AUSTRALIAN PRODUCT INFORMATION – AMGEVITA® (ADALIMUMAB) SOLUTION FOR SUBCUTANEOUS INJECTION

1. NAME OF THE MEDICINE

Adalimumab.

AMGEVITA is a biosimilar medicine to the reference product Humira® (adalimumab). The evidence for comparability supports the use of AMGEVITA for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMGEVITA (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 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

AMGEVITA 20 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains adalimumab 20 mg in 0.4 mL solution (50 mg/mL).

Each pre-filled syringe contains adalimumab 20 mg in 0.2 mL solution (100 mg/mL).

AMGEVITA 40 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains adalimumab 40 mg in 0.8 mL solution (50 mg/mL).

Each pre-filled syringe contains adalimumab 40 mg in 0.4 mL solution (100 mg/mL).

AMGEVITA 40 mg solution for injection in pre-filled pen

Each pre-filled pen contains adalimumab 40 mg in 0.8 mL solution (50 mg/mL).

Each pre-filled pen contains adalimumab 40 mg in 0.4 mL solution (100 mg/mL).

AMGEVITA 80 mg solution for injection in pre-filled pen

Each pre-filled pen contains adalimumab 80 mg in 0.8 mL solution (100 mg/mL).

Excipients

AMGEVITA contains no antimicrobial agent. For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

AMGEVITA is a sterile, preservative free solution of adalimumab for subcutaneous administration. The solution of AMGEVITA is a clear liquid with a pH of 5.2. AMGEVITA is supplied as either a single use pre-filled glass syringe or as a single use pre-filled SureClick® pen. Enclosed within the pre-filled pen is a single use, pre-filled glass syringe.

The presentation for paediatric use contains 20 mg adalimumab per 0.4 mL (50 mg/mL) or 20 mg adalimumab per 0.2 mL (100 mg/mL). The adult presentations contain 40 mg adalimumab per 0.8 mL (50 mg/mL), 40 mg adalimumab per 0.4 mL (100 mg/mL) or 80 mg adalimumab per 0.8 mL (100 mg/mL).

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 RA. 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 pJIA in patients 2 years of age and older who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). 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 ERA in children, 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 moderately to severely active PsA 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 AS.

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

AMGEVITA is indicated for the treatment of moderate to severe CD, 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,
- lost response to or are intolerant of infliximab.

Ulcerative colitis (UC)

AMGEVITA is indicated for the treatment of moderate to severe UC in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have

medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see section 5.1 Pharmacodynamic properties - Clinical trials).

Psoriasis (Ps) in children 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 adults and adolescents (from 12 years of age)

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 pan-uveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.

4.2 Dose and method of administration

Dosage (dose and interval)

Rheumatoid arthritis

The recommended dose of AMGEVITA for adult patients with RA 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 40 mg every week, or 80 mg fortnightly.

Juvenile idiopathic arthritis

The recommended dose of AMGEVITA for patients 2 years of age and older with pJIA and ERA is based on weight as shown in Table 1 below. MTX, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with AMGEVITA.

Table 1. Dose regimen for Juvenile idiopathic arthritic patients (2 years of age and older) based on body weight

Body weight of paediatric patients	Dose
10 kg to <30 kg	20 mg fortnightly (20 mg Pre-filled Syringe)
≥ 30 kg	40 mg fortnightly (40 mg Pre-filled Pen or Pre-filled Syringe)

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

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 ERA aged less than 6 years or any child weighing less than 10 kg.

Psoriatic arthritis

The recommended dose of AMGEVITA for patients with PsA 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 AS 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.

Crohn's disease

Children and adolescents (6 to 17 years)

The recommended dose of AMGEVITA for patients from 6 to 17 years of age with CD is given in Table 2.

Table 2. Recommended dose regimen for children and adolescents (6 to 17 years of age) with Crohn's Disease

Patients < 40 kg body weight		
Therapy	**Moderate to severe CD**	**Frequency**
Induction	80 mg	Initial Dose (Day 0) given as one 80 mg injection **OR** two 40 mg injections in one day
	40 mg	Second Dose (Day 14) given in one day as **either**: one 40 mg injection **OR** two 20 mg injections.
Maintenance*	20 mg	One 20 mg injection starting Day 28 & continuing fortnightly
Patients ≥ 40 kg body weight		
Therapy	**Moderate to severe CD**	**Frequency**
Induction	160 mg	Initial Dose (Day 0) given as two 80 mg injections in one day **OR** four 40 mg injections in one day **OR** as one 80 mg injection per day for two consecutive days **OR** two 40 mg injections per day for two consecutive days
	80 mg	Second Dose (Day 14) given as one 80 mg injection OR two 40 mg injections in one day
Maintenance*	40 mg	One 40 mg injection starting Day 28 & continuing fortnightly

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

- Patients < 40 kg body weight: 20 mg every week;
- Patients ≥ 40 kg body weight: 40 mg every week or 80 mg fortnightly.

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

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

The recommended AMGEVITA dose regimen for adult patients with CD is given in Table 3.

Table 3. Recommended dose regimen for adult patients with Crohn's Disease

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

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

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

Ulcerative colitis

The recommended AMGEVITA dose regimen for adult patients with UC is given in Table 4.

Table 4. Recommended dose regimen for adult patients with Ulcerative colitis

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

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg AMGEVITA every week, or 80 mg fortnightly.

AMGEVITA should not be continued in patients who do not achieve a clinical response in the first 8 weeks of treatment. The efficacy of AMGEVITA in the treatment of UC has not been demonstrated in patients who have failed previous anti-TNF therapy (see section 5.1 Pharmacodynamic properties, Clinical trials).

Psoriasis

Paediatric plaque psoriasis (4 to 17 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. Recommended dose regimen for patients with paediatric plaque psoriasis(4 to 17 years) based on body weight

Paediatric Patients (4 years of age and older)	Dose
< 40 kg	20 mg fortnightly (20 mg Pre-filled Syringe)
≥ 40 kg	40 mg fortnightly (40 mg Pre-filled Pen or 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 aged less than 4 years in this indication.

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

Adults

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

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

Hidradenitis suppurativa

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

The recommended adalimumab dose is given in Table 6.

Table 6. Recommended dose regimen for adolescent patients (from 12 years of age, weighing at least 30 kg) with Hidradenitis suppurativa

Recommended Dose	Frequency
80 mg	Initial Dose (Day 0) given as one 80 mg injection **OR** two 40 mg injections
40 mg	Second Dose (Day 7) & continuing fortnightly

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

Antibiotics may be continued during treatment with adalimumab 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 adalimumab.

In patients without any benefit after 12 weeks of treatment, therapy should be discontinued (see section 5.1 Pharmacodynamic properties - Clinical trials).

Should treatment be interrupted, adalimumab 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 trials – HS adults).

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

<u>Adults</u>

The recommended adalimumab dose regimen for adult patients with HS is given in Table 7.

Table 7. Recommended dose regimen for adult patients with Hidradenitis suppurativa

Day	Recommended dose and frequency
1	160 mg given as two 80 mg injections in one day **OR** four 40 mg injections in one day **OR** as one 80 mg injection per day over two consecutive days **OR** two 40 mg injections per day for two consecutive days
15	80 mg given as one 80 mg injection **OR** two 40 mg injections
29	Continue with a dose of 40 mg every week or 80 mg fortnightly

Antibiotics may be continued during treatment with adalimumab if necessary. Should treatment need to be interrupted, adalimumab may be re-introduced. In patients without any benefit after 12 weeks of treatment, therapy should be discontinued.

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

Uveitis

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

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

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

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

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

Special populations

Use in hepatic impairment

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

Use in renal impairment

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

Paediatric use

Refer to the specific paediatric dosage information provided in the indication sections above.

Method of administration

AMGEVITA is for one dose in one patient only.

AMGEVITA is intended for use under the guidance and supervision of a physician. AMGEVITA is administered by subcutaneous injection. 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 the 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 contains no antimicrobial agent. Discard any residue (see section 6.6 Special precautions for disposal).

4.3 Contraindications

AMGEVITA should not be administered to patients with:

- known hypersensitivity to adalimumab or any of its excipients.
- severe infections including sepsis, active tuberculosis and opportunistic infections (see section 4.4 Special warnings and precautions for use).
- 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

In order to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.

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 adalimumab 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 adalimumab should be considered prior to initiating therapy (see Other opportunistic infections).

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

Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab 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 adalimumab 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, adalimumab 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 adalimumab, 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 adalimumab. 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, adalimumab therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of adalimumab in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of adalimumab 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, consult a physician with expertise in the treatment of tuberculosis. The benefit/risk balance of therapy with adalimumab should be very carefully considered.

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

Patients receiving adalimumab 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 adalimumab.

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

Haematologic events

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF blocking agents.   Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with adalimumab (see section 4.8 Adverse effects (Undesirable effects)).   The causal relationship of these reports to adalimumab remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor) while on adalimumab. Discontinuation of adalimumab 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 RA 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 sections 4.4 Special

warnings and precautions for use, Infections and 4.8 Adverse effects (Undesirable effects), Infections and Malignancies.)

Vaccinations

In a randomised, double-blind, placebo-controlled study in 226 adult RA 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 adalimumab 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 adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab 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 adalimumab therapy.

Congestive heart failure (CHF)

In a clinical trial with another TNF-antagonist, worsening CHF and increased mortality due to CHF were observed. Cases of worsening CHF have been reported in patients receiving adalimumab. Adalimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Adalimumab is contraindicated in moderate or severe heart failure (see section 4.3 Contraindications). Treatment with adalimumab 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 were observed among patients receiving a TNF-antagonist, including adalimumab, compared with control patients (see section 4.8 Adverse effects (Undesirable effects), Malignancies). However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk in RA patients with long-standing, highly active inflammatory disease, which complicates the risk estimation.

Very rare post marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and adalimumab should be carefully considered. The causal association of HSTCL with adalimumab is not clear.

With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

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

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving adalimumab. Thus, additional caution should be exercised in considering adalimumab treatment of 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 psoralen and ultraviolet A (PUVA) treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8 Adverse effects (Undesirable effects)).

Cases of acute and chronic leukaemia have been reported in association with post marketing TNF blocker use in RA and other indications. Patients with RA 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 UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC 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 adalimumab, treatment should be discontinued (see section 4.8 Adverse effects (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 (see section 5.2 Pharmacokinetic properties) if a surgical procedure is planned. A patient who requires surgery while on adalimumab should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab.

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

Of the total number of subjects in clinical studies of adalimumab 10.4% were 65 years and over, while approximately 2.2% were 75 and over. A total of 519 RA patients 65 years of age and older, including 107 patients 75 years and older, received adalimumab in clinical RA studies I-IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among adalimumab-treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly (see section 4.2 Dose and method of administration).

Paediatric use

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

Effects on laboratory tests

There is no known interference between Amgevita and laboratory tests.

4.5 Interactions with other medicines and other forms of interactions

Methotrexate (MTX)

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

TNF-antagonists or biologic DMARDS

Concurrent administration of AMGEVITA and anakinra (interleukin-1 receptor antagonist) is contraindicated (see section 4.3 Contraindications).

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effect of adalimumab on fertility has not been investigated.

Use in pregnancy

Category C

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to adalimumab *in utero* suggest it crosses the placenta. Consequently, these infants maybe at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

There are no adequate and well-controlled studies in pregnant women and therefore adalimumab should only be used during pregnancy if clearly needed. Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy, and continue contraception for at least 5 months after the last adalimumab treatment.

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

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

Although the registry has methodological limitations, including small sample size and non-randomised study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with

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

Also refer to section 5.3 Preclinical safety data – Animal studies.

Use in lactation

Limited information from three cases in the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown.

There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects on the breastfed child from adalimumab or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Clinical trials

Adalimumab was studied in 9316 patients in controlled and open-label trials. These trials included RA patients with short term and long-standing disease, JIA (pJIA and enthesitis-related arthritis) as well as PsA, AS, CD, UC, Ps, HS and uveitis patients. The pivotal controlled studies involved 5994 patients receiving adalimumab and 3704 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies across all indications was 5.9% for patients taking adalimumab and 5.5% for control-treated patients. The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of RA studies I, II, III and IV was 6.6% for patients taking adalimumab and 4.2% for placebo-treated patients.

Approximately 13% of patients can be expected to experience injection site reactions, based on the most common adverse event with adalimumab in controlled clinical studies. Undesirable effects in paediatric patients with polyarticular JIA: In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Adverse events at least possibly causally-related to adalimumab for clinical studies, both clinical and laboratory, are displayed by system organ class and frequency:

very common ≥ 1/10;

common ≥ 1/100 to <1/10;

uncommon ≥ 1/1000 to < 1/100 and

rare ≥ 1/10000 to < 1000.

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

Table 8 contains adverse 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 clinical studies

System organ class [a]	Frequency	Adverse reaction [a]
Infections and infestations	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	Lymphoma*, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma*
Blood and the lymphatic system disorders	Very common	Leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	Thrombocytopenia, leucocytosis
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders	Common	Hypersensitivity, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalemia, increased uric acid, abnormal serum sodium, hypocalcemia, hyperglycemia, hypophosphotemia, dehydration
Psychiatric disorders	Common	Mood alterations (including depression), anxiety, insomnia

System organ class [a]	Frequency	Adverse reaction [a]
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 (CHF)
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	Vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	Common	Cough, asthma, dyspnoea
	Uncommon	Chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	Pancreatitis, dysphagia, face oedema
Hepato-biliary disorders	Very common	Liver enzymes elevated
	Uncommon	Cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very Common	Rash (including exfoliative rash)
	Common	Pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis (e.g. nail disorders), hyperhydrosis
	Uncommon	Night sweats, scar
Musculoskeletal, connective tissue and bone 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

System organ class [a]	Frequency	Adverse reaction [a]
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

* including open-label extension studies

[a] MedDRA

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

Table 9. Adverse reactions reported by patients treated with adalimumab during placebo-controlled period of RA studies

System organ class[a]	Adverse reaction[a]	adalimumab (n = 1380) %	control (n = 690) %
Infections and infestations	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)	39	33
	Oral infections (including herpes simplex, oral herpes and tooth infections)	7	5
	Reproductive tract infections (including vulvovaginal mycotic infection)	3	1
Blood and the lymphatic system disorders	Anaemia	13	8
	Leucopenia (including neutropenia and agranulocytosis)	14	8
	Leucocystosis	1	0
	Thrombocytopenia	1	0
Metabolism and nutrition disorders	Lipids increased	17	8
	Uric acid increased	6	3
	Blood sodium abnormal	10	3
	Hypokalemia	3	2
	Hypophosphotemia	2	1
	Blood potassium increased	3	1
Nervous system disorders	Headache	14	8
Vascular disorders	Hypertension	6	3
	Flushing	2	1

System organ class[a]	Adverse reaction[a]	adalimumab (n = 1380) %	control (n = 690) %
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

[a] MedDRA

Study V (DE013)

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

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

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

Uveitis
The safety profile for patients with non-infectious uveitis treated with adalimumab 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 7.3% of patients receiving control treatments. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

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

In the controlled and open-label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most, but not all of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies
During the controlled portions of pivotal adalimumab trials in adults at least 12 weeks in duration in patients with moderately to severely active RA, PsA, AS, CD, UC, psoriasis, HS, and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% CI) of 6.9 (4.4, 10.6) per 1000 patients years among 5196 adalimumab-treated patients versus a rate of 6.4 (3.5, 11.9) per 1000 patient years among 3347 control patients (median duration of treatment was 4.0 months for adalimumab and 3.9 months for control-treated patients).

The rate (95% CI) of non-melanoma (basal cell and squamous cell) skin cancers was 8.9 (6.1, 13.1) per 1000 patient years among adalimumab-treated patients and 3.2 (1.3, 7.7) per 1000 patient years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% CI) of 2.7 (1.4, 5.5) per 1000 patient years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1000 patient years among control patients.

The rate (95% CI) of lymphomas was 0.7 (0.2, 2.7) per 1000 patient years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1000 patient years among control patients.

When combining controlled portions of these trials and ongoing open-label extension studies with a median duration of approximately 3.3 years including 6279 patients and over 26045 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.6 per 1000 patient years.

The observed rate of non-melanoma skin cancers is approximately 9.8 per 1000 patient years and the observed rate of lymphomas is approximately 1.3 per 1000 patient years.

No malignancies were observed in 217 paediatric patients with an exposure of 610.4 patient years during adalimumab trials in patients with pJIA and ERA. 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 CD.

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.

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

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

Autoantibodies
Patients had serum samples tested for autoantibodies at multiple time points in RA studies I-V. In these adequate and well-controlled trials, 11.9% of patients treated with 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, PsA, and AS studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown.

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

Liver Enzyme Elevations

RA and PsA clinical trials

In controlled Phase III trials of adalimumab (40 mg fortnightly), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g. NSAIDS, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear.

JIA clinical trials

In a controlled Phase III trial of adalimumab in patients with polyarticular JIA who were 4 to 17 years and ERA 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

III trial of adalimumab in patients with polyarticular JIA who were 2 to <4 years or aged 4 years and above weighing <15 kg.

AS clinical trials

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

HS clinical *trials*

In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with HS 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.

CD clinical trials

In controlled Phase III 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 CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of control-treated patients.

Paediatric CD clinical trials

In the Phase III trial of adalimumab in patients with paediatric CD 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.

UC clinical trials

In controlled Phase III 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 UC with a control period duration ranging from 1 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 1.5% of adalimumab-treated patients and 1.0% of control-treated patients.

Psoriasis clinical trials

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

Paediatric patients with plaque psoriasis clinical trials

No ALT elevations ≥ 3 x ULN occurred in the Phase III trial.

Uveitis clinical trials

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

In all indications patients with raised ALT were asymptomatic and, in most cases, elevations were transient and resolved on continued treatment. However, there have been very rare post marketing reports of severe hepatic reactions including liver failure 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 azathioprine/6-mercaptopurine compared with adalimumab alone.

Polyarticular Juvenile Idiopathic Arthritis clinical trials

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

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

In pJIA study I, 45% of patients experienced an infection while receiving adalimumab with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in pJIA 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 pJIA 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.

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

Approximately 15% of patients treated with adalimumab developed mild-to-moderate elevations of creatine phosphokinase (CPK) in pJIA study I. Elevations > 5 x ULN were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue adalimumab without interruption.

In pJIA study II, adalimumab was studied in 32 patients who were 2 to < 4 years of age or 4 years of age and older weighing < 15 kg with polyarticular JIA. Thirty-one of 32 patients (97%) received the required minimum of 24 weeks of adalimumab treatment. Patients were able to continue up to a maximum of 120 weeks of treatment. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In pJIA study II, 78% of patients experienced an infection while receiving adalimumab. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving adalimumab in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In pJIA study II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

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

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

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

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

Table 10. Additional adverse reactions from post marketing surveillance or phase IV clinical trials

Body System	Adverse Reaction
Infections and infestations	Diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Hepatosplenic T-cell lymphoma, leukaemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin), Karposi's sarcoma*
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

* occurring in patients receiving a TNF-antagonist including adalimumab

Comparability of AMGEVITA with Humira®

Both the AMGEVITA RA and Ps studies showed clinical equivalence between AMGEVITA and Humira (see section 5.1 Pharmacodynamic properties, Clinical trials). Table 11 and Table 12 below show comparative data for adverse events between AMGEVITA and Humira from the RA and Ps studies respectively.

The data in Table 11 reflects exposure to AMGEVITA in 264 subjects and Humira in 262 subjects in the RA study treated at the recommended dose and schedule for a median of 480 mg doses (see section 5.1 Pharmacodynamic properties, Clinical trials). 52.3% of all subjects had at least 1 treatment-emergent adverse event during the study, and similar proportions were reported in each treatment group (50.0% in AMGEVITA group and 54.6% in Humira group). The overall safety profile of AMGEVITA is similar to that of Humira.

Table 11. Adverse events reported by ≥ 2% of patients treated with AMGEVITA and Humira in RA study

Adverse events (preferred term)	AMGEVITA (n = 264)	Humira (n = 262)
Nasopharyngitis	6.4%	7.3%
Headache	4.5%	4.2%
Arthralgia	3.0%	3.4%
Cough	2.7%	3.1%
Upper respiratory tract infection	1.5%	3.8%
Hypertension	2.3%	1.9%
Bronchitis	2.3%	1.9%
Back pain	1.9%	2.3%
Alanine aminotransferase increased	2.7%	1.1%
Diarrhoea	2.3%	1.5%
Rheumatoid arthritis	1.5%	2.3%
Pharyngitis	0.8%	2.7%

The data in Table 12 reflects exposure to AMGEVITA/AMGEVITA in 152 subjects, Humira/Humira in 79 subjects, and Humira/AMGEVITA in 77 subjects in the Ps study treated at the recommended dose and schedule for a median of 1040 mg doses (see section 5.1 Pharmacodynamic properties, Clinical trials). 82.1% of subjects, from baseline to end of study, had at least 1 treatment emergent adverse event and similar proportions were reported across treatment groups (86.2% of subjects in Treatment Group A (AMGEVITA/AMGEVITA), 78.5% of subjects in Treatment Group B1 (Humira/Humira), and 85.7% of subjects in Treatment Group B2 (Humira/AMGEVITA).

The overall safety profiles of the AMGEVITA/AMGEVITA, Humira/Humira and Humira/AMGEVITA groups were similar.

Table 12. Adverse events reported by ≥ 2% of patients treated with AMGEVITA, adalimumab or adalimumab switched to AMGEVITA in psoriasis study

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%
Toothache	3.3%	2.5%	5.2%
Gastroenteritis	3.9%	2.5%	2.6%
Psoriatic arthropathy	2.6%	0.0%	2.6%
Sinusitis	2.6%	3.8%	2.6%
Abdominal pain	1.3%	2.5%	3.9%
Cough	2.0%	2.5%	3.9%
Pain in extremity	2.6%	3.8%	1.3%
Nausea	2.0%	1.3%	3.9%
Conjunctivitis	0.7%	3.8%	2.6%
Bronchitis	0.7%	0.0%	5.2%
Gamma-glutamyltransferase increased	3.9%	1.3%	0.0%
Pharyngitis	2.6%	2.5%	1.3%
Injection site pain	0.0%	5.1%	2.6%
Tonsillitis	2.0%	2.5%	0.0%
Dyspnoea	1.3%	1.3%	2.6%
Contusion	0.7%	0.0%	6.5%
Dermatitis contact	3.9%	0.0%	0.0%
Influenza	1.3%	1.3%	3.9%
Alanine aminotransferase increased	3.3%	0.0%	1.3%
Myalgia	2.6%	2.5%	0.0%
Oral herpes	1.3%	1.3%	2.6%
Blood pressure increased	1.3%	3.8%	0.0%
Musculoskeletal pain	0.7%	1.3%	2.6%

Adverse events (preferred term)	AMGEVITA/ AMGEVITA (n = 152)	Humira/ Humira (n = 79)	Humira/ AMGEVITA[a] (n = 77)
Dental caries	2.0%	2.5%	0.0%
Gastroeosophageal reflux disease	0.7%	1.3%	3.9%
Injection site reaction	1.3%	1.3%	2.6%
Seasonal allergy	2.0%	0.0%	2.6%
Depression	1.3%	2.5%	0.0%
Muscle spasm	2.6%	0.0%	0.0%
Urinary tract infection	1.3%	0.0%	2.6%
Dyspepsia	0.7%	2.5%	1.3%
Ligament strain	1.3%	2.5%	0.0%
Skin papilloma	0.7%	1.3%	2.6%
Injection site swelling	0.0%	1.3%	2.6%
Migraine	0.0%	2.5%	1.3%
Pulpitis dental	0.7%	0.0%	2.6%
Excoriation	0.7%	0.0%	2.6%
Intertrigo	0.7%	0.0%	2.6%
Spinal pain	0.0%	1.3%	2.6%
Thermal burn	0.7%	0.0%	2.6%
Tinea pedis	0.7%	2.5%	0.0%
Decreased appetite	0.0%	0.0%	2.6%
Neutropenia	0.0%	0.0%	2.6%
Cystitis	0.0%	2.5%	0.0%
Diffuse alopecia	0.0%	0.0%	2.6%
Hypercholesterolaemia	0.0%	0.0%	2.6%
Rhinorrhoea	0.0%	0.0%	2.6%
Urticaria	0.0%	0.0%	2.6%

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

Reporting of suspected adverse effects

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

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tumour necrosis factor alpha (TNF-alpha) inhibitors.
ATC code: L04AB04

Mechanism of action

Adalimumab binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of RA, including JIA, PsA and 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 (PD)

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

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR20) appears to follow the Hill E_{max} equation as shown in Figure 1.

Figure 1. Concentration-Efficacy Relationship
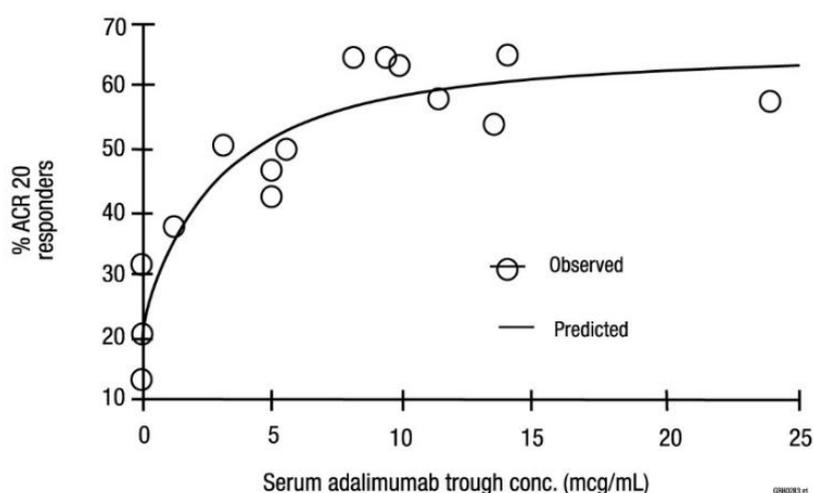
EC_{50} estimates ranging from 0.8 to 1.4 micrograms/mL (µm/mL) were obtained through PK/PD modelling of swollen joint count, tender joint count and ACR20 response from patients participating in Phase II and III trials.

Clinical trials

Clinical trials with Humira

Clinical trials for Rheumatoid arthritis (RA)

Adalimumab was evaluated in over 3000 patients in all RA 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 efficacy endpoint in those 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 adalimumab 20, 40 or 80 mg 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 adalimumab 20 or 40 mg 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 adalimumab 20 mg every week for 52 weeks. The third group received adalimumab 40 mg 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 adalimumab 40 mg/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 ≥ 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 adalimumab 40 mg or placebo fortnightly for 24 weeks.

RA study V (DE013) was an active comparator trial of 2 years duration, which randomised 799 adult MTX (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 adalimumab 40 mg 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 RA Studies I-V were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary endpoint in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR20 response at 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, 50 and 70 responses was consistent across all three trials. The results for the 40 mg fortnightly dose are summarised in Table 13.

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
ACR 20						
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%
ACR 50						
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%
ACR 70						
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] adalimumab 40 mg 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

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 (see Figure 2).

Figure 2. RA study II ACR20 responses over 26 weeks
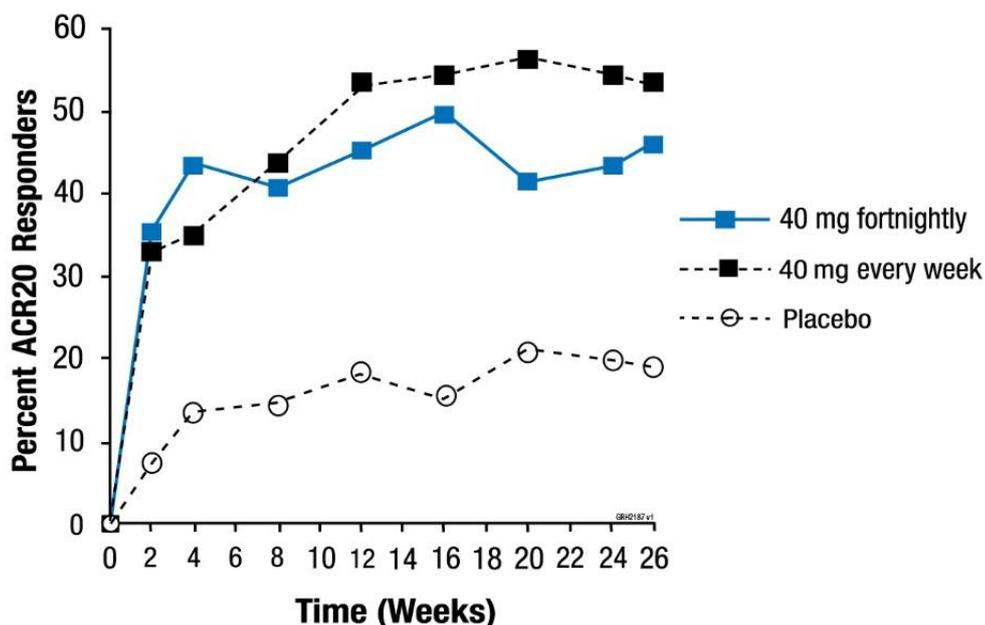
The results of the components of the ACR response criteria for RA study III are shown in Figure 3 and Table 14. ACR response rates and improvement in all ACR response criteria were maintained to week 104. Over the 2 years in RA study III, 20% of adalimumab patients achieved a major clinical response, 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-II			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. 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 2 and Figure 3 illustrate the durability of ACR20 responses to adalimumab in RA Studies II and III.

Figure 3. RA study III ACR20 responses over 52 weeks
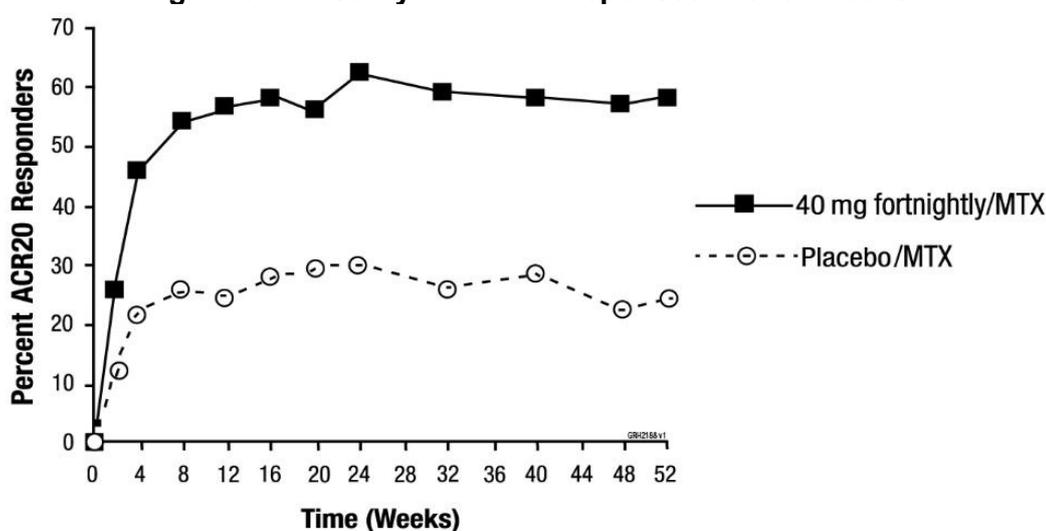
RA STUDY IV

The ACR20 response of patients treated with adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p<0.001). In RA Studies I-IV, adalimumab-treated patients achieved statistically significant ACR20 and 50 responses compared to placebo as early as 1-2 weeks after initiation of treatment.

RA STUDY V

In RA study V for early RA 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 > 6 continuous months) compared to 27.2% of patients who received MTX monotherapy (p<0.001).

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

Note: Subjects with missing values were counted as non-responders.
[a] p-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using 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

In the open-label extension for RA study V, ACR responses were maintained when followed for up to 10 years. However, no statistical hypothesis was tested in the OLE period. Of 542 patients who were randomised to adalimumab 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.

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 RA for approximately 11 years and a mean ± standard deviation baseline modified Total Sharp Score for the adalimumab 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).

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

Table 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% CI*)	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] adalimumab 40 mg administered fortnightly; [b] Based on rank analysis
MTX: Methotrexate; CI: confidence interval; *95% confidence intervals for the differences in change scores between MTX and adalimumab

In RA study V, adalimumab-treated patients had a mean duration of RA of less than 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.

Table 18. Change in Modified total sharp score from baseline at weeks 52 and104 (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) week 52 (mean) change at week 52 (mean ± SD)	21.8 ± 22.2 27.6 ± 24.6 5.7 ± 12.7	18.8 ± 19.0 21.8 ± 19.7 3.0 ± 11.2	18.1 ± 20.1 19.4 ± 19.9 1.3 ± 6.5	< 0.001	< 0.002
Week 104 baseline (mean) week 104 (mean) change at week 104 (mean ± SD)	21.8 ± 22.2 32.3 ± 30.0 10.4 ± 21.7	18.8 ± 19.0 24.3 ± 23.2 5.5 ± 15.8	18.1 ± 20.1 20.0 ± 20.5 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.

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

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

There were 619 patients enrolled in RA study III also known as the DE019 study. The patients were divided into three groups. The first group received placebo injections every week for 52 weeks. The second group received adalimumab 20 mg every week for 52 weeks. The third group received adalimumab 40 mg fortnightly with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase (DE019OLE) in which 40 mg of adalimumab/MTX was administered fortnightly. Maintenance of physical function was defined as maintaining a reduction in HAQ of -0.5 over the second year of active treatment.

Results

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

Table 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%)

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

Quality of life

Results from the Short Form Health Survey (SF-36) for all doses/schedules of adalimumab in all four studies support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the adalimumab 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 (measured by HAQ-DI response) were maintained through 10 years of treatment. No statistical hypothesis was tested in the OLE phase.

Clinical trials for polyarticular juvenile idiopathic arthritis (pJIA)

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

pJIA study I

The safety and efficacy of adalimumab were assessed in a multi-centre, randomised, withdrawal, double blind, parallel-group study in 171 patients (4 to 17 years of age) with

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/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) fortnightly. In the OLE-FD phase, the patients were treated with 20 mg of adalimumab SC fortnightly if their weight was less than 30 kg and with 40 mg of adalimumab SC fortnightly if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or 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 double blind phase significantly, fewer patients who received adalimumab experienced disease flare compared to placebo, both without MTX (43% vs. 71%) and with MTX (37% vs. 65%). More patients treated with adalimumab continued to show paediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of adalimumab and MTX compared to adalimumab alone.

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

pJIA study II

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

PJIA STUDY II CLINICAL RESPONSE

At week 12 and week 24, paediatric ACR 30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of patients with Paediatric ACR 50/70/90 at week 12 and week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Paediatric ACR 30) at week 24 (n = 27 out of 30 patients), the paediatric ACR 30 responses were maintained for up to 60 weeks in

patients who continued with adalimumab treatment throughout this time period. Overall, 20 patients were treated for 60 weeks or longer.

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

Clinical trials for enthesitis-related arthritis (ERA)

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind study (M11-328) in 46 paediatric patients (6 to 17 years old) with ERA. 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 adalimumab 24 mg/m^2 body surface area (BSA) 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 adalimumab 24 mg/m^2 BSA up to a maximum of 40 mg fortnightly subcutaneously for up to an additional 192 weeks.

The primary endpoint was the percent change from baseline to week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved (p = 0.039) with mean percent decrease of -62.6% in patients in the adalimumab group compared to -11.6% in patients in the placebo group. Decreases in the mean percent change from baseline in the number of active joints with arthritis was maintained through week 156 with a mean decrease from baseline of -88.3%. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count, swollen joint count, paediatric ACR 30 response, paediatric ACR 50 response, and paediatric ACR 70 response, and maintained these results during the OL period through week 156 of the study.

Clinical trials for psoriatic arthritis (PSA)

Adalimumab 40 mg fortnightly was studied in patients with moderately to severely active PsA 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 nonsteroidal 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 adalimumab 40 mg 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 20 and Table 21. Among patients with PsA 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 20. ACR and PASI response in placebo-controlled PsA study (% of patients)

Response*	placebo n = 162	adalimumab n = 151
ACR20		
week 12	14%	58%
week 24	15%	57%
ACR50		
week 12	4%	36%
week 24	6%	39%
ACR70		
week 12	1%	20%
week 24	1%	23%
	n = 69	**n = 69**
PASI 50		
week 12	15%	72%
week 24	12%	75%
PASI 75		
week 12	4%	49%
week 24	1%	59%

* p< 0.001 for all comparisons between adalimumab and placebo

Table 21. Components of disease activity in PsA

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

[a] As observed analysis presented. N at 24 weeks may be less than 162 for placebo or 151 for
  adalimumab.
[b] Scale 0 – 78
[c] Scale 0 – 76
[d] Visual analog scale; 0 = best, 100 = worst.
[e] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst; measures the patient's
  ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and
  maintain daily activity.
[f] Normal range: 0-2.87 mg/L.
*p< 0.001 for adalimumab vs. placebo comparisons based on mean changes.

Radiographic response
Radiographic changes were assessed in the PsA 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 RA), 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 22).

Table 22. Change in Modified total sharp score in PsA

	placebo	adalimumab
MODIFIED TOTAL SHARP SCORE*		
Baseline to week 24	*n = 162*	*n = 151*
baseline mean	19.0	22.6
mean change from baseline	1.6	1.0[a]
	placebo to adalimumab**	**adalimumab**
Baseline to week 48	*n = 141*	*n = 133*
baseline mean	21.2	22.2
mean change from baseline	0.9	0.0
Week 48 to week 144	*n = 128*	*n = 115*
Week 48 mean	22.7	22.3
mean change from 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
Week 48 to week 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
Week 48 to week 144	*n = 128*	*n = 115*
Week 48 mean	10.6	10.2
mean change from baseline	0.3	0.4

[a] p-value < 0.001
* Baseline to week 24 data represents Intention to treat (ITT) data and belongs to a different X-ray reading than baseline to week 48 and week 48 to week 144 data.
**Patients changed over to adalimumab at week 24

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

Quality of life and physical function

In PsA study VI, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the Short Form Health Survey (SF-36). Patients treated with adalimumab 40 mg fortnightly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at weeks 12 and 24 respectively).

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

CLINICAL TRIALS FOR ANKYLOSING SPONDYLITIS (AS)

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 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 4 and Table 23.

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

Figure 4. ASAS 20 response by visit, AS study I
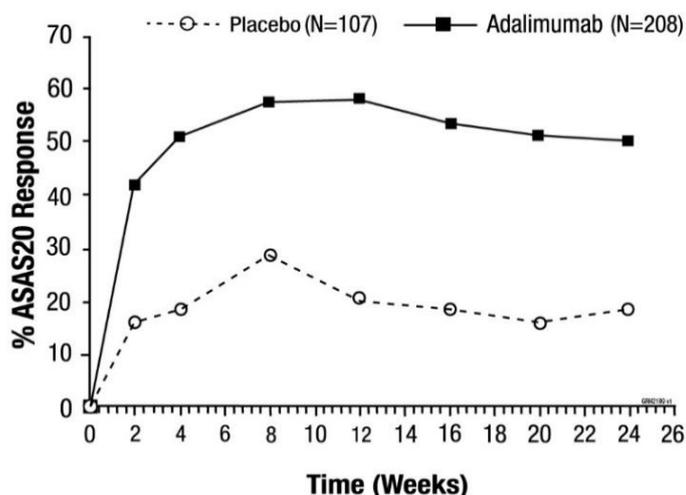
Table 23. ASAS[a] responses in placebo-controlled AS study

Response	placebo n = 107	adalimumab n = 208
ASAS 20		
week 12	21%	58%*
week 24	19%	51%*
ASAS 50		
week 12	10%	38%*
week 24	11%	35%*
ASAS 70		
week 12	5%	23%*
week 24	8%	24%*

* Statistically significant at p<0.001 for all comparisons between adalimumab and placebo at weeks 12 and 24
[a] Assessments in Ankylosing Spondylitis

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

Table 24.   Components of Ankylosing spondylitis disease activity

ASAS 20 response criteria*	placebo n = 107		adalimumab n = 208	
	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 (PROs) 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.

Clinical trials for Crohn's disease
Adults
The safety and efficacy of multiple doses of adalimumab were assessed in over 1500 patients with moderately to severely active CD (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 adalimumab 160 mg at week 0 and adalimumab 80 mg at week 2, the 80/40 group received adalimumab 80 mg at week 0 and adalimumab 40 mg at week 2, and the 40/20 group received adalimumab 40 mg at week 0 and adalimumab 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 adalimumab 160 mg at week 0 and adalimumab 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 adalimumab 80 mg at week 0 and adalimumab 40 mg at week 2. Patients were then randomised at week 4 to adalimumab 40 mg fortnightly, adalimumab 40 mg 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 adalimumab 160/80 mg 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 25).

Table 25. Induction of clinical remission and response (percent of patients)

Week 4	CD study I		CD study II	
	placebo (n = 74)	adalimumab 160/80 mg (n = 76)	placebo (n = 166)	adalimumab 160/80 mg (n = 159)
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 27). Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at week 56 (see Table 26).

Table 26. Hospitalisations to week 56 (ITT population)

	Placebo n = 261 n (%)	adalimumab 40 mg fortnightly n = 260 n (%)	adalimumab 40 mg every week n = 257 n (%)	Combined adalimumab 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 ≤ 0.05

Clinical remission results presented in Table 27 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 that patients in the placebo maintenance group (see Figure 5). Among patients who were not in response by week 12, therapy continued beyond 12 weeks did not result in significantly more responses. The group that received adalimumab every week did not show significantly higher remission rates than the group that received adalimumab fortnightly.

Table 27. Maintenance of clinical remission and response (percent of patients)

Outcome	placebo	adalimumab 40 mg fortnightly	adalimumab 40 mg 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.

One hundred and seventeen (117) out of 276 patients from CD study I and 272 out of 777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. Eighty-eight (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 CD given either adalimumab or placebo. After 8 weeks of randomised treatment (week 12 of study) there was a trend towards higher levels of mucosal healing in subjects given adalimumab compared with subjects given placebo but the differences were not statistically significant (healing in 27.4% (17/62) adalimumab vs 13.1% (8/61) given placebo; p = 0.056). Subjects who continued randomised adalimumab for 52 weeks (n = 135) were more likely to experience mucosal healing relative to placebo (healing in 24.2% [15/62] adalimumab vs 0% [0/61] given placebo; p < 0.001).

Figure 5. Days in clinical remission for patients who achieved clinical remission in CD study III
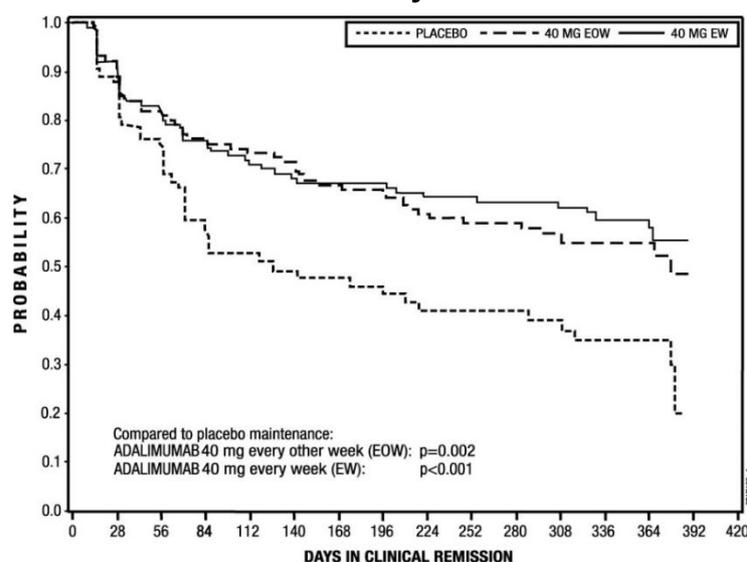
PATIENT REPORTED OUTCOMES (PRO)

In CD study I and CD study II, statistically significant improvement in disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomised to adalimumab 160/80 mg compared to placebo. Statistically significant improvement from baseline in IBDQ scores was seen at weeks 26 and 56 in CD study III among the adalimumab treatment groups compared to the placebo group.

Children and adolescents

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

All subjects received open-label induction therapy at a dose based on their baseline body weight: adalimumab 160 mg at week 0 and adalimumab 80 mg at week 2 for subjects ≥ 40 kg, and adalimumab 80 mg and adalimumab 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 28.

Table 28. Maintenance regimen

Patient weight	adalimumab low dose	adalimumab 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 29.

Table 29. Paediatric CD study PCDAI clinical remission and response

Outcome	adalimumab standard dose 40/20 mg fortnightly n = 93	adalimumab 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

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 30.

Table 30. Paediatric CD study discontinuation of corticosteroids or immunomodulators and fistula remission

	adalimumab standard Dose 40/20 mg fortnightly	adalimumab 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 adalimumab standard dose versus adalimumab low dose comparison.

[2] Immunosuppressant therapy could only be discontinued at or after week 26 at the investigator's discretion if the subject met the clinical response criterion

[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits
Statistically significant increases (improvement) from baseline to week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups. Statistically and clinically significant improvements from baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

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

In study UC-I, 576 TNF-antagonist naïve patients were randomised to receive either placebo at weeks 0 and 2, adalimumab 160 mg at week 0 followed by adalimumab 80 mg at week 2, or adalimumab 80 mg at week 0 followed by adalimumab 40 mg at week 2. After week 2, patients in both adalimumab arms received adalimumab 40 mg fortnightly. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at week 8. The primary endpoint was evaluated based on the 390 patients recruited after the adalimumab 80/40 induction group was added by protocol amendment.

In study UC-II, 248 patients received adalimumab 160 mg at week 0, 80 mg at week 2 and adalimumab 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 adalimumab 160/80 mg achieved clinical remission versus placebo at week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p = 0.031) and study UC-II (17% vs. 9% respectively, p = 0.019). In study UC-II, among those treated with adalimumab who were in clinical remission at week 8, 21/41 (51%) were in clinical remission at week 52. The percentage of subjects induced with adalimumab 80/40 mg in study UC-I who achieved clinical remission at week 8 was not statistically significantly different versus placebo. Results from the overall UC-II study population are shown in Table 32.

Table 31. Clinical remission, clinical response and mucosal healing in study UC-II (percent of patients)

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

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

Clinical Response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30%, and rectal bleeding subscore of 0 or 1 or its decrease from baseline ≥ 1 point.

Mucosal healing is defined as endoscopy 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

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

Table 32. Remission, response and mucosal healing at week 52 among week 8 responders in study UC-II (percent of patients)

Week 52 outcomes	ITT Population		Adalimumab-treated patients	
	adalimumab 40 mg fortnightly n = 248	placebo n = 246	week 8 responders per full Mayo Score n = 125	week 8 responders per partial Mayo score n = 123
Clinical remission	17%	9%	29%	31%
Clinical response	30%	18%	47%	50%
Mucosal healing	25%	15%	41%	43%
Steroid-free remission[a]	-	-	20%	-

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

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

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients.

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

Patients from UC studies I and II had the option to roll over into an open-label long-term extension study.

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

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

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

Adalimumab clinical trials for psoriasis (Ps)
Adults
The safety and efficacy of adalimumab were assessed in over 1600 patients 18 years of age or older with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy in randomised, double- blind, well-controlled studies. The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy.

Ps study I (M03-656) evaluated 1212 patients with chronic plaque psoriasis with ≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 within 3 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 adalimumab 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 adalimumab 40 mg 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 adalimumab 40 mg 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 MTX 25 mg or an initial dose of adalimumab 80 mg followed by adalimumab 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 adalimumab 40 mg fortnightly starting at week 1 after an initial dose of adalimumab 80 mg at week 0 or an initial dose of adalimumab 80 mg at week 0 followed by a dose of adalimumab 40 mg weekly.

Patients participating in all Phase II and Phase III 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 adalimumab 40 mg fortnightly, with the option to dose-escalate to adalimumab 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 34 and Table 35).

Table 33. Psoriasis study I (M03-656)

	Period A		Period B	Period C	
	Efficacy results at 16 weeks (percent of patients)		**Efficacy results at 33 weeks (percent of patients)**	**Among PASI 75 responders at week 33, efficacy results at 52 weeks (percent of patients)**	
	placebo n = 398	**adalimumab 40 mg fortnightly n = 814**	**adalimumab 40 mg fortnightly n = 580**	**placebo n = 240**	**adalimumab 40 mg fortnightly n = 250**
≥ PASI 75	6.5	70.9 [a]	84.5	42.5	79.2
PASI 100	0.8	20.0 [a]	30.3	7.5	32.0
PGA: Clear/minimal	4.3	62.2 [a]	73.3	27.9	68.0

[a] p < 0.001, adalimumab vs. placebo

Table 34. Psoriasis study II (M04-716) efficacy results at 16 weeks (percent of patients)

	placebo n = 53	MTX n = 110	adalimumab 40 mg fortnightly n = 108
≥ PASI 75	18.9	35.5	79.6 [a,b]
PASI 100	1.9	7.3	16.7 [c,d]
PGA: Clear/minimal	11.3	30.0	73.1 [a,b]

[a] p < 0.001, adalimumab vs. placebo

[b] p < 0.001 adalimumab vs. MTX

[c] p < 0.01 adalimumab vs. placebo

[d] p < 0.05 adalimumab vs. MTX

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

Two hundred and fifty (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 adalimumab 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.

One hundred and eight (108) subjects in the adalimumab group of study II received continuous therapy at adalimumab 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 adalimumab 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 adalimumab 40 mg fortnightly to adalimumab 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 weeks 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 adalimumab 80 mg, followed by adalimumab 40 mg fortnightly (starting one week after the initial dose), or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received adalimumab achieved a PGA score of "clear" or "almost clear" for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [p = 0.014]).

Psoriasis study IV (M13-674) compared efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by adalimumab 40 mg fortnightly (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks.

This study evaluated the proportion of subjects who achieved at least a 75% improvement from baseline in the Modified Nail Psoriasis Severity Index (mNAPSI 75) and the proportion of subjects who achieved "clear" or "minimal" assessment with at least a 2-grade improvement on the PGA-F scale at week 26 (see Table 37). The mNAPSI is a numeric index for the evaluation of nail psoriasis. The index assessed each nail abnormality for each of a subject's fingernails. Pitting, onycholysis and oil-drop dyschromia and crumbling of each fingernail were graded on a scale from 0 to 3. Leuconychia, splinter haemorrhages, hyperkeratosis and red spots in the lunula were graded as either present (scored as 1) or absent (scored as 0) for each fingernail. The mean (±SD) severity of mNAPSI at baseline was 58.11 ± 21.550 and 57.59 ± 20.159 in the placebo and adalimumab treatment group, respectively.

Of those who continued to receive adalimumab treatment until week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response. The percent improvement in NAPSI was also statistically significantly greater in adalimumab patients compared with placebo at week 16 (44.2% vs 7.8%).

Table 35. Ps Study IV (M13-674) Efficacy Results at 26 weeks in ranked order

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

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

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

B-SNIPI 50: At least a 50% reduction in scalp component of Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis index (B-SNIPI) among subjects with Baseline scalp score of 6 or greater).

QUALITY OF LIFE (QOL)
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 MTX groups at week 16, and clinically meaningful improvement in pain compared to the placebo group at week 16.

The Short form health survey (SF-36) was used to assess general health-related quality of life in Ps study I. The adalimumab-treated patients had significantly greater improvement in the SF-36 Physical component summary (PCS) and Mental component summary (MCS) scores.

In Ps Study IV, patients receiving adalimumab showed clinically meaningful improvements at week 26 from baseline compared with placebo in the DLQI.

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

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

Table 36. Paediatric plaque psoriasis efficacy results at 16 weeks

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

[a] MTX = methotrexate

[b] p = 0.027, adalimumab 0.8 mg/kg versus MTX

[c] p = 0.083, adalimumab 0.8 mg/kg versus MTX

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (loss of PGA response). Patients were then re-treated with adalimumab 0.8 mg/kg fortnightly for an additional 16 weeks. Among patients who were responders to the initial 16 weeks of treatment but who relapsed upon withdrawal and were retreated, PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects) was observed.

In the open-label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings. A total of 91 subjects received only adalimumab 0.8 mg/kg in period D, the mean duration of treatment with adalimumab 0.8 mg/kg in period D was 315.0 days (range 42 to 380 days). Of the 91 subjects who only received adalimumab 0.8 mg/kg in period D, the PASI 75 response rate and PGA clear/minimal response rate at week 52 were 69.2% and 59.3%, respectively.

Clinical trials for hidradenitis suppurativa (HS)

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 HS who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in studies HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (M11-313) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or an initial dose of adalimumab 160 mg at week 0, adalimumab 80 mg at week 2, and adalimumab 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 an initial dose of adalimumab 160 mg at week 0 and adalimumab 80 mg at week 2 and adalimumab 40 mg every week starting at week 4 to week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg fortnightly, or placebo from week 12 to week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in studies HS-I and HS-II were eligible to enrol into an open-label extension study in which adalimumab 40 mg was administered every week. Mean exposure in all adalimumab population was 762 days (standard deviation: 397 days). Throughout all 3 studies patients used topical antiseptic wash daily.

CLINICAL RESPONSE

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

At week 12, a significantly higher proportion of patients treated with adalimumab versus placebo achieved HiSCR. At week 12, a significantly higher proportion of patients in study HS II experienced a clinically relevant decrease in HS-related skin pain (see Table 38). Patients treated with adalimumab had reduced risk of disease flare during the initial 12 weeks of treatment.

Table 37. Efficacy results at 12 weeks, HS studies I and II

| Endpoint | HS study 1 | | HS study II | |
	placebo	adalimumab 40 mg weekly	placebo	adalimumab 40 mg weekly
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	n = 154 40 (26.0%)	n = 153 64 (41.8%)*	n = 163 45 (27.6%)	n = 163 96 (58.9%)**
≥30% Reduction in Skin Pain[b]	n = 109 27 (24.8%)	n = 122 34 (27.9%)	n = 111 23 (20.7%)	n = 105 48 (45.7%)**

* p < 0.05

**p < 0.001, adalimumab versus placebo

[a] Among all randomised patients.

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

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

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

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

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

Adolescents

There are no clinical trials in adolescent patients with hidradenitis suppurativa (HS). Efficacy of adalimumab for the treatment of adolescent patients from 12 years of age with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels (see section 5.2 Pharmacokinetic properties).

Clinical trials for uveitis

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

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

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). A majority of the 217 patients were female and Caucasian with mean age of 42.7 years. There was no statistically significant demographic difference between the placebo and adalimumab groups. All patients received a standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. A majority of the 226 patients were female and Caucasian with mean age of 42.5 years. There was no statistically significant demographic difference between the placebo and adalimumab groups. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by week 19.

CLINICAL RESULTS

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo (see Table 39). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see Figure 6 and Figure 7). In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups (Table 39).

Table 38. Time to treatment failure in uveitis studies UV I and UV II

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

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

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

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

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

Figure 6. Kaplan-Meier curves summarising the time to treatment failure on-or-after week 6 (study UV I)
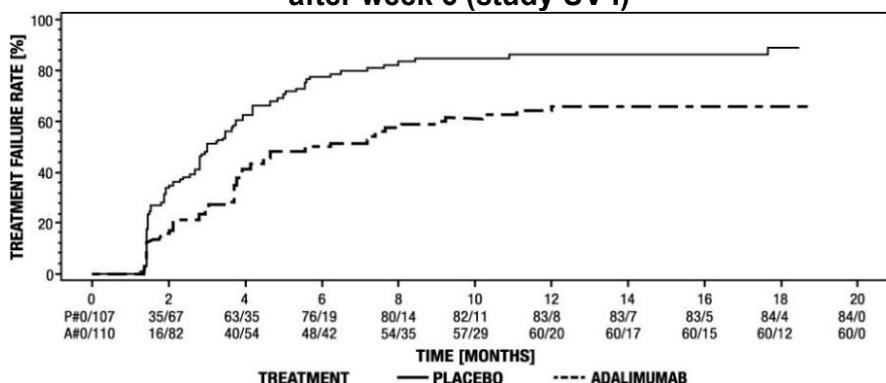
Figure 7. Kaplan-Meier curves summarising the time to treatment failure on-or-after week 2 (study UV II)
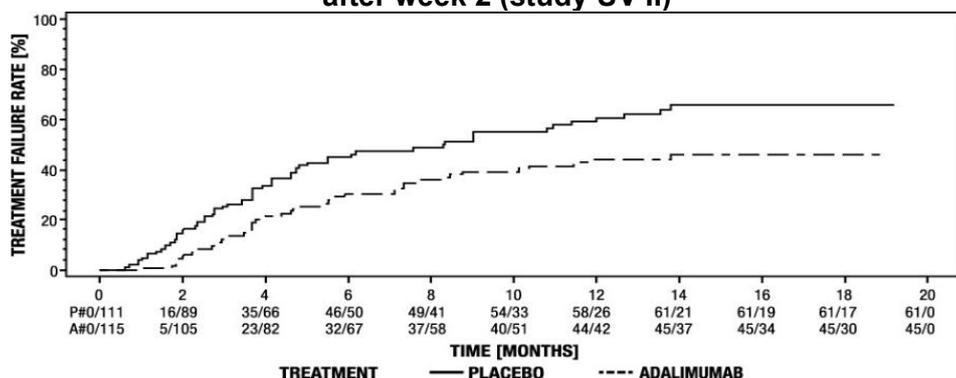
Table 39. Treatment failure components in studies UV I and UV II

Component of Time-to-treatment failure	UV I			UV II		
	HR[a]	CI 95%	p value[b]	HR[a]	CI 95%	p value[b]
New active inflammatory lesions	0.38	0.21-0.69	0.001	0.55	0.26-1.15	0.105
Anterior chamber cells grade	0.51	0.30-0.86	0.01	0.7	0.42-1.18	0.18
Vitreous haze grade	0.32	0.18-0.58	<0.001	0.79	0.34-1.81	0.569
Deterioration of best corrected visual acuity	0.56	0.32-0.98	0.04	0.33	0.16-0.70	0.002

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

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

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

Additionally, in study UV I, statistically significant differences in favour of adalimumab versus placebo were observed for the secondary endpoints changes in AC cell grade, vitreous haze grade, and logMAR BCVA (mean change from best state prior to week 6 to the final visit; p values: 0.011, < 0.001 and 0.003, respectively).

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

QUALITY OF LIFE

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

Comparability of Amgevita with Humira

CLINICAL TRIAL FOR RHEUMATOID ARTHRITIS

The efficacy and safety of AMGEVITA compared with Humira were assessed in a randomised active-control, double-blind study in patients ≥ 18 years of age with moderate to severe active RA with inadequate response to MTX. The patients had either rheumatoid factor or anti-cyclic citrullinated peptide positivity. The study evaluated 526 patients on stable doses of MTX. Patients were randomised to receive AMGEVITA or Humira 40 mg subcutaneously every other week for up to 22 weeks.

The percent of AMGEVITA-treated subjects achieving ACR 20 at week 24 in the RA study is shown in Table 41. At week 24, 74.6% (194/260) subjects in the AMGEVITA group and 72.4% (189/261) subjects in the Humira group met the ACR 20 response criteria. The risk ratio (RR) of ACR 20 for AMGEVITA versus Humira was 1.039 with the 2-sided 90% CI of (0.954, 1.133).

Table 40. Clinical responses in RA study of similarity: AMGEVITA vs Humira

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

The RR of ACR 20 primary endpoint was within the pre-specified margin and showed clinical equivalence between AMGEVITA and Humira. The results of the components of the ACR response criteria for RA ABP-study 1 are shown in Table 42. 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 8.

Table 41. Components of ACR response

Parameter (median)	AMGEVITA[a] N = 264		Humira[a] N = 262	
	baseline	week 24	baseline	week 24
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] adalimumab 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

Figure 8. RA study with AMGEVITA and Humira ACR20 responses over 24 weeks
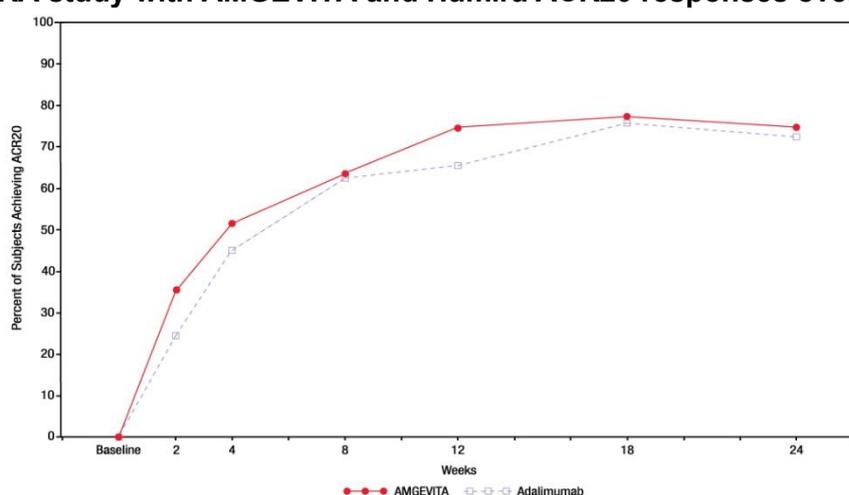
Clinical Trial for Psoriasis

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 Humira at an initial loading dose of 80 mg administered SC on week 1/day 1, followed by AMGEVITA or Humira 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 pre-specified equivalence margin to demonstrate clinical equivalence between AMGEVITA and Humira.

Table 42. Efficacy results at week 16 in psoriasis study: AMGEVITA vs Humira

|	AMGEVITA n = 175	Humira n = 175

PASI % Improvement from baseline	80.91	83.06
SDa	24.237	25.195

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 Humira group. The least-squares (LS) mean difference of PASI percent improvement from baseline to week 16 between AMGEVITA and Humira was -2.18 with the 2-sided 95% CI of (-7.39, 3.02). The 95% CI was within the predefined equivalence margin (-15,15), thus demonstrating clinical equivalence of AMGEVITA and Humira.

The Ps study was also designed to evaluate clinically meaningful differences in safety and immunogenicity in subjects who underwent a single transition from Humira to AMGEVITA at week 16 and to provide a descriptive comparison with patients who continued on Humira. The 350 subjects in the Ps study 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 Humira, Treatment Group B1 (Humira/Humira) or were transitioned to AMGEVITA, Treatment Group B2 (Humira/ AMGEVITA). Subjects continued with their assigned treatment until week 48, when the last dose of assigned investigational product was administered and week 52 was the end of study.

The overall safety profile of the subjects who transitioned from Humira to AMGEVITA was similar to the subjects who remained on Humira throughout the study. The mean PASI percent improvement from baseline over the duration of the study is shown in Figure 9.

Figure 9. Mean PASI percent improvement from baseline over the duration of psoriasis study for AMGEVITA and Humira (represented as adalimumab)
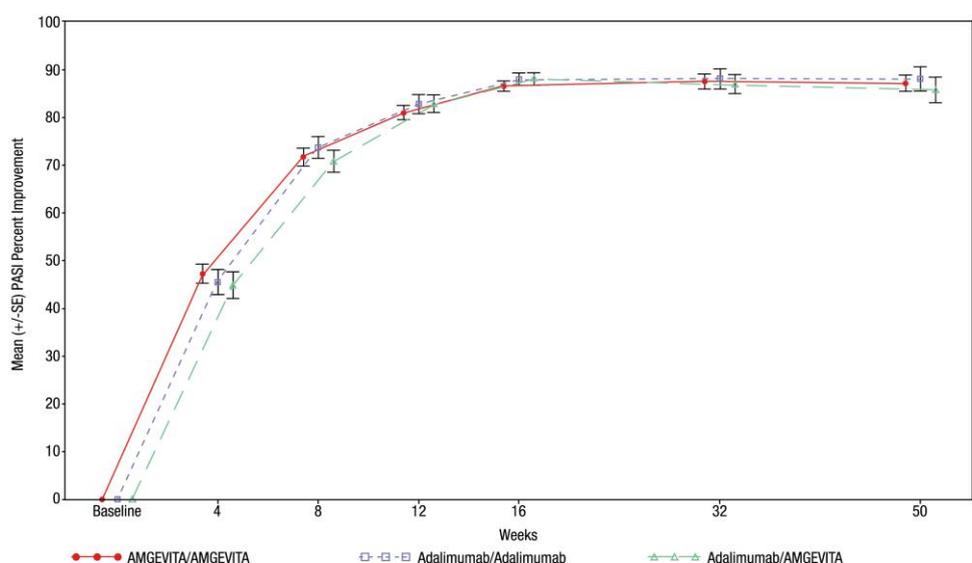
IMMUNOGENICITY OF HUMIRA

Patients in RA studies I, II, and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. Approximately 5.5% (58 of 1062) of adult RA

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

In pJIA study I a greater percentage of patients developed antibodies to adalimumab compared to adult RA patients. Antibody formation was lower when adalimumab was given together with MTX in comparison with use as monotherapy. There was no apparent correlation between the presence of antibodies and adverse events. Anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant MTX, the incidence was 25.6% (22/86), compared to 5.9% (5/85) when adalimumab was used as add-on to MTX.

In pJIA study II anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant MTX.

In patients with ERA, 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 add-on to MTX.

In paediatric patients with moderately to severely active CD, the rate of antibody development in patients receiving adalimumab was 3.3%.

In patients with AS, the rate of development of anti-adalimumab antibodies in adalimumab-treated patients was comparable to patients with RA. In patients with PsA, the rate of antibody development in patients receiving adalimumab monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA. The immunogenicity rate was 8% for psoriasis patients who were treated with adalimumab monotherapy.

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

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

In plaque psoriasis patients on long-term adalimumab without 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. Thirty-seven (37) out of the 38 subjects completed the initial double-blind period (16 weeks) of study M04-717, and one subject entered the long-term follow-up period after week 4.

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

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

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

IMMUNOGENICITY OF AMGEVITA

Differences in assay methodology for measuring immunogenicity prevents direct comparison of immunogenicity rates between AMGEVITA and Humira or other biologics in different studies. In the RA and Ps studies, binding ADA activity was determined using a bridging immunoassay and the neutralising ADA activity was determined using a TNFα-ligand binding based bioassay.

Immunogenicity in the RA study

Patients were tested at multiple time points for antibodies to AMGEVITA and Humira 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 Humira group; the incidence of developing neutralising antibodies was 9.1% (24/264) in the AMGEVITA group and 11.1% (29/262) in the Humira group. The immunogenicity profile of AMGEVITA was similar to Humira.

Immunogenicity in the Ps study

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

5.2 Pharmacokinetic properties

Absorption
Following single adalimumab 40 mg subcutaneous (SC) administration to 59 healthy adult subjects, adalimumab absorption 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 adalimumab 40 mg subcutaneous dose was 64%. The pharmacokinetics (PK) of adalimumab was linear over the dose range of 0.5 to 10 mg/kg following a single intravenous dose.

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

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 µg/mL (without concomitant MTX and 8 to 9 µg/mL (with concomitant MTX), respectively. These trough concentration levels are well above the EC_{50} estimates of 0.8 to 1.4 µg/mL and consistent with those at which ACR20 responses appear to reach a maximum (Figure 2). The serum adalimumab trough levels at steady state increased approximately proportionally with dose following adalimumab 20 mg, 40 mg 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 µg/mL during adalimumab 40 mg fortnightly without concomitant MTX treatment (after an initial loading dose of adalimumab 80 mg subcutaneously).

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

In patients with CD, 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 µg/mL at weeks 2 and 4. The mean steady state trough concentration at weeks 24 and 56 were 6.6 µg/mL and 7.2 µg/mL respectively. The range of trough concentrations in patients who received a maintenance dose of adalimumab 40 mg every fortnight was 0-21.7 µg/mL.

In patients with UC, 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 µg/mL during the induction period. Mean steady-state trough levels of approximately 8 µg/mL were observed in UC patients who received a maintenance dose of 40 mg adalimumab fortnightly in a 52-week study.

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

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

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

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

Special populations

PK in special populations were investigated using population PK analyses.

Race/ethnicity

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

Gender/weight

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

Paediatrics

In pJIA study I for patients with pJIA (4 to 17 years of age), the mean steady-state trough serum adalimumab concentrations for patients weighing < 30 kg receiving adalimumab 20 mg subcutaneously fortnightly without concomitant MTX or with concomitant MTX were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥ 30 kg receiving adalimumab 40 mg subcutaneously fortnightly without concomitant MTX, or with concomitant MTX, were 6.6 µg/mL and 8.1 µg/mL, respectively. In pJIA study II for patients with pJIA who were 2 to < 4 years old, or aged 4 years and above weighing < 15 kg, the mean steady-state trough serum adalimumab concentrations for patients receiving adalimumab subcutaneously fortnightly were 6.0 ± 6.1 µg/mL (101% CV) for adalimumab without concomitant MTX, and 7.9 ± 5.6 µg/mL (71.2% CV) with concomitant MTX.

Table 43. Summary of serum adalimumab trough concentrations (µg/mL) inpatients with Polyarticular JIA by week 24 (n = 15) (pJIA study II)

Treatment Groups	Mean ± SD (CV%) Min – Max, N_{nmiss}		
	Week		
	0	**12**	**24**
Adalimumab 24 mg/m² BSA fortnightly (All patients n = 15)	0 ± 0 (0%) 0 – 0, 14	6.97 ± 5.69 (81.6%) 0 – 14.9, 15	7.78 ± 5.85 (75.2%) 0 – 14.7, 15
Adalimumab 24 mg/ m² BSA fortnightly, with MTX (All patients n = 11)	0 ± 0 (0%) 0 – 0, 10	7.27 ± 5.71 (78.5%) 0 – 14.8, 11	8.45 ± 5.69 (67.3%) 0 – 14.7, 11
Adalimumab 24 mg/ m² BSA fortnightly, without MTX (All patients n = 4)	0 ± 0 (0%) 0 – 0, 4	6.13 ± 6.41 (104.6%) 0 – 14.9, 4	5.95 ± 6.74 (113.3%) 0 – 12.7, 4

BSA = Body surface area

N_{nmiss} = number of non-missing observations

Following the administration of adalimumab 24 mg/m² (up to a maximum of adalimumab 40 mg) subcutaneously fortnightly to patients with ERA, the mean trough steady-state (values measured at week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/mL for adalimumab without concomitant MTX and 11.8 ± 4.3 µg/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 (adalimumab 20 mg fortnightly for body weight < 30 kg and adalimumab 40 mg fortnightly for body weight ≥ 30 kg) were comparable to the simulated trough concentrations for the body surface area-based regimen.

In paediatric patients with moderately to severely active CD, the open-label induction dose was adalimumab 160/80 mg or adalimumab 80/40 mg at weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At week 4, patients were randomised 1:1 to either the standard dose (adalimumab 40/20 mg fortnightly) or low dose (adalimumab 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 µg/mL for patients ≥ 40 kg (adalimumab 160/80 mg) and 10.6 ± 6.1 µg/mL for patients < 40 kg (adalimumab 80/40 mg).

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

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously 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 µg/mL (79% CV). Serum concentrations after adalimumab 40 mg fortnightly in adult psoriasis patients are comparable to those following 0.8 mg/kg fortnightly in paediatric psoriasis patients in study M04-717 (range 7-11 µg/mL).

Adalimumab exposure in adolescent HS patients was predicted using population PK modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, JIA, paediatric CD, and ERA). The recommended adolescent HS dosing schedule of adalimumab 40 mg fortnightly is predicted to provide serum adalimumab exposure and efficacy similar to that observed in adult HS patients receiving the recommended adult dose of adalimumab 40 mg every week.

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

Hepatic insufficiency
No pharmacokinetic data are available in patients with hepatic impairment.

Renal insufficiency
No pharmacokinetic data are available in patients with renal impairment.

Disease states
Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Drug interactions, Methotrexate
When adalimumab was administered to 21 RA patients on stable 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).

Comparability of AMGEVITA with Humira

AMGEVITA is pharmacokinetically similar to Humira.
PK similarity was demonstrated between AMGEVITA and Humira following administration of a single adalimumab 40 mg dose subcutaneously in 203 healthy adult subjects. PK parameters including maximum serum concentrations and area under the serum concentration time curves were compared. According to the bioequivalence testing, the 90% CI of the geometric mean test-to-reference ratios for these parameters fell within the

protocol-specified criteria of 0.80 to 1.25 and concluded PK similarity between AMGEVITA and Humira.

Bioequivalence of Amgevita 50mg/mL and 100mg/mL concentrations

Study 20200286 was a randomised, single-blind, single-dose, 2-arm, parallel-group study in healthy adult male and female subjects.

The primary objective of the study was to determine the PK comparability of AMGEVITA 100 mg/mL compared to AMGEVITA 50 mg/mL following single dose SC injection, as assessed principally by area under the serum concentration time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) and maximum observed serum concentration (C_{max}) in healthy adult subjects.

Prior to dosing, subjects were randomised through the interactive voice/web response system (IXRS) to receive either AMGEVITA 100 mg/mL or AMGEVITA 50 mg/mL in a 1:1 ratio. Randomisation was stratified by gender. Each randomised subject was assigned a unique randomisation number. Pharmacokinetic parameters were summarised descriptively by treatment; this summary was repeated for neutralising ADA negative subjects.

For the comparisons of AMGEVITA 100 mg/mL to AMGEVITA 50 mg/mL, the point estimates and 90% CIs of the Geometric Mean Ratios (GMRs) were fully contained within the prespecified equivalence margin of 0.8 to 1.25 for both the primary PK endpoints (AUC_{inf} and C_{max}) and the secondary PK endpoint of AUC_{last} for the PK parameter analysis set. Therefore, PK comparability was demonstrated between AMGEVITA 100 mg/mL and AMGEVITA 50 mg/mL.

Table 44 Summary of Statistical Assessment of PK Parameters (ANCOVA with Baseline Weight) (PK Parameter Analysis Set)

Treatment and Comparison	AUC_{inf} (hr*ng/mL) LS Geometric Mean [n]	C_{max} (ng/mL) LS Geometric Mean [n]	AUC_{last} (hr*ng/mL) LS Geometric Mean [n]
ABP 501 100 mg/mL	2176667.1 [154]	3749.1 [180]	2058821.4 [177]
ABP 501 50 mg/mL	2086410.1 [153]	3521.5 [184]	2066337.7 [176]
Ratio of LS Geometric Means (90% CI)			
ABP 501 100 mg/mL vs ABP 501 50 mg/mL	1.0433 (0.9634, 1.1297)	1.0646 (0.9960, 1.1380)	0.9964 (0.9264, 1.0716)

ANCOVA = analysis of covariance; AUC = area under the serum concentration-time curve; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum concentration; LS = least squares; PK = pharmacokinetic; ABP = Amgen Biosimilar Product (ie, AMGEVITA)
Note: Geometric LS mean, ratio of geometric LS means and 90% CI were estimated based on the ANCOVA model with a fixed effect for treatment and adjusting for baseline weight.

Figure 10. Mean (± SD) PK Concentrations Over Time by Treatment (PK Concentration Analysis Set)
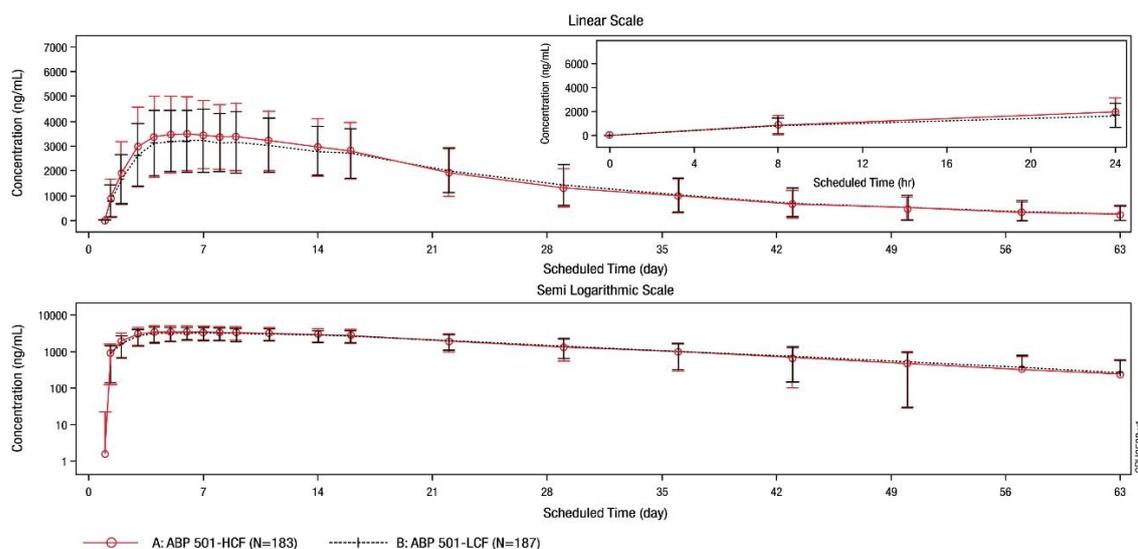
5.3 Preclinical safety data

Animal studies

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 adalimumab 40 mg fortnightly. Parturition was unaffected by both doses.

Because animal studies are not always predictive of human responses, the use of adalimumab during pregnancy is not recommended.

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For 50 mg/mL formulation: AMGEVITA pre-filled syringes and pre-filled SureClick® pen contain the following inactive ingredients: 9.0 % (w/v) sucrose, polysorbate 80, glacial acetic acid, sodium hydroxide, and water for injections. The solution is adjusted to pH 5.2.

For 100 mg/mL formulation: AMGEVITA pre-filled syringes and pre-filled SureClick® pen contain the following inactive ingredients: 24 mM s-lactic acid, 8.4 % (w/v) sucrose, 0.1% (w/v) polysorbate 80, sodium hydroxide, and water for injections. The solution is adjusted to pH 5.2.

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

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

Do not use AMGEVITA beyond the expiration date.

Storage at room temperature for not more than 14 days (only if necessary).

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 single maximum period of 14 days and must be protected from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator afterwards.

The date of removal from the refrigerator should be recorded to allow the pre-filled syringe and pre-filled pen to be discarded after the maximum 14 days if not used.

6.5 Nature and contents of container

AMGEVITA (adalimumab) solution for injection is supplied as a sterile single-use liquid solution practically free from particles.
The solution for injection is available in 50 mg per mL or 100 mg per mL in a pre-filled syringe or pre-filled SureClick® pen for subcutaneous administration.

Pre-filled syringe

Each pre-filled syringe is fitted with an in-place needle, glass barrel, plunger, and needle shield. Supplied in the following presentations. Not all pack sizes are distributed in Australia.

AMGEVITA 20 mg solution for injection in single-use pre-filled syringe
50 mg/mL presentation
- 20 mg in 0.4 mL solution for subcutaneous administration (in paediatric patients), available in packs containing 1 or 2 pre-filled syringes.

100 mg/mL presentation
- 20 mg in 0.2 mL solution for subcutaneous administration (in paediatric patients), available in packs containing 1 pre-filled syringe.

AMGEVITA 40 mg solution for injection in a single-use pre-filled syringe
 50 mg/mL presentation
- 40 mg in 0.8 mL solution for subcutaneous administration available in packs containing 1, 2, 4 or 6 pre-filled syringes.

100 mg/mL presentation
- 40 mg in 0.4 mL solution for subcutaneous administration, available in packs containing 2 pre-filled syringes.

Pre-filled SureClick® pen

Each pen is a disposable, handheld, spring-based, plastic injection device with a small clear window and cap. It contains an AMGEVITA adalimumab 40 mg or 80 mg pre-filled syringe. Supplied in the following presentations. Not all pack sizes are distributed in Australia.

AMGEVITA 40 mg solution for injection in a single-use SureClick® pen
50 mg/mL presentation
- ^40 mg in 0.8 mL solution for subcutaneous administration available in packs containing 1, 2, 4 or 6 SureClick® pens

100 mg/mL presentation
- 40 mg in 0.4 mL solution for subcutaneous administration, available in packs containing 1 or 2 SureClick® pens.

AMGEVITA 80 mg solution for injection in a single-use SureClick® pen
100 mg/mL presentation
- 80 mg in 0.8 mL solution for subcutaneous administration, available in packs containing 1 SureClick® pen.

6.6 Special precautions for disposal
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties
Chemical structure

Adalimumab consists of 2 heavy chains (HC) of the lgG1 subclass and 2 light chains (LC) of the human kappa subclass, which are covalently linked through disulfide bonds. It consists of 1330 amino acids.

Molecular weight
Approximately 148 kilodaltons (kDa).

CAS Number

1446410-95-2

AMGEVITA is produced by recombinant DNA technology in a mammalian cell expression system. AMGEVITA (adalimumab) is a fully human anti-TNFα monoclonal antibody expressed in a Chinese hamster ovary (CHO) cell line.

The amino acid sequence of AMGEVITA is identical to that of Humira. The comparability of AMGEVITA with Humira has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see sections 4.8 Adverse effects (Undesirable effects), 5.1 Pharmacodynamic properties, Clinical trials, and 5.2 Pharmacokinetic properties). The evidence for comparability supports the use of AMGEVITA for the listed indications.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4) – Prescription Only Medicine

8. SPONSOR

Amgen Australia Pty Ltd
Level 11, 10 Carrington Street
Sydney NSW 2000
Ph: 1800 803 638
www.amgenmedinfo.com.au
Email: medinfo.JAPAC@amgen.com.

9. DATE OF FIRST APPROVAL

AMGEVITA 20 mg/0.4mL and 40 mg/0.8 mL (50 mg/mL)

09 November 2017.

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

22 September 2025

10.   DATE OF REVISION

12 February 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Reference to the 40 mg/0.8mL pre-filled SureClick pen containing latex has been removed
6.4	Removed restrictions on storage at room temperature for the 100 mg/mL presentations.
6.5	Reference to the 40 mg/0.8mL pre-filled SureClick pen containing latex has been removed

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SureClick® is a registered trademark of Amgen Inc
Humira® is a registered trademark of AbbVie Biotechnology Ltd