AMGEVITA® SOLUTION FOR INJECTION

1. PRODUCT NAME

AMGEVITA® adalimumab (rch) solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

AMGEVITA 20 mg

Each 0.4 mL single-use pre-filled syringe contains 20 mg of adalimumab.

AMGEVITA 40 mg

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

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

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. AMGEVITA was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human tumour necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. AMGEVITA binds with high affinity and specificity to soluble tumour necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons.

AMGEVITA is a biosimilar medicine. The prescribing clinician should be involved in any decision regarding interchangeability (see https://medsafe.govt.nz/profs/riss/Biosimilars.asp). Data comparing AMGEVITA with the reference product Humira® can be found in sections 4.8 and 5.1 of this data sheet.

Excipients

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis (RA)

AMGEVITA 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 (MTX).

AMGEVITA can be used alone or in combination with MTX.

Juvenile Idiopathic Arthritis (JIA)

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

AMGEVITA in combination with MTX is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 years of age and older.

AMGEVITA can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.

Enthesitis-Related Arthritis (ERA)

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

Psoriatic Arthritis (PsA)

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

Ankylosing spondylitis (AS)

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

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

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

Crohn's Disease (CD) in children (≥ 6 years) and adults

AMGEVITA 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 in children (≥ 5 years) and adults

AMGEVITA is indicated for:

- inducing and maintaining clinical remission in paediatric patients 5 years of age or older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
- treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Psoriasis in children (≥ 4 years) and adults

AMGEVITA 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.

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

Hidradenitis Suppurativa (HS) in adolescents (from 12 years of age) and adults

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

Uveitis

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

Paediatric uveitis (≥ 2 years)

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

4.2 Dose and method of administration

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

AMGEVITA should not be mixed in the same syringe with any other medicine. Any unused product or waste material should be disposed of in accordance with local requirements. AMGEVITA contains no antimicrobial agent. Discard any residue.

Dose

Rheumatoid arthritis

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

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

Psoriatic arthritis

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

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

Ankylosing spondylitis

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

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

Non-radiographic axial spondyloarthritis

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

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

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

Crohn's disease in adults

The recommended AMGEVITA dose regimen for adults with CD is given in Table 1.

Table 1. AMGEVITA recommended dosages for adults with CD

Therapy	Dose	Frequency
Induction	160 mg	Initial Dose (Day 0) as **either**: • Four 40 mg injections in one day **OR** • 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

Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-MP and AZA) may be continued during treatment with AMGEVITA.

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

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

Ulcerative colitis in adults

The recommended AMGEVITA induction dose regimen for adult patients with moderate to severe ulcerative colitis is given in Table 2.

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

Some patients who experience a decrease in their response may benefit from increasing the dosage to 40 mg AMGEVITA every week or 80 mg fortnightly (as two 40 mg injections).

Table 2. AMGEVITA recommended dosages for adults with ulcerative colitis

Therapy	Dose	Frequency
Induction	160 mg	Initial Dose (Day 0) can be administered as **either**: • Four 40 mg injections in one day **OR** • 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

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

Psoriasis

The recommended dose of AMGEVITA for adult patients with psoriasis 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.

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

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

Uveitis

The recommended dose of AMGEVITA 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 AMGEVITA can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents.

Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with AMGEVITA. There is limited experience in the initiation of treatment with AMGEVITA alone.

Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with AMGEVITA.

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

Hidradenitis suppurativa

Adults

The recommended AMGEVITA 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 as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg fortnightly (as two 40 mg injections). Antibiotics may be continued during treatment with AMGEVITA if necessary.

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

In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered. The benefit and risk of continued long-term treatment should be periodically evaluated (See Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

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

The recommended AMGEVITA dose is 80 mg at week 0, followed by 40 mg fortnightly, starting at week 1 via subcutaneous injection.

In adolescent patients with inadequate response to AMGEVITA 40 mg fortnightly, an increasing dosage to 40 mg every week or 80 mg fortnightly (given as two 40 mg injections) may be considered.

Antibiotics may be continued during treatment with AMGEVITA 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 AMGEVITA.

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

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

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

Special populations

Elderly

No dose adjustment is needed for this population (See Section 4.4 Special warnings and precautions for use, Elderly).

Renal Impairment

AMGEVITA has not been studied in this patient population. No dose recommendations can be made.

Hepatic Impairment

AMGEVITA has not been studied in this patient population. No dose recommendations can be made.

Paediatric population

Juvenile Idiopathic Arthritis (Polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis)

The recommended dose of AMGEVITA for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis or patients 6 years of age and older with enthesitis-related arthritis are based on weight as shown in Table 3. MTX, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with AMGEVITA.

Adalimumab has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg. Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years of age. The safety and efficacy of adalimumab has not been established in systemic juvenile idiopathic arthritis or oligoarticular juvenile idiopathic arthritis.

Table 3. AMGEVITA recommended dosages for paediatrics patients aged 2 years and older with Polyarticular Juvenile Idiopathic Arthritis and paediatrics patients 6 years of age and older with Enthesitis Related Arthritis

Patient's body weight	Dose
10 kg to < 30 kg	20 mg fortnightly (with the AMGEVITA 20 mg pre-filled syringe)
≥ 30 kg	40 mg fortnightly (with either the AMGEVITA 40 mg pen or 40 mg prefilled syringe)

Paediatric Crohn's Disease (≥ 6 years)

The recommended doses of AMGEVITA for patients from 6 to 17 years of age with CD are given in Table 4. Some patients may benefit from increasing the dosage if a disease flare or an inadequate response is experienced during maintenance dosing:

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

Continued therapy should be carefully considered in a subject not responding by week 12. AMGEVITA has not been studied in children with Crohn's disease aged less than 6 years of age.

Table 4. AMGEVITA recommended dosages for moderate to severe paediatric CD

Patients < 40 kg body weight		
Therapy	Dose	Frequency
Induction	80 mg	Initial Dose (Day 0) as two 40 mg injections
	40 mg	Second Dose (Day 14) as **either**: • One 40 mg injection **OR** • Two 20 mg injections
Maintenance	20 mg	Starting Day 28 and continuing fortnightly
Patients ≥ 40 kg body weight		
Therapy	**Dose**	**Frequency**
Induction	160 mg	Initial Dose (Day 0) as **either**: • Four 40 mg injections in one day **OR** • 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

Paediatric plaque psoriasis (≥ 4 years)

The recommended dose of AMGEVITA is based on body weight as shown in Table 5. 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.

Table 5. AMGEVITA recommended dosages for paediatric plaque psoriasis in patients aged 4 years and older

Patient's body weight	**Dose**
< 30 kg	20 mg fortnightly (AMGEVITA 20 mg Pre-filled Syringe)
≥ 30 kg	40 mg fortnightly (AMGEVITA 40 mg Pen or 40 mg Pre-filled Syringe)

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

There is no relevant use of AMGEVITA in children with chronic plaque psoriasis aged less than 4 years of age.

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

Paediatric uveitis (≥ 2 years)

The recommended dose of AMGEVITA for paediatric patients with uveitis from 2 years of age is based on body weight as shown in Table 6. AMGEVITA is administered via subcutaneous injection. AMGEVITA may be available in different strengths and/or presentations depending on the individual treatment needs.

In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with MTX.

Table 6. AMGEVITA recommended dosages for paediatric uveitis patients aged 2 years and older

Patient's body weight	Dose
< 30 kg	20 mg fortnightly in combination with MTX
≥ 30 kg	40 mg fortnightly in combination with MTX

When AMGEVITA is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of an AMGEVITA loading dose in children < 6 years of age (see section 5.2 Pharmacokinetics in Special Populations, Paediatrics).

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

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

Paediatric Hidradenitis Suppurativa (2 to less than 12 years)

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

Paediatric Ulcerative Colitis (5 to 17 years)

The recommended dose of AMGEVITA for patients 5 to 17 years of age with ulcerative colitis is based on body weight as given in Table 7.

AMGEVITA may be available in different strengths and/or presentations. Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

Patients who experience a disease flare after beginning maintenance therapy may benefit from a one-time re-induction dose of 80 mg (<40 kg) or 160 mg (≥40 kg), followed by maintenance dosing.

There is no relevant use of AMGEVITA in children aged less than 5 years of age for this indication.

Table 7. AMGEVITA recommended dosages for paediatric ulcerative colitis patients aged from 5 to 17 years)

Patient's body weight	Induction dose	Maintenance dose starting at week 4*
< 40 kg	• 80 mg at Week 0 • 40 mg at Week 2	40 mg fortnightly **OR** 20 mg every week
≥ 40 kg	• 160 mg at Week 0 • 80 mg at Week 2	80 mg fortnightly **OR** 40 mg every week

* Paediatric patients who turn 18 years of age while on AMGEVITA should continue their prescribed maintenance dose.

Paediatric psoriatic Arthritis and Axial Spondyloarthritis including Ankylosing Spondylitis

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

Method of administration

AMGEVITA is administered by subcutaneous injection (see section 6.6 for more information). This product is for one dose in one patient only. Comprehensive instructions for the administration of AMGEVITA are provided in the Instructions for Use leaflet in the pack.

4.3 Contraindications

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

AMGEVITA is contraindicated in severe infections including sepsis, active tuberculosis and opportunistic infections (see Section 4.4 Special warnings and precautions for use).

AMGEVITA is contraindicated in moderate to severe heart failure (NYHA class III/IV).

Concurrent administration of AMGEVITA and anakinra (interleukin-1 receptor antagonist) is contraindicated (see Section 4.4 Special warnings and precautions for use).

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 AMGEVITA 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 AMGEVITA should be considered prior to initiating therapy (see Section 4.4 Special warnings and precautions for use, Other opportunistic infections).

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

Patients who develop a new infection while undergoing treatment with AMGEVITA should be monitored closely and undergo a complete diagnostic evaluation. Administration of AMGEVITA 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 AMGEVITA 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,

AMGEVITA 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 extrapulmonary (i.e. disseminated).

Before initiation of therapy with AMGEVITA, 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 AMGEVITA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG).

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or 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, AMGEVITA therapy must not be initiated.

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

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with AMGEVITA. 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 AMGEVITA 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 AMGEVITA.

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 AMGEVITA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of AMGEVITA 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 AMGEVITA 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 AMGEVITA should be discontinued immediately and appropriate therapy initiated.

Dry natural rubber

The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex).

The needle cover of the pre-filled syringes does not contain latex.

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, leucopenia) have been infrequently reported with adalimumab (see section 4.8 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 AMGEVITA. Discontinuation of AMGEVITA therapy should be considered in patients with confirmed significant haematologic abnormalities.

Immunosuppression

The possibility exists for TNF blocking agents, including adalimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis

treated with 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 section 4.4 Special warnings and precautions for use, Infections and Section 4.8 Undesirable effects, Infections and Malignancies).

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 AMGEVITA 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 AMGEVITA in utero is not recommended for 5 months following the mother's last AMGEVITA 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 AMGEVITA therapy.

Congestive Heart Failure (CHF)

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

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 section 4.8 Undesirable effects, Malignancies). However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active inflammatory disease, which complicates the risk estimation.

Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and AMGEVITA 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 AMGEVITA 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 AMGEVITA.

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 AMGEVITA, treatment should be discontinued (see Section 4.8 Undesirable effects, Autoantibodies).

Concurrent administration of biologic DMARDS or TNF-antagonists

Concurrent administration of etanercept and anakinra has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, combination of adalimumab and anakinra is contraindicated.

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

Use in Psoriasis

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

Surgery

There is limited safety experience of surgical procedures in patients treated with 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 AMGEVITA should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab.

Special populations

Paediatric population

See Vaccinations.

The long term effects of adalimumab on the growth and development of children have not been studied. The safety and efficacy of AMGEVITA in paediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), paediatric Crohn's disease, paediatric plaque psoriasis, adolescent hidradenitis suppurativa, paediatric uveitis and paediatric ulcerative colitis have not been established.

Elderly

Of the total number of subjects in clinical studies of adalimumab 10.2% were 65 years and over, while approximately 2.2% were 75 and over. A total of 519 RA patients 65 years of age and older, including 107 patients 75 years and older, received 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. Two patients older than 65 years of age received adalimumab in the clinical non-radiographic axial spondyloarthritis study (see Section 4.2 Dose and method of administration).

Renal Impairment

Adalimumab has not been studied in this patient population. No dose recommendations can be made.

Hepatic Impairment

Adalimumab has not been studied in this patient population. No dose recommendations can be made.

4.5 Interaction with other medicines and other forms of interaction

Methotrexate

Adalimumab has been studied in RA patients taking concomitant MTX (see section 5.1 Pharmacodynamic properties, Clinical efficacy and safety and section 5.2 Pharmacokinetic properties, Steady-State). The data do not suggest the need for dose adjustment of either AMGEVITA or MTX. Interactions between adalimumab and medicines other than MTX have not been evaluated in formal pharmacokinetic studies.

TNF-alpha inhibitors

Concurrent administration of TNF-alpha inhibitors with anakinra or abatacept has been associated with an increased risk of serious infections (see section 4.4 Special warnings and precautions for use).

Laboratory tests

There is no known interference between adalimumab and laboratory tests.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

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

In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. There were no significant differences in the overall rates for the primary endpoint of major birth defects (adjusted Odds Ratio 0.84, 95% Confidence Interval (CI) 0.34, 2.05) as well as the secondary endpoints which included minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections. No stillbirths or malignancies were reported.

Although the registry has methodological limitations, including small sample size and non-randomised study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not treated with adalimumab. In addition, data from post-marketing surveillance does not establish the presence of a drug-associated risk.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not

recommended for 5 months following the mother's last adalimumab injection during pregnancy.

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

Lactation

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

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

Fertility

The effect of adalimumab on fertility has not been investigated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

Adalimumab was studied in 9506 patients in controlled and open-label trials.

These trials included rheumatoid arthritis patients with short term and long-standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving adalimumab and 3,801 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 5.4% for control treated patients. The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of RA Studies I, II, III and IV was 6.6% for patients taking 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.

Tabulated list of adverse reactions

The following convention has been used for the classification of frequencies:

Very common:	≥ 1 in 10
Common:	≥ 1 in 100 and < 1 in 10
Uncommon:	≥ 1 in 1,000 and < 1 in 100
Rare:	≥1/10,000 and <1/1,000

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

Table 8 contains adverse drug reactions (ADRs), which in some cases represent groups of related preferred terms to represent a medical concept. The ADRs presented in the table were included based on criteria including statistical significance, doubling in rate in adalimumab-treated patients compared to placebo-treated patients, a rate greater than 1% for adalimumab-treated patients and medical importance assessment.

Table 8. Adverse drug reactions in adalimumab clinical studies (listed by MEDRA system organ class)

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	leucopenia (including neutropenia and agranulocytosis), anaemia
Common	thrombocytopenia, leucocytosis
Uncommon	idiopathic thrombocytopenic purpura
Rare	Pancytopenia
Immune system disorders*	
Common	hypersensitivity, allergies (including seasonal allergy)

Metabolism and nutrition disorders	
Very common	lipids increased
Common	hypokalaemia, uric acid increased, blood sodium, abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
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), hyperhidrosis
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

*see information in section 4.3, 4.4 and 4.8
** includes open-label extension studies

Rheumatoid arthritis

Table 9 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 studies I to IV). In general, the adverse reactions across all indications were similar to those seen in RA patients.

Table 9. Adverse reactions (by MedDRA system organ class) reported by patients treated with adalimumab during placebo-controlled period of RA studies

Adverse Reaction	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
leucopenia (including neutropenia and agranulocytosis)	14	8

Adverse Reaction	Adalimumab (N = 1380) (%)	Control (N = 690) (%)
Leucocystosis	1	0
thrombocytopenia	1	0
Metabolism and nutrition disorders		
lipids increased	17	8
uric acid increased	6	3
blood sodium abnormal	10	3
Hypokalaemia	3	2
hypophosphatemia	2	1
blood potassium increased	3	1
Nervous system disorders		
Headache	14	8
Vascular disorders		
Hypertension	6	3
Flushing	2	1
Respiratory, thoracic and mediastinal disorders		
Cough	7	6
Gastrointestinal disorders		
nausea and vomiting	12	11
abdominal pain	10	6
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

Polyarticular Juvenile Idiopathic Arthritis

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

Uveitis

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

Hidradenitis suppurativa

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

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 7.2% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections

In pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the 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, non-radiographic axial spondyloarthritis, Crohn's disease, ulcerative colitis psoriasis, hidradenitis suppurativa and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patients years among 5,291 adalimumab-treated patients versus a rate of 6.3 (3.4, 11.8) per 1,000 patient years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control treated patients).

The rate (95% confidence interval) of non-melanoma (basal cell and squamous cell) skin cancers was 8.8 (6.0, 13.0) per 1,000 patient years among adalimumab-treated patients and 3.2 (1.3, 7.6) per 1,000 patient years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient years among control patients.

The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 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 6,427 patients and over 26,439 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

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

In addition, no malignancies were observed in 192 paediatric patients with an exposure of 258.9 patient years during an 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 an adalimumab trial in paediatric patients with plaque psoriasis.

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

No malignancies were observed in 93 paediatric patients with an exposure of 65.3 patient years during an adalimumab trial in paediatric patients with ulcerative colitis.

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 1,000 patient treatment years. The reported rates for non-melanoma skins cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (See Section 4.4 Special warnings and precautions for use).

Autoantibodies

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

Liver Enzyme Elevations

In controlled Phase 3 trials of adalimumab (40 mg SC fortnightly), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN

occurred in 3.7% of 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.

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.

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.

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.

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.

In controlled Phase 3 trials of adalimumab (initial dose of 80 mg then 40 mg fortnightly), in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of adalimumab-treated patients and 1.8% of control-treated patients. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in paediatric patients with plaque psoriasis.

In controlled Phase 3 trials of adalimumab (40 mg fortnightly), in patients with axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2.1% of adalimumab-treated patients and 0.8% of control-treated patients.

In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of adalimumab-treated patients and 1.3% of

control-treated patients. Most ALT elevations occurred with concomitant MTX use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

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 166.5 days and 105.0 days in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

In the controlled Phase 3 trial of adalimumab in patients with paediatric ulcerative colitis (N=93), which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every week (N=32), following body weight adjusted induction doses of 2.4 mg/kg (maximum dose of 160 mg) at week 0 and week 1, and 1.2 mg/kg (maximum dose of 80 mg) at week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum dose of 160 mg) at week 0, placebo at week 1, and 1.2 mg/kg (maximum dose of 80 mg) at week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of patients.

Across all indications in clinical trials, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving TNF blockers, including adalimumab.

Concurrent Treatment with Azathioprine/6-Mercaptopurine

In adult CD studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of adalimumab and AZA/6-MP compared with adalimumab alone.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) clinical trials

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

pJIA Study I

Adalimumab was studied in 171 patients, who were 4 to 17 years of age with polyarticular juvenile idiopathic arthritis. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster,

myositis, metrorrhagia and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with adalimumab and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

45% of patients experienced an infection while receiving adalimumab with or without concomitant MTX 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 MTX. In general, these elevations did not lead to discontinuation of adalimumab treatment.

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.

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. Most patients received at least 24 weeks of adalimumab treatment up to a maximum of 120 weeks duration. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

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.

Non-serious allergic reactions were observed in 6% of patients and included intermittent urticarial and rash, which were all mild in severity.

Additional adverse reactions from post-marketing surveillance or phase IV clinical trials

Adverse events have been reported during post-approval use of adalimumab (see Table 10). 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 10. Additional adalimumab adverse reactions from post-marketing surveillance or phase IV clinical trials

System Organ Class	Adverse Reaction
Infections and infestations	diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	hepatosplenic T-cell lymphoma, leukaemia, merkel cell carcinoma (neuroendocrine carcinoma of the skin)
Immune system disorders*	anaphylaxis, sarcoidosis
Nervous system disorders*	cerebrovascular accident, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome)
Cardiac disorders	myocardial infarction
Vascular disorders	thrombosis
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, autoimmune hepatitis
Skin and subcutaneous tissue disorders	alopecia, angioedema, cutaneous vasculitis, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), erythema multiforme, Stevens Johnson Syndrome, lichenoid skin reaction**
Musculoskeletal and connective tissue disorders	lupus-like syndrome
General disorders and administration site conditions	pyrexia

* further information found in sections 4.3, 4.4 and 4.8

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

Similarity of AMGEVITA with Humira®

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a medicine cannot be directly compared to rates in the clinical trials of another medicine and may not reflect the rates observed in practice.

Comparative studies between AMGEVITA and Humira

AMGEVITA-Humira RA study 1 and AMGEVITA-Humira Ps study 1 showed clinical equivalence between AMGEVITA and Humira. Table 11 and Table 12 show comparative data for adverse events between AMGEVITA and Humira from RA study 1 and Ps study 1 respectively.

The data in Table 11 reflects exposure to AMGEVITA in 264 patients and Humira in 262 subjects in the AMGEVITA RA study 1 treated at the recommended dose and schedule for a median of 480 mg doses of AMGEVITA. The overall safety profile of AMGEVITA is similar to that of Humira.

Table 11. Adverse events reported by ≥ 5% of patients treated with AMGEVITA and Humira in RA ABP Study 1

Adverse events (Preferred term)	AMGEVITA (n = 264)	Humira (n = 262)
Nasopharyngitis	6.4%	7.3%

Three hundred and fifty (350) subjects in Ps ABP Study 1 were initially randomised (1:1) to Treatment Group A (AMGEVITA) or Treatment Group B (Humira). At week 16, subjects with a PASI 50 response (50% or better improvement) continued on study for up to 52 weeks. Subjects who continued treatment beyond week 16 were re-randomised in a blinded fashion such that all subjects initially randomised to Treatment Group A (AMGEVITA) continued treatment with AMGEVITA (AMGEVITA/AMGEVITA) and subjects initially randomised to Treatment Group B (Humira) were re-randomised (1:1) to either continue treatment with adalimumab (Treatment Group B1 [Humira/Humira]) or were transitioned to AMGEVITA (Treatment Group B2 [Humira/AMGEVITA]). All subjects continued with their assigned treatment until week 48, when the last dose of assigned investigational product was administered. All subjects continued in the study until week 52, which was the end of the study.

The data in Table 12 reflect exposure to AMGEVITA/AMGEVITA in 152 subjects, Humira/Humira in 79 subjects, and Humira/AMGEVITA in 77 subjects in Psoriasis study 1 treated at the recommended dose and schedule for a median of 1,040 mg doses. The overall safety profiles of the AMGEVITA/AMGEVITA, Humira/Humira and Humira/AMGEVITA groups were similar.

Table 12. Adverse events reported by ≥ 5% of patients treated with AMGEVITA, Humira or Humira switched to AMGEVITA in Psoriasis ABP study 1

Adverse events (preferred term)	AMGEVITA/ AMGEVITA (n = 152)	Humira/ Humira (n = 79)	Humira/ AMGEVITA[a] (n = 77)
Nasopharyngitis	27.0%	27.8%	32.5%
Headache	8.6%	17.7%	9.1%
Upper respiratory tract infection	11.8%	11.4%	10.4%
Arthralgia	5.9%	10.1%	6.5%
Psoriasis	7.2%	6.3%	5.2%
Diarrhoea	3.3%	6.3%	13.0%
Back pain	6.6%	6.3%	2.6%
Oropharyngeal pain	2.6%	7.6%	3.9%
Pruritus	2.6%	2.5%	9.1%
Hypertension	5.3%	6.3%	0.0%
Rhinitis	2.6%	5.1%	3.9%
Adverse events (preferred term)	**AMGEVITA/ AMGEVITA (n = 152)**	**Humira/ Humira (n = 79)**	**Humira/ AMGEVITA[a] (n = 77)**
Toothache	3.3%	2.5%	5.2%
Bronchitis	0.7%	0.0%	5.2%
Injection site pain	0.0%	5.1%	2.6%
Contusion	0.7%	0.0%	6.5%

[a]This group reflects data for subjects exposed to both adalimumab and AMGEVITA before and after the transition of adalimumab subjects to AMGEVITA.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicine is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions to: https://pophealth.my.site.com/carmreportnz/s/

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour necrosis factor alpha (TNF-α) inhibitors.

ATC code: L04AB04.

Pharmacodynamic effects

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.

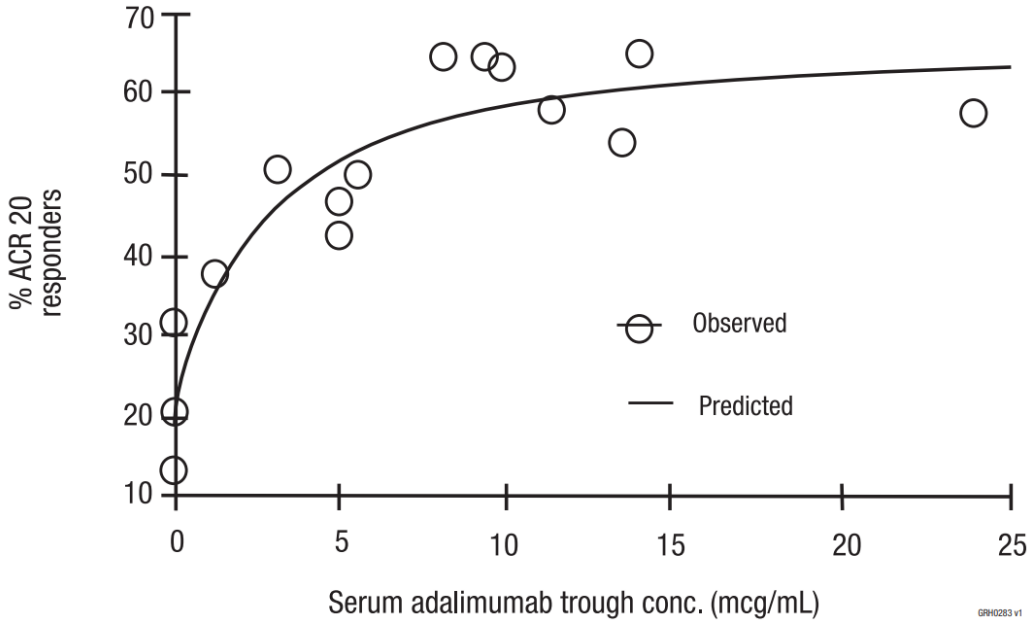
Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leucocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10} M).

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, 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 Emax equation as shown in Figure 1.

Figure 1. Concentration-efficacy relationship



EC_{50} estimates ranging from 0.8 to 1.4 microgram/mL were obtained through PK/ pharmacodynamic modelling of swollen joint count, tender joint count and ACR20 response from patients participating in Phase II and III trials.

Clinical efficacy and safety

Rheumatoid arthritis

Adalimumab was evaluated in over 3,000 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.

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 MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained

constant at 10 to 25 mg every week. Patients had ≥ 6 swollen joints and ≥ 9 tender joints and RA diagnosed according to ACR criteria. Doses of 20, 40 or 80 mg of 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 MTX 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 MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained constant at 12.5 to 25 mg every week. 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 MTX-naïve patients with early RA (mean disease duration less than 9 months) to treatment with adalimumab 40 mg fortnightly alone, MTX 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 40 mg 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.

Results of all five trials were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary endpoint in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR20 response at weeks 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.

Clinical Response

RA Studies I, II and III

The percent of adalimumab-treated patients achieving ACR20, ACR50 and ACR70 responses was consistent across all three trials. The results for the 40 mg fortnightly dose are summarised in Table 13. Patients receiving adalimumab 40 mg every week in RA Study II also achieved statistically significant ACR20, 50 and 70 response rates of 53.4%, 35.0% and 18.4%, respectively, at six months.

The ACR20 responses over 26 weeks in RA Study II for patients receiving adalimumab 40 mg weekly and adalimumab 40 mg fortnightly compared to placebo are presented in Figure 2.

Table 13. ACR responses in placebo-controlled trials (percent of patients)

Response	RA study I[a]*		RA study II[a]*		RA study III[ac]*	
	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	N/A	N/A	N/A	N/A	24.0%	58.9%
ACR50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	N/A	N/A	N/A	N/A	9.5%	41.5%
ACR70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	N/A	N/A	N/A	N/A	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

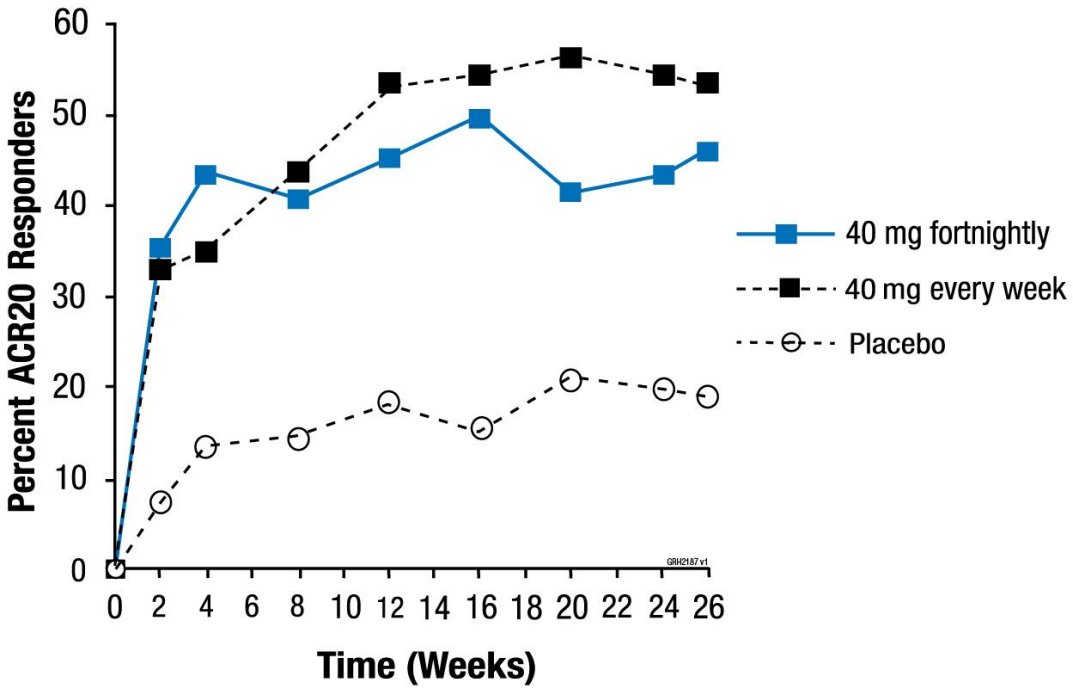
[b] 40 mg adalimumab administered every other week

[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 versus placebo at all time points for ACR20, ACR50, and ACR70

MTX = Methotrexate

Figure 2. RA Study II ACR20 Responses over 26 weeks



The results of the components of the ACR response criteria for RA Study III are shown in Table 14. 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 over a > 6 month period.

Table 14. Components of ACR Response in RA Study III

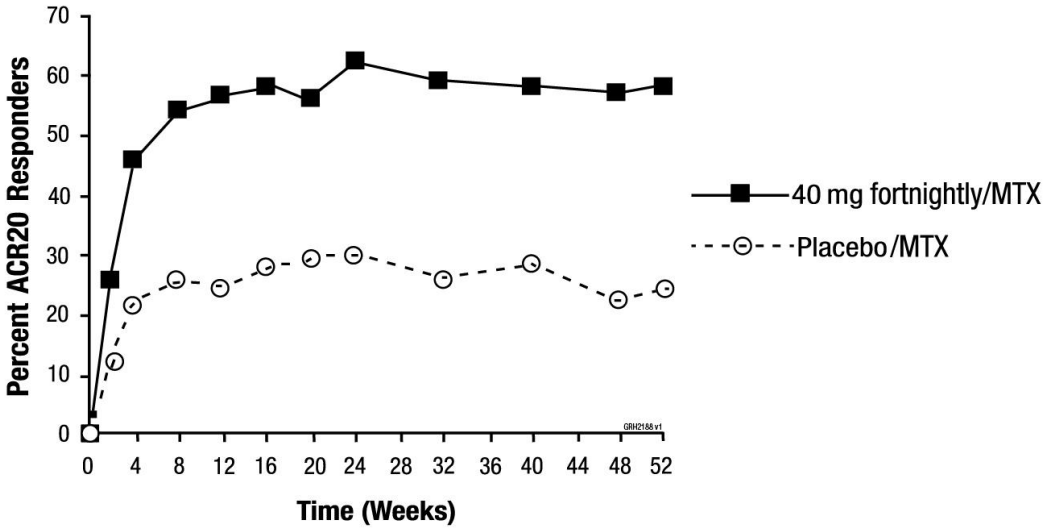
Parameter (median)	Study RA-III					
	Placebo/MTX (n = 200)			Adalimumab[a] /MTX (n = 207)		
	Baseline	week 24	week 52	Baseline	week 24	week 52
Number of tender joints (0-68)	26.0	15.0	15.0	24.0	8.0*	6.0*
Number of swollen joints (0-66)	17.0	11.0	11.0	18.0	5.0*	4.0*
Physician global assessment disease 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, 10 = 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 (Figure 3). 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 MTX 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. Figure 3 illustrates the durability of ACR20 responses to adalimumab in RA study III.

Figure 3. ACR20 Responses over 52 weeks in RA Study III



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

RA Study V

In RA Study V for early rheumatoid arthritis patients who were MTX naïve, combination therapy with adalimumab plus MTX led to significantly greater ACR responses than MTX monotherapy at week 52 and responses were sustained at week 104 (see Table 15).

At week 52 all individual components of the ACR response criteria improved with adalimumab/MTX therapy and improvements were maintained to week 104. Over the two-year study, 48.5% patients who received adalimumab/MTX combination therapy achieved a major clinical response (ACR70 for > six continuous months) compared to 27.2% of patients who received MTX monotherapy ($p < 0.001$).

In the open-label extension for RA study V, ACR responses were maintained when followed for up to 10 years. Of 542 patients who were randomised to adalimumab 40 mg fortnightly, 170 patients continued on adalimumab 40 mg 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.

Table 15. ACR20/50/70 response at weeks 26, 52, 76 and 104 (all randomised subjects) in RA study V

Response	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.

MTX: Methotrexate

In RA Study V, adalimumab/MTX combination therapy was superior to MTX monotherapy in achieving clinical remission defined as Disease Activity Score (DAS28) (CRP) < 2.6 at

week 52 (see Table 16). Of the 342 subjects originally randomised to adalimumab monotherapy or adalimumab/ MTX 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 16. Subjects in remission as defined by DAS28 < 2.6 at week 52 (all randomised subjects in RA study V)

Response	MTX N = 257	Adalimumab N = 274	Adalimumab/MTX N = 268	p-value[a]	p-value[b]
		n (%)			
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 the Pearson's chi-square test.

[b] p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the 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/MTX-treated patients demonstrated less radiographic progression than patients receiving placebo/MTX (see Table 17).

Table 17. 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

JSN: Joint space narrowing score

	Placebo/ MTX N = 200	Adalimumab[a] / MTX N = 207	Difference between adalimumab[a]/ MTX and Placebo/ MTX (95% Confidence interval*)	p-value

MTX: Methotrexate

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

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.

In RA Study V, adalimumab-treated patients had a mean duration of RA of < 9 months and had not previously received MTX. Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score. The week 52 results are shown in Table 18. 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 MTX monotherapy, adalimumab monotherapy and adalimumab/MTX combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Table 18. 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		

	MTX N = 257	Adalimumab N = 274	Adalimumab + MTX n = 268	p-value[a]	p-value[b]
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.

MTX: Methotrexate

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 (Table 19).

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.

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.

Table 19. 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%)

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 RA, the improvement in the HAQ disability index and the physical component of the SF-36 showed greater improvement ($p < 0.001$) for adalimumab/MTX combination therapy versus MTX monotherapy at week 52, which was maintained through week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Similarity of AMGEVITA with Humira in RA

The efficacy and safety of AMGEVITA compared with adalimumab were assessed in a randomised active control, double blind study in patients ≥ 18 years of age with active rheumatoid arthritis diagnosed according to 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria. Patients had RA for at least 3 months duration and at least 6 swollen and 6 tender joints and high ESR or CRP at the study entry. The patients had either rheumatoid factor or anti cyclic citrullinated peptide positivity. The study evaluated 526 patients who had an inadequate response to

MTX at doses of 7.5 mg to 25 mg. Patients received 40 mg of AMGEVITA or adalimumab subcutaneously every other week for up to 22 weeks.

Clinical Response

The percent of AMGEVITA treated subjects achieving ACR20 at week 24 in RA AMGEVITA and Humira Study 1 is shown in Table 20. The risk ratio (RR) of ACR 20 primary endpoint was within the prespecified equivalence margin and showed clinical equivalence between AMGEVITA and adalimumab.

Table 20. Clinical responses in RA study 1 of AMGEVITA and Humira at week 24 (percent of patients achieving responses)

	AMGEVITA (24 weeks)	Humira (24 weeks)
ACR20	74.6%	72.4%

At week 24, 74.6% (194/260) subjects in the AMGEVITA group and 72.4% (189/261) subjects in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for AMGEVITA versus adalimumab was 1.039 with the 2 sided 90% confidence interval (CI) of (0.954, 1.133). The 90% CI fell within the predefined equivalence margin. The risk difference (RD) of ACR20 for AMGEVITA versus adalimumab was 2.604% with the 2 sided 90% confidence interval (CI) of (3.728%, 8.936%). Thus clinical equivalence between AMGEVITA and adalimumab was demonstrated.

The results of the components of the ACR response criteria for RA AMGEVITA and Humira (adalimumab) Study 1 are shown in Table 21. ACR response rates and improvement in all components of ACR response showed an absence of clinically meaningful differences between the two groups at week 24. The time course of ACR20 response is shown in Figure 4.

Table 21. Components of ACR Response

	AMGEVITA[a] (N = 162)		Humira[a] (N = 151)	
Parameter (median)	**baseline**	**24 weeks**	**baseline**	**24 weeks**
Number of tender joints (0-68)	21.0	4.0	20.5	4.0
Number of swollen joints (0-66)	12.0	2.0	12.0	2.0
Physician global assessment[b]	7.0	2.0	7.0	2.0
Patient global assessment[b]	7.0	3.0	7.0	3.0
Pain[c]	60.0	19.0	65.0	21.0
Disability index (HAQ)[d]	1.5	1.0	1.5	0.9
CRP (mg/L)	6.1	3.0	7.6	3.0

[a] 40 mg administered every other week

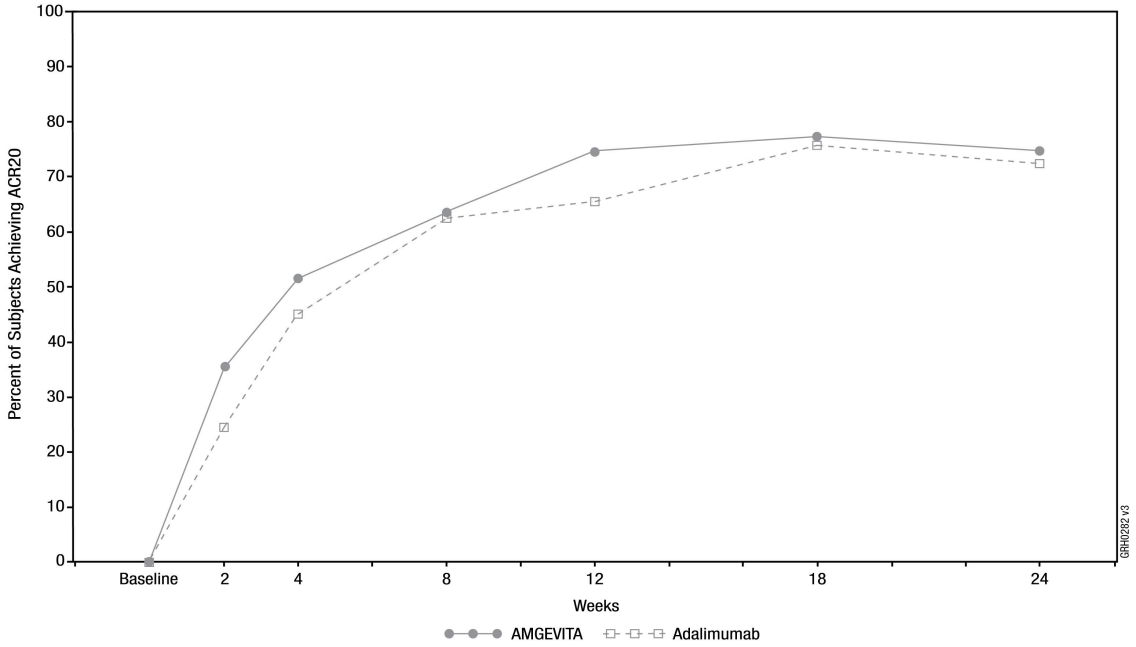
[b] Visual analogue scale; 0 = best, 10 = worst

[c] Pain scale; 0 = no pain; 100 = severe pain

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

CRP: C-reactive protein

Figure 4. AMGEVITA and Humira RA study 1: ACR20 responses over 24 weeks



Adalimumab = Humira®

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 or positive polyarthritis and 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 (pJIA). In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All patients had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDs. Patients who received prior treatment with any biologic DMARDs were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomised withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, adalimumab was administered based on body surface area at a dose of 24 mg/m2 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 prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a paediatric ACR 30 response at the end of OL-LI phase were randomised into the double blind (DB) phase of the study and received either 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 ACR30/50/70 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 two years in the OLE phase in patients who received adalimumab throughout the study.

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

pJIA Study II

The safety and efficacy of adalimumab was assessed in an open-label, multi-centre study in 32 patients (2 to < 4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active pJIA. The patients received 24 mg/m^2 body surface area (BSA) of 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 subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

PJIA STUDY II CLINICAL RESPONSE

At week 12 and week 24, paediatric ACR30 responses were 93.5% and 90.0% respectively, using the observed data approach. The proportions of patients with paediatric ACR50/70/90 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 ACR30) at week 24 (n = 27 out of 30 patients), the paediatric ACR30 responses were maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period. Overall, 20 patients were treated for 60 weeks or longer.

Enthesitis-related arthritis (ERA)

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

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. Improvement in number of active joints with arthritis was maintained during the open label period through week 156. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), paediatric ACR30 response, paediatric ACR50 response, and Paediatric ACR70 response, and maintained these improvements during the OL period through week 156 of the study.

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 MTX. 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 22 and Table 23. 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 MTX therapy. ACR responses were maintained in the open-label extension study for up to 136 weeks.

Table 22. ACR and PASI response in placebo-controlled psoriatic arthritis study (percent of patients)

ACR 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%

PASI response*	placebo N = 69	adalimumab 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

ACR = American College of Rheumatology

PASI = Psoriasis Area and Severity Index

Table 23. 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)

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

CRP: C-reactive protein

[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 analogue 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.

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 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.

Table 24. Change in modified Total sharp score in psoriatic arthritis

MODIFIED TOTAL SHARP SCORE*	**placebo**	**adalimumab**
baseline to week 24	n = 162	n = 151
baseline mean	19.0	22.6
mean change from baseline	1.6	1.0[a]
p-value	< 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
weeks 48 to 144	n = 128	n = 115
week 48 mean	22.7	22.3
mean change from baseline	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
weeks 48 to 144	n = 128	n = 115
week 48 mean	12.1	12.1
mean change from baseline	-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
weeks 48 to 144	n = 128	n = 115
week 48 mean	10.6	10.2
mean change from baseline	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.

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 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.

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 analogue 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 5, Table 25, and Table 26. Patients with total spinal ankylosis were included in the larger study (n = 11). Responses of these patients were similar to those without total ankylosis. 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 ($p < 0.001$).

Figure 5. ASAS 20 response by visit, AS study I

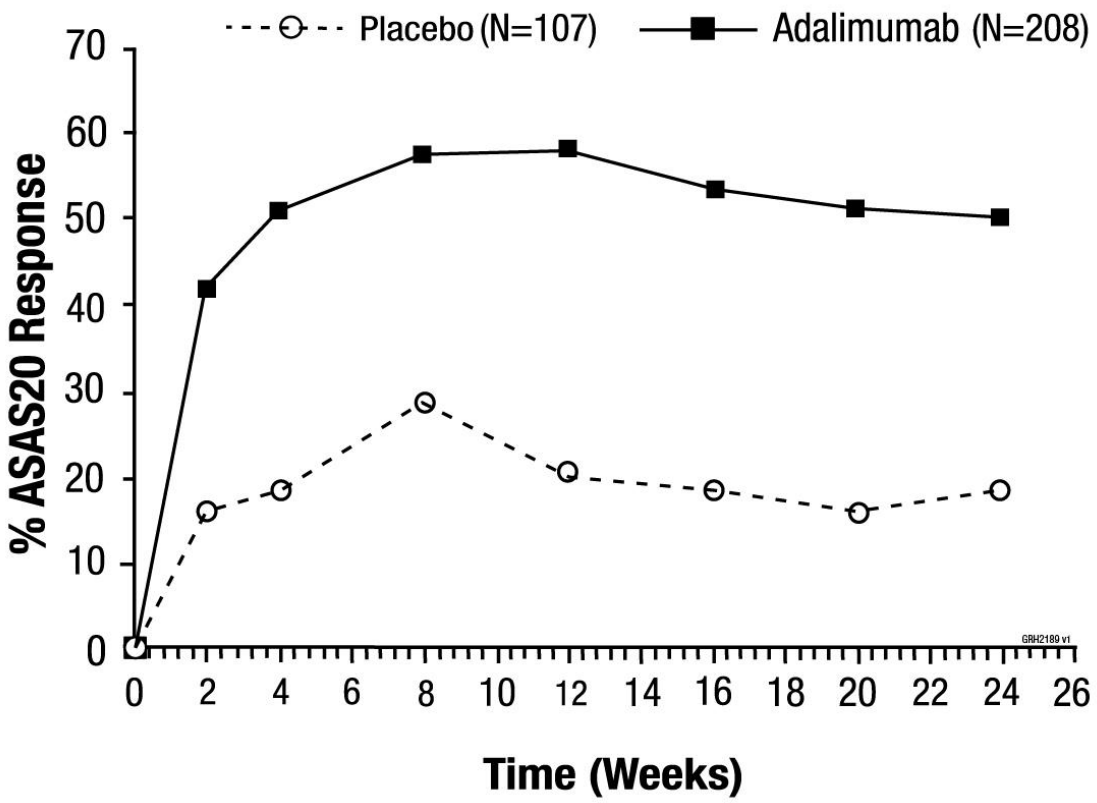


Table 25. Assessments in Ankylosing Spondylitis (ASAS) responses in placebo-controlled Ankylosing Spondylitis study

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

Table 26. Components of Ankylosing spondylitis disease activity

	placebo N = 107		adalimumab N = 208	
ASAS 20 Response Criteria*	baseline mean	week 24 mean	baseline mean	week 24 mean
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] (mg/dL)	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 Analogue 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

* 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 multicentre, double-blind, placebo-controlled study of 82 patients with AS. Patient Reported Outcomes were assessed in both AS studies using the generic health status questionnaire SF-36 and the disease-specific AS 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.

Non-radiographic axial spondyloarthritis

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

Study nr-ax SpA I

In Study nr-ax SpA I Adalimumab 40 mg fortnightly was assessed in 185 patients in a randomised, 12 week double-blind, placebo-controlled study in patients with active nr-axSpA who have had an inadequate response to or intolerance to ≥ 1 NSAIDs, or a contraindication for NSAIDSs (Study M10-791). Patients included were classified according to the ASAS axial SpA criteria, excluding patients fulfilling modified New York criteria for ankylosing spondylitis and those with psoriasis or psoriatic arthritis. The primary efficacy endpoint was the proportion of patients who achieved the ASAS40 response criteria at week 12. Mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with adalimumab and 6.5 for those on placebo. Thirty-three (18%) of patients were treated concomitantly with disease-modifying anti-rheumatic drugs and 146 (79%) with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients received adalimumab 40 mg fortnightly SC for up to an additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active nr-axSpA in patients treated with adalimumab compared to placebo in both the overall population and in patients with a positive MRI or elevated CRP (see Table 27 and Table 28).

Table 27. Efficacy Response in the Placebo-Controlled Study nr-axSpA I[#]

Double-blind response at week 12	Placebo N = 94	Adalimumab N = 91
ASAS 40	15%	36%*
ASAS 20	31%	52%**
ASAS 5/6	6%	31%*
ASAS Partial Remission	5%	16%***
BASDAI 50	15%	35%**
ASDAS[a,b]	-0.3	-1.0*
ASDAS Inactive Disease	4%	24%*
SF-36 PCS[a]	2.0[f]	5.5**
HAQ-S[a]	-0.1	-0.3***
Hs-CRP[a,c]	-0.3	-4.7*
SPARCC MRI Sacroiliac Joints[a,d]	-0.6	-3.2**
SPARCC MRI Spined[a,e]	-0.2	-1.8**

* p-value < 0.001

** p-value < 0.01

*** p-value < 0.05

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

ASAS: Assessment of Spondyloarthritis International Society

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

ASDAS: Ankylosing Spondylitis Disease Activity Score

SF-36 PCS: Short Form-36 Health Status Survey™ Version 2 Physical Component Summary score

HAQ-S: Health Assessment Questionnaire modified for the spondyloarthropathies

Hs-CRP: high sensitivity C-Reactive Protein (mg/L)

SPARCC: Spondyloarthritis Research Consortium of Canada

[a] Mean change from baseline

[b] n = 91 placebo and n = 87 adalimumab

[c] n = 73 placebo and n = 70 adalimumab

[d] n = 84 placebo and adalimumab

[e] n = 82 placebo and n = 85 adalimumab

[f] n = 93

Table 28. Efficacy Response in the Placebo-Controlled Study nr-axSpA I (Population with either a positive MRI or Elevated CRP)[#]

Double-Blind response at week 12	placebo N = 73	adalimumab N = 69
ASAS 40	14%	41%***
ASAS 20	32%	59%***
ASAS 5/6	8%	35%***
ASAS Partial Remission	5%	19%*
BASDAI 50	14%	39%***
ASDAS[a,b]	-0.3	-1.2***
ASDAS Inactive Disease	4%	29%***
SF-36 PCS[a]	2.3[f]	6.9***
HAQ-S[d]	-0.1	-0.3**
Hs-CRP[d,]	-0.8	-6.5***
SPARCC[j] MRI Sacroiliac Joints[a,d]	-0.9	-4.3**
SPARCC MRI Spine[a]	-0.5	-2.3**

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

* p-value < 0.05

** p-value < 0.01

*** p-value < 0.001

ASAS: Assessment of Spondyloarthritis International Society

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

ASDAS: Ankylosing Spondylitis Disease Activity Score

SF-36 PCS: Short Form-36 Health Status Survey™ Version 2 Physical Component Summary score

[g] HAQ-S: Health Assessment Questionnaire modified for the spondyloarthropathies

Hs-CRP: High sensitivity C-Reactive Protein (mg/L)

[j] SPARCC: Sponyloarthritis Research Consortium of Canada

[a] mean change from baseline

[b] n = 72 placebo and n = 66 adalimumab

[c] n = 54 placebo and n = 50 adalimumab

[d] n = 64 placebo and adalimumab

[e] n = 62 placebo and n = 65 adalimumab [f] n = 72

[m] n = 72

Variables demonstrating a reduction in signs and symptoms of nr-axSpA were sustained or continued to improve at week 24 and week 68 and were maintained through week 156 (see Table 29 and Table 30).

Table 29. Efficacy response in the Open-label extension of Study nr-axSpA I (observed case analysis)

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

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] Mean change from baseline

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

[f] Health Assessment Questionnaire modified for the spondyloarthropathies

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

[h] n = 170

[i] n = 120

[j] n = 163

[k] n = 140

[l] n = 118

[m] n = 177

[n] n = 151, week 52

[o] n = 121

[p] n = 131

[q] n = 112

[r] n = 97

Table 30. Efficacy response in the open-label extension of the study nr-axSpA I (population with either a positive MRI or elevated CRP) (observed case analysis)

Endpoint	Response at		
	week 24	week 68	week 156
ASAS[a] 40	70/133 (52.6%)	78/112 (69.6%)	67/97 (69.1%)
ASAS 20	96/133 (72.2%)	94/112 (83.9%)	83/97 (85.6%)
ASAS 5/6	61/133 (45.9%)	63/112 (56.3%)	49/97 (50.5%)
ASAS Partial Remission	37/133 (27.8%)	45/112 (40.2%)	45/97 (46.9%)b
BASDAI[b] 50	68/133 (51.1%)	75/112 (67.0%)	70/97 (72.2%)
ASDAS[c,d]	-1.6[i]	-1.9[j]	-1.9[k]
ASDAS inactive disease	48/133 (36.1%)	54/112 (48.2%)	45/97 (47.4%)[l]
SF-36 PCS[d,e]	7.7[m]	10.5[n]	11.5[o]
HAQ-S[d,f]	-0.39	-0.48	-0.50
Hs-CRP[d,g]	-6.0[p]	-5.9[q]	-4.2[r]

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] Mean change from baseline

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

[f] Health Assessment Questionnaire modified for the sponyloarthropathies

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

[h] n = 96

[i] n = 129

[j] n = 110

[k] n = 93

[l] n = 95

[m] n = 138

[n] n = 116, week 52

[o] n = 96

[p] n = 97

[q] n = 83

[r] n = 75

Inhibition of Inflammation

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

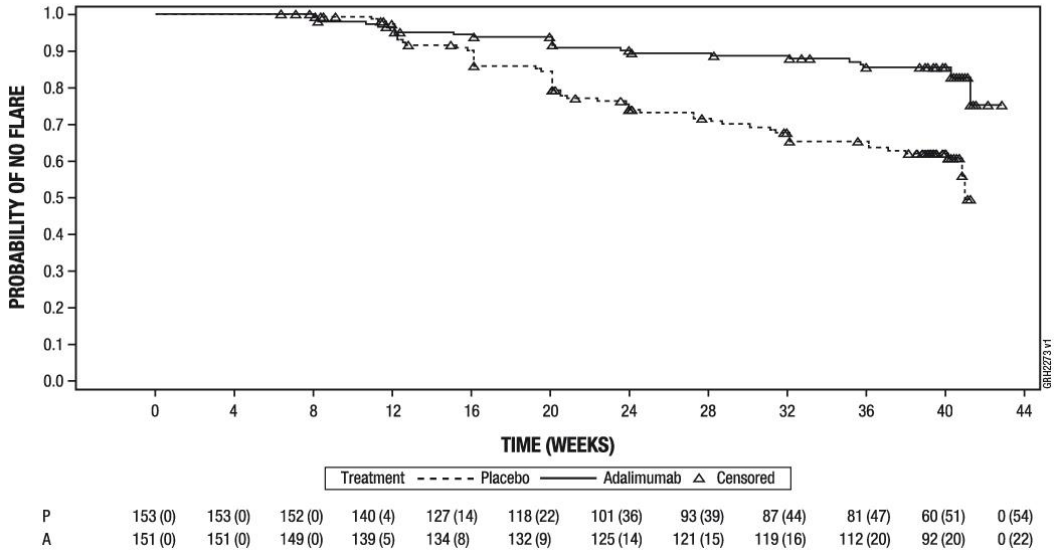
Quality of Life and Physical Function

Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Adalimumab showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to week 12 compared to placebo. Results for the SF-36 PCS score and the HAQ-S total score were sustained through week 52, week 68 and week 156 respectively (see Table 29 and Table 30).

Study nr-axSpA II

673 patients with active nr-axSpA (mean baseline disease activity [BASDAI] was 7.0) who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into the open-label period of Study nr-axSpA II during which they received adalimumab 40 mg fortnightly for 28 weeks. These patients also had objective evidence of inflammation in the sacroiliac joints or spine on MRI or elevated Hs-CRP. Patients who achieved sustained remission for at least 12 weeks (N = 305) (ASDAS < 1.3 at weeks 16, 20, 24, and 28) during the open-label period were then randomised to receive either continued treatment with adalimumab 40 mg fortnightly (N = 152) or placebo (N = 153) for an additional 40 weeks in a double-blind, placebo- controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed adalimumab 40 mg fortnightly rescue therapy for at least 12 weeks. The primary efficacy endpoint was the proportion of patients with no flare by Week 68 of the study. Flare was defined as ASDAS ≥ 2.1 at two consecutive visits four weeks apart. A greater proportion of patients on adalimumab had no disease flare during the double-blind period, when compared with those on placebo (70.4% vs. 47.1%, p<0.001) (Figure 6).

Figure 6. Kaplan-Meier Curves Summarising Time to Flare in Study nr-axSpA II



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

Among the 68 patients who flared in the group allocated to treatment withdrawal, 65 completed 12 weeks of rescue therapy with adalimumab, out of which 37 (56.9%) had regained remission (ASDAS < 1.3) after 12 weeks of restarting the open-label treatment. By week 68, patients receiving continuous adalimumab treatment showed statistically significant greater improvement of the signs and symptoms of active nr- axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study (see Table 31).

Table 31. Efficacy Response in Placebo-Controlled Period for Study nr-axSpA II

Double-blind response at week 68	placebo N = 153	adalimumab N = 152
ASAS[a] 20	47.1%	70.4%***
ASAS[a] 40	45.8%	65.8%***
ASAS Partial Remission	26.8%	42.1%**
ASDAS Inactive Disease	33.3%	57.2%***
Partial Flare[b]	64.1%	40.8%***

ASAS: Assessment of Spondyloarthritis International Society
ASDAS: Ankylosing Spondylitis Disease Activity Score
[a] Baseline is defined as open label baseline when patients have active disease
[b] Partial flare is defined as ASDAS ≥1.3 but < 2.1 at 2 consecutive visits
** p < 0.01
*** p < 0.001

Crohn's disease

Adults

The safety and efficacy of multiple doses of adalimumab were assessed in over 1,500 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 32).

Table 32. Induction of clinical remission and response (% 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 34). Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at week 56 (see Table 33).

Table 33. Hospitalisations to week 56 (ITT population) in CD study III

	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) *

* $p \leq 0.05$

Clinical remission results presented in Table 34 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 7). 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 34. Maintenance of clinical remission and response (% of patients) in CD study III

	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

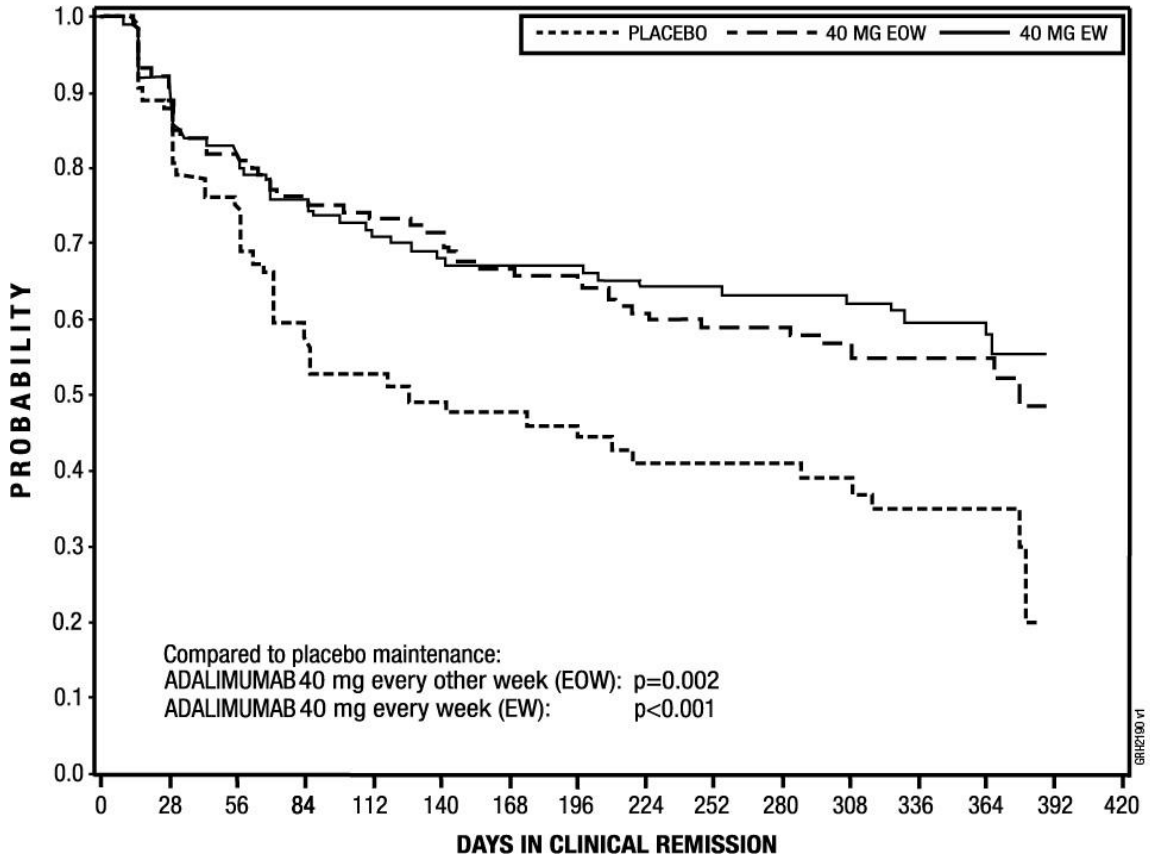
* $p < 0.001$ for adalimumab vs. placebo pairwise comparisons of proportions

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

[a] Of those receiving corticosteroids at baseline

One hundred and seventeen (117) out of 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.

Figure 7. Days in Clinical remission for patients who achieved clinical remission in CD study III



40 MG EOW = adalimumab 40 mg every other week;
40 MG EW = adalimumab 40 mg every week.

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).

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.

Paediatric Crohn's disease (≥ 6 years)

Adalimumab was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at week 0 and 80 mg at week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg. At week 4, subjects were randomised 1:1 based on their body weight at the time to either the low dose or standard dose maintenance regimens as shown in Table 35.

Table 35. 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

The primary endpoint of the study was clinical remission at week 26, defined as PCDAI score ≤ 10. Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 36. Rates of discontinuation of corticosteroids or immunomodulators and fistula remission (defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits) are presented in Table 37.

Table 36. 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 37. 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).

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 subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In Study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at weeks 0 and 2, 160 mg 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. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at week 8.

In study UC-II, 248 patients received 160 mg of 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 remission at week 8, 21/41 (51%) were in remission at week 52. Results from the overall UC-II study population are shown in Table 38.

Table 38. Response, remission and mucosal healing in study UC-II (% of patients)

	placebo	**adalimumab 40 mg fortnightly**
week 52	**N = 246**	**N = 248**
Clinical response	18%	30%*
Clinical remission	9%	17%*
Mucosal healing	15%	25%*
Steroid-free remission for ≥ 90 days[a]	6%(N = 140)	13% * (N = 150)
weeks 8 and 52		
Sustained response	12%	24%**
Sustained remission	4%	8%*
Sustained mucosal healing	11%	19%*

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

* p < 0.05 for 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

Statistically significant reductions of both all-cause and UC-related rates of hospitalisation were observed in a pooled analysis of studies UC I and II. Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

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

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

Quality of Life

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

Psoriasis

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

Ps Study I (M03-656) evaluated 1,212 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 MTX 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 MTX (see Table 39 and Table 40).

Table 39. Psoriasis study I (M03-656) Efficacy results at 16, 33, and 52 weeks (% of patients)

	Period A		Period B	Period C	
	Efficacy results at 16 weeks		Efficacy results at 33 weeks	Among PASI 75 responders at week 33, efficacy results at 52 weeks	
	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

PASI: Psoriatic Area and Severity Index

PGA: Physician's Global Assessment

[a] p < 0.001, adalimumab vs. placebo

Table 40. Psoriasis study II (M04-716) efficacy results at 16 weeks (% 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. MTX

[c] p < 0.01 adalimumab vs. placebo

[d] p < 0.05 adalimumab vs. MTX

MTX = 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 ≥ 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 week16, 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 clinical study did not include dose escalation to weekly dosing. Nail psoriasis assessments included the modified Nail Psoriasis Severity Index (mNAPSI)

and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). Of those who continued to receive adalimumab treatment until week 52, 71.4% achieved mNAPSI 75 response and 57.1% achieved PGA-F response (see Table 41).

Table 41. Psoriasis study IV (M13-674) efficacy results at 26 weeks

	placebo N = 108	**adalimumab 40 mg fortnightly N = 109**
≥ mNAPSI 75 (%)	3.4	46.6[a]
PGA-F clear/minimal and ≥ 2-grade improvement (%)	6.9	48.9[a]
Percent Change in Total Fingernail NAPSI (%)	-11.5	-56.2[a]
mNAPSI = 0 (%)	0	6.6[b]
Change in Nail Pain Numeric Rating Scale	-1.1	-3.7[a]
Change in Nail Psoriasis Physical functioning severity score	-0.8	-3.7[a]
	N = 12	**N = 18**
B-SNIPI50 Scalp (%)	0.4	58.3[b]

mNAPSI: modified Nail Psoriasis Severity Index

PGA-F: Physician's Global Assessment of Fingernail Psoriasis

B-SNIPI: Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index

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

[b] $p < 0.05$, adalimumab vs. placebo

Adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA ≥ 10% and BSA < 10% and ≥ 5%) and a statistically significant improvement in scalp psoriasis compared with placebo. The percent improvement in NAPSI was also statistically significantly greater in 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 statistically significant improvements at week 26 from baseline compared with placebo in the DLQI.

Paediatric plaque psoriasis (≥ 4 years)

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 MTX 0.1 to 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 (see Table 42).

Table 42. Paediatric plaque psoriasis efficacy results at 16 weeks

	MTX[a] weekly 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%)

PASI: Psoriatic Area and Severity Index

PGA: Physician's Global Assessment

[a] MTX = methotrexate 0.1 to 0.4 mg/kg weekly (up to 25 mg)

[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 and responses observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

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

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

Similarity of AMGEVITA with Humira in Psoriasis

The efficacy and safety of AMGEVITA were assessed in a randomised active control, double blind study in 350 patients ≥ 18 years of age with moderate to severe plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy. Patients had stable moderate to severe plaque Ps for at least 6 months, a body surface area (BSA) ≥ 10%, and Psoriasis Area and Severity Index (PASI) ≥ 12 at study entry. The patients received AMGEVITA or adalimumab at an initial loading dose of 80 mg administered SC on week 1/day1, followed by 40 mg SC given every other week starting one week after the loading dose. The PASI percent improvement from baseline was measured and compared with adalimumab (see Table 43) and it was within the prespecified equivalence margin to demonstrate clinical equivalence between AMGEVITA and adalimumab.

Table 43. AMGEVITA and Humira efficacy results at week 16 in psoriasis study 1

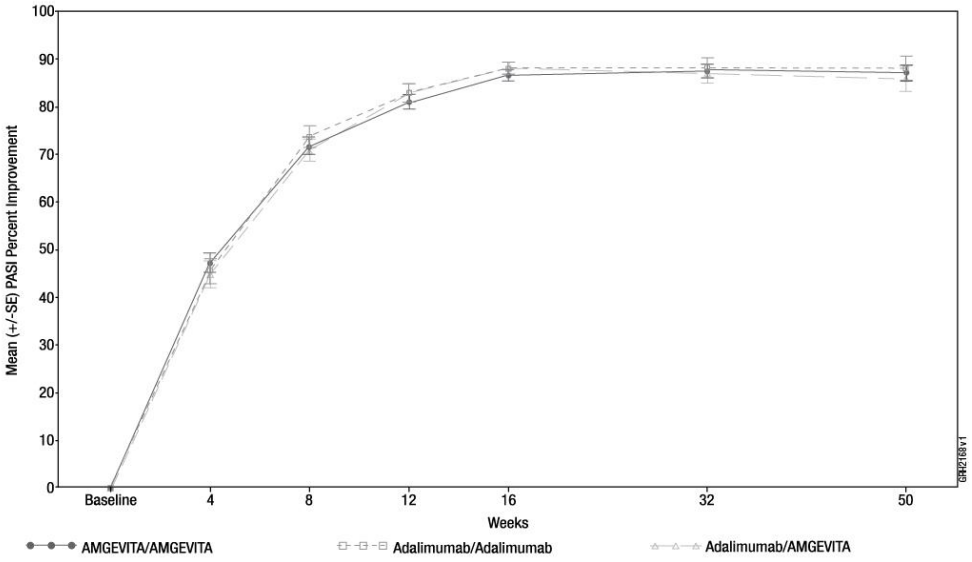
	AMGEVITA (N = 175)	**Humira (N = 175)**
PASI % Improvement from baseline	80.91	83.06

The primary endpoint was PASI percent improvement from baseline to week 16. At week 16, the PASI percent improvement from baseline was 80.9 in the AMGEVITA group and 83.1 in the adalimumab group. The least squares (LS) mean difference of PASI percent improvement from baseline to week 16 between AMGEVITA and adalimumab was -2.18 with the 2 sided 95% CI of (-7.39, 3.02). The 95% CI was within the predefined equivalence margin, thus demonstrating clinical equivalence of AMGEVITA and adalimumab.

After subjects with a PASI 50 response (50% or better improvement) were re-randomised at week 16 to continue on study, similar results were observed at week 50 (end of study), where the mean PASI percent improvement from baseline was similar across the treatment groups: AMGEVITA/AMGEVITA was 87.16; adalimumab/adalimumab was 88.11, and adalimumab/AMGEVITA was 85.82.

The mean PASI percent improvement from baseline over the duration of the study is shown in Figure 8.

Figure 8. Mean PASI Percent improvement from baseline over the duration of Amgevita/Humira psoriasis study 1



AMGEVITA/AMGEVITA = AMGEVITA/AMGEVITA arm;
Adalimumab/Adalimumab = Humira/Humira arm;
Adalimumab/AMGEVITA = Humira/AMGEVITA arm

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 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. 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 44). Patients treated with adalimumab had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 44. Efficacy results at 12 weeks, HS Studies I and II

Endpoint	HS Study I		HS Study II	
	placebo	**adalimumab 40 mg weekly**	**placebo**	**adalimumab 40 mg weekly**
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%)**

HiSCR: Hidradenitis Suppurativa Clinical Response

* $p < 0.05$; ** $p < 0.001$, adalimumab versus placebo

[a] Among all randomised patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on the numeric rating scale: 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

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

Greater improvements at week 12 from baseline compared to placebo were demonstrated in skin- specific health-related quality of life, as measured by the Dermatology Life Quality

Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

Adolescents

There are no clinical trials in adolescent patients with hidradenitis suppurativa (HS). Efficacy of 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. The recommended adolescent HS dosing schedule of 40 mg fortnightly is predicted to provide similar efficacy to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see Section 5.2 Pharmacokinetic properties).

Uveitis

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg fortnightly starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by week 15.

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

Clinical results

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo

(see Table 45). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see Figure 9 and Figure 10).

Table 45. Time to Treatment Failure in UV studies I and II

Analysis treatment	N	Failure N (%)	Median time to failure (months)	HR[a]	CI 95% for HR[a]	p value[b]
Time to treatment failure at or after week 6 in UV study I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	-	-	-
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to treatment failure at or after week 2 in UV study II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	-	-	-
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

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

CI: Confidence interval

HR: Hazard ratio

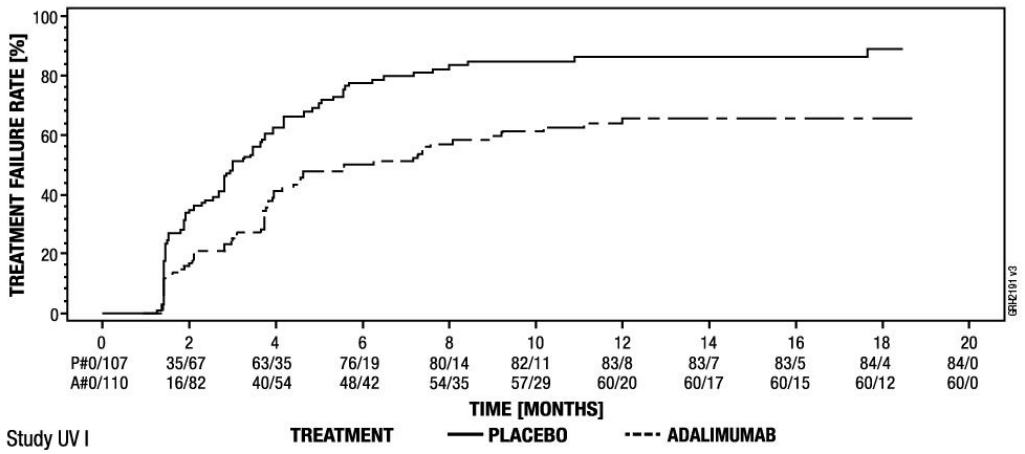
ITT: intention-to-treat

[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

[b] 2-sided p value from log rank test.

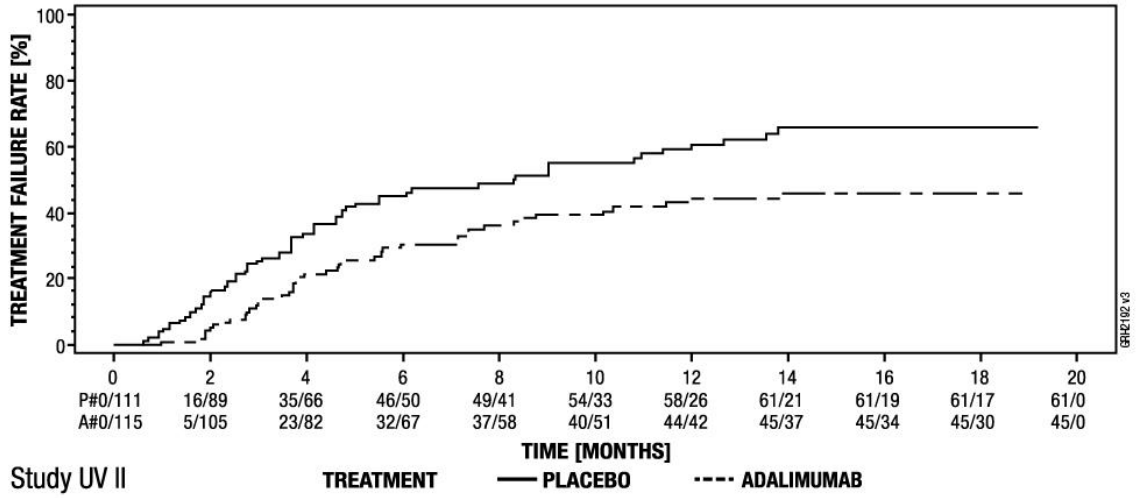
[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 9. Kaplan-Meier curves summarising time to treatment failure on or after week 6 (Study UV I)



Note:
P# = placebo (number of events/number at risk);
A# = adalimumab (Number of Events/ Number at Risk);

Figure 10. Kaplan-Meier curves summarising time to treatment failure on or after week 2 (study UV II)



Note:
P# = placebo (number of events/number at risk);
A# = adalimumab (number of events/ number at risk);

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

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

Quality of life

Patient reported outcomes regarding vision related functioning were measured in both clinical studies, using the NEI VFQ-25. Adalimumab was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision

and mental health in Study UV II. Vision related effects were not numerically in favour of adalimumab for colour vision in Study UV I and for colour vision, peripheral vision and near vision in Study UV II.

Paediatric uveitis

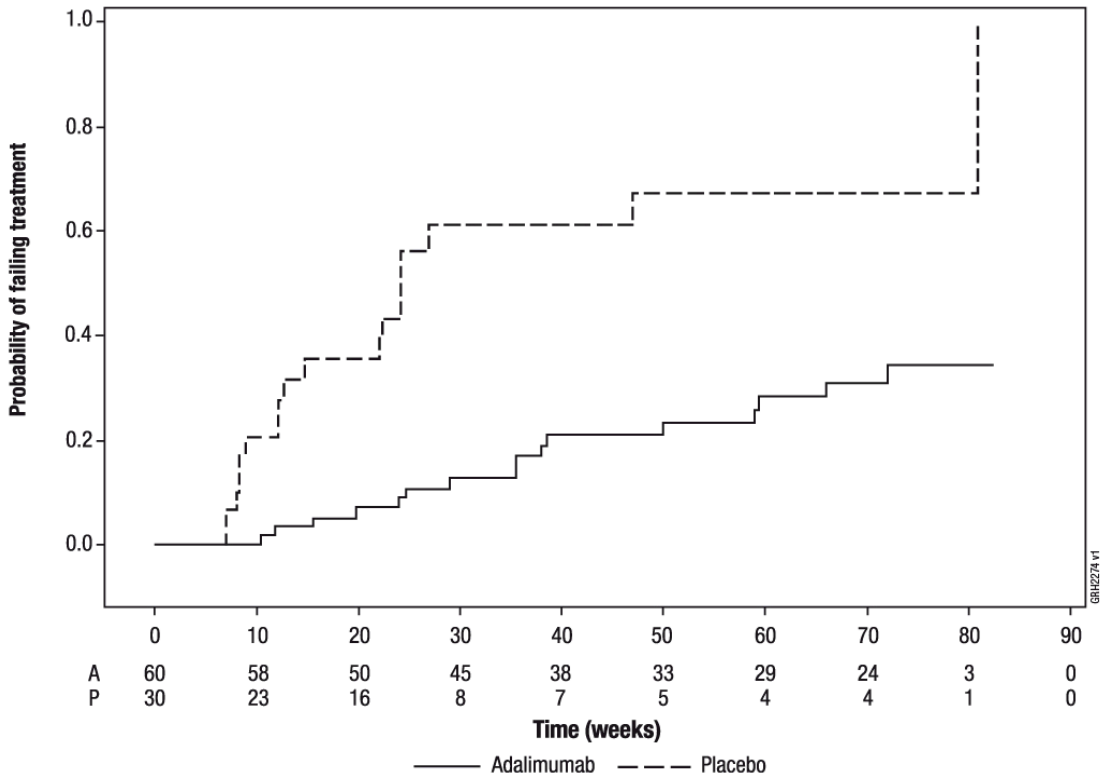
The safety and efficacy of adalimumab was assessed in a randomised, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated non- infectious anterior uveitis who were refractory to at least 12 weeks of MTX treatment. Patients received either placebo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

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

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (see Figure 11, $p < 0.0001$ from log rank test). The median time to treatment failure was 24.1 weeks for patients treated with placebo, whereas the median time to treatment failure was not estimable for patients treated with Humira because less than one-half of these patients experienced treatment failure. Humira significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 11. Kaplan-Meier curves summarising time to treatment failure in the paediatric uveitis study



Paediatric Ulcerative Colitis

The safety and efficacy of adalimumab was assessed in a multicentre, randomised, double-blind, trial in 93 paediatric patients from 5 to 17 years of age with moderate to severe ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3 points, confirmed by centrally read endoscopy) who had an inadequate response or intolerance to conventional therapy. Approximately 16% of patients in the study had failed prior anti-TNF treatment. Patients who received corticosteroids at enrolment were allowed to taper their corticosteroid therapy after week 4.

In the induction period of the study, 77 patients were randomised 3:2 to receive double-blind treatment with adalimumab at an induction dose of 2.4 mg/kg (up to a maximum of 160 mg) at week 0 and week 1, and 1.2 mg/kg (up to a maximum of 80 mg) at week 2; or an induction dose of 2.4 mg/kg (up to a maximum of 160 mg) at week 0, placebo at week 1, and 1.2 mg/kg (maximum dose of 80 mg) at week 2. Both groups received 0.6 mg/kg (maximum dose of 40 mg) at week 4 and week 6. Following an amendment to the study design, the remaining 16 patients who enrolled in the induction period received open-label treatment with adalimumab at the induction dose of 2.4 mg/kg (up to a maximum of 160 mg) at week 0 and week 1, and 1.2 mg/kg (up to a maximum of 80 mg) at week 2.

At week 8, 62 patients who demonstrated clinical response per Partial Mayo Score (PMS; defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) were randomised equally to receive double-blind maintenance treatment at a dose of 0.6 mg/kg (maximum of 40 mg) every week, or a maintenance dose. of 0.6 mg/kg (maximum dose of 40 mg) fortnightly. Prior to an amendment to the study design, 12 additional patients who demonstrated clinical response per PMS were randomised to receive placebo but were not included in the confirmatory analysis of efficacy.

Disease flare was defined as an increase in PMS of 3 points (for patients with PMS of 0 to 2 at week 8), 2 points (for patients with PMS of 3 to 4 at week 8), or 1 point (for patients with PMS of 5 to 6 at week 8). Patients who met criteria for disease flare at or after week 12 were randomised to receive a re-induction dose of 2.4 mg/kg (maximum dose of 160 mg) or a dose of 0.6 mg/kg (maximum dose of 40 mg) and continued to receive their respective maintenance dose regimen afterwards.

Efficacy Results

The co-primary endpoints of the study were clinical remission per PMS (defined as PMS ≤ 2 and no individual subscore > 1) at week 8, and clinical remission per FMS (Full Mayo Score) (defined as a Mayo Score ≤ 2 and no individual subscore > 1) at week 52 in patients who achieved clinical response per PMS at week 8.

Clinical remission rates per PMS were compared to external placebo at week 8 for patients in each of the adalimumab double-blind induction groups, and for the combined double-blind induction dose groups (Table 46).

Table 46. Paediatric Ulcerative Colitis: Clinical remission per Partial Mayo Score at 8 weeks

	External placebo	adalimumab[a] maximum of 160 mg at week 0/ placebo at week 1	adalimumab[b, c] maximum of 160 mg at weeks 0 and 1	Combined adalimumab induction dose groups[c]
Clinical remission	19.83%	13/30 (43.3%)	28/47 (59.6%)[d]	41/77 (53.2%)[d]

[a] Humira 2.4 mg/kg (max of 160 mg) at week 0, placebo at week 1, and 1.2 mg/kg (max of 80 mg) at week 2

[b] Humira 2.4 mg/kg (max of 160 mg) at week 0 and week 1, and 1.2 mg/kg (max of 80 mg) at week 2

[c] Not including open-label Induction dose of adalimumab 2.4 mg/kg (max of 160 mg) at week 0, placebo at week 1, 1.2 mg/kg (max of 80 mg) at week 2, and 0.6 mg/kg (max of 40 mg) at weeks 4 and 6

[d] Statistically significant vs. External placebo

Note 1: Both induction groups received 0.6 mg/kg (maximum dose of 40 mg) at weeks 4 and 6

Note 2: Patients with missing values at Week 8 were considered as not having met the endpoint

At week 52, clinical remission per FMS in week 8 responders, clinical response per FMS (defined as a decrease in Mayo score ≥ 3 points and ≥ 30% from baseline) in week 8

responders, mucosal healing (defined as Mayo endoscopy subscore ≤ 1) in week 8 responders, clinical remission per FMS in week 8 remitters, and the proportion of subjects in corticosteroid-free remission per FMS in week 8 responders were assessed in patients who received Humira at the double-blind max 40 mg fortnightly (0.6 mg/kg) and max 40 mg weekly (0.6 mg/kg) maintenance doses, and for the combined double-blind maintenance groups (Table 47).

Table 47. Paediatric Ulcerative Colitis: efficacy results at 52 weeks

	External Placebo	**adalimumab[a] maximum of 40 mg fortnightly**	**adalimumab[b] maximum of 40 mg weekly**	**Combined adalimumab maintenance dose groups**
Clinical remission in week 8 PMS responders	18.37%	9/31 (29.0%)	14/31 (45.2%)[c]	23/62 (37.1%)[c]
Clinical response in week 8 PMS responders	26.10%	19/31 (61.3%)[c]	21/31 (67.7%)[c]	40/62 (64.5%)[c]
Mucosal healing in week 8 PMS responders	22.03%	12/31 (38.7%)	16/31 (51.6%)[c]	28/62 (45.2%)[c]
Clinical remission in week 8 PMS remitters	14.79%	9/21 (42.9%)	10/22 (45.5%)[c]	19/43 (44.2%)[c]
Corticosteroid-free remission in week 8 PMS responders[d]	24.08%	4/13 (30.8%)	5/16 (31.3%)	9/29 (31.0%)

Note: Patients with missing values at week 52 or who received re-induction treatment were considered non-responders for week 52 endpoints

PMS Partial Mayo Score

[a] Humira 0.6 mg/kg (max of 40 mg) every other week

[b] Humira 0.6 mg/kg (max of 40 mg) every week

[c] Statistically significant vs. External Placebo

[d] In patients receiving concomitant corticosteroids at baseline

Additional exploratory efficacy endpoints included clinical response per the paediatric Ulcerative Colitis Activity Index (PUCAI) (defined as a decrease in PUCAI ≥ 20 points from Baseline) and clinical remission per PUCAI (defined as PUCAI < 10) at week 8 and week 52. The number of adalimumab treated patients in clinical response per PUCAI at week 8 and week 52 were 47/77 (61.0%) and 34/62 (54.8%), respectively, and in clinical remission per PUCAI at week 8 and week 52 were 32/77 (41.6%) and 32/62 (51.6%), respectively.

Of the adalimumab-treated patients who received re-induction treatment during the maintenance period, 2/6 (33%) achieved clinical response per FMS at week 52.

Quality of Life

Clinically meaningful improvements from baseline were observed in IMPACT III and the caregiver Work Productivity and Activity Impairment (WPAI) scores for the groups treated with adalimumab.

Clinically meaningful increases (improvement) from Baseline in height velocity were observed for the groups treated with adalimumab, and clinically meaningful increases (improvement) from Baseline in Body Mass Index were observed for subjects on the adalimumab maintenance dose of Maximum 40 mg (0.6 mg/kg) weekly.

Immunogenicity

Patients in rheumatoid arthritis studies I, II, and III were tested at multiple time points for anti- adalimumab antibodies during the 6 to 12 month period. Approximately 5.5% (58 of 1,062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titre anti-adalimumab antibodies at least once during treatment, which were neutralising in vitro. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab without concomitant MTX (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. Without concomitant MTX, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg fortnightly without concomitant MTX, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

In the patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, a greater percentage of patients developed anti-adalimumab antibodies compared to adult rheumatoid arthritis patients. Antibody formation was lower when adalimumab was given together with MTX in comparison to use without concomitant MTX. 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 MTX, the incidence was 25.6% (22/86), compared to 5.9% (5/85) when adalimumab was used as an add-on to MTX.

In patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years old or aged 4 and above weighing < 15 kg, anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant MTX.

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 MTX, the incidence was 14% (3/22), compared to 8% (2/24) when adalimumab was used as an add-on to MTX.

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

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

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

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

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

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

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

In patients with moderately to severely active paediatric ulcerative colitis, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3%.

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

Immunogenicity of AMGEVITA

RA data with AMGEVITA

Differences in assay methodology for measuring immunogenicity prevents direct comparison of immunogenicity rates between AMGEVITA and adalimumab or other biologics in different studies. In RA ABP Study 1, binding ADA activity was determined

using a bridging immunoassay and the neutralising ADA activity was determined using a ligand binding assay.

Patients in RA ABP Study 1 were tested at multiple time points for antibodies to adalimumab and AMGEVITA during the 26 week study period. The incidence of developing binding antibodies was 38.3% (101/264) in the AMGEVITA group and 38.2% (100/262) in the adalimumab group; the incidence of developing neutralising antibodies was 9.1% (24/264) in the AMGEVITA group and 11.1% (29/262) in the adalimumab group. Based on the data from RA AMGEVITA/Humira Study 1, the immunogenicity profile of AMGEVITA was found to be similar to adalimumab.

Psoriasis data with AMGEVITA

Differences in assay methodology for measuring immunogenicity prevents direct comparison of immunogenicity between AMGEVITA and adalimumab or other biologics in different studies. In Ps ABP Study 1, binding ADA activity was determined using a bridging immunoassay and the neutralising ADA activity was determined using a ligand binding assay.

Patients in Ps ABP Study 1 were tested at multiple time points for antibodies to adalimumab and AMGEVITA during the 52 week study period. The incidence of developing binding antibodies through the duration of the entire study was 68.4% (104/152) in the AMGEVITA/AMGEVITA group, 74.7% (59/79) in the adalimumab/adalimumab group, and 72.7% (56/77) in the adalimumab/AMGEVITA group; the incidence of developing neutralising antibodies was 13.8% (21/152) in the AMGEVITA/AMGEVITA group, 20.3% (16/79) in the adalimumab/adalimumab group, and 24.7% (19/77) in the adalimumab/AMGEVITA group. The adalimumab/AMGEVITA group reflects data for subjects exposed to both adalimumab and AMGEVITA before and after the transition of adalimumab subjects to AMGEVITA. The safety and immunogenicity profiles of patients who transitioned from adalimumab to AMGEVITA were comparable to those who continued on adalimumab until the end of the study (week 52).

5.2 Pharmacokinetic properties

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption of adalimumab was slow, with mean peak serum concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab was linear over the dose range of 0.5 to 10 mg/kg following a single intravenous dose.

Distribution and Elimination

The single dose pharmacokinetics of adalimumab in rheumatoid arthritis (RA) patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (Vss) ranged from 4.7 to 6.0 L. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-State

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab fortnightly to patients with RA, with mean steady-state trough concentrations of approximately 5 microgram/mL (without concomitant methotrexate (MTX)) and 8 to 9 microgram/mL (with concomitant MTX), respectively. These trough concentration levels are well above the EC50 estimates of 0.8 to 1.4 microgram/mL and consistent with those at which ACR20 responses appear to reach a maximum (Figure 1). The serum adalimumab trough levels at steady-state increased approximately proportionally with dose following 20, 40 and 80 mg fortnightly and every week SC dosing. In long-term studies with dosing for more than two years, there was no evidence of changes in clearance over time.

In patients with psoriasis, the mean steady-state trough concentration was 5 microgram/mL during adalimumab 40 mg fortnightly without concomitant MTX 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 microgram/mL at week 2 and week 4. The mean steady-state trough concentrations at week 12 through week 36 were approximately 8 to 10 microgram/mL during adalimumab 40 mg every week treatment.

In patients with Crohn’s disease, the loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 12 microgram/mL at weeks 2 and 4. The mean steady-state trough concentration at weeks 24 and 56 were 6.6 microgram/mL and 7.2 microgram/mL respectively. The range of trough concentrations in patients who received a maintenance dose of 40 mg adalimumab every fortnight was 0 to 21.7 microgram/mL.

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

approximately 12 microgram/mL during the induction period. Mean steady-state trough levels of approximately 8 microgram/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab fortnightly.

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

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

Population pharmacokinetic analyses with data from over 1,200 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 (13.1 mL/hr at 4 weeks) vs. long term (16.8 mL/hr at 56 weeks).

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

Pharmacokinetics (PK) in Special Populations

Pharmacokinetics in special populations were investigated using population PK analyses.

Elderly

Adalimumab's apparent clearance decreases slightly with increasing age. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n = 850) and ≥ 65 years (n = 287) were 0.33 and 0.30 mL/h/kg, respectively.

Paediatrics

Polyarticular juvenile idiopathic arthritis

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 MTX or with concomitant MTX were 6.8 microgram/mL and 10.9

microgram/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥ 30 kg receiving 40 mg adalimumab subcutaneously fortnightly without concomitant MTX or with concomitant MTX were 6.6 microgram/mL and 8.1 microgram/mL, respectively. In pJIA Study II for patients with polyarticular JIA who were 2 to < 4 years old, or aged 4 and above weighing < 15 kg, the mean trough steady-state serum adalimumab concentrations for patients receiving adalimumab subcutaneously fortnightly was 6.0 ± 6.1 microgram/mL (101% CV) for adalimumab without concomitant MTX, and 7.9 ± 5.6 microgram/mL (71.2% CV) with concomitant MTX.

Enthesitis-related arthritis

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

Crohn's disease

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

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

Chronic plaque psoriasis

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

Adolescent hidradenitis suppurativa

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

Ulcerative colitis

Following the subcutaneous administration of body weight-based dosing of 0.6 mg/kg (maximum dose of 40 mg) every other week to paediatric patients with ulcerative colitis, the mean trough steady-state serum adalimumab concentration was 5.01±3.28 µg/mL at week 52. For patients who received 0.6 mg/kg (maximum dose of 40 mg) every week, the mean (±SD) trough steady-state serum adalimumab concentrations were 15.7±5.60 µg/mL at week 52.

Uveitis

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

Gender

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

Race

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

Renal Impairment

No pharmacokinetic data are available in patients with renal impairment.

Hepatic Impairment

No pharmacokinetic data are available in patients with hepatic impairment.

Disease States

Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Drug Interactions - Methotrexate (MTX)

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

5.3 Preclinical safety data

Carcinogenicity

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

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, polysorbate 80, glacial acetic acid, sodium hydroxide (for pH adjustment), and Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

Do **not** use if it has been thawed from frozen.

Do **not** use beyond the expiration date.

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

The date of removal from the refrigerator should be recorded on the Instructions for Use leaflet, to allow the pre-filled syringe or pre-filled pen to be discarded after the maximum 14 days if not used.

6.5 Nature and contents of container

AMGEVITA 20 mg solution for injection in single-use pre-filled syringe:

AMGEVITA solution for injection for paediatric use is supplied as a sterile solution of 20 mg adalimumab in 0.4 mL sterile solution for subcutaneous administration in the following pack configuration(s):

- Carton containing 1 pre-filled syringe
- Carton containing 2 pre-filled syringes*

AMGEVITA 40 mg solution for injection in single-use pre-filled syringe (for patient use):

AMGEVITA solution for injection in pre-filled syringes are supplied as a sterile solution of 40 mg adalimumab in 0.8 mL sterile solution for subcutaneous administration in the following pack configurations.

- Carton containing 1 pre-filled syringe*
- Carton containing 2 pre-filled syringes
- Carton containing 4 pre-filled syringes*
- Carton containing 6 pre-filled syringes*

AMGEVITA 40 mg solution for injection in single-use pre-filled pen (for patient use):

AMGEVITA solution for injection in pre-filled pens are supplied as a sterile solution of 40 mg adalimumab in 0.8 mL sterile solution for subcutaneous administration in the following pack configurations.

- Carton containing 1 pre-filled pen*
- Carton containing 2 pre-filled pens
- Carton containing 4 pre-filled pens*
- Carton containing 6 pre-filled pens*

* Not all presentations may be marketed.

The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex) – see section 4.4 Special warnings and Precautions for use.

6.6 Special precautions for disposal <and other handling>

Prior to subcutaneous administration, allow the AMGEVITA pre-filled syringe or pre-filled pen to sit at room temperature for 15-30 minutes. Do not warm in any other way.

Avoid vigorous shaking of the product.

Visually inspect the solution for particles and discolouration. Do not use if the solution is discoloured, cloudy, or if flakes or particles are present.

AMGEVITA does not contain preservatives. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Amgen (New Zealand) Limited
Level 22, PwC Tower, 15 Customs Street West
AUCKLAND 1010 NEW ZEALAND
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9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 05 September 2019

10. DATE OF REVISION OF THE TEXT

23 April 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Update to table 10 to include autoimmune hepatitis. Amended paragraph under ‘Liver Enzyme Elevations’ section. Editorial changes to section on reporting of suspected adverse reactions.
5.1	Editorial changes to tables and figures

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