[a)]	Adverse Reaction[a)]	Adalimumab (N = 1380) (%)	Control (N = 690) (%)
	sicca syndrome	3	2
	GI haemorrhage	2	1
Hepato-biliary disorders	liver enzymes elevated	12	8
Skin and subcutaneous tissue disorders	rash (including exfoliative rash)	14	7
	pruritus	5	1
	dermatitis (including eczema)	3	1
	bruising (including purpura)	2	0
Musculoskeletal, connective tissue and bone disorders	musculoskeletal pain	14	9
	muscle spasms (including blood creatine phosphokinase increased)	5	4
Renal and urinary disorders	haematuria	9	4
	renal impairment	8	4
General disorders and administration site conditions	injection site reaction (including injection site erythema)	20	13
	oedema	5	4
Investigations	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged)	9	4
	blood lactate dehydrogenase increased	2	1

[a)] MedDRA

Polyarticular Juvenile Idiopathic Arthritis

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

Uveitis

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

Hidradenitis Suppurativa

The safety profile for patients with hidradenitis suppurativa treated with Humira weekly was consistent with the known safety profile of Humira.

Description of selected adverse reactions

Injection Site Reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, 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 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 infections consisted primarily of nasopharyngitis, upper respiratory tract infections and sinusitus. Most patients continued on Humira after the infection resolved. The incidence of serious infections was 0.04 per patient year in Humira-treated patients and 0.03 per patient year in control treated patients.

In the controlled and open label adult and paediatric 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).

Most, but not all of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies

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, ankylosing spondylitis, non-radiographic axial spondyloarthritis, Crohn's disease, ulcerative colitis psoriasis, hidradenitis suppurativa 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 patients 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 (basal cell and squamous cell) 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.

When combining controlled portions of these trials and ongoing open label extension studies with a median duration of approximately 3.3 years including 6427 patients and over 26439 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1000 patient years. 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.

No malignancies were observed in 249 paediatric patients with an exposure of 656.6 patient years during Humira trials in patients with polyarticular juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 paediatric patients with an exposure of 258.9 patient years during a Humira trial in paediatric patients with Crohn's disease.

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

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

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1000 patient treatment years. The reported rates for non-melanoma skins cancers and lymphomas are approximately 0.2 and 0.3 per 1000 patient treatment years, respectively.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I to 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 antinuclear antibody titres reported positive titres at Week 24. Two patients out of 3989 treated with Humira in all rheumatoid, psoriatic arthritis, and ankylosing spondylitis 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 hospitalisation. 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 fortnightly), 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 fortnightly), 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 trials of Humira (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of Humira-treated patients and 0.6% of control-treated patients.

In the Phase 3 trial of Humira in patients with paediatric 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 Phase 3 trials of Humira (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg fortnightly), in patients with ulcerative colitis with a control period duration ranging from 1 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients.

In controlled Phase 3 trials of Humira (initial dose of 80 mg then 40 mg fortnightly), in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.

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

In controlled Phase 3 trials of Humira (40 mg fortnightly), in patients with axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2.1% of Humira-treated patients and 0.8% 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 controlled trials of Humira (initial doses of 80 mg at Week 0 followed by 40 mg fortnightly starting at Week 1) in patients with uveitis with an exposure of 166.5 days and 105.0 days 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.

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 post-marketing 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.

Polyarticular Juvenile Idiopathic Arthritis Clinical Trials

In general, the adverse reactions in patients with polyarticular juvenile idiopathic arthritis trials (pJIA Studies I and II) were similar in frequency and type to those seen in adult patients. Important findings and differences from adults are discussed in the following paragraphs.

In pJIA Study I, Humira was studied in 171 patients, who were 4 to 17 years of age with polyarticular juvenile idiopathic arthritis. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with Humira and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In pJIA Study I, 45% of patients experienced an infection while receiving Humira with or without concomitant methotrexate in the first 16 weeks of treatment. The types of infections reported in polyarticular juvenile idiopathic arthritis (JIA) patients were generally similar to those commonly seen in outpatient polyarticular JIA populations. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with Humira were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving Humira was granuloma annulare which did not lead to discontinuation of Humira treatment.

In the first 48 weeks of treatment in pJIA Study I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localised allergic hypersensitivity reactions and allergic rash. Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in patients with polyarticular JIA exposed to Humira alone; liver function tests (LFT) elevations were more frequent among those treated with the combination of Humira and methotrexate. In general, these elevations did not lead to discontinuation of Humira treatment.

In the pJIA Study I trial, 10% of patients treated with Humira who had negative baseline anti-dsDNA antibodies developed positive titres after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with Humira developed mild-to-moderate elevations of creatine phosphokinase (CPK) in pJIA Study I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue Humira without interruption.

In pJIA Study II, Humira was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing < 15 kg with polyarticular JIA. Most patients received at least 24 weeks of Humira treatment up to a maximum of 120 weeks duration. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In pJIA Study II, 78% of patients experienced an infection while receiving Humira. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate

in severity. Serious infections were observed in 9% of patients receiving Humira in the study and included dental caries, rotavirus gastroenteritis, and varicella.
In pJIA Study II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticarial and rash, which were all mild in severity.

Additional Adverse Reactions from Post-Marketing 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 3: Additional Adverse Reactions from Post-Marketing Surveillance or Phase IV Clinical Trials

System Organ Class	Adverse Reaction
Infections and infestations	diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	hepatosplenic T-cell lymphoma, leukaemia, merkel cell carcinoma (neuroendocrine carcinoma of the skin)
Immune system disorders*	anaphylaxis, sarcoidosis
Nervous system disorders*	cerebrovascular accident, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome)
Cardiac disorders	myocardial infarction
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, pulmonary fibrosis; pleural effusion
Gastrointestinal disorders*	intestinal perforation
Hepato-biliary disorders	reactivation of hepatitis B, liver failure, hepatitis
Skin and subcutaneous tissue disorders	alopecia, angioedema, cutaneous vasculitis, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), erythema multiforme, Stevens Johnson Syndrome, lichenoid skin reaction**
Musculoskeletal and connective tissue disorders	lupus-like syndrome
General disorders and administration site conditions	pyrexia
*Further information found in sections 4.3, 4.4 and 4.8 ** occurring in patients receiving a TNF-antagonist including Humira	

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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 over dosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

For advice on the management of overdose please contact the National Poisons Information Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-alpha) inhibitors. ATC code: L04AB04.

Mechanism of action

Adalimumab binds to TNF and neutralises 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 (RA), including juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) 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, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease.

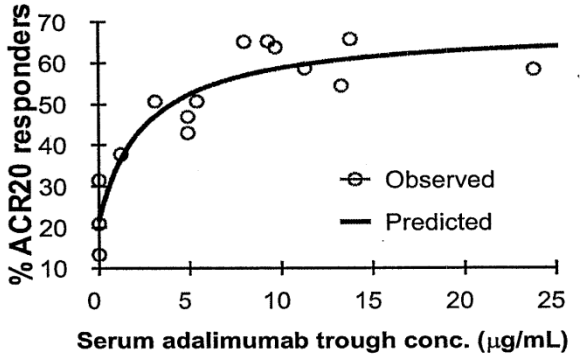
Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10} M).

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. In patients with Crohn's disease, a decrease in CRP levels was observed by week 1, After 12 weeks of treatment with adalimumab, subjects with CD had lower levels of expression of TNF-alpha and the inflammatory markers, human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon but not in the ileum, compared with subjects with CD given placebo. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation. A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR20) 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 microgram/mL were obtained through pharmacokinetic/ pharmacodynamic modelling of swollen joint count, tender joint count and ACR20 response from patients participating in Phase II and III trials.

Clinical efficacy and safety

Rheumatoid Arthritis

Humira was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for greater than 60 months duration. The efficacy and safety of Humira were assessed in five randomised, double-blind and well-controlled studies. Injection site pain of Humira 40mg/0.4mL was assessed in two randomised, active control, single-blind, two-period crossover studies.

The primary endpoint in the efficacy studies was ACR20 response, equating to an at least 20% improvement from baseline in tender joint count, swollen joint count, and at least 3 of the 5 remaining ACR core set measures: Patient assessment of pain, patient global assessment of disease activity, physician global assessment of disease activity, patient self-assessed disability (HAQ), and erythrocyte sedimentation rate or CRP.

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) and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate 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 fortnightly 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. Patients, who were not permitted methotrexate or

other DMARDs during the study, 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 subcutaneous injection fortnightly 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 methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. 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 fortnightly 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 fortnightly, for up to 5 years. The objectives of this open-label extension were to evaluate the long-term safety and maintenance of efficacy of Humira in subjects with RA receiving concurrent MTX. The maintenance of efficacy was assessed by evaluating the effect of Humira on the signs and symptoms of RA, physical function, structural damage, rates of clinical remission and patient-reported outcomes. Of the 457 patients who entered the open-label extension, 53/457 (11.6%) subjects discontinued the study due to adverse events, and 16/457 (3.5%) subjects discontinued because of a lack of efficacy/disease progression.

RA Study IV (DE031) primarily assessed safety in 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 naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomised to 40 mg of Humira or placebo fortnightly for 24 weeks.

RA Study V (DE013) was an active comparator trial of 2 years duration, which randomised 799 adult methotrexate (MTX)-naïve patients with early RA (mean disease duration less than 9 months) to treatment with adalimumab 40 mg fortnightly alone, methotrexate up to 20 mg/week alone, or the combination of the two, for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40mg of adalimumab was administered fortnightly for up to 10 years. 31.5% of patients in the MTX group, 33.2% in the adalimumab group, and 32.5% in the combination group had taken previous DMARDs. The mean duration of RA was 0.8 years, 0.7 years, and 0.7 years in the MTX alone, adalimumab alone, and combination groups, respectively. The mean Tender Joint Count (TJC 68) at baseline was 32.3, 31.8 and 30.7 for the three groups, and the Erosion Score was 13.6, 11.3 and 11.0, respectively.

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 patients who were starting Humira 40 mg/0.8 mL. Patients were randomised 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 trials were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary endpoint in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR20 response at Week 24 or 26. The primary endpoint in RA Study V was the percent of patients who achieved an ACR50 response at Week 52. RA Studies 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

RA Studies I, II and III

The percent of Humira-treated patients achieving ACR20, 50 and 70 responses was consistent across all three trials. The results for the 40 mg fortnightly dose are summarised in Table 4.

Table 4: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a]*		RA Study II[a]*		RA Study III[a, c] *	
	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
ACR20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR70						
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 fortnightly

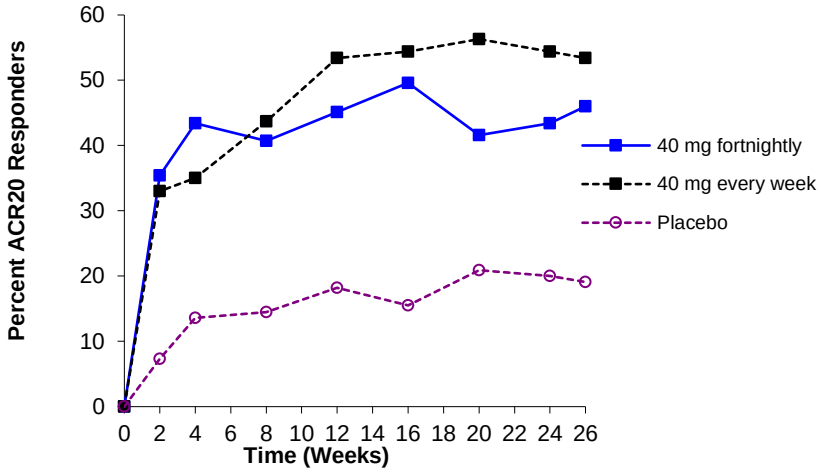
[c] The 12 months placebo-controlled phase of RA Study III was followed by 12 months of open-label treatment with ACR responses at 24 months of 48.8% (ACR20), 36.2% (ACR50) and 22.7% (ACR70).

* $p < 0.01$, Humira vs. placebo at all timepoints for ACR20, 50, 70

MTX Methotrexate

Patients receiving Humira 40 mg every week in RA Study II also achieved statistically significant ACR20, 50 and 70 response rates of 53.4%, 35.0% and 18.4%, respectively, at six months.

Figure 2: RA Study II ACR20 Responses over 26 Weeks



The results of the components of the ACR response criteria for RA Study III are shown in Table 5. ACR response rates and improvement in all ACR response criteria were maintained to Week 104. Over the 2 years in RA Study III, 20% of Humira patients achieved a major clinical response, defined as maintenance of an ACR70 response over a > 6 month period.

Table 5: Components of ACR Response in RA Study III

Parameter (median)	Placebo/MTX (N = 200)			Humira[a] /MTX (N = 207)		
	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
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 fortnightly

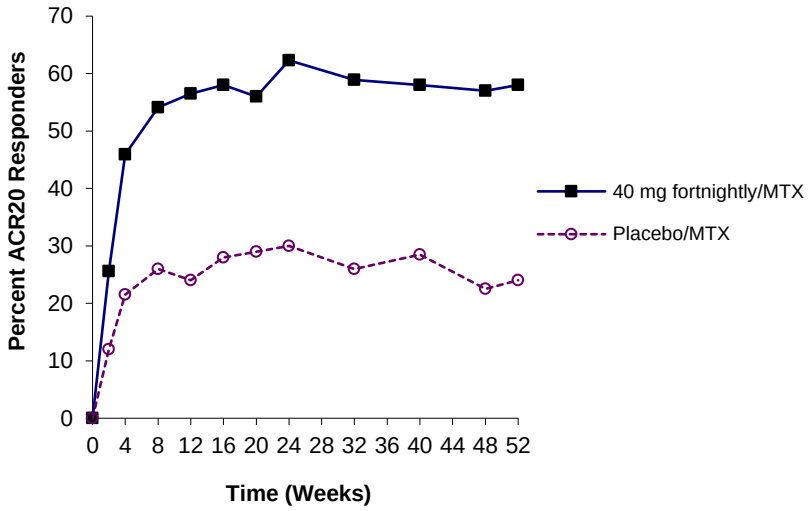
[b] Visual analogue scale; 0 = best, 100 = worst

[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 ACR20 responses at Week 24 maintained the response at 52 weeks. Clinical responses were maintained for up to 5 years in the open-label portion of RA Study III. ACR responses observed at Week 52 were maintained or increased through 5 years of continuous treatment with 22% (115/534) of patients achieving major clinical response. A total of 372 (67.8%) subjects had no change in their methotrexate dose during the study, 141 (25.7%) subjects had a dose reduction and 36 (6.6%) subjects required a dose increase. A total of 149 (55.6%) subjects had no change in their corticosteroid dose during the study, 80 (29.9%) subjects had a dose reduction and 39 (14.6%) subjects required a dose increase. The following figures illustrate the durability of ACR20 responses to Humira in RA Studies III and II.

Figure 3: RA Study III ACR20 Responses over 52 Weeks



RA Study IV

The ACR20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In RA Studies I to IV, Humira-treated patients achieved statistically significant ACR20 and 50 responses compared to placebo as early as 1 to 2 weeks after initiation of treatment.

RA Study V

In RA Study V for early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira plus methotrexate led to significantly greater ACR responses than methotrexate monotherapy at Week 52 and responses were sustained at Week 104 (see Table 6).

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 (ACR70 for > six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ($p < 0.001$).

Table 6: ACR20/50/70 Response at Weeks 26, 52, 76 and 104 (All Randomised Subjects) in RA Study V

	MTX N=257	Adalimumab N=274	Adalimumab + MTX N=268	p-value[a]	p-value[b]
		N (%)			
ACR20					
Week 26	158 (61.5)	146 (53.3)	184 (68.7)	0.084	< 0.001
Week 52	161 (62.6)	149 (54.4)	195 (72.8)	0.013	< 0.001
Week 76	154 (59.9)	137 (50.0)	185 (69.0)	0.029	< 0.001
Week 104	144 (56.0)	135 (49.3)	186 (69.4)	0.002	< 0.001
ACR50					
Week 26	104 (40.5)	96 (35.0)	157 (58.6)	< 0.001	< 0.001
Week 52	118 (45.9)	113 (41.2)	165 (61.6)	< 0.001	< 0.001
Week 76	114 (44.4)	114 (41.6)	161 (60.1)	< 0.001	< 0.001
Week 104	110 (42.8)	101 (36.9)	158 (59.0)	< 0.001	< 0.001
ACR70					
Week 26	57 (22.2)	54 (19.7)	114 (42.5)	< 0.001	< 0.001
Week 52	70 (27.2)	71 (25.9)	122 (45.5)	< 0.001	< 0.001
Week 76	75 (29.2)	79 (28.8)	127 (47.4)	< 0.001	< 0.001
Week 104	73 (28.4)	77 (28.1)	125 (46.6)	< 0.001	< 0.001

Note: Subjects with missing values were counted as non-responders.

a. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

b. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

In the open-label extension for RA study V, ACR responses were maintained when followed for up to 10 years. Of 542 patients who were randomised to Humira 40mg fortnightly, 170 patients continued on Humira 40mg fortnightly for 10 years. Among those, 154 patients (90.6%) had ACR20 responses; 127 patients (74.7%) had ACR50 responses and 102 patients (60.0%) had ACR70 responses.

In RA Study V, Humira/methotrexate combination therapy was superior to methotrexate monotherapy in achieving clinical remission defined as Disease Activity Score (DAS28) (CRP) < 2.6 at Week 52 (see Table 7).

Of the 342 subjects originally randomised 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 7: Subjects in Remission as Defined by DAS28 < 2.6 at Week 52 (All Randomised Subjects) in RA Study V

	MTX N=257	Adalimumab N=274	Adalimumab + MTX N=268		
	N (%)			p-value[a]	p-value[b]
Subjects in Remission at Week 52	53 (20.6)	64 (23.4)	115 (42.9)	< 0.001	< 0.001

a. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

b. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

MTX Methotrexate

Radiographic Response

In RA Study III, Humira-treated patients had a mean duration of rheumatoid arthritis for approximately 11 years and a mean ± standard deviation baseline modified Total Sharp Score for the 40 mg fortnightly group of 72.1 ± 60.7 and placebo group of 66.4 ± 47.4. Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, erosion score and joint space narrowing score (JSN) at month 12 compared to baseline. Humira/methotrexate-treated patients demonstrated less radiographic progression than patients receiving placebo/methotrexate (see Table 8).

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; 54% had no progression of structural damage as defined by a change in the TSS of zero or less.

Fifty-five percent (113/207) of patients originally treated with 40 mg Humira fortnightly have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with approximately 50% (57/113) showing no progression of structural damage defined by a change in the TSS of zero or less.

Table 8: Radiographic Mean Changes Over 12 Months in RA Study III with Background MTX

	Placebo/ MTX N = 200	Humira[a]/MTX N = 207	Difference Between Humira[a]/MTX and Placebo/MTX (95% Confidence Interval*)	p-value
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	≤ 0.001[b]
Erosions	1.6	0.0	1.6 (0.9, 2.2)	≤ 0.001
No New Erosions (% of Patients)	46.2	62.9	16.7	≤ 0.001
JSN Score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a] 40 mg administered fortnightly

[b] Based on rank analysis

MTX Methotrexate

* 95% confidence intervals for the differences in change scores between MTX and Humira

In RA Study V, Humira-treated patients had a mean duration of rheumatoid arthritis of less than 9 months and had not previously received methotrexate. Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score. The Week 52 results are shown in Table 9. A statistically significant difference for change in modified Total Sharp Score and the erosion score was observed at Week 52 and maintained at Week 104.

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 randomised 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.

Table 9: Change in Modified Total Sharp Score from Baseline at Weeks 52 and 104 (All Randomised Subjects) in RA Study V					
	MTX N=257	Adalimumab N=274	Adalimumab + MTX N=268	p-value[a]	p-value[b]
Week 52					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 52 (mean)	27.6 ± 24.6	21.8 ± 19.7	19.4 ± 19.9		
Change at Week 52 (mean ± SD)	5.7 ± 12.7	3.0 ± 11.2	1.3 ± 6.5	< 0.001	0.002
Week 104					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 104 (mean)	32.3 ± 30.0	24.3 ± 23.2	20.0 ± 20.5		
Change at Week 104 (mean ± SD)	10.4 ± 21.7	5.5 ± 15.8	1.9 ± 8.3	< 0.001	< 0.001

Note: Primary analysis imputation used for missing data.

a. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

b. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

Physical Function

Health-related quality of life and physical function was assessed using the disability index of the Stanford Health Assessment Questionnaire (HAQ), which was a pre-specified primary endpoint at Week 52 in RA Study III.

The HAQ was developed as a disease-specific outcome measure for rheumatoid arthritis and has been extensively studied in RA. HAQ has been shown to correlate with mortality, work disability, functional limitations, pain, fatigue and psychological relief. The score is based on 8 questions and normalised to a scale of 0 to 3, where higher scores indicate more disability, and lower scores indicate less disability. Studies have shown that a change in HAQ score of 0.22 or greater represents an improvement in disability that is perceptible and meaningful to the patient. All doses/schedules of Humira in RA Study III showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and the same was seen at Week 52.

There were 619 patients enrolled in RA Study III also known as the DE019 study. The patients were divided into three groups. The first group received placebo injections every week for 52 weeks. The second group received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of

Humira fortnightly with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase (DE019OLE) in which 40 mg of Humira/MTX was administered fortnightly. Maintenance of physical function was defined as maintaining a reduction in HAQ of -0.5 over the second year of active treatment.

Results

In RA Study III, the mean (95% CI) improvement in HAQ from baseline at Week 52 was -0.60 (-0.65, -0.55) for the Humira patients and -0.25 (-0.33, -0.17) for the placebo/MTX ($p < 0.001$) patients. At Week 104, the mean improvement in HAQ from baseline was -0.70 (-0.8, -0.6) for the Humira patients.

Table 10: Percentage of Patients Achieving Improvement in Physical Function After One and Two Years of Treatment In RA Study III

Reduction in HAQ from Baseline	**Proportion of patients who achieved HAQ reduction at Week 52**		**Proportion of patients who received adalimumab 40 mg fortnightly and who achieved HAQ reduction at Week 104**	**Proportion of all adalimumab-treated patients with HAQ reduction at Week 52 that was maintained at Week 104**
Treatment arm	**Adalimumab 40 mg fortnightly**	**Placebo**	**Adalimumab 40 mg fortnightly**	**All adalimumab**
-0.22	150/207 (72.5%)	96/200 (48%)	123/207 (59.4%)	231/258 (89.5%)
-0.5	114/207 (55.1%)	56/200 (28%)	94/207 (45.4%)	167/204 (81.9%)
-0.75	82/207 (39.6%)	40/200 (20%)	71/207 (34.3%)	124/149 (83.2%)
-1.0	56/207 (27.1%)	22/200 (11%)	40/207 (19.3%)	69/103 (67.0%)

At Year 2, 94/207 (45.4%) of patients who originally entered the study achieved a -0.5 reduction in HAQ. 79.5% (115/195) of the patients who achieved a reduction in HAQ of -0.5 at the end of one year of Humira treatment maintained this response over 5 years of active treatment.

Quality of Life

Results from the Short Form Health Survey (SF-36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg fortnightly dose. A statistically significant decrease in fatigue as measured by Functional Assessment of Chronic Illness Therapy (FACIT) scores was seen in all three studies in which it was assessed (RA Studies I, III, IV). Improvement in SF-36 was measured up to Week 156 (3 years) and improvement was maintained through this time.

In RA Study V, the active-comparator controlled study in early rheumatoid arthritis, the improvement in the HAQ disability index and the physical component of the SF-36 showed greater improvement ($p < 0.001$) for

Humira/methotrexate combination therapy versus methotrexate monotherapy at Week 52, which 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.

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The safety and efficacy of Humira was assessed in two clinical studies (pJIA Studies I and II) in patients 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 Study I

The safety and efficacy of Humira were assessed in a multi-centre, randomised, withdrawal, double blind, parallel-group study in 171 patients (4 to 17 years of age) with polyarticular juvenile idiopathic arthritis (pJIA). In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All patients had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDs. Patients who received prior treatment with any biologic DMARDs were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomised withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, Humira was administered based on body surface area at a dose of 24 mg/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) fortnightly. In the OLE-FD phase, the patients were treated with 20 mg of Humira SC fortnightly if their weight was less than 30 kg and with 40 mg of Humira SC fortnightly if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a Paediatric ACR 30 response at the end of OL-LI phase were randomised into the double blind (DB) phase of the study and received either Humira or placebo fortnightly for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥ 30% from baseline in ≥ 3 of 6 Paediatric ACR core criteria, ≥ 2 active joints, and improvement of > 30% in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

pJIA Study I Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Paediatric ACR 30 responders. In the DB phase significantly fewer patients who received Humira experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%)

and with MTX (37% *vs.* 65%). More patients treated with Humira continued to show paediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone.

Paediatric ACR responses were maintained for up to two years in the OLE phase in patients who received Humira throughout the study.

The long term effects of Humira on the growth and development of children have not been studied.

pJIA Study II

The safety and efficacy of Humira was assessed in an open-label, multi-centre study in 32 patients (2 to < 4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active pJIA. The patients received 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 20 mg fortnightly 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.

pJIA Study II Clinical Response

At Week 12 and Week 24, Paediatric ACR 30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of patients with Paediatric 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 (Paediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Paediatric 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 patients were treated for 60 weeks or longer.

Enthesitis-Related Arthritis (ERA)

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with enthesitis-related arthritis (M11-328). Subjects had to have a diagnosis of ERA prior to their sixteenth birthday, at least 3 active joints (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), evidence of past or present enthesitis in at least 1 location and an inadequate response or intolerance to at least 1 nonsteroidal anti-inflammatory drug (NSAID). In addition, subjects had to have an inadequate response or intolerance to at least 1 disease-modifying anti-rheumatic drug, either sulfasalazine or methotrexate.

Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo fortnightly for 12 weeks. The double-blind period was 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 fortnightly 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), Paediatric ACR 30 response, Paediatric ACR 50 response, and Paediatric ACR 70 response, and maintained these improvements during the OL period through Week 156 of the study.

Psoriatic Arthritis

Humira, 40 mg fortnightly, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, PsA Studies I (M02-518) and II (M02-570). PsA Study I with 24-week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50% were taking methotrexate. PsA Study II with 12-week duration treated 100 patients who had an inadequate response to DMARD therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg Humira was administered fortnightly.

ACR and PASI response

Humira was superior to placebo in all measures of disease activity ($p < 0.001$) as shown in Table 11 and 12. Among patients with psoriatic arthritis who received Humira, the clinical responses were apparent at the time of the first visit (2 weeks), significant at 12 weeks and were maintained through 24 weeks of therapy. Patients with a psoriasis involvement of at least 3% Body Surface Areas (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) response. In these patients the skin lesions of psoriasis were improved with Humira, relative to placebo, as measured by PASI. Responses were similar with and without concomitant methotrexate therapy. ACR responses were maintained in the open-label extension study for up to 136 weeks.

Table 11: ACR and PASI Response in Placebo-Controlled Psoriatic Arthritis Study (Percent of Patients)

Response*	Placebo N=162	Humira N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%
	N=69	N=69
PASI 50		
Week 12	15%	72%
Week 24	12%	75%
PASI 75		
Week 12	4%	49%
Week 24	1%	59%

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

Table 12: Components of Disease Activity in Psoriatic Arthritis				
	Placebo N=162[a]		Humira* N=151[a]	
Parameter: mean (median)	Baseline	24 Weeks	Baseline	24 Weeks
Number of tender joints[b]	25.8 (23.0)	22.3 (17.0)	23.3 (19.0)	11.8 (5.0)
Number of swollen joints[c]	14.6 (11.0)	12.1 (8.0)	13.4 (10.0)	7.6 (3.0)
Physician global assessment[d]	53.2 (53.0)	46.0 (48.0)	53.5 (54.0)	21.4 (16.0)
Patient global assessment[d]	47.2 (49.0)	47.6 (49.0)	47.5 (48.0)	24.2 (18.5)
Pain[d]	47.6 (47.5)	47.9 (49.0)	50.6 (53.0)	25.4 (19.0)
Disability index (HAQ)[e]	1.0 (1.0)	0.9 (0.8)	1.0 (0.9)	0.6 (0.4)
CRP (mg/L)[f]	13.9 (7.8)	14.3 (7.4)	14.3 (8.0)	5.5 (2.1)

[a] As observed analysis presented. N at 24 weeks may be less than 162 for placebo or 151 for Humira.

[b] Scale 0 – 78

[c] Scale 0 – 76

[d] Visual analog scale; 0 = best, 100 = worst.

[e] 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.

[f] Normal range: 0-2.87 mg/L.

* $p < 0.001$ for Humira vs. placebo comparisons based on mean changes.

Radiographic Response

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

Humira-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 13).

Table 13: Change in Modified Total Sharp Score in Psoriatic Arthritis			
Modified Total Sharp Score*	Placebo	Adalimumab	*p*-value
Baseline to Week-24	n = 162	n = 151	
• baseline mean	19.0	22.6	
• mean change from baseline	1.6	1.0	< 0.001
	Placebo to adalimumab**	Adalimumab	
Baseline to Week-48	n = 141	n = 133	
• baseline mean	21.2	22.2	
• mean change from baseline	0.9	0.0	
Week-48 to Week-144	n = 128	n = 115	
• Week-48 mean	22.7	22.3	
• mean change from Week-48	0.1	0.4	
Erosion Score	Placebo to adalimumab**	Adalimumab	
Baseline to Week 48	n = 141	n = 133	
• baseline mean	11.2	11.9	
• mean change from baseline	0.6	0.1	
Week-48 to Week-144	n = 128	n = 115	
• Week-48 mean	12.1	12.1	
• Mean change from Week 48	-0.2	0.0	
Joint Space Narrowing Score	Placebo to adalimumab**	Adalimumab	
Baseline to Week 48	n = 141	n = 133	
• baseline mean	10.0	10.4	
• mean change from baseline	0.3	-0.1	
Week-48 to Week-144	n = 128	n = 115	
• Week-48 mean	10.6	10.2	
• Mean change from Week 48	0.3	0.4	

* Baseline to Week-24 data represents ITT data and belongs to a different x-ray reading than baseline to Week-48 and Week-48 to Week-144 data.

**Patients changed over to adalimumab at Week 24

In subjects treated with Humira with no radiographic progression from baseline to Week 48 (n = 102), 84% continued to show no radiographic progression through 144 weeks of treatment.

Quality of Life and Physical Function

In PsA study VI, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the Short Form Health Survey (SF-36). Patients treated with 40 mg of Humira fortnightly showed

greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively).

Results from the Short Form Health Survey (SF-36) support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores. At Weeks 12 and 24, patients treated with Humira showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function and disability measures were maintained for up to 136 weeks through the open label portion of the study.

Ankylosing Spondylitis

The safety and efficacy of Humira 40 mg fortnightly was assessed in 393 adult patients in two randomised, 24-week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (AS). The larger study (AS Study I or M03-607) enrolled 315 adult patients with active AS (defined as fulfilling at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score $\geq$ 4 cm, (2) a visual analog score (VAS) for total back pain $\geq$ 40 mm, (3) morning stiffness $\geq$ 1 hour), who had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open-label period. Subjects (N=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg fortnightly SC and were subsequently treated as non-responders in double-blind statistical analyses.

Results showed statistically significant improvement of signs and symptoms of AS in patients treated with Humira compared to placebo. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 4 and Table 14.

Patients with total spinal ankylosis were included in the larger study (n=11). Responses of these patients were similar to those without total ankylosis.

Figure 4. ASAS 20 Response By Visit, AS Study I

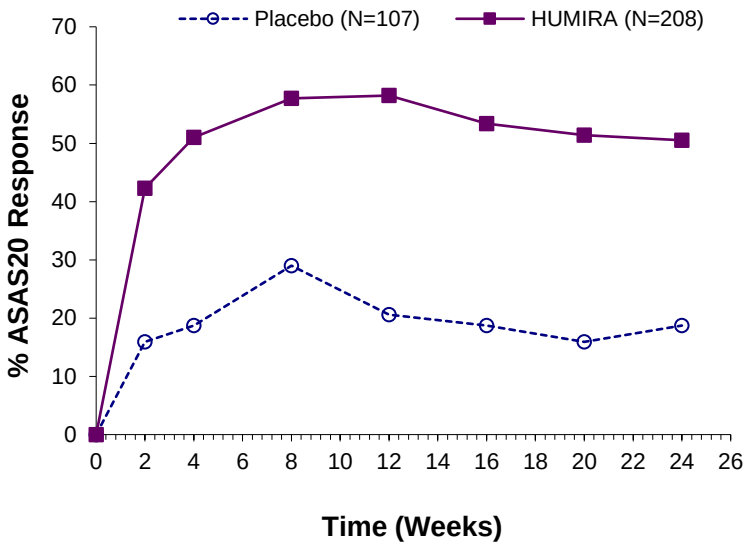


Table 14. ASAS[a] Responses in Placebo-Controlled AS Study		
Response	Placebo N=107	Humira N=208
ASAS 20		
Week 12	21%	58%*
Week 24	19%	51%*
ASAS 50		
Week 12	10%	38%*
Week 24	11%	35%*
ASAS 70		
Week 12	5%	23%*
Week 24	8%	24%*

* Statistically significant at p<0.001 for all comparisons between Humira and placebo at Weeks 12 and 24

[a] Assessments in Ankylosing Spondylitis

A low level of disease activity (defined as a value < 20 [on a scale of 0-100 mm] in each of the four ASAS response parameters) was achieved at 24 weeks in 22% of Humira-treated patients vs. 6% in placebo-treated patients (p < 0.001).

Table 15. Components of Ankylosing Spondylitis Disease Activity				
	Placebo N=107		Humira N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a]	65	60	63	38
Total back pain	67	58	65	37
Inflammation[b]	6.7	5.6	6.7	3.6
BASFI[c]	56	51	52	34
BASDAI[d] score	6.3	5.5	6.3	3.7
CRP[e]	2.2	2.0	1.8	0.6

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

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

[c] Bath Ankylosing Spondylitis Functional Index

[d] Bath Ankylosing Spondylitis Disease Activity Index

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

* Statistically significant as p<0.001 for all comparisons between Humira and placebo at Week 24

Results of this study were similar to those seen in the second randomised trial (AS Study II or M03-606), a multicentre, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis. Patient Reported Outcomes were assessed in both ankylosing spondylitis studies using the generic health status questionnaire SF-36 and the disease specific Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL). The Humira-treated patients had significantly greater improvement in SF-36 Physical Component Score (mean change: 6.93) compared to placebo-treated patients (mean change: 1.55; $p < 0.001$) at Week 12, which was maintained through Week 24.

Results from the ASQoL support these findings demonstrating improvement in overall quality of life. The Humira-treated patients had statistically significant improvement (mean change: -3.15) compared to placebo-treated patients (mean change: -0.95; $p < 0.001$) at Week 12, which was maintained through Week 24.

Non-Radiographic Axial Spondyloarthritis

The safety and efficacy of Humira were assessed in two randomised, double-blind placebo-controlled studies in patients with non-radiographic axial spondyloarthritis (nr-axSpA). Study nr-axSpA I evaluated patients with active nr-axSpA. Study n-axSpA II was a treatment withdrawal study in active nr-axSpA patients who achieved remission during open-label treatment with Humira.

Study nr-axSpA I

In Study nr-axSpA I, Humira 40 mg fortnightly was assessed in 185 patients in a randomised, 12 week double-blind, placebo-controlled study in patients with active nr-axSpA who have had an inadequate response to or intolerance to ≥ 1 NSAIDs, or a contraindication for NSAIDSs (Study M10-791). Patients included were classified according to the ASAS axial SpA criteria, excluding patients fulfilling modified New York criteria for ankylosing spondylitis and those with psoriasis or psoriatic arthritis. The primary efficacy endpoint was the proportion of patients who achieved the ASAS40 response criteria at Week 12. Mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with Humira and 6.5 for those on placebo. Thirty-three (18%) of patients were treated concomitantly with disease-modifying anti-rheumatic drugs and 146 (79%) with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients received Humira 40 mg fortnightly SC for up to an additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active nr-axSpA in patients treated with Humira compared to placebo in both the overall population and in patients with a positive MRI or elevated CRP (see Tables 16 and 17).

Variables demonstrating a reduction in signs and symptoms of nr-axSpA were sustained or continued to improve at Week 24 and Week 68 and were maintained through Week 156 (see Tables 18 and 19).

Table 16: **Efficacy Response in the Placebo-Controlled Study nr-axSpA I**[#]		
Double-Blind **Response at Week 12**	**Placebo** **N=94**	**Humira** **N=91**
ASAS[a] 40	15%	36%*
ASAS 20	31%	52%**
ASAS 5/6	6%	31%*
ASAS Partial Remission	5%	16%***
BASDAI[b] 50	15%	35%**
ASDAS[c,d,e]	-0.3	-1.0*
ASDAS Inactive Disease	4%	24%*
SF-36 PCS[d, f]	2.0[m]	5.5**
HAQ-S[d,g]	-0.1	-0.3***
Hs-CRP[d,h,i]	-0.3	-4.7*
SPARCC[j] MRI Sacroiliac Joints [d,k]	-0.6	-3.2**
SPARCC MRI Spine [d,l]	-0.2	-1.8**

a Assessment of Spondyloarthritis International Society

b Bath Ankylosing Spondylitis Disease Activity Index

c Ankylosing Spondylitis Disease Activity Score

d Mean change from baseline

e n=91 placebo and n=87 Humira

f Short Form-36 Health Status SurveyTM Version 2 Physical Component Summary score

g Health Assessment Questionnaire modified for the spondyloarthropathies

h high sensitivity C-Reactive Protein (mg/L)

i n=73 placebo and n= 70 Humira

j Spondyloarthritis Research Consortium of Canada

k n=84 placebo and Humira

l n=82 placebo and n=85 Humira

m n=93

* P-value < 0.001

** P-value < 0.01

*** P-value < 0.05

Last observation carried forward (LOCF) analysis for HAQ-S and hs-CRP, observed case analysis for SF-36 and SPARCC MRI scores, and non-responder imputation (NRI) analysis for all other categorical endpoints

Table 17: Efficacy Response in the Placebo-Controlled Study nr-axSpA I (Population with either a positive MRI or Elevated CRP)[#]		
Double-Blind **Response at Week 12**	**Placebo** **N = 73**	**Humira** **N = 69**
ASAS[a] 40	14%	41%***
ASAS 20	32%	59%***
ASAS 5/6	8%	35%***
ASAS Partial Remission	5%	19%*
BASDAI[b] 50	14%	39%***
ASDAS[c,d,e]	-0.3	-1.2***
ASDAS Inactive Disease	4%	29%***
SF-36 PCS[d,f]	2.3[m]	6.9***
HAQ-S[d,g]	-0.1	-0.3**
hs-CRP[d,h,i]	-0.8	-6.5***
SPARCC[j] MRI Sacroiliac Joints[d,k]	-0.9	-4.3**
SPARCC MRI Spine[d,l]	-0.5	-2.3**

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] mean change from baseline

[e] n = 72 placebo and n = 66 Humira

[f] Short Form-36 Health Status Survey™ Version 2 Physical Component Summary score

[g] Health Assessment Questionnaire modified for the spondyloarthropathies

[h] high sensitivity C-Reactive Protein (mg/L)

[i] n = 54 placebo and n=50 Humira

[j] Spondyloarthritis Research Consortium of Canada

[k] n = 64 placebo and Humira

[l] n = 62 placebo and n=65 Humira

[m] n = 72

*** p-value < 0.001

** p-value < 0.01

* p-value < 0.05

[#] LOCF analysis for HAQ-S and hs-CRP, observed case analysis for SF-36 and SPARCC MRI scores, and NRI analysis for all other categorical endpoints

Table 18: Efficacy Response in the Open-label Extension of the Study nr-axSpA I[#]			
Endpoint	**Week 24** **N=171**	**Week 68** **N=145**	**Week 156** **N=122**
ASAS[a] 40	89/171 (52.0%)	97/145 (66.9%)	81/122 (66.4%)
ASAS 20	117/171 (68.4%)	116/145 (80.0%)	101/122 (82.8%)
ASAS 5/6	73/171 (42.7%)	72/145 (49.7%)	58/122 (47.5%)
ASAS Partial Remission	45/170 (26.5%)[h]	53/145 (36.6%)	52/120 (43.3%)[i]
BASDAI[b] 50	86/171 (50.3%)	93/145 (64.8%)	85/122 (69.7%)
ASDAS[c,d]	-1.5[j]	-1.8[k]	-1.7[l]
ASDAS Inactive Disease	60/170 (35.3%)[h]	69/145 (47.6%)	55/120 (45.8%)[i]
SF-36 PCS[d,e]	7.2[m]	9.6[n]	10.5[o]
HAQ-S[d,f]	-0.39	-0.47[i]	-0.48
hs-CRP[d,g]	-4.6[p]	-4.4[q]	-3.3[r]

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] Mean change from baseline

[e] Short Form-36 Health Status Survey TM Version 2 Physical Component Summary score

[f] Health Assessment Questionnaire modified for the spondyloarthropathies

[g] high sensitivity C-Reactive Protein (mg/L)

[h] n=170

[i] n=120

[j] n=163

[k] n=140

[l] n=118

[m] n=177

[n] n=151, Week 52

[o] n=121

[p] n=131

[q] n=112

[r] n=97

[#] Observed case analysis

Table 19: Efficacy Response in the Open-label Extension of the Study nr-axSpA I **(Population with either a positive MRI or Elevated CRP)[#]**			
Endpoint	**Week 24** **N = 133**	**Week 68** **N = 112**	**Week 156** **N = 97**
ASAS[a] 40	70/133 (52.6%)	78/112 (69.6%)	67/97 (69.1%)
ASAS 20	96/133 (72.2%)	94/112 (83.9%)	83/97 (85.6%)
ASAS 5/6	61/133 (45.9%)	63/112 (56.3%)	49/97 (50.5%)
ASAS Partial Remission	37/133 (27.8%)	45/112 (40.2%)	45/97 (46.9%)[h]
BASDAI[b] 50	68/133 (51.1%)	75/112 (67.0%)	70/97 (72.2%)
ASDAS[c,d]	-1.6[i]	-1.9[j]	-1.9[k]
ASDAS Inactive Disease	48/133 (36.1%)	54/112 (48.2%)	45/97 (47.4%)[l]
SF-36 PCS[d,e]	7.7[m]	10.5[n]	11.5[o]
HAQ-S[d,f]	-0.39	-0.48	-0.50
hs-CRP[d,g]	-6.0[p]	-5.9[q]	-4.2[r]

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] Mean change from baseline

[e] Short Form-36 Health Status Survey TM Version 2 Physical Component Summary score

[f] Health Assessment Questionnaire modified for the spondyloarthropathies

[g] high sensitivity C-Reactive Protein (mg/L)

[h] n=96

[i] n=129

[j] n=110

[k] n=93

[l] n=95

[m] n=138

[n] n=116, Week 52

[o] n=96

[p] n=97

[q] n=83

[r] n=75

[#] Observed case analysis

Inhibition of Inflammation

Significant improvements of signs of inflammation as measured by hS-CRP, and MRI of both Sacroiliac Joints and the Spine was maintained in Humira-treated patients through Week 156 and Week 104 respectively. SPARCC MRI for Sacroiliac Joints was available for 131 patients and SPARCC MRI for Spine was available for 130 patients with a mean change from baseline -3.8 and -1.4, respectively at Week 104.

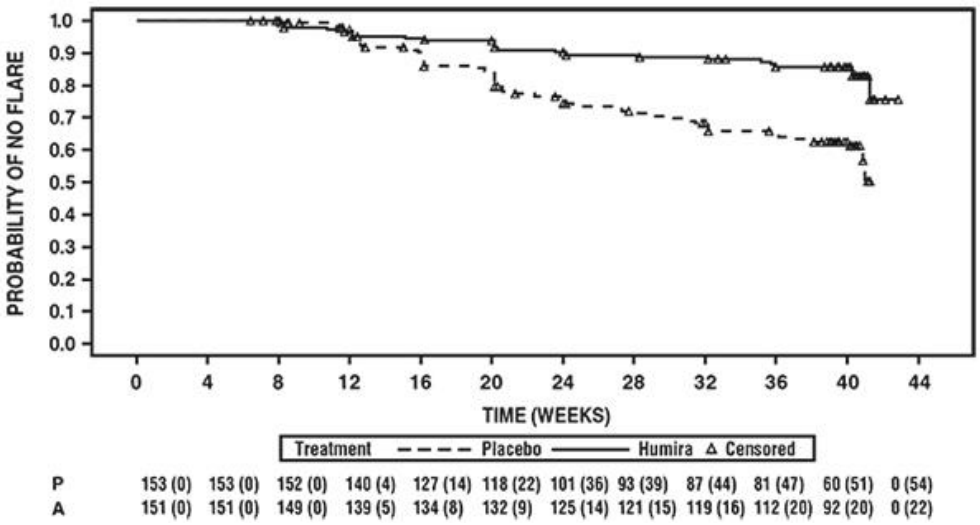
Quality of Life and Physical Function

Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Humira showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to Week 12 compared to placebo. Results for the SF-36 PCS score and the HAQ-S total score were sustained through Week 52, Week 68 and Week 156 respectively (see Tables 18 and 19).

Study nr-axSpA II

673 patients with active nr-axSpA (mean baseline disease activity [BASDAI] was 7.0) who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into the open-label period of Study nr-axSpA II during which they received Humira 40 mg fortnightly for 28 weeks. These patients also had objective evidence of inflammation in the sacroiliac joints or spine on MRI or elevated hs-CRP. Patients who achieved sustained remission for at least 12 weeks (N = 305) (ASDAS < 1.3 at Weeks 16, 20, 24, and 28) during the open-label period were then randomised to receive either continued treatment with Humira 40 mg fortnightly (N = 152) or placebo (N = 153) for an additional 40 weeks in a double-blind, placebo-controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed Humira 40 mg fortnightly rescue therapy for at least 12 weeks. The primary efficacy endpoint was the proportion of patients with no flare by Week 68 of the study. Flare was defined as ASDAS ≥ 2.1 at two consecutive visits four weeks apart. A greater proportion of patients on Humira had no disease flare during the double-blind period, when compared with those on placebo (70.4% vs. 47.1%, p<0.001) (Figure 5).

Figure 5: Kaplan-Meier Curves Summarising Time to Flare in Study nr-axSpA II



Note: P = Placebo (Number at Risk (flared)); A = HUMIRA (Number at Risk (flared)).

Among the 68 patients who flared in the group allocated to treatment withdrawal, 65 completed 12 weeks of rescue therapy with Humira, out of which 37 (56.9%) had regained remission (ASDAS < 1.3) after 12 weeks of restarting the open-label treatment. By Week 68, patients receiving continuous Humira treatment showed statistically significant greater improvement of the signs and symptoms of active nr-axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study (Table 20).

Table 20: Efficacy Response in Placebo-Controlled Period for Study nr-axSpA II		
Double-Blind **Response at Week 68**	**Placebo** **N = 153**	**Humira** **N = 152**
ASAS[a,b] 20	47.1%	70.4%***
ASAS[a,b] 40	45.8%	65.8%***
ASAS[a] Partial Remission	26.8%	42.1%**
ASDAS[c] Inactive Disease	33.3%	57.2%***
Partial Flare[d]	64.1%	40.8%***

[a] Assessment of SpondyloArthritis international Society

[b] Baseline is defined as open label baseline when patients have active disease.

[c] Ankylosing Spondylitis Disease Activity Score

[d] Partial flare is defined as ASDAS ≥ 1.3 but < 2.1 at 2 consecutive visits.

*** p-value < 0.001

** p-value < 0.01

Crohn's Disease in Adults

The safety and efficacy of multiple doses of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (M02-403) and CD Study II (M04-691). In CD Study I, 299 TNF-antagonist naïve patients were randomised to one of four treatment groups; the placebo group received placebo at Weeks 0 to 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. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2.

Maintenance of clinical remission was evaluated in a third study, CD Study III (M02-404). In CD Study III, 854 patients received open-label 80 mg Humira at Week 0 and 40 mg Humira at Week 2. Patients were then randomised at Week 4 to 40 mg Humira fortnightly, 40 mg Humira every week or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8. Fistula healing was an important pre-determined secondary endpoint for this study.

Clinical Results

CD Study I / CD Study II

A statistically significantly greater percentage of the groups treated with 160/80 mg Humira achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF antagonist naïve (CD Study I) or had been previously exposed to infliximab (CD Study II) (see Table 21).

Table 21: Induction of Clinical Remission and Response (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 (CR-100)	24%	49%**	25%	38%**
Clinical response (CR-70)	34%	58%**	34%	52%**

Clinical remission is CDAI score <150; clinical response (CR-100) is decrease in CDAI ≥ 100 points; clinical response (CR-70) is decrease in CDAI ≥ 70 points

All p-values are pairwise comparisons of proportions for Humira *vs*. placebo

* $p < 0.001$

** $p < 0.01$

CD Study III (M02-404)

At Week 4, 58% (499/854) patients were in clinical response (decrease in CDAI ≥ 70 points) and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other anti-TNF therapy. At Weeks 26 and 56, statistically significantly greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the Humira maintenance groups compared to patients in the placebo maintenance group. Additionally, statistically significantly greater proportions of patients receiving concomitant corticosteroids at baseline were in clinical remission and were able to discontinue corticosteroid use for at least 90 days in the Humira maintenance groups compared to patients in the placebo maintenance group at Weeks 26 and 56 (see Table 23).

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56 (see Table 22).

Table 22: Hospitalisations to Week 56 (ITT population)				
	Placebo	**40 mg Humira fortnightly**	**40 mg Humira every week**	**Combined Humira**
	N=261 n (%)	**N=260 n (%)**	**N=257 n (%)**	**N= 517 n (%)**
All-cause Hospitalisation	47 (18)	25 (9.6) *	29 (11.3) *	54 (10.4) *
CD – Related Hospitalisation	31 (11.9)	16 (6.2) *	18 (7.0)*	34 (6.6) *
Major Surgery	11 (4.2)	1 (0.4) *	2 (0.8) *	3 (0.6) *

* $p \leq 0.05$

Clinical remission results presented in Table 23 remained relatively constant irrespective of previous TNF antagonist exposure.

Of those in response at Week 4 who attained remission during the study, patients in Humira maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group (see Figure 6). Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses. The group that received Humira every week did not show significantly higher remission rates than the group that received Humira fortnightly.

Table 23: Maintenance of Clinical Remission and Response (Percent of Patients)			
	Placebo	**40 mg Humira fortnightly**	**40 mg Humira every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Clinical response (CR-70)	28%	54%*	56%*
Patients in steroid-free remission for ≥ 90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Clinical response (CR-70)	18%	43%*	49%*
Patients in steroid-free remission for ≥ 90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

Clinical remission is CDAI score < 150; clinical response (CR-100) is decrease in CDAI ≥ 100 points; clinical response (CR-70) is decrease in CDAI ≥ 70 points

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

** p<0.02 for Humira *vs*. placebo pairwise comparisons of proportions

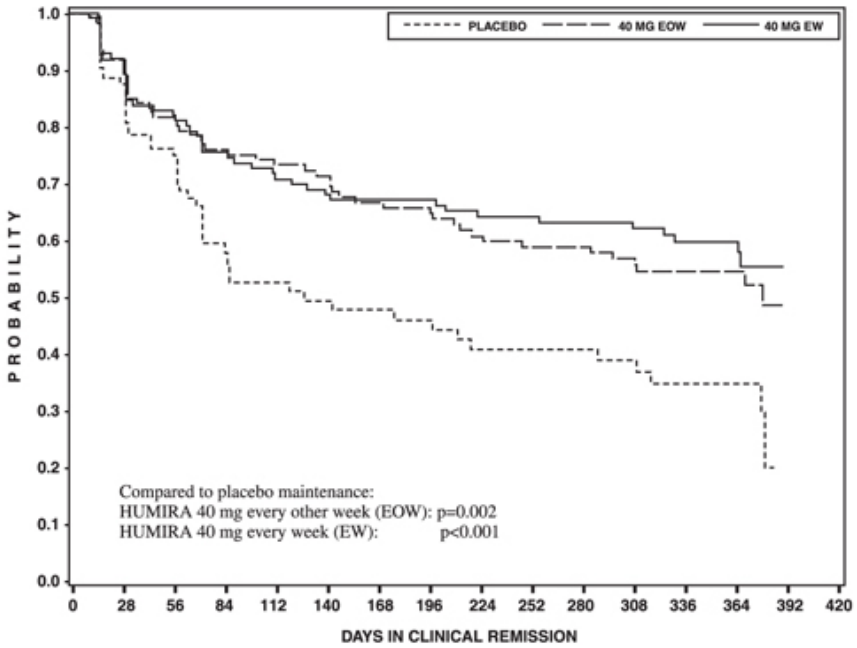
[a] Of those receiving corticosteroids at baseline

117/854 patients 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 (ITT population) 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 (ITT population) in the adalimumab and placebo groups, respectively

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 adalimumab therapy. 88 (75.2%) and 189 (69.5%) patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 (87.2%) and 233 (85.7%) patients, respectively.

An endoscopy study (n=135) assessed rates of mucosal healing in patients with moderate to severe Crohn's Disease given either adalimumab or placebo. After 8 weeks of randomised treatment (Week 12 of study) there was a trend towards higher levels of mucosal healing in subjects given adalimumab compared with subjects given placebo but the differences were not statistically significant (healing in 27.4% (17/62) adalimumab vs 13.1% (8/61) given placebo; p = 0.056). Subjects who continued randomised adalimumab for 52 weeks (n=135) were more likely to experience mucosal healing relative to placebo (healing in 24.2% [15/62] adalimumab vs 0% [0/61] given placebo; p < 0.001).

Figure 6: Days in Clinical Remission for Patients Who Achieved Clinical Remission in CD Study III



Patient Reported Outcomes

In CD Study I and CD Study II, statistically significant improvement in disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 160/80

mg compared to placebo. Statistically significant improvement from baseline in IBDQ scores was seen at Weeks 26 and 56 in CD Study III among the adalimumab treatment groups compared to the placebo group.

Paediatric Crohn's Disease (≥ 6 years)

Humira was assessed in a multicentre, randomised, 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 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric 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 randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 24.

Table 24: Maintenance Regimen

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

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 25.

Rates of discontinuation of corticosteroids or immunomodulators and fistula remission (defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits) are presented in Table 26.

Table 25: Paediatric CD Study PCDAI Clinical Remission and Response

	Standard Dose 40/20 mg fortnightly N =93	Low Dose 20/10 mg fortnightly 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 26: Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission			
	Standard Dose 40/20mg fortnightly	**Low Dose 20/10mg fortnightly**	**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).

Ulcerative Colitis

The safety and efficacy of Humira was assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In Study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg Humira at Week 0 followed by 80 mg at Week 2, or 80 mg Humira at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg fortnightly. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of Humira at Week 0, 80 mg at Week 2 and 40 mg fortnightly thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Subjects induced with 160/80 mg Humira achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with Humira who were in

remission at Week 8, 21/41 (51%) were in remission at Week 52. Results from the overall UC-II study population are shown in Table 27.

Table 27: Response, Remission and Mucosal Healing in Study UC-II (Percent of Patients)

	Placebo	**Humira 40 mg fortnightly**
Week 52	**N=246**	**N=248**
Clinical Response	18%	30%*
Clinical Remission	9%	17%*
Mucosal Healing	15%	25%*
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13% * (N=150)
Week 8 and 52		
Sustained Response	12%	24%**
Sustained Remission	4%	8%*
Sustained Mucosal Healing	11%	19%*

Clinical remission is Mayo score ≤ 2 with no subscore > 1;

*p < 0.05 for Humira *vs.* placebo pairwise comparison of proportions

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

[a] Of those receiving corticosteroids at baseline

Statistically significant reductions of both all-cause and UC-related rates of hospitalisation were observed in a pooled analysis of studies UC I and II.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

Patients from UC studies I and II had the option to roll over into an open-label long-term extension study (UC-III). Following 3 years of Humira therapy, 74% (268/360) continued to be in clinical remission per partial Mayo score, and of those who had received at least 4 years of Humira therapy, 75% (97/130) were in clinical remission per partial Mayo score.

Patients, who lose response may benefit from an increase of dosing frequency to 40 mg weekly.

Quality of Life

In UC Study II, improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 52 in patients randomised to Humira 160/80 mg compared to placebo (p=0.007).

Psoriasis

The safety and efficacy of Humira were assessed in over 1,600 patients 18 years of age or older with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy in randomised, double-blind, well-controlled studies. The safety and efficacy of Humira were also studied in adult patients with moderate to severe plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in an additional Ps Study (M10-405).

Ps Study I (M03-656) evaluated 1212 patients with chronic plaque psoriasis with ≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 within three treatment periods. In period A, patients received placebo or Humira subcutaneously at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg fortnightly starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open label 40 mg Humira fortnightly. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomised to active therapy in Period A were re-randomised in period C to receive 40 mg Humira fortnightly 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" (52.6%) to "severe" (41.3%) to "very severe" (6.1%).

Ps Study II (M04-716) compared the efficacy and safety of Humira versus methotrexate and placebo in 271 patients with 10% BSA involvement and PASI ≥ 10. 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 fortnightly (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%).

Ps Study III (M02-528) evaluated 148 patients with chronic plaque psoriasis with ≥ 5% BSA involvement for at least 1 year. Patients received placebo or Humira subcutaneously at a dose of 40 mg fortnightly starting at Week 1 after an initial dose of 80 mg at Week 0 or Humira at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg weekly.

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial (M03-658) where Humira was given for at least an additional 108 weeks at 40 mg fortnightly, with the option to dose-escalate to 40 mg weekly if response was sub-optimal.

Clinical Results

In Ps Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 for Ps Studies I and II and Week 12 for Ps Study III. Other evaluated outcomes in Ps Studies I, II, and III included the PGA and other PASI measures.

Ps Study I had an additional primary endpoint of loss of adequate response after Week 33 and on or before Week 52. Loss of adequate response is defined as a 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. In Ps Studies I and II, more patients randomised to Humira than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16. Other relevant clinical parameters including PASI 100 (i.e. complete clearance of psoriasis skin signs) and PGA of "clear or minimal" were also improved over placebo. Patients with ≥PASI 75 response continued to Week 33. In Ps Study I, patients who were PASI 75 responders and were re-randomised to continue Humira therapy at Week 33 were less likely to experience a loss of adequate response on or before Week 52 than the PASI 75 responders who were re-randomised to placebo at Week 33 (4.9% versus 28.4%, $p < 0.001$). In Ps Study II, superior results were achieved for PASI 75, PASI 100 and PGA of "clear or minimal" in patients randomised to the Humira treatment group versus those randomised to receive methotrexate (see Tables 28 and 29).

Table 28: Ps Study I (M03-656)

	Period A		Period B	Period C	
	Efficacy Results at 16 Weeks (Percent of Patients)		Efficacy Results at 33 Weeks (Percent of Patients)	Among PASI 75 Responders at Week 33, Efficacy Results at 52 Weeks (Percent of Patients)	
	Placebo N=398	Humira 40 mg fortnightly N=814	Humira 40 mg fortnightly N=580	Placebo N=240	Humira 40 mg fortnightly N=250
≥PASI 75	6.5	70.9[a]	84.5	42.5	79.2
PASI 100	0.8	20.0[a]	30.3	7.5	32.0
PGA: Clear/minimal	4.3	62.2[a]	73.3	27.9	68.0

[a] $p < 0.001$, Humira vs. placebo

Table 29: Ps Study II (M04-716) Efficacy Results at 16 Weeks (Percent of Patients)

	Placebo N=53	MTX N=110	Humira 40 mg fortnightly N=108
≥ PASI 75	18.9	35.5	79.6 [a, b]
PASI 100	1.9	7.3	16.7 [c,d]
PGA: Clear/minimal	11.3	30.0	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

Two of the continuous treatment populations entering trial M03-658 were those from Period C of Study I and those from Study II.

250 subjects in the Humira group in Period C of Study I achieved PASI 75 at Weeks 16 and 33 and received continuous Humira therapy at 40 mg fortnightly for up to 52 weeks. Of these, 233 entered the extension trial M03-658 and the proportion of patients with PGA of "clear or minimal" response was 70.0% at entry to the extension trial (52 weeks Humira treatment), 73.4% after 76 weeks treatment, and 59.0% after 160 weeks treatment. The corresponding percentages for PASI 75 were 83.7% at entry, 86.5% after 76 weeks treatment, and 74.7% after 160 weeks treatment.

108 subjects in the Humira group of Study II received continuous Humira therapy at 40 mg fortnightly for 16 weeks. Of these, 94 entered the extension trial M03-658, and the proportion of these patients with PGA of "clear or minimal" response was 68.1% at entry to the extension trial (16 weeks Humira treatment) and 46.2% after 124 weeks treatment. The corresponding percentages for PASI 75 were 74.5% at entry and 58.1% after 124 weeks treatment.

There was a withdrawal and retreatment evaluation in the extension trial (M03-658) after subjects had received at least 2 years of treatment with Humira. A pre-specified evaluable population of stable responders to Humira was assessed after withdrawal of Humira. This population consisted of subjects with stable psoriasis defined as PGA clear or minimal at the last 2 visits at least 12 weeks apart and receiving Humira 40 mg fortnightly during the last 12 weeks. If subjects relapsed (PGA became moderate or worse) during the withdrawal period, Humira was recommenced at an initial dose of 80 mg and then, from the following week, at 40 mg fortnightly. After 178 subjects had relapsed and recommenced Humira, the remaining subjects who had not relapsed were also eligible for retreatment with Humira.

Of 347 stable responders withdrawn from Humira, 339 had at least one post-baseline evaluation. Approximately half (55.5%) of these subjects relapsed. The median time to relapse was approximately 5 months. None of the subjects experienced rebound of disease (PASI ≥ 125% or new generalised erythrodermic or pustular psoriasis within 3 months of withdrawal of Humira). The number of retreated subjects was 285, of whom 178 had relapsed during the withdrawal period. At week 16 of retreatment, PGA "clear or minimal" increased from 0% to 69.1% in relapsed subjects and from 59.8% to 88.8% in non-relapsed subjects. Therefore, after withdrawal of Humira and relapse, most subjects responded to retreatment within 16 weeks.

In the open-label extension trial (M03-658), patients who dose escalated from 40 mg fortnightly to 40 mg every week 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.

An additional Ps Study (M10-405) 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 of Humira, followed by 40 mg fortnightly (starting one week after the initial dose), or placebo for 16 weeks. At Week16, a statistically significantly greater proportion of patients who received Humira achieved a PGA score 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 (M13-674) compared 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 fortnightly (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. This clinical study did not include dose escalation to weekly dosing. Nail psoriasis assessments included the modified Nail Psoriasis Severity Index (mNAPSI) and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) (see Table30).

Table 30: **Ps Study IV (M13-674)** Efficacy Results at 26 Weeks

	Placebo **N = 108**	**Humira 40 mg fortnightly** **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, 71.4% achieved mNAPSI 75 response and 57.1% achieved PGA-F response.

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. The percent improvement in NAPSI was also statistically significantly greater in Humira patients compared with placebo at Week 16 (44.2% vs 7.8%).

Quality of Life

Patient Reported Outcomes (PRO) were evaluated by several measures. Quality of Life was assessed using the disease-specific Dermatology Life Quality Index (DLQI) in Ps Study I and Ps Study II. In Ps Study I, patients receiving Humira demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 and 16. The DLQI result was maintained at Week 52. In Ps Study II, patients receiving Humira demonstrated clinically meaningful improvement in the DLQI total score, disease severity, and pruritus compared to the placebo

and methotrexate groups at Week 16, and clinically meaningful improvement in pain compared to the placebo group at Week 16.

The Short Form Health Survey (SF-36) was used to assess general health-related quality of life in Ps Study I. The Humira-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

In Ps Study IV, patients receiving Humira showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI.

Paediatric Plaque Psoriasis (≥ 4 years)

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric 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 fortnightly (up to 40 mg), 0.4 mg/kg fortnightly (up to 20 mg), or methotrexate 0.1 to 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g. PASI 75) than those randomised to MTX.

Table 31: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	**Humira 0.8 mg/kg fortnightly 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 fortnightly 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.

The safety and efficacy of adalimumab has not been studied in children with paediatric psoriasis weighing < 15kg.

Hidradenitis Suppurativa

Adults

The safety and efficacy of Humira were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to systemic antibiotic therapy.

The patients in Studies HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (M11-313) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg fortnightly, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

Study HS-II (M11-810) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg fortnightly, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enroll into an open-label extension study in which Humira 40mg was administered every week. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on an 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS -II experienced a clinically relevant decrease in HS-related skin pain (see Table 32). Patients treated with HUMIRA had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 32: Efficacy Results at 12 Weeks, HS Studies I and II				
	HS Study I		HS Study II	
Endpoint	Placebo	Humira 40 mg Weekly	Placebo	Humira 40 mg Weekly
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain [b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a.] Among all randomised patients.

[b.] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Among patients who were randomised to Humira continuous weekly dosing, the overall HiSCR rate at Week 12 was maintained through Week 96. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

Adolescents

There are no clinical trials in adolescent patients with hidradenitis suppurativa (HS). Efficacy of Humira for the treatment of adolescent patients from 12 years of age with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. The recommended adolescent HS dosing schedule of 40 mg fortnightly is predicted to provide similar efficacy to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week. Safety of the recommended Humira dose in the adolescent HS population is based on cross-indication safety profile of Humira in both adults and paediatric patients at similar or more frequent doses (see section 5.2 Pharmacokinetic properties).

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of

80 mg followed by 40 mg fortnightly starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV 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 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV 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 Results

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 34). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 7).

Table 33: 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	--	--	--
Humira	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	--	--	--
Humira	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

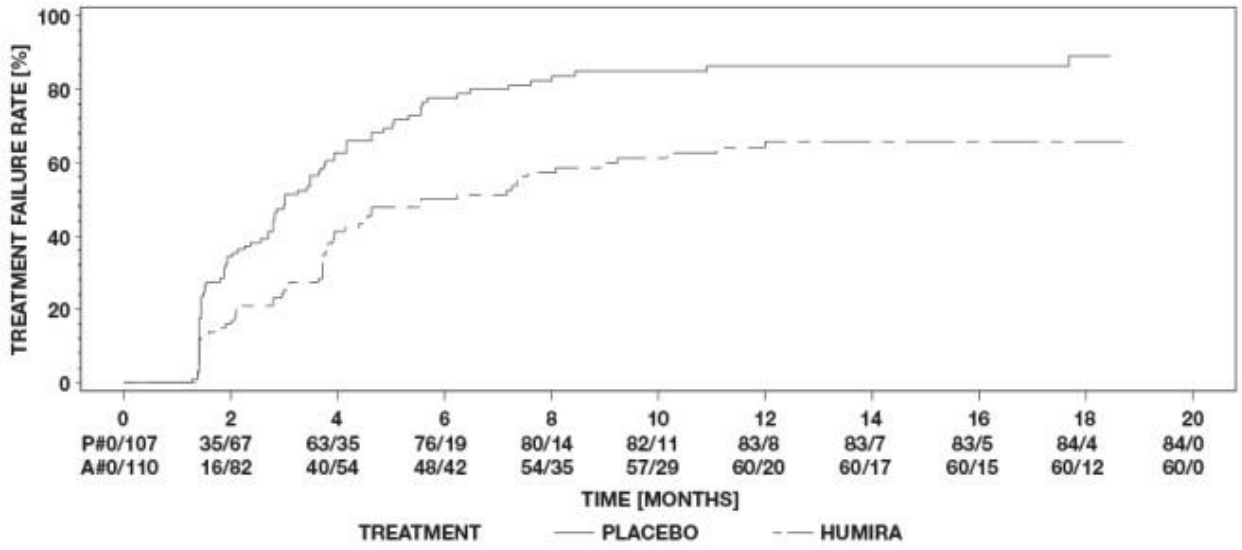
Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

a. HR of Humira vs placebo from proportional hazards regression with treatment as factor.

b. 2-sided *P* value from log rank test.

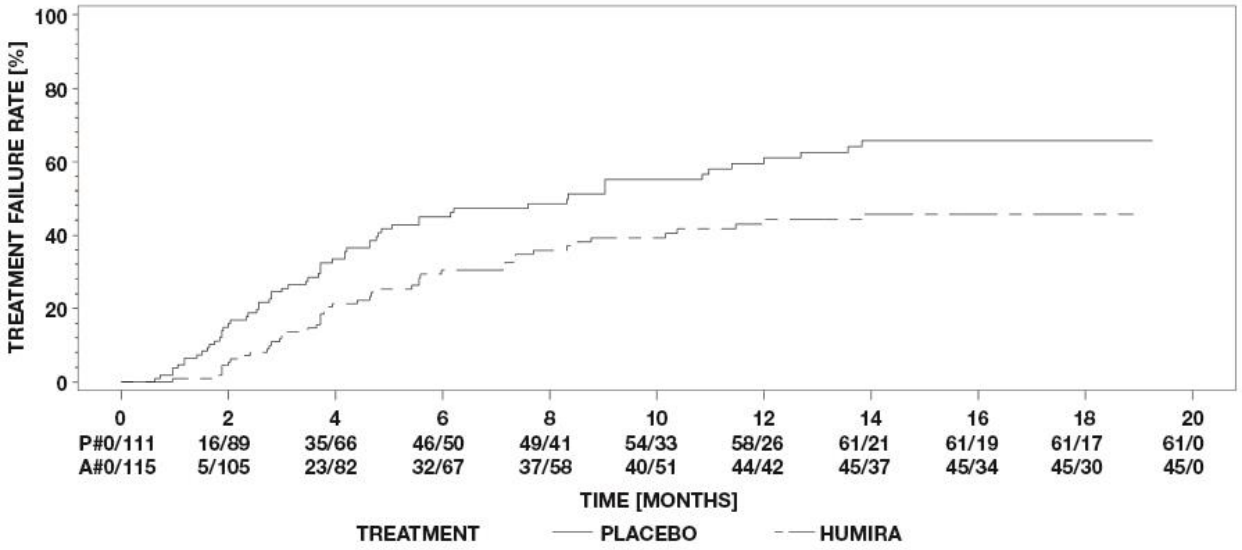
c. NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 7: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I)



Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

Figure 8: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 2 (Study UV II)



Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I, statistically significant differences in favour of Humira versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

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 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

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of sub-scores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UV I and for colour vision, peripheral vision and near vision in Study UV II.

Paediatric Uveitis

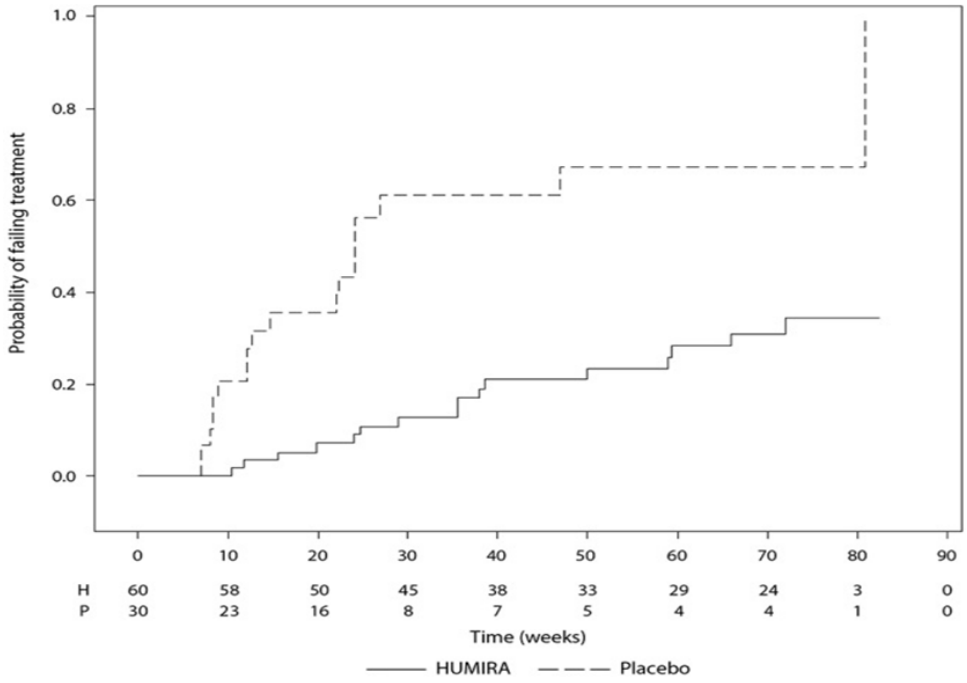
The safety and efficacy of Humira was assessed in a randomised, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated non-infectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) fortnightly 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

Humira significantly delayed the time to treatment failure, as compared to placebo (see Figure 9, $p < 0.0001$ from log rank test). The median time to treatment failure was 24.1 weeks for patients treated with placebo, whereas the median time to treatment failure was not estimable for patients treated with Humira because less than one-half of these patients experienced treatment failure. Humira 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 9: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Immunogenicity

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. Approximately 5.5% (58 of 1,062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titre anti-adalimumab antibodies at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab without concomitant methotrexate (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. Without concomitant methotrexate, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg fortnightly without concomitant methotrexate, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

In the patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, a greater percentage of patients developed anti-adalimumab antibodies compared to adult rheumatoid arthritis patients. Antibody formation was lower when adalimumab was given together with methotrexate in comparison to use without concomitant methotrexate. There was no apparent correlation between the presence of antibodies and adverse events. Anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86), compared to 5.9% (5/85) when adalimumab was used as an 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 an add-on to methotrexate.

In paediatric patients with moderately to severely active Crohn's disease, the rate of antibody development in patients receiving Humira was 3.3%.

In patients with ankylosing spondylitis, the rate of development of anti-adalimumab antibodies in adalimumab-treated patients was comparable to patients with rheumatoid arthritis.

In patients with psoriatic arthritis, the rate of antibody development in patients receiving adalimumab without concomitant methotrexate was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. The immunogenicity rate was 8% for psoriasis patients who were treated with adalimumab without concomitant methotrexate.

In patients with non-radiographic axial spondyloarthritis, anti-adalimumab antibodies were identified in 8/152 subjects (5.3%) who were treated continuously with adalimumab.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab and in 3.9% (19/487) patients with ulcerative colitis treated with adalimumab.

In plaque psoriasis patients on long term adalimumab with concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was similar to the rate observed prior to withdrawal.

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

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 subjects (10.1%) treated with adalimumab.

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

The data reflect the percentage of patients whose test results were considered positive for anti-adalimumab antibodies in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. For these reasons, comparison of the incidence of anti-adalimumab antibodies with the incidence of antibodies to other products may be misleading.

5.2 Pharmacokinetic properties

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption 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%. The pharmacokinetics of adalimumab was linear over the dose range of 0.5 to 10 mg/kg following a single intravenous dose.

Distribution and Elimination

The single dose pharmacokinetics of adalimumab in rheumatoid arthritis (RA) patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. 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. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-State

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab fortnightly to patients with RA, with mean steady-state trough concentrations of approximately 5 microgram/mL (without concomitant methotrexate (MTX)) and 8 to 9 microgram/mL (with concomitant MTX), respectively. These trough concentration levels are well above the EC_{50} estimates of 0.8 to 1.4 microgram/mL and consistent with those at which ACR20 responses appear to reach a maximum (Figure 1). The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg fortnightly and every week SC dosing. In long-term studies with dosing for 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 microgram/mL during adalimumab 40 mg fortnightly without concomitant methotrexate treatment (after an initial loading dose of 80 mg SC).

In adult patients with hidradenitis suppurativa, a dose of 160 mg Humira on Week 0, followed by 80 mg on Week 2, achieved serum adalimumab trough concentrations of approximately 7 to 8 microgram/mL at Week 2 and Week 4. The mean steady-state trough concentrations at Week 12 through Week 36 were approximately 8 to 10 microgram/mL during adalimumab 40 mg every week treatment.

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 serum adalimumab trough concentrations of approximately 12 microgram/mL at Weeks 2 and 4. The mean steady state trough concentration at Weeks 24 and 56 were 6.6 microgram/mL and 7.2 microgram/mL respectively. The range of trough concentrations in patients who received a maintenance dose of 40 mg adalimumab every fortnight was 0 to 21.7 microgram/mL.

In patients with ulcerative colitis, a loading dose of 160mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12

microgram/mL during the induction period. Mean steady-state trough levels of approximately 8 microgram/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab fortnightly.

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

Population pharmacokinetic and pharmacokinetic/pharmacodynamics modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg fortnightly when compared with 40 mg weekly (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS and paediatric patients ≥ 40 kg with CD.

Population pharmacokinetic analyses with data from over 1200 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight and in patients who developed the presence of anti-adalimumab antibodies.

Minor increases in apparent clearance were predicted in RA patients receiving doses lower than the recommended dose, and in RA patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important. However, there is a significant difference in mean apparent clearance in patients with Crohn's disease studied short term (4 weeks – 13.1 mL/hr) vs. long term (56 weeks – 16.8 mL/hr).

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

Pharmacokinetics in Special Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Elderly

Adalimumab's apparent clearance decreases slightly with increasing age. 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.

Paediatrics

In pJIA Study I for patients with polyarticular juvenile idiopathic arthritis (4 to 17 years of age), the mean steady-state trough serum adalimumab concentrations for patients weighing < 30 kg receiving 20 mg adalimumab subcutaneously fortnightly without concomitant methotrexate or with concomitant methotrexate were 6.8 microgram/mL and 10.9 microgram/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥ 30 kg receiving 40 mg adalimumab subcutaneously fortnightly without concomitant methotrexate or with concomitant methotrexate were 6.6 microgram/mL and 8.1 microgram/mL, respectively. In pJIA Study II for patients with polyarticular JIA who were 2 to < 4 years old, or aged 4 and above weighing < 15 kg, the mean trough steady-state serum adalimumab concentrations for patients receiving adalimumab subcutaneously fortnightly was 6.0 ± 6.1

microgram/mL (101% CV) for adalimumab without concomitant methotrexate, and 7.9 ± 5.6 microgram/mL (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously fortnightly to patients with enthesitis-related arthritis, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 microgram/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 microgram/mL with concomitant methotrexate. Based on a population pharmacokinetic (PK) modelling approach, simulated steady-state adalimumab serum trough concentrations for a weight-based dosing regimen (20 mg adalimumab fortnightly for body weight < 30 kg and 40 mg adalimumab fortnightly for body weight ≥ 30 kg) were comparable to the simulated trough concentrations for the body surface area-based regimen.

In paediatric 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, subjects were randomised 1:1 to either the Standard Dose (40/20 mg fortnightly) or Low Dose (20/10 mg fortnightly) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 microgram/mL for subjects ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 microgram/mL for patients < 40 kg (80/40 mg).

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

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously fortnightly to paediatric patients with chronic plaque psoriasis, the mean ±SD steady-state adalimumab trough concentration (measured at Week 11) was approximately 7.4 ± 5.8 microgram/mL (79% CV).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of 40 mg fortnightly 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.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

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.

Renal Impairment and Hepatic Impairment

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

Disease States

Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Drug Interactions, Methotrexate

When Humira was administered to 21 RA patients on stable methotrexate therapy, there were no statistically significant changes in the serum methotrexate concentration profiles. In contrast, after single and multiple dosing, methotrexate reduced adalimumab's apparent clearances by 29% and 44% respectively (see section 4.5). This is consistent with the higher trough concentrations of adalimumab found in patients treated with concomitant methotrexate (see section 5.2 - Steady State).

5.3 Preclinical safety data

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of adalimumab.

Genotoxicity

No genotoxicity was observed in an *in-vitro* test for bacterial gene mutation or in an *in-vivo* mouse micronucleus test for clastogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Humira 40 mg/0.8 mL, 20 mg/0.4 mL (50 mg/mL)

Citric acid monohydrate

Dibasic sodium phosphate dihydrate

Mannitol

Monobasic sodium phosphate dihydrate

Polysorbate 80

Sodium chloride

Sodium citrate dihydrate

Sodium hydroxide

Water for injections

Humira 20 mg/0.2 mL, 40 mg/0.4 mL, 80 mg/0.8mL (100 mg/mL)

Mannitol

Polysorbate 80

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

Do not use beyond the expiration date.

When required (for example, when travelling), a single Humira pre-filled syringe or pen may be stored below 25°C (room temperature) for a maximum period of 14 days but must be protected from light. Once removed from the refrigerator for room temperature storage, the syringe or pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

The date of removal from the refrigerator should be recorded on the syringe or pen label, to allow the syringe or pen to be discarded after the maximum 14 days if not used.

6.5 Nature and contents of container

Humira solution for injection for paediatric use is supplied as a sterile solution of either 20 mg adalimumab dissolved in 0.4 mL sterile solution or 20 mg adalimumab dissolved in 0.2 mL sterile solution sterile solution for subcutaneous administration in the following pack configurations:

Humira 20 mg per 0.4 mL solution for injection in single-use pre-filled syringe:

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

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

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

Humira solution for injection is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 mL sterile solution for subcutaneous administration in the following pack configurations:

Humira 40 mg per 0.8 mL solution for injection in single-use pre-filled syringe (for **patient use**):

- Carton containing 1 alcohol pad and 1 blister with 1 pre-filled syringe
- Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled syringe

- Carton containing 3 alcohol pads and 3 blisters, each containing 1 pre-filled syringe
- Carton containing 6 alcohol pads and 6 blisters, each containing 1 pre-filled syringe

Humira 40 mg per 0.8 mL solution for injection in single-use pre-filled pen (for **patient use**):

- Carton containing 2 alcohol pads and 1 blister with 1 pre-filled pen
- Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled pen
- Carton containing 4 alcohol pads and 3 blisters, each containing 1 pre-filled pen
- Carton containing 4 alcohol pads and 4 blisters, each containing 1 pre-filled pen
- Carton containing 6 alcohol pads and 6 blisters, each containing 1 pre-filled pen

Humira (adalimumab) solution for injection is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.4 mL sterile solution for subcutaneous administration in the following packaging configurations:

Humira 40 mg per 0.4 mL solution for injection in a single-use pre-filled syringe (for **patient use**):

- Carton containing 1 alcohol pad and 1 blister with 1 pre-filled syringe
- Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled syringe
- Carton containing 4 alcohol pads and 4 blisters, each containing 1 pre-filled syringe
- Carton containing 6 alcohol pads and 6 blisters, each containing 1 pre-filled syringe

Humira 40 mg per 0.4 mL solution for injection in a single-use pre-filled pen (for **patient use**):

- Carton containing 2 alcohol pads and 1 blister with 1 pre-filled pen
- Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled pen
- Carton containing 4 alcohol pads and 4 blisters, each containing 1 pre-filled pen
- Carton containing 6 alcohol pads and 6 blisters, each containing 1 pre-filled pen

Humira (adalimumab) solution for injection is supplied as a sterile solution of 80 mg adalimumab dissolved in 0.8 mL sterile solution for subcutaneous administration in the following packaging configurations:
Humira 80 mg per 0.8 mL solution for injection in a single use pre-filled syringe (for **patient use**):

- Carton containing 2 alcohol pads and 1 blister with 1 pre-filled syringe

Humira 80 mg per 0.8 mL solution for injection in a single-use pre-filled pen (for **patient use**):

- Carton containing 2 alcohol pads and 1 blister with 1 pre-filled pen
- Carton containing 4 alcohol pads and 3 blisters, each containing 1 pre-filled pen

Not all presentations may be marketed.

6.6 Special precautions for disposal

Humira does not contain preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AbbVie Limited

6th Floor, 156-158 Victoria St

Wellington, 6011

New Zealand

Phone: 0800 900 030.

9. DATE OF FIRST APPROVAL

30 September 2004.

10. DATE OF REVISION OF THE TEXT

21 October 2020

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of new information**
2 Qualitative and Quantitative composition	Deletion of reference to vial
4.2 Dose and method of administration	Deletion of reference to vial
6.4 Special warnings for storage	Deletion of reference to vial
6.5 Nature of contents and container	Deletion of reference to 40mg per 0.8mL vial dosage presentation

Version 51