AUSTRALIAN PI – IDACIO®
(ADALIMUMAB) – SOLUTION FOR SUBCUTANEOUS INJECTION

1 NAME OF THE MEDICINE

Adalimumab (rch)
Idacio (adalimumab) is a biosimilar of Humira®.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Idacio 40 mg solution for injection in pre-filled syringe

Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 mL solution.

Idacio 40 mg solution for injection in pre-filled pen

Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 mL solution.

Idacio 40 mg/0.8 mL solution for injection in a vial

Each single dose vial contains 40 mg of adalimumab in 0.8 mL solution.
Adalimumab is a recombinant human monoclonal antibody (mAb) which binds to Tumor Necrosis Factor-alpha (TNF) and blocks TNF interaction with the p55 and p75 cell surface receptors and inhibits the biological function of TNF.
Adalimumab is an IgG1 antibody composed of two kappa light chains each with a molecular weight of approximately 24 kilo Daltons (kDa) and two IgG1 heavy chains each with a molecular weight of approximately 49 kDa based on the amino acid sequence. The total molecular weight of adalimumab with post-translational modifications is approximately 148 kDa. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues resulting in a total of 1330 amino acids for the entire IgG1 molecule. For the full list of excipients, **see Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Idacio is a clear solution for injection for subcutaneous administration and is to be used on one patient on one occasion only. Idacio is practically free from visible particles with, pH 5.2 with an osmolality of approximately 325 mOsm/Kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis

Idacio 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.

Idacio can be used alone or in combination with methotrexate.

Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

Idacio in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Idacio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis

Idacio is indicated for the treatment of enthesitis-related arthritis in children, who have had an inadequate response to, or who are intolerant to, conventional therapy.

Psoriatic Arthritis

Idacio 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

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

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

Idacio 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

Idacio is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time. (see **5.1 PHARMACODYNAMIC PROPERTIES-CLINICAL TRIALS**).

Psoriasis in Adults and Children

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

Idacio 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)

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

Uveitis

Idacio is indicated for the treatment of non-infectious intermediate, posterior and pan-uveitis 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.

4.2 Dose and method of administration

Paediatric patients requiring a dose less than 40mg should use the vial presentation of Idacio. Healthcare providers should consider the risk of medication errors and the appropriateness of using the vial presentation for any dose less than 40mg.

Idacio is administered by subcutaneous injection. This product is for one dose in one patient only.

Idacio is intended for use under the guidance and supervision of a physician. Patients may self-inject Idacio 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.

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

Idacio contains no antimicrobial agent. Discard any residue.

Rheumatoid Arthritis

The recommended dose of Idacio 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 Idacio

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

Juvenile Idiopathic Arthritis

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

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

Available data suggest that a 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.

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

Idacio has not been studied in patients with enthesitis-related arthritis aged less than 6 years or any child weighing less than 10 kg.

Psoriatic Arthritis

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

	Dose	Frequency
Induction	160 mg	Initial Dose (Day 0) 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) two 40 mg injections
Maintenance	40 mg	Starting Day 28 and continuing fortnightly

Some patients who experience a decrease in their response may benefit from an increase in dosage to 40 mg Idacio every week, or 80 mg fortnightly.

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

Paediatric Crohn's Disease (6 to 17 years)

The recommended dose of Idacio for patients from 6 to 17 years of age with Crohn's disease:

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

Patients ≥ 40kg body weight		
	Moderate to Severe CD	**Frequency**
Induction	160 mg	Initial Dose (Day 0) 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 two 40 mg injections
Maintenance	40 mg	Starting Day 28 and continuing fortnightly

Some patients may benefit from increasing the frequency to weekly if a disease flare or an inadequate response is experienced during maintenance dosing:

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

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

Good nutrition should be encouraged alongside pharmacological therapy to allow appropriate growth.

Ulcerative Colitis

The recommended Idacio dose regimen for adult patients is:

	Dose	Frequency
Induction	160 mg	Initial Dose (Day 0) 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 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 decrease in their response may benefit from an increase in dosing frequency to 40 mg Idacio every week, or 80 mg fortnightly.
Idacio should not be continued in patients who do not achieve a clinical response in the first 8 weeks of treatment. Efficacy of Idacio in the treatment of ulcerative colitis has not been demonstrated in patients who have failed previous anti-TNF therapy (see **5.1 PHARMACODYNAMIC PROPERTIES-CLINICAL TRIALS**).

Psoriasis

Adults

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

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week or 80mg fortnightly. Response should be periodically evaluated (for example, every 12 weeks). Patients with continued inadequate response should discontinue treatment. If an adequate response is achieved with an increased dosing frequency, the dose may

subsequently be reduced to 40 mg fortnightly.

Paediatric Plaque Psoriasis (4 to 17 years)

The recommended dose of Idacio 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.

Paediatric Patients (4 years of age and older)	**Dose**
< 40 kg	20 mg fortnightly
≥ 40 kg	40 mg fortnightly (Idacio 40 mg Pen, 40 mg Vial or 40 mg Pre-filled Syringe)

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

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

There is limited data on the efficacy or safety of the use of adalimumab for paediatric plaque psoriasis beyond 52 weeks.

Hidradenitis Suppurativa

Adults

The recommended Idacio dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given 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 a two 40 mg injections). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80mg fortnightly. Antibiotics may be continued during treatment with Idacio if necessary. Should treatment need to be interrupted, Idacio may be re-introduced. In patients without any benefit after 12 weeks of treatment, therapy should be discontinued.

Ongoing evidence of benefit, potential loss of response and the risks of treatment in patients continuing adalimumab beyond 12 weeks should be periodically evaluated (for example, after a further 12 weeks and every 6 months thereafter). In the two pivotal studies, the primary measure of efficacy was hidradenitis suppurativa clinical response (HiSCR), defined as ≥ 50% reduction from baseline in total abscess and inflammatory nodule (AN) count, with no observed increase in either abscess or draining fistula counts (see **5.1 PHARMACODYNAMIC PROPERTIES- CLINICAL TRIALS**).

Adolescents (from 12 years of age, weighing at least 30 kg)

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

In adolescent patients with inadequate response to Idacio 40 mg fortnightly, an increase in dosing frequency to 40 mg every week or 80mg fortnightly may be considered.

Antibiotics may be continued during treatment with Idacio 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 Idacio.

In patients without any benefit after 12 weeks of treatment, therapy should be discontinued. (see **5.1 PHARMACODYNAMIC PROPERTIES-CLINICAL TRIALS** - HS Adults).

Should treatment be interrupted, Idacio may be re-introduced as appropriate. The benefit and risk of continued long-term treatment should be periodically evaluated (see **5.1 PHARMACODYNAMIC PROPERTIES-CLINICAL TRIALS** - HS Adults).

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

Uveitis

Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Idacio. Use of Idacio for uveitis should be supervised by an ophthalmologist or other appropriate specialist. Patients treated with Idacio should be given the patient reminder card.

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

Treatment with Idacio can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. There is limited experience in the initiation of treatment with Idacio alone.

Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Idacio.

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

4.3 Contraindications

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

Idacio is contraindicated in severe infections including sepsis, active tuberculosis and opportunistic infections (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Concurrent administration of Idacio and anakinra (interleukin-1 receptor antagonist) is contraindicated (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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 adalimumab. Sepsis, rare cases of tuberculosis and candidiasis have also been reported with the use of TNF antagonists, including adalimumab. 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 Idacio 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 Idacio should be considered prior to initiating therapy (see **Other Opportunistic Infections).**

Patients should be monitored closely for infections – including tuberculosis before, during and after treatment with Idacio.

Patients who develop a new infection while undergoing treatment with Idacio should be monitored closely and undergo a complete diagnostic evaluation. Administration of Idacio 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 Idacio 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 adalimumab, 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, Idacio 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 adalimumab. Reports included cases of pulmonary and extra pulmonary (i.e., disseminated).

Before initiation of therapy with Idacio, 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 Idacio. 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, Idacio therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of Idacio in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of Idacio 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 Idacio should be very carefully considered.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with adalimumab. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Also, active tuberculosis has developed in patients receiving adalimumab 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 Idacio 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 Idacio.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. 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

Adalimumab 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 Idacio in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Idacio 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 Idacio therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Hypersensitivity Reactions

Serious allergic reactions associated with adalimumab 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 adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Idacio 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 adalimumab (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS**). The causal relationship of these reports to adalimumab 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 Idacio. Discontinuation of Idacio therapy should be considered in patients with confirmed significant haematologic abnormalities.

Immunosuppression

The possibility exists for TNF blocking agents, including adalimumab, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with adalimumab, 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 adalimumab on the development and course of malignancies, as well as active and/or chronic infections is not fully understood. The safety and efficacy of adalimumab in patients with immunosuppression have not been evaluated. (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS -** and **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) -**

Vaccinations

In a randomised, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with adalimumab, 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 adalimumab group compared to 82% in the placebo group. A total of 37% of

adalimumab-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 adalimumab group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of adalimumab-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 Idacio may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

Administration of live vaccines to infants exposed to Idacio *in utero* is not recommended for 5 months following the mother's last Idacio 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 Idacio 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 adalimumab. Idacio should be used with caution in patients with mild heart failure (NYHA class I/II). Adalimumab is contraindicated in moderate or severe heart failure. Treatment with Idacio 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 adalimumab, compared with control patients (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) –**). 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 adalimumab 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 adalimumab. Thus, additional caution should be exercised in considering Idacio 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 Idacio. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (See **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS**).

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 adalimumab may result in the formation of autoantibodies and rarely in the

development of a lupus-like syndrome. The impact of long-term treatment with adalimumab on the development of autoimmune disease is unknown.

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Idacio, treatment should be discontinued (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) –**).

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

Use in Hepatic Impairment

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

Use in Renal Impairment

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

Use in the elderly

Of the total number of subjects in clinical studies of adalimumab 10.4% 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 adalimumab 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 adalimumab-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. (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Paediatric use

The safety and efficacy of adalimumab has not been established in other forms of JIA such as systemic JIA or oligoarticular JIA. The long term effects of adalimumab on the growth and development of children have not been studied. Treatment with Idacio should only be initiated in patients with paediatric Crohn's disease following diagnosis by a specialist gastroenterologist, where other diseases with potentially similar presentations (e.g., Inflammatory Bowel Disease (IBD) associated with chronic granulomatous disease) have been ruled out. Adalimumab has not been studied in children with Crohn's disease aged less than 6 years.

Effects on Laboratory Tests

There is no known interference between adalimumab and laboratory tests.

4.5 Interactions with other medicines and other forms of interactions

Adalimumab has been studied in RA patients taking concomitant methotrexate (see **5.1 PHARMACODYNAMIC PROPERTIES-CLINICAL STUDIES** and **5.1 PHARMACODYNAMIC PROPERTIES – Steady State**). The data do not suggest the need for dose adjustment of either adalimumab or methotrexate. Interactions between adalimumab 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 **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effect of adalimumab on fertility has not been investigated.

Use in pregnancy (Pregnancy Category C)

Due to its inhibition of TNF-alpha, adalimumab administered during pregnancy could affect immune response in the in utero-exposed newborn and infant. Data from eight infants exposed to adalimumab in utero suggest it crosses the placenta. 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. There are no adequate and well-controlled studies in pregnant women and therefore adalimumab should only be used during pregnancy if clearly needed. Women of child bearing potential should consider the use of adequate contraception to prevent pregnancy and continue for at least 5 months after the last Idacio treatment.

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.

Results obtained with a very high intravenous adalimumab dose (100 mg/kg/week) in an embryofetal 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.

Use in lactation

Limited information from three cases in 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. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. 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.

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 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

Clinical Trials

Adalimumab was studied in 9316 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, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 5994 patients receiving adalimumab and 3704 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 adalimumab and 5.5% 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 adalimumab 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.

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	Very common	lipids increased

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
disorders	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphotemia, dehydration
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

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
	Uncommon	night sweats, scar
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis, systemic lupus erythematosus
Renal and urinary disorders	Common	haematuria, renal impairment
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions	Very common	injection site reaction (including injection site erythema)
	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

* 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.

Rheumatoid Arthritis

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-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 adalimumab 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 neutropaenia 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
	hypophosphotaemia	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.

Hidradenitis Suppurativa

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

Uveitis

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

Study V (DE013)

The safety profile for patients with rheumatoid arthritis treated with adalimumab for up to 10 years was consistent with the known safety profile of adalimumab. The following adverse events were observed in the study: RA (worsening of RA) in 32.6% patients (corresponding to 13.2 events per 100 patient years), arthralgia in 19.5% (5.9 E/100 PY), bronchitis in 16.2% (5.4 E/100 PY), diarrhoea in 15.1% (4.0 E/100 PY), fatigue in 14.1% (3.1 E/100 PY), pain in extremity in 10.6% (2.5 E/100 PY), osteoarthritis in 10.5% (3.1 E/100 PY), dizziness in 9.8% (2.4 E/100 PY), contusion in 7.3% (1.6 E/100 PY), fall in 6.7% (1.6 E/100 PY), cataract in 6% (1.5 E/100 PY), and tendonitis in 6% (1.5 E/100 PY). These events were not considered adverse drug reactions in that they were not observed in a statistically significantly higher percentage of patients in the adalimumab group than in the control (methotrexate) group.

Description of selected adverse reactions

Injection Site Reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.3% of patients receiving control treatments. 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 adalimumab-treated patients and 1.46 per patient year in the control treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infections and sinusitis. Most patients continued on adalimumab after the infection resolved. The incidence of serious infections was 0.04 per patient year in adalimumab-treated patients and 0.03 per patient year in control treated patients.

In the controlled and open label adult and paediatric studies with adalimumab, 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 adalimumab trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, 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 6.9 (4.4, 10.6) per 1000 patients years among 5196 adalimumab-treated patients versus a rate of 6.4 (3.5, 11.9) per 1000 patient years among 3347 control patients (median duration of treatment was 4.0 months for adalimumab and 3.9 months for control-treated patients).

The rate (95% confidence interval) of non-melanoma (basal cell and squamous cell) skin cancers was 8.9 (6.1, 13.1) per 1000 patient years among adalimumab-treated patients and 3.2 (1.3, 7.7) 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, 5.5) per 1000 patient years among adalimumab-treated patients and 0.6 (0.1, 4.6) 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 adalimumab-treated patients and 0.6 (0.1, 4.6) 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 6279 patients and over 26045 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.6 per 1000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.8 per 1000 patient years and the observed rate of lymphomas is approximately 1.3 per 1000 patient years.

No malignancies were observed in 217 paediatric patients with an exposure of 610.4 patient years during adalimumab trials in patients with 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 adalimumab 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 adalimumab trial in paediatric patients with plaque psoriasis.

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 years. The reported rates for non-melanoma skins cancers and lymphomas is approximately 0.3 per 1000 patient years.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I – V. In these adequate and well-controlled trials, 11.9% of patients treated with adalimumab 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 adalimumab in all rheumatoid and 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 adalimumab 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 adalimumab. 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 adalimumab should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations

Rheumatoid Arthritis and Psoriatic Arthritis Clinical Trials: In controlled Phase 3 trials of adalimumab (40 mg 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 adalimumab-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 adalimumab and the liver enzyme elevations is not clear.

Juvenile Idiopathic Arthritis Clinical Trials: In a controlled Phase 3 trial of adalimumab in patients with polyarticular JIA 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 adalimumab-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 adalimumab in patients with polyarticular JIA who were 2 to < 4 years or aged 4 years and above weighing <15 kg.

Ankylosing Spondylitis Clinical Trials: In controlled Phase 3 trials of adalimumab (40 mg fortnightly), in patients with ankylosing spondylitis with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2.44% of adalimumab-treated patients and 0.66% of control-treated patients.

Hidradenitis Suppurativa clinical Trials: In controlled trials of adalimumab (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 adalimumab-treated patients and 0.6% of control-treated patients.

Crohn's Disease Clinical Trials: In controlled Phase 3 trials of adalimumab (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 adalimumab-treated patients and 0.9% of control-treated patients.

Paediatric Crohn's Disease Clinical Trials: In the Phase 3 trial of adalimumab 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.

Ulcerative Colitis Clinical Trials: In controlled Phase 3 trials of adalimumab (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 adalimumab-treated patients and 1.0% of control-treated patients.

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

Paediatric Patients with Plaque Psoriasis Clinical Trial: No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial.

Uveitis Clinical Trials: In controlled trials of adalimumab (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 165.4 patient years and 119.8 patient years in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3x ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

In all indications 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 adalimumab and azathioprine/6-mercaptopurine compared with adalimumab alone.

Polyarticular Juvenile Idiopathic Arthritis Clinical Trials

In general, the adverse reactions in patients with polyarticular juvenile idiopathic arthritis (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, adalimumab was studied in 171 patients, 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 adalimumab 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 adalimumab 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 adalimumab were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving adalimumab was granuloma annulare which did not lead to discontinuation of adalimumab 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 adalimumab alone; liver function tests (LFT) elevations were more frequent among those treated with the combination of adalimumab and methotrexate. In general, these elevations did not lead to discontinuation of adalimumab treatment.

In the pJIA Study I, 10% of patients treated with adalimumab 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 adalimumab 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 adalimumab without interruption.

In pJIA Study II, adalimumab 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. Thirty-one of 32 patients (97%) received the required minimum of 24 weeks of adalimumab treatment. Patients were able to continue up to a maximum of 120 weeks of treatment. 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 adalimumab. 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 adalimumab 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 urticaria and rash, which were all mild in severity.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

Adverse events have been reported during post-approval use of adalimumab. 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 adalimumab exposure.

Table 3: Additional Adverse Reactions from Post marketing Surveillance or Phase IV Clinical Trials

Body System	**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
* occurring in patients receiving a TNF-antagonist including adalimumab	

Comparability of Idacio with Humira® - Adverse Effects

Plaque Psoriasis:

In the randomized, double-blind, Phase III study in subjects with moderate to severe plaque psoriasis

performed with Idacio (EMR200588-002, Auriel-PsO), no discernable differences in the proportion of subjects with liver enzyme elevations were observed.

4.9 Overdose

The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with adalimumab. 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tumour necrosis factor alpha (TNF-alpha) inhibitors.

ATC code: L04AB04

Idacio is a biosimilar medicine to Humira. The evidence for comparability supports the use of Idacio for the listed indications.
Clinical studies have been conducted with Idacio in healthy subjects and in patients with moderate to severe plaque psoriasis. The description of these studies comparing the biosimilar with the adalimumab reference product are presented at the end of section- CLINICAL TRIAL FOR COMPARABILITY OF IDACIO WITH HUMIRA®.

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,

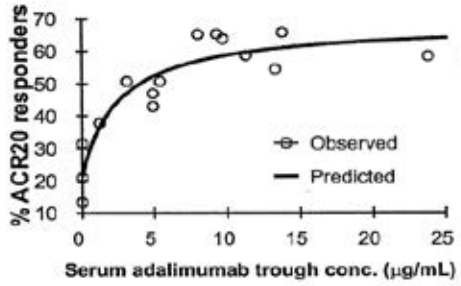
and ICAM-1 with an IC_{50} of 1-2 X 10^{-10} M).

Pharmacodynamics

After treatment with adalimumab, 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 (CD), 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 adalimumab administration. Patients treated with adalimumab 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 micrograms/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.

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 micrograms/mL (without concomitant methotrexate (MTX)) and 8 to 9 micrograms/mL (with concomitant MTX), respectively. These trough concentration levels are well above the EC_{50} estimates of 0.8 to 1.4 micrograms/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 micrograms/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 adalimumab on Week 0, followed by 80 mg on Week 2, achieved serum adalimumab trough concentrations of approximately 7 to 8 micrograms/mL at Week 2 and Week 4. The mean steady-state trough concentrations at Week 12 through Week 36 were approximately 8 to 10 micrograms/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 micrograms/mL at Weeks 2 and 4. The mean steady state trough concentration at Weeks 24 and 56 were 6.6 micrograms/mL and 7.2 micrograms/mL respectively. The range of trough concentrations in patients who received a maintenance dose of 40 mg adalimumab every fortnight was 0 – 21.7 micrograms/mL.

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 micrograms/mL during the induction period. Mean steady-state trough levels of approximately 8 micrograms/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab fortnightly in a 52-week study.

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 80mg fortnightly when compared with 40mg weekly (including adults with RA, HS, UC, CD or Ps, adolescent patients with HS and paediatric patients ≥ 49 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).

Comparability of Idacio with Humira®

Pharmacodynamic comparability between Idacio and Humira was demonstrated in in vitro studies as well as in in vivo studies using transgenic mouse models of polyarthritis and TNBS induced colitis (Tg197). The in vitro assays assessed functional characteristics of innovator adalimumab (Humira) against biosimilar (Idacio

– -target binding to other cytokines. Other cell-based assays such as Antibody Dependent Cell-mediated Cytotoxicity (ADCC), Complement Dependent Cytotoxicity (CDC) and apoptosis demonstrated similarity between Idacio and Humira. An in vivo study using the Tg197 transgenic mouse model of arthritis demonstrated similar reductions in arthritic and histopathologic scores between Idacio and Humira. In another in vivo study using the Tg197 transgenic mouse model of colitis, Idacio showed similar efficacy compared to Humira.

Clinical trials with Humira®

CLINICAL TRIALS FOR RHEUMATOID ARTHRITIS

Adalimumab 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 adalimumab were assessed in five randomised, double-blind and well-controlled studies. Injection site pain of adalimumab 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 adalimumab 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 adalimumab 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 adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab 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 adalimumab/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 adalimumab in subjects with RA receiving concurrent MTX. The maintenance of efficacy was assessed by evaluating the effect of adalimumab 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 adalimumab 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 adalimumab 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 adalimumab 40 mg/ 0.8 mL. Patients were randomised to receive a single dose of adalimumab 40 mg/ 0.8 mL or adalimumab 40 mg/ 0.4 mL, followed by a single injection of the

opposite treatment at their next dose.

Results of RA Study I-V were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary 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 adalimumab-treated patients achieving ACR 20, 50 and 70 responses was consistent across all three trials. The results for the 40 mg fortnightly dose are summarised in Table 4.

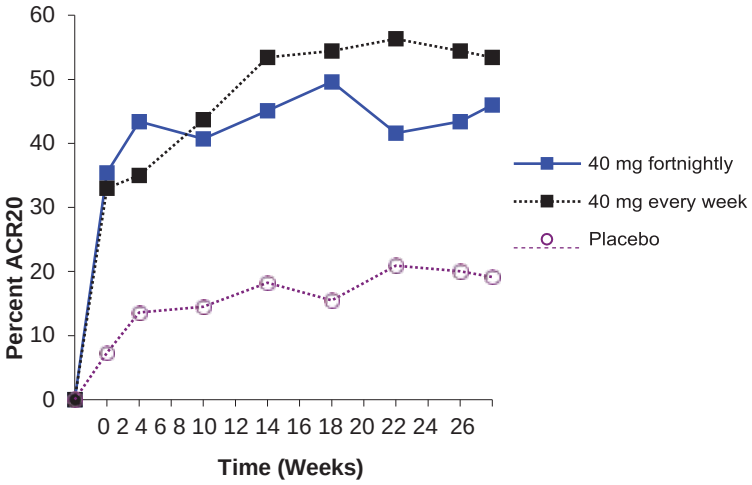
Table 4: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a]*		RA Study II[a]*		RA Study III[a, c]*	
	Placebo/ MTX N=60	Adalimumab[b] / MTX N=63	Placebo N=110	Adalimumab[b] *N=113	Placebo/ MTX N=200	Adalimumab[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 adalimumab 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, adalimumab vs. placebo at all time points for CR20,50, 70
MTX Methotrexate

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

Figure 2: RA Study II ACR20 Responses over 26 Weeks



The results of components of the ACR response criteria 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 adalimumab patients achieved a major clinical response, defined as maintenance of an ACR70 response > 6 month period.

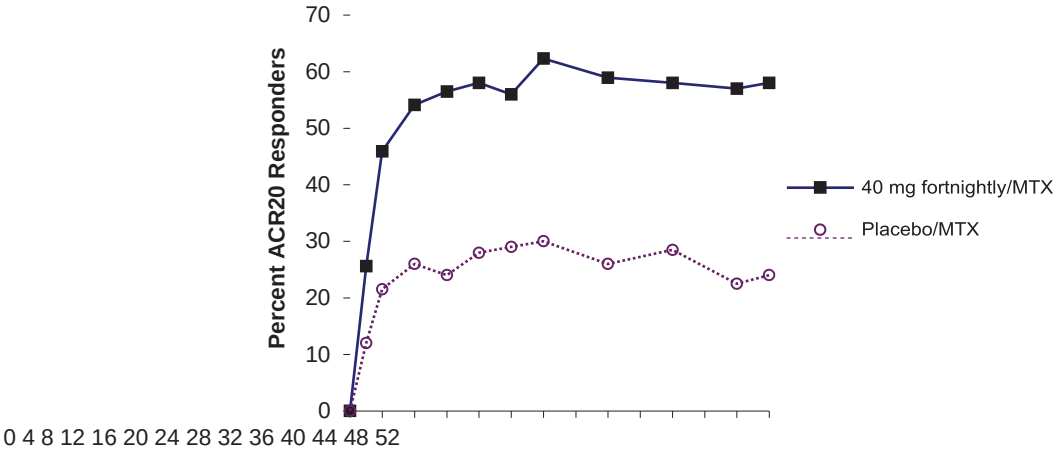
Table 5: Components of ACR Response in RA Study III

Parameter (median)	Placebo/MTX (N = 200)			Adalimumab[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 adalimumab 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, adalimumab 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 adalimumab 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 adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p<0.001$).

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

RA Study V

In RA Study V for early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with adalimumab 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 adalimumab/methotrexate therapy and improvements were maintained to Week 104.

Over the two-year study, 48.5% patients who received adalimumab/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		
		N (%)		p-value[a]	p-value[b]
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. However, no statistical hypothesis was tested in the OLE period. Of 542 patients who were randomised to adalimumab 40mg fortnightly, 170 patients continued on adalimumab 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, adalimumab/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 adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of

adalimumab 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, adalimumab-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. adalimumab/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 adalimumab 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 adalimumab 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	Adalimumab [a]/MTX N=207	Difference Between Adalimumab[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 adalimumab

In RA Study V, adalimumab-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, adalimumab monotherapy and adalimumab/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 adalimumab 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 adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab 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 adalimumab/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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab/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 (measured by HAQ-DI response) were maintained through 10 years of treatment. No statistical hypothesis was tested in the OLE phase.

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 adalimumab 40 mg/ 0.8 mL and adalimumab 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.

CLINICAL TRIALS FOR JUVENILE IDIOPATHIC ARTHRITIS

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The safety and efficacy of adalimumab 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 polyarthritis, rheumatoid-factor positive polyarthritis or extended oligoarthritis).

pJIA Study I

The safety and efficacy of adalimumab 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 (JIA). 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, adalimumab 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 adalimumab SC fortnightly if their weight was less than 30 kg and with 40 mg of adalimumab SC fortnightly if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or 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 adalimumab 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 adalimumab experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with adalimumab 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 adalimumab and MTX compared to adalimumab alone.

Paediatric ACR responses were maintained for up to six years in the OLE phase in patients who received adalimumab throughout the study. Overall 19 patients were treated for 6 years or longer, with 11 of the 19 patients in the 4 to 12 year age group, and 8 of the 19 patients being between 13 and 17 years of age.

pJIA Study II

The safety and efficacy of adalimumab was assessed in an open-label, multi-centre, uncontrolled study in 32 patients (2 to < 4 years old or aged 4 years and above weighing < 15 kg) with moderately to severely active polyarticular or polyarticular-course JIA. The patients received 24 mg/m^2 body surface area (BSA) of adalimumab up to a maximum of 20 mg fortnightly as a single dose via SC injection for at least 24 weeks. During the study, most patients 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 patients who continued with adalimumab treatment throughout this time period. Overall, 20 patients were treated for 60 weeks or longer.

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

Enthesitis-Related Arthritis (ERA)

The safety and efficacy of adalimumab were assessed in a multi-centre, 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 adalimumab 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 adalimumab 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 adalimumab group compared to -11.6% in patients in the placebo group. Decreases in the mean percent change from baseline in the number of active joints with arthritis was maintained through Week 156 with a mean decrease from baseline of -88.3%. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count, swollen joint count, Paediatric ACR 30 response, Paediatric ACR 50 response, and Paediatric ACR 70 response, and maintained these results during the OL period through Week 156 of the study.

CLINICAL TRIALS FOR PSORIATIC ARTHRITIS

Adalimumab, 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 adalimumab was administered fortnightly.

ACR and PASI response

Adalimumab 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 adalimumab, 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 adalimumab, 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	Adalimumab 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 adalimumab and placebo

Table 12: Components of Disease Activity in Psoriatic Arthritis

	Placebo (N=162[a])		Adalimumab (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 adalimumab.
[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 adalimumab 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

adalimumab or placebo and at Week 48 when all patients were on open-label adalimumab. 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.

Adalimumab-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 adalimumab 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 adalimumab 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 adalimumab 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.

CLINICAL TRIALS FOR ANKYLOSING SPONDYLITIS

The safety and efficacy of adalimumab 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 ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, (3) morning stiffness ≥ 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 adalimumab 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

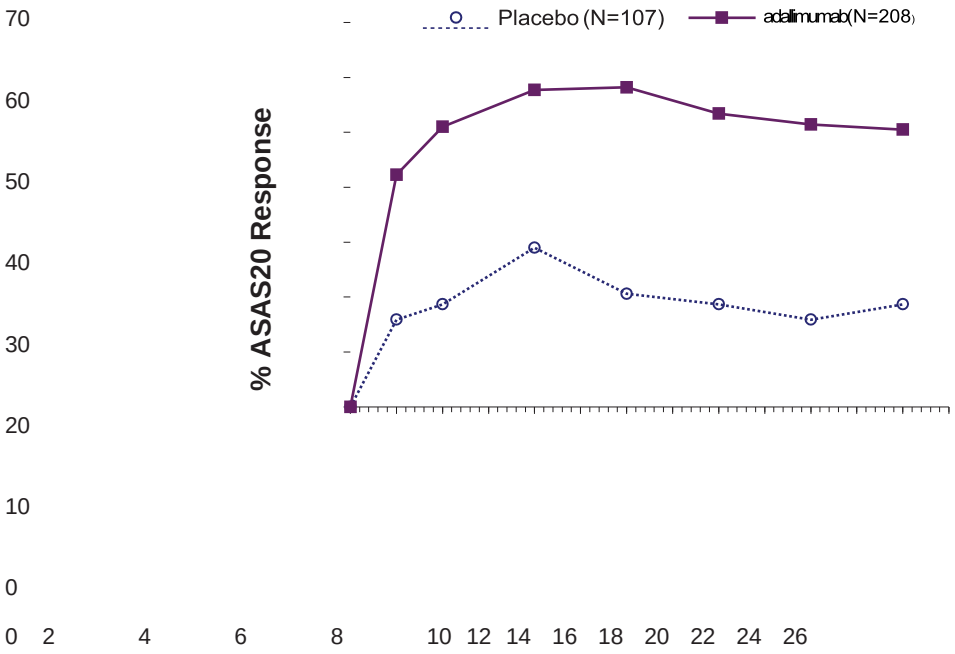


Table 14: ASAS[a] Responses in Placebo-Controlled AS Study

Response	Placebo N=107	Adalimumab 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 adalimumab 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 adalimumab-treated patients vs. 6% in placebo-treated patients (p<0.001).

Table 15: Components of Ankylosing Spondylitis Disease Activity				
	Placebo N=107		Adalimumab 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 adalimumab 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 multicenter, 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 adalimumab-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 adalimumab-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.

CLINICAL TRIALS FOR CROHN'S DISEASE

Adults

The safety and efficacy of multiple doses of adalimumab 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 adalimumab 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 adalimumab 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 adalimumab at Week 0 and 40 mg adalimumab at Week 2. Patients were then randomised at Week 4 to 40 mg adalimumab fortnightly, 40 mg adalimumab 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 adalimumab 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 16).

Table 16: Induction of Clinical Remission and Response (Percent of Patients)

	CD Study I		CD Study II	
	Placebo N=74	**Adalimumab 160/80 mg N=76**	**Placebo N=166**	**Adalimumab 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 adalimumab *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 adalimumab 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 adalimumab maintenance groups compared to patients in the placebo maintenance group at Weeks 26 and 56 (see Table 18).

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56 (see Table 17).

Table 17: Hospitalisations to Week 56 (ITT population)

	Placebo	**40 mg adalimumab fortnightly**	**40 mg adalimumab every week**	**Combined adalimumab**
	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) *

Clinical remission results presented in Table 18 remained relatively constant irrespective of previous TNF antagonist exposure.

Of those in response at Week 4 who attained remission during the study, patients in adalimumab maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group (see Figure 5). 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 adalimumab every week did not show significantly higher remission rates than the group that received adalimumab fortnightly.

Table 18: Maintenance of Clinical Remission and Response (Percent of Patients)

	Placebo	**40 mg adalimumab fortnightly**	**40 mg adalimumab 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 Adalimumab *vs*. placebo pairwise comparisons of proportions

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

[a] Of those receiving corticosteroids at baseline

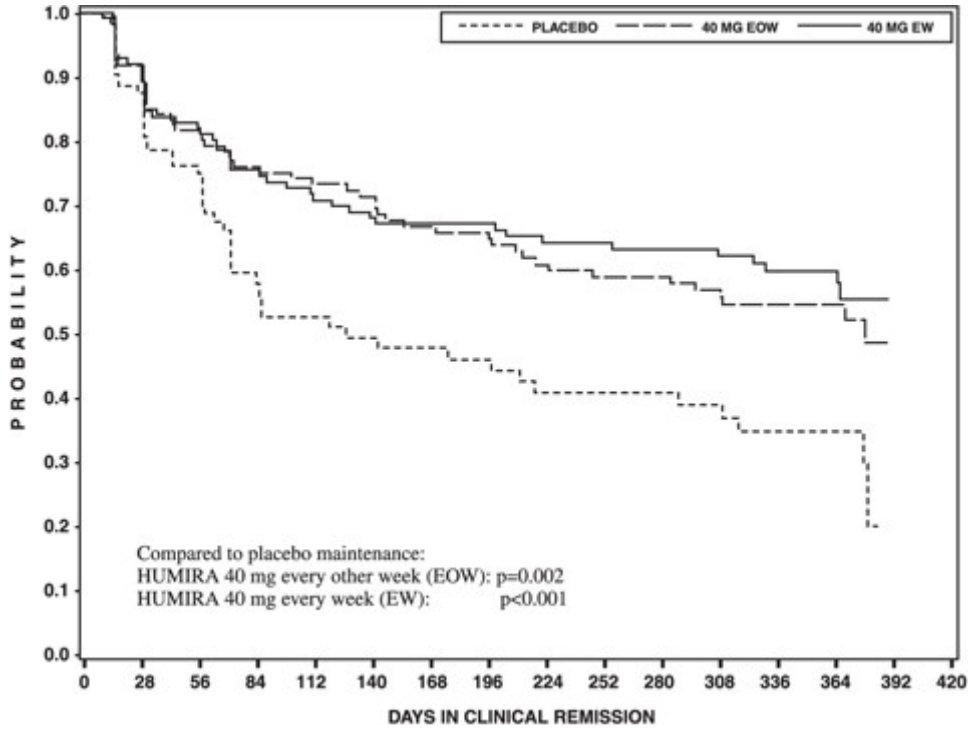
117/854 patients had draining fistulas both at screening and at baseline. For the assessment of fistula healing, the data for both doses of adalimumab used in the study were pooled. The proportion of subjects (ITT population) with fistula healing at Week 26 was statistically significantly greater in 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 5: 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 adalimumab 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.

Children and Adolescents

Adalimumab was assessed in a multi-centre, 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 19.

Table 19: Maintenance Regimen

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

Efficacy Results

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 20.

Table 20: 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 21:Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission

	Standard Dose 40/20 mg fortnightly	Low Dose 20/10 mg 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).

CLINICAL TRIALS FOR ULCERATIVE COLITIS

The safety and efficacy of adalimumab was assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy sub score of 2 to 3) in randomised, double-blind, placebo-controlled studies. Enrolled patients received concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP.

In Study UC-I, 576 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg adalimumab at Week 0 followed by 80 mg at Week 2, or 80 mg adalimumab at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg fortnightly.

Week 8. The primary endpoint was evaluated based on the 390 patients recruited after the 80/40 induction group was added by protocol amendment.

In Study UC-II, 248 patients received 160 mg of adalimumab 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 adalimumab 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 adalimumab who were in clinical remission at Week 8, 21/41 (51%) were in clinical remission at Week 52. The percentage of subjects induced with 80/40 mg adalimumab in Study UC-I who achieved clinical remission at Week 8 was not statistically significantly different versus placebo.

Results from the overall UC-II study population are shown in Table 22.

Table 22: Clinical Remission, Clinical Response and Mucosal Healing in Study UC-II (Percent of Patients)

	Placebo	**Adalimumab 40 mg fortnightly**
Week 8	**N = 246**	**N = 248**
Clinical Remission	9%	17%*
Clinical Response	35%	50%**
Mucosal Healing	32%	41%*
Week 52	**N = 246**	**N = 248**
Clinical Remission	9%	17%*
Clinical Response	18%	30%*
Mucosal Healing	15%	25%*
Steroid-free remission [a]	6% (N=140)	13% * (N=150)
Week 8 and 52	**N = 246**	**N = 248**
Sustained Clinical Remission	4%	8%*
Sustained Clinical Response	12%	24%**
Sustained Mucosal Healing	11%	19%*

Clinical Response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30%, and rectal bleeding sub score of 0 or 1 or its decrease from baseline ≥ 1 point.
Mucosal healing is defined as endos
*p<0.05 for adalimumab *vs.* placebo pairwise comparison of proportions
**p<0.001 for adalimumab *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Adalimumab should be discontinued in patients who do not achieve a clinical response during the first 8 weeks of therapy because very few patients will achieve clinical remission with continuing treatment. In UC-1 and UC-2, of patients given adalimumab 160/80 mg at baseline who did not achieve a clinical response at Week 8, 5.2%, and 17.0% went on to be in remission and response, respectively at Week 52.

Table 23: Remission, Response and Mucosal Healing at Week 52 Among Week 8 Responders in Study UC-II (Percent of Patients)

	ITT Population		Adalimumab-Treated Patients	
Week 52 Outcome	**Adalimumab 40 mg fortnightly N = 248**	**Placebo N = 246**	**Week 8 Responders per Full Mayo Score N = 125**	**Week 8 Responders per Partial Mayo Score N = 123**
Clinical Remission	17%	9%	29%	31%
Clinical Response	30%	18%	47%	50%
Mucosal healing	25%	15%	41%	43%
Steroid-free remission[a]	-	-	20%	-

[a] Of those receiving corticosteroids at baseline (N=90)

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.

The effectiveness of adalimumab in patients who have lost response to infliximab has not been established, statistically significant differences for Week 8 clinical remission and Week 8 clinical response were not observed for adalimumab versus placebo in those patients. However, at Week 52, clinical remission and clinical response were achieved in a statistically significantly greater number of patients on adalimumab versus placebo in patients who had failed prior anti-TNF treatment (i.e. remission: 3% on placebo versus 10% on adalimumab, and response: 10% on placebo versus 20% on adalimumab).

Patients who completed 52 weeks in UC Study I and II continued in an open, uncontrolled extension study (UC-III). Of the 588 patients who entered in the open-label study, 299 (51%) were in remission at year 3 and 273 (46%) were in remission at year 4.

Patients, who lose response may benefit from an increase of dosing frequency to 40 mg weekly. 17% of patients initially responding to treatment with adalimumab required an increase in dosing frequency to 40 mg adalimumab every week.

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 adalimumab 160/80 mg compared to placebo (p=0.007).

CLINICAL TRIALS FOR PSORIASIS

Adults

The safety and efficacy of adalimumab were assessed in over 1600 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 adalimumab 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.

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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab followed by 40 mg fortnightly (starting one week after the initial dose) for 16 weeks. There are no data available comparing adalimumab 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 adalimumab subcutaneously at a dose of 40 mg fortnightly starting at Week 1 after an initial dose of 80 mg at Week 0 or adalimumab 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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab treatment group versus those randomised to receive methotrexate (see Tables 24 and 25).

Table 24: 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	Adalimumab 40 mg fortnightly N = 814	Adalimumab 40 mg fortnightly N = 580	Placebo N = 240	Adalimumab 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, Adalimumab vs. placebo

Table 25: Ps Study II (M04-716)
Efficacy Results at 16 Weeks (Percent of Patients)

	Placebo N = 53	MTX N = 110	Adalimumab 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, Adalimumab vs. placebo
[b] p<0.001 Adalimumab vs. methotrexate
[c] p< 0.01 Adalimumab vs. placebo
[d] p< 0.05 Adalimumab 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 adalimumab group in Period C of Study I achieved PASI 75 at Weeks 16 and 33 and received continuous adalimumab 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 adalimumab 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 adalimumab group of Study II received continuous adalimumab 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 adalimumab 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 adalimumab. A pre-specified evaluable population of stable responders to adalimumab was assessed after withdrawal of adalimumab. 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 adalimumab 40 mg fortnightly during the last 12 weeks. If subjects relapsed (PGA became moderate or worse) during the withdrawal period, adalimumab 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 adalimumab, the remaining subjects who had not relapsed were also eligible for retreatment with adalimumab.

Of 347 stable responders withdrawn from adalimumab, 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 $\geq$ 125% or new generalised erythrodermic or pustular psoriasis within 3 months of withdrawal of adalimumab). 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 adalimumab 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 adalimumab 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 adalimumab, followed by 40 mg fortnightly (starting one week after the initial dose), or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received adalimumab 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 adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg fortnightly (starting one week after the initial dose) or placebo for 26

weeks followed by open-label adalimumab treatment for an additional 26 weeks.

This study evaluated the proportion of subjects who achieved at least a 75% improvement from baseline in the Modified Nail Psoriasis Severity Index (mNAPSI 75) and the proportion of subjects who achieved “clear” or “minimal” assessment with at least a 2-grade improvement on the PGA-F scale at week 26 (see Table 26). The mNAPSI is a numeric index for the evaluation of nail psoriasis. The index assessed each nail abnormality for each of a subject’s fingernails. Pitting, onycholysis and oil-drop dyschromia and crumbling of each fingernail were graded on a scale from 0 to 3. Leukonychia, splinter hemmorrhages, hyperkeratosis and red spots in the lunula were graded as either present (scored as 1) or absent (scored as 0) for each fingernail. The mean (±SD) severity of mNAPSI at baseline was 58.11 ± 21.550 and 57.59 ± 20.159 in the placebo and adalimumab treatment group, respectively.

Table 26: Ps Study IV (M13-674)

Efficacy Results at 26 Weeks in ranked order

	Placebo N = 108	**Adalimumab 40 mg fortnightly N = 109**
≥ mNAPSI 75 (%)	3.4	46.6[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]
PGA-F clear/minimal and ≥2-grade improvement (%)	6.9	48.9[a]
B-SNIPI 50 Scalp (%)	N=12 0.4	N=18 58.3[b]

[a] p<0.001, Adalimumab *vs.* placebo

[b] p<0.05, Adalimumab *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 adalimumab treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response.

The percent improvement in NAPSI was also statistically significantly greater in adalimumab 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 adalimumab 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 adalimumab 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 adalimumab-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 adalimumab showed clinically meaningful improvements at Week 26 from baseline compared with placebo in the DLQI.

Children and Adolescents

The efficacy of adalimumab 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 adalimumab 0.8 mg/kg fortnightly (up to 40 mg), 0.4 mg/kg fortnightly (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to adalimumab 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to MTX.

Table 27: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N = 37	Adalimumab 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, Adalimumab 0.8 mg/kg versus MTX
[c] p=0.083, Adalimumab 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. Among patients who were responders to the initial 16 weeks of treatment but who relapsed upon withdrawal and were retreated, PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects) was observed.

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. A total of 91 subjects received only adalimumab 0.8mg/kg in period D, the mean duration of treatment with adalimumab 0.8mg/kg in period D was 315.0 days (range 42 to 380 days). Of the 91 subjects who only received adalimumab 0.8mg/kg in period D, the PASI 75 response rate and PGA clear/minimal response rate at week 52 were 69.2% and 59.3%, respectively.

CLINICAL TRIALS FOR HIDRADENITIS SUPPURATIVA

Adults

The safety and efficacy of adalimumab 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 at least a 3-month trial of 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 adalimumab 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 adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 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 adalimumab 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 adalimumab 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 adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 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 enrol into an open-label extension study in which adalimumab 40 mg was administered every week. Mean exposure in all adalimumab population was 762 days (standard deviation: 397 days). 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 adalimumab 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 29). Patients treated with adalimumab had reduced risk of disease flare during the initial 12 weeks of treatment.

Table 28: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		HS Study II	
Endpoint	**Placebo**	**Adalimumab 40 mg Weekly**	**Placebo**	**Adalimumab 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%) ***

* $P < 0.05$, *** $P < 0.001$, Adalimumab 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.

There is a statistically significantly higher HiSCR rate at Week 36 in patients who continued to receive weekly adalimumab compared to those who stopped adalimumab at Week 12.

At Week 36 HiSCR was achieved by 43% of the patients receiving ongoing weekly adalimumab and 28% of the patients who were withdrawn from adalimumab treatment after Week 12 ($p<0.05$), in the pooled Study HS-I and Study HS-II population.

Of the 88 patients randomised to adalimumab continuous weekly dosing who were at least partial responders at Week 12 and subsequently entered the open-label extension study, 81 and 53 patients had observed efficacy assessments at Week 48 and Week 96, respectively. The overall HiSCR response rate at Week 12 was maintained through Week 96.

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; Study

HS-II), and patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Study HS-II).

Adolescents

There are no clinical trials in adolescent patients with hidradenitis suppurativa (HS). Efficacy of adalimumab 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. (see **5.2 PHARMACOKINETIC PROPERTIES**).

CLINICAL TRIALS FOR UVEITIS

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

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

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). A majority of the 217 patients were female and Caucasian with mean age of 42.7 years. There was no statistically significant demographic difference between the placebo and adalimumab groups. All patients received a 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. A majority of the 226 patients were female and Caucasian with mean age of 42.5 years. There was no statistically significant demographic difference between the placebo and adalimumab groups. 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 adalimumab versus patients receiving placebo (See Table 29). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo

(see Figure 6).

Table 29: Time to Treatment Failure in Studies UV I and UV II

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

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

a. HR of Adalimumab vs placebo from proportional hazards regression with treatment as factor.
b. 2-sided *P* value from log rank test.
c. NE = not estimable. Fewer than half of at-risk subjects had an event.

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

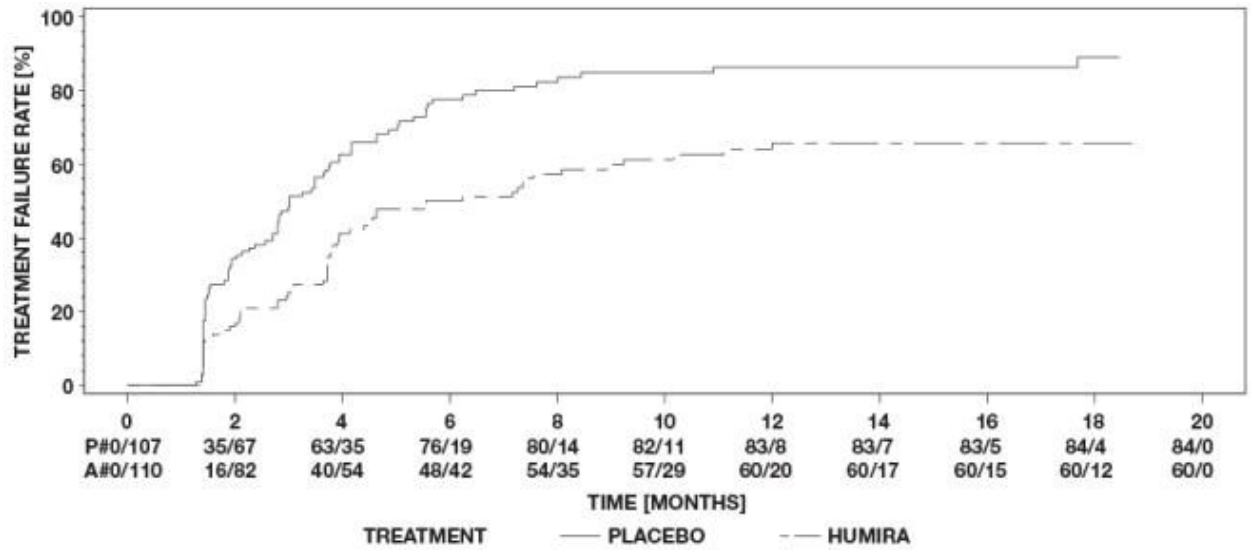
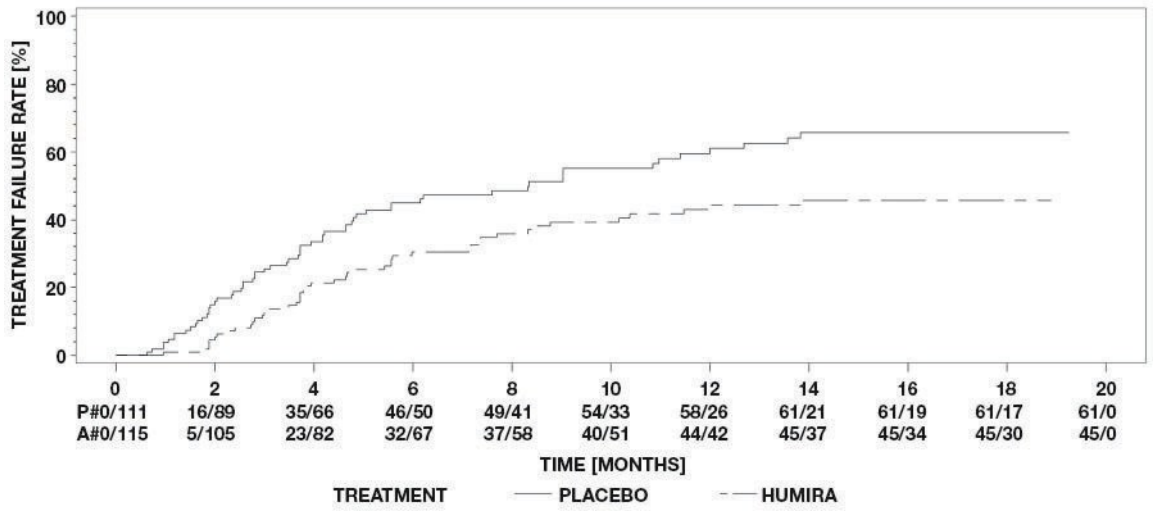


Figure 7: Kaplan-Meier Curves Summarizing Time to Treatment Failure on-or-after Week 2 (Study UV II)



In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups (Table 29).

Table 30: Treatment Failure Components in Study UV I and UV II

UV I				UV II		
Component of Time-to-Treatment Failure	HR[a]	CI 95%	*p Value*[b]	HR[a]	CI 95%	*p Value*[b]
New Active Inflammatory Lesions	0.38	(0.21- 0.69)	*0.001*	0.55	(0.26-1.15)	*0.105*
Anterior Chamber Cells Grade	0.51	(0.30- 0.86)	*0.01*	0.7	(0.42- 1.18)	*0.18*
Vitreous Haze Grade	0.32	(0.18- 0.58)	*<0.001*	0.79	(0.34- 1.81)	*0.569*
Deterioration of Best Corrected Visual Acuity	0.56	(0.32- 0.98)	*0.04*	0.33	(0.16- 0.70)	*0.002*

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

a. HR of Adalimumab vs placebo from proportional hazards regression with treatment as factor.
b. 2-sided *P* value from log rank test.

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

In the long-term extension of studies UV I and UV II, 276 of 371 eligible patients reached 78 weeks of open-label adalimumab treatment. Of these, 222 (80.4%) were quiescence (no active inflammatory

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.

Quality of Life

In Study UV 1, treatment with adalimumab resulted in maintenance of vision-related functioning and health- related quality of life, as measured by the National Eye Institute Visual Functioning Questionnaire - 25 (NEI VFQ-25).

CLINICAL TRIAL FOR COMPARABILITY OF IDACIO WITH HUMIRA®

Plaque psoriasis

The safety, efficacy and immunogenicity of Idacio was assessed in a randomized, double-blind equivalence study in 443 adult patients with moderate to severe chronic plaque psoriasis (Auriel-Pso) who were candidates for systemic therapy or phototherapy.

The primary objective was the demonstration of therapeutic equivalence between Idacio and Humira, in terms of the proportion of subjects achieving a PASI score reduction of ≥ 75% from baseline (PASI

75) at Week 16.

Study Auriel-Pso evaluated 443 patients with chronic Ps with ≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12. Patients received Idacio or reference product at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 50 response at Week 16, defined as a PASI score improvement of at least 50% relative to baseline, entered extended treatment period and continued receiving 40 mg reference product every other week for an additional 37 weeks.

Efficacy Results after 16 Weeks of treatment in Auriel-Pso (primary endpoint)

	Idacio	**Reference product**
ITT set	**N=222**	**N=221**
95% stratified Newcombe CI (%)	-4.00, 9.57	

Equivalence results for Idacio were further confirmed by similarity of efficacy responses observed up to 1 year in the follow-up of the 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 1062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titre antibodies to adalimumab at least once during treatment, which were neutralising *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg fortnightly as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

In pJIA Study I a greater percentage of patients developed antibodies to adalimumab compared to adult rheumatoid arthritis patients. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. 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 pJIA Study II 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 adalimumab 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 monotherapy 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 monotherapy.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab. In patients with ulcerative colitis, anti-adalimumab antibodies were identified in 3.9% (19/487) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 micrograms/mL. Among the patients whose serum adalimumab levels were < 2 micrograms/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In plaque psoriasis patients on long term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was 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. 37 of the 38 subjects completed the initial double blind period (16 weeks) of Study M04-717, and one subject entered the long term follow up period after Week 4.

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 antibodies

to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Comparability of Idacio and Humira® Immunogenicity Results:

The immunogenicity comparison of Idacio and Humira® in plaque psoriasis patients showed that the incidences of immunogenicity (ADA and Nab) were similar through the primary analysis at Week 16 and across treatment groups up to Week 52. In the Safety Analysis Set, the incidence of ADA at Week 52 was 91.5 % for Idacio and 93.9% for EU Humira®.

Switching from the EU adalimumab reference product to Idacio did not result in clinically meaningful differences on immunogenicity.

Safety Results:

Frequencies of subjects with TEAEs and ADR were similar between treatment groups. Most TEAE were classified as of mild or moderate severity. SAE were distributed in a balanced manner across treatment groups. The proportion of subjects reporting hypersensitivity reactions, injection site reactions, and serious infections was similar between Idacio and the EU Humira.

When extending the observation period to 66 weeks (Overall Treatment Period) similar findings were observed. The majority of SAE were classified as unrelated to the exposure. SAE were observed in 9.0% of subjects allocated only to Idacio, 6.7% of subjects allocated to only EU Humira, and 5.0% of subjects who have undergone a single treatment transition.

Most TEAE were of mild or moderate intensity, distributing proportionally across treatment groups. ADR distributed proportionally across treatment groups for the clinical studies performed with Idacio didn't reveal any clinically meaningful differences in efficacy, safety, PK and immunogenicity between Idacio and Humira.

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 was 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.

Specific Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Race/ethnicity

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

Gender/weight

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

Paediatric Patients

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 micrograms/mL and 10.9 micrograms/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 micrograms/mL and 8.1 micrograms/mL, respectively. In pJIA Study II for patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years old, or aged 4 years and above weighing < 15 kg, the mean steady-state trough serum adalimumab concentrations for patients receiving adalimumab subcutaneously fortnightly were 6.0 ± 6.1 micrograms/mL (101% CV) for adalimumab without concomitant methotrexate, and 7.9 ± 5.6 micrograms/mL (71.2% CV) with concomitant methotrexate.

Table 31: Summary of Serum Adalimumab Trough Concentrations (microgram/mL) in Patients with Polyarticular JIA by Week 24 (N = 15) (pJIA Study II)

Treatment Groups	Mean ± SD (CV%) Min – Max, N_{nmiss}		
	Week		
	0	12	24
Adalimumab 24 mg/m^2 BSA fortnightly (All patients N = 15)	0 ± 0 (0%) 0 – 0, 14	6.97 ± 5.69 (81.6%) 0 – 14.9, 15	7.78 ± 5.85 (75.2%) 0 – 14.7, 15
Adalimumab 24 mg/m^2 BSA fortnightly, with Methotrexate (All patients N = 11)	0 ± 0 (0%) 0 – 0, 10	7.27 ± 5.71 (78.5%) 0 – 14.8, 11	8.45 ± 5.69 (67.3%) 0 – 14.7, 11
Adalimumab 24 mg/m^2 BSA fortnightly, without Methotrexate (All patients N = 4)	0 ± 0 (0%) 0 – 0, 4	6.13 ± 6.41 (104.6%) 0 – 14.9, 4	5.95 ± 6.74 (113.3%) 0 – 12.7, 4

BSA = Body surface area

N_{nmiss} = number of non-missing observations

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 micrograms/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 micrograms/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 micrograms/mL for patients ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 micrograms/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 micrograms/mL for the Standard Dose group and 3.5 ± 2.2

micrograms/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 micrograms/mL (40/20 mg, weekly) and 6.7 ± 3.5 micrograms/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 micrograms/mL (79% CV). Serum adalimumab concentrations after 40mg fortnightly in adult psoriasis patients are comparable to those following 0.8 mg/kg fortnightly in paediatric psoriasis patients in study M04-717 (range 7-11 micrograms/mL).

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 and efficacy similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.

Geriatric Patients

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.

Hepatic and Renal Insufficiency

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

Disease States

Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Drug Interactions, Methotrexate

When adalimumab 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 **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)**.** This is consistent with the higher trough concentrations of adalimumab found in patients treated with concomitant methotrexate (see **5.1 PHARMACODYNAMIC PROPERTIES** - **Steady State**).

Comparability of Idacio and Humira® in healthy volunteers

Statistical comparison of primary PK parameters between treatment arms for all subjects in the PK

analysis set is presented below.

The analysis of variance (ANOVA) geometric least-squares mean ratios for the comparison of Idacio versus the US Humira for $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$, and C_{max} were 90.46, 96.03, and 97.22, respectively, and the corresponding 90% CIs were all entirely contained within the predefined equivalence interval of 80.00% to 125.00%, demonstrating that the 2 products had equivalent PK profiles.

The ANOVA geometric least-squares mean ratios for the comparison of Idacio versus EU Humira for $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$, and C_{max} were 89.12, 91.53, and 95.38, respectively, and the corresponding 90% CIs were all entirely contained within the predefined equivalence interval of 80.00% to 125.00%, demonstrating that the 2 products had equivalent PK profiles.

The ANOVA geometric least-squares mean ratios for the comparison of US Humira versus EU Humira for $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$, and C_{max} were 98.52, 95.32, and 98.10, respectively, and the corresponding 90% CIs were all entirely contained within the predefined equivalence interval of 80.00% to 125.00%, indicating that the 2 products had equivalent PK profiles.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monobasic sodium phosphate dihydrate
Dibasic sodium phosphate dihydrate
Mannitol
Sodium chloride
Citric acid monohydrate
Sodium citrate dihydrate
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C (in a refrigerator) and store the syringe or vial 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 Idacio vial, 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 vial **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 label, to allow the syringe to be discarded after the maximum 14 days if not used.

6.5 Nature and contents of container

Idacio 40 mg solution for injection in single use pre-filled syringe

0.8 mL solution in pre-filled syringe (type I glass) with needle guard, finger flanges, a plunger stopper (bromobutyl rubber), and a needle with a needle shield (thermoplastic elastomer).

Pack Sizes:

1 pre-filled syringe + 1 alcohol pad
2 pre-filled syringes + 2 alcohol pads
3 pre-filled syringes + 3 alcohol pads
4 pre-filled syringes + 4 alcohol pads
6 pre-filled syringes + 6 alcohol pads

Idacio 40 mg solution for injection in single use pre-filled pen

0.8 mL solution in pre-filled pen containing a pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer). The pen is a single use, disposable, handheld, mechanical injection device.

Pack Sizes:

1 pre-filled pen + 1 alcohol pad

2 pre-filled pens + 2 alcohol pads

3 pre-filled pens + 3 alcohol pads

4 pre-filled pens + 4 alcohol pads

6 pre-filled pens + 6 alcohol pads

Idacio 40 mg/0.8 mL solution for injection for paediatric use in single-use vial

0.8 mL solution in vial (type I glass) with a rubber stopper (bromobutyl rubber) and aluminium crimp seal.

Pack sizes:

1 vial + 1 syringe + 1 needle + 1 adaptor + 2 alcohol pads

2 vial + 2 syringes + 2 needles + 2 adaptors + 4 alcohol pads

*Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 Physicochemical properties

CAS number

CAS Registry Number: 331731-18-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4- Prescription only Medicine

8 SPONSOR

Fresenius Kabi Australia Pty Limited
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9 DATE OF FIRST APPROVAL

15/06/2020

10 DATE OF REVISION

15/06/2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information