1. NAME OF THE MEDICINAL PRODUCT

AMGEVITA 20 mg solution for injection in pre-filled syringe.
AMGEVITA 40 mg solution for injection in pre-filled syringe.
AMGEVITA 40 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMGEVITA 20 mg solution for injection in pre-filled syringe
Each single dose pre-filled syringe contains 20 mg of adalimumab in 0.4 mL (50 mg/mL) solution.

AMGEVITA 40 mg solution for injection in pre-filled syringe
Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 mL (50 mg/mL) solution.

AMGEVITA 40 mg solution for injection in pre-filled pen
Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 mL (50 mg/mL) solution.

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

Patient safety information card

The marketing of AMGEVITA is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AMGEVITA 20 mg solution for injection in pre-filled syringe
AMGEVITA 40 mg solution for injection in pre-filled syringe

Solution for injection (injection).

AMGEVITA 40 mg solution for injection in pre-filled pen (SureClick)
Solution for injection (injection).

Clear and colorless to slightly yellow solution.

AMGEVITA is a biosimilar medicinal product, that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Humira. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. The biosimilar is not to be switched with the reference medicinal product unless specifically stated otherwise. More detailed information regarding biosimilar medicinal products is available on the website of the Ministry of Health:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/Registration/Pages/Biosimilars.aspx

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

AMGEVITA in combination with methotrexate is indicated for:

- The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

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

AMGEVITA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Axial spondyloarthritis

Ankylosing spondylitis (AS):

AMGEVITA is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS:

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

Psoriatic arthritis

AMGEVITA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Psoriasis

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

Hidradenitis suppurativa (HS)

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

Crohn’s disease

AMGEVITA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. AMGEVITA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative colitis

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

Uveitis

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

Intestinal Behcet's disease

AMGEVITA is indicated for the treatment of intestinal Behcet's disease in patients who have had an inadequate response to conventional therapy.

4.2 Posology and method of administration

AMGEVITA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which AMGEVITA is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with AMGEVITA (see section 4.4). Patients treated with AMGEVITA should be given the Patient safety information card.

After proper training in injection technique, patients may self-inject with AMGEVITA if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with AMGEVITA, other concomitant therapies (e.g. corticosteroids and/or immunomodulatory agents) should be optimized.

Posology

Rheumatoid arthritis

The recommended dose of AMGEVITA for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with AMGEVITA.

Glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, or analgesics can be continued during treatment with AMGEVITA. Regarding combination with disease-modifying anti-rheumatic drugs other than methotrexate, see sections 4.4 and 5.1.

In monotherapy, some patients who experience a decrease in their response to AMGEVITA 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week.

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

Dose interruption

There may be a need for dose interruption, for instance before surgery or if a serious infection occurs.

Available data suggest that re-introduction of AMGEVITA after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis

The recommended dose of AMGEVITA for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

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

Psoriasis

The recommended dose of AMGEVITA for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week 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 to AMGEVITA 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency (see section 5.1). If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

Hidradenitis suppurativa

The recommended AMGEVITA dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at day 15 (given as two 40 mg injections in one day). Two weeks later (day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day). Antibiotics may be continued during treatment with AMGEVITA if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with AMGEVITA.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, AMGEVITA 40 mg every week or 80 mg every other week may be re-introduced (see section 5.1).

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

Crohn's disease

The recommended AMGEVITA induction dose regimen for adult patients with moderately to severely active Crohn's disease is 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at week 2 (given as two 40 mg injections in one day), followed by a maintenance dose of 40 mg every other week via subcutaneous injection beginning at week 4.

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

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

Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ulcerative colitis

The recommended AMGEVITA induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

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

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

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. AMGEVITA therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of AMGEVITA for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with adalimumab alone. Treatment with AMGEVITA can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with AMGEVITA.

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

Intestinal Behcet's disease

The initial dose of AMGEVITA for adult intestinal Behcet's disease patients is 160 mg as subcutaneous injection. The initial dose is followed by 80 mg two weeks later. From four weeks after the initial dose, 40 mg is administered every other week.

AMGEVITA should be used when the signs and symptoms caused by intestinal Behcet's disease remain clearly even if patients have appropriate treatment with existing drug (steroids or immunomodulator, etc.).

Continued therapy with the same regimen should be carefully reconsidered in a patient not responding such as clinical symptoms and/or endoscopic findings within 12 weeks of treatment

Special populations

Elderly

No dose adjustment is required.

Renal and/or hepatic impairment

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

Method of administration

AMGEVITA is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with AMGEVITA. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

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

Patients who develop a new infection while undergoing treatment with AMGEVITA, should be monitored closely and undergo a complete diagnostic evaluation. Administration of AMGEVITA should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of AMGEVITA in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving adalimumab.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalization or fatal outcomes associated with infections have been reported.

Tuberculosis

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

Before initiation of therapy with AMGEVITA, all patients must be evaluated for both active or inactive (“latent”) tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and

previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the 'Patient safety information card'. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromized.

If active tuberculosis is diagnosed, AMGEVITA therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of AMGEVITA, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of AMGEVITA in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab.

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

Other opportunistic infections

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

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of AMGEVITA should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including adalimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with AMGEVITA. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with AMGEVITA should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in

conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, AMGEVITA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of AMGEVITA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of AMGEVITA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of AMGEVITA therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

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

Dry natural rubber for AMGEVITA 40 mg solution for injection in pre-filled pen

The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause allergic reactions.

Immunosuppression

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

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post-marketing setting, cases of leukemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukemia in rheumatoid arthritis patients with long-standing highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy $\leq$ 18 years of age), including adalimumab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for

inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and AMGEVITA should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with AMGEVITA cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with adalimumab is continued following development of malignancy. Thus, additional caution should be exercised in considering AMGEVITA treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with AMGEVITA. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, 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 increased risk for malignancy due to heavy smoking.

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

Hematologic reactions

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

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

Patients on AMGEVITA may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to AMGEVITA *in utero* is not recommended for 5 months following the mother's last AMGEVITA injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving adalimumab. AMGEVITA should be used with caution in patients with mild heart failure (NYHA class I/II). AMGEVITA is contraindicated in

moderate to severe heart failure (see section 4.3). Treatment with AMGEVITA must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with AMGEVITA may result in the formation of autoimmune antibodies. The impact of long-term treatment with AMGEVITA on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with AMGEVITA and is positive for antibodies against double-stranded DNA, further treatment with AMGEVITA should not be given (see section 4.8).

Concurrent administration of biologic DMARDs or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of AMGEVITA and anakinra is not recommended (see section 4.5).

Concomitant administration of AMGEVITA with other biologic DMARDs (e.g. anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions (see section 4.5).

Surgery

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

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that adalimumab does not worsen or cause strictures.

Elderly

The frequency of serious infections among adalimumab-treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Excipients with known effects

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 mL dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Adalimumab has been studied in rheumatoid arthritis and psoriatic arthritis patients taking adalimumab as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. Administration of adalimumab without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of AMGEVITA and anakinra is not recommended (see section 4.4 “Concurrent administration of biologic DMARDs or TNF-antagonists”).

The combination of AMGEVITA and abatacept is not recommended (see section 4.4 “Concurrent administration of biologic DMARDs or TNF-antagonists”).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last AMGEVITA treatment.

Pregnancy

A large number (approximately 2,100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1,500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn’s disease (CD) treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8.7%) in the adalimumab-treated women with RA and 5/74 (6.8%) in the untreated women with RA (unadjusted OR 1.31, 95% CI 0.38-4.52) and 16/152 (10.5%) in the adalimumab-treated women with CD and 3/32 (9.4%) in the untreated women with CD (unadjusted OR 1.14, 95% CI 0.31-4.16). The adjusted OR (accounting for baseline differences) was 1.10 (95% CI 0.45-2.73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. AMGEVITA should only be used during pregnancy if clearly needed.

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

Breast-feeding

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, AMGEVITA can be used during breast-feeding.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

AMGEVITA may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of AMGEVITA (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Adalimumab was studied in 9,506 patients in pivotal controlled and open-label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long-standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving adalimumab and 3,801 patients receiving placebo or active comparator during the controlled period.

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

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, hemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for adalimumab. TNF-antagonists, such as AMGEVITA affect the immune system and their use may affect the body's defence against infection and cancer.

Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukemia, lymphoma and HSTCL) have also been reported with use of adalimumab.

Serious hematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on post-marketing experience and are displayed by system organ class and frequency in table 1 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 1. Undesirable effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza), Intestinal infections (including gastroenteritis viral), Skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotizing 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	Neurological infections (including viral meningitis), Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), Bacterial infections, Eye infections, Diverticulitis[1]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), Benign neoplasm
	Uncommon	Lymphoma**, Solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), Melanoma**
	Rare	Leukemia[1]
	Not known	Hepatosplenic T-cell lymphoma[1], Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1] Kaposi's sarcoma

System Organ Class	Frequency	Adverse Reaction
Blood and the lymphatic system disorders*	Very common	Leukopenia (including neutropenia and agranulocytosis), Anemia
	Common	Leukocytosis, Thrombocytopenia
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders*	Common	Hypersensitivity, Allergies (including seasonal allergy)
	Uncommon	Sarcoidosis[1], Vasculitis
	Rare	Anaphylaxis[1]
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalemia, Uric acid increased, Blood sodium abnormal, Hypocalcemia, Hyperglycemia, Hypophosphatemia, Dehydration
Psychiatric disorders	Common	Mood alterations (including depression), Anxiety, Insomnia
Nervous system disorders*	Very common	Headache
	Common	Paresthesias (including hypoesthesia), Migraine, Nerve root compression
	Uncommon	Cerebrovascular accident[1], Tremor, Neuropathy
	Rare	Multiple sclerosis, Demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome)[1]

System Organ Class	Frequency	Adverse Reaction
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	Myocardial infarction[1], Arrhythmia, Congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, Flushing, Hematoma
	Uncommon	Aortic aneurysm, Vascular arterial occlusion, Thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	Asthma, Dyspnea, Cough
	Uncommon	Pulmonary embolism[1], Interstitial lung disease, Chronic obstructive pulmonary disease, Pneumonitis, Pleural effusion[1]
	Rare	Pulmonary fibrosis[1]

System Organ Class	Frequency	Adverse Reaction
Gastrointestinal disorders	Very common	Abdominal pain, Nausea and vomiting
	Common	GI hemorrhage, Dyspepsia, Gastroesophageal reflux disease, Sicca syndrome
	Uncommon	Pancreatitis, Dysphagia, Face edema
	Rare	Intestinal perforation[1]
Hepato-biliary disorders*	Very common	Elevated liver enzymes
	Uncommon	Cholecystitis and cholelithiasis, Hepatic steatosis, Bilirubin increased
	Rare	Hepatitis, Reactivation of hepatitis B[1], Autoimmune hepatitis[1]
	Not known	Liver failure[1]
Skin and subcutaneous tissue disorders	Very common	Rash (including exfoliative rash)
	Common	Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis)[1], Urticaria, Bruising (including purpura), Dermatitis (including eczema), Onychoclasis, Hyperhidrosis, Alopecia[1], Pruritus
	Uncommon	Night sweats, Scar

System Organ Class	Frequency	Adverse Reaction
	Rare	Erythema multiforme[1], Stevens-Johnson syndrome[1], Angioedema[1], Cutaneous vasculitis[1], Lichenoid skin reaction[1]
	Not known	Worsening of symptoms of dermatomyositis[1]
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis, Systemic lupus erythematosus
	Rare	Lupus-like syndrome[1]
Renal and urinary disorders	Common	Renal impairment, Hematuria
	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, Edema, Pyrexia[1]
	Uncommon	Inflammation
Investigations*	Common	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), Autoantibody test positive (including double stranded DNA antibody), Blood lactate dehydrogenase increased
	Not known	Weight increased[2]
Injury, poisoning and procedural complications	Common	Impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

** including open-label extension studies

[1)] including spontaneous reporting data

[2)] The mean weight change from baseline for adalimumab ranged from 0.3 kg to 1.0 kg across adult indications compared to (minus) -0.4 kg to 0.4 kg for placebo over a treatment period of 4-6 months. Weight increase of 5-6 kg has also been observed in long-term extension studies with mean exposures of approximately 1-2 years without control group, particularly in patients with Crohn's disease and Ulcerative colitis. The mechanism behind this effect is unclear but could be associated with the anti-inflammatory effect of adalimumab.

Hidradenitis suppurativa

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

Uveitis

The safety profile for patients with uveitis treated with adalimumab every other week 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, hemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the 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 placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, 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 placebo and active control-treated patients.

In controlled and open-label adult and pediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% CI) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 adalimumab-treated patients versus a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients).

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

years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% CI) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open-label extension studies of adalimumab, with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient-years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient-years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient-years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

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

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I–V. In these trials, 11.9% of patients treated with adalimumab and 8.1% of placebo and active control-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3,441 treated with adalimumab in all rheumatoid arthritis and psoriatic arthritis 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.

Hepato-biliary events

In controlled phase 3 trials of adalimumab in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 × ULN occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients.

In controlled phase 3 trials of adalimumab in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥ 3 × ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of controlled-treated patients.

In controlled phase 3 trials of adalimumab in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 × ULN occurred in 1.8% of adalimumab-treated patients and 1.8% of control-treated patients.

In controlled trials of adalimumab (initial doses of 160 mg at week 0 and 80 mg at week 2, followed by 40 mg every week starting at week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 × ULN occurred in 0.3% of adalimumab-treated patients and 0.6% of control-treated patients.

In controlled trials of adalimumab (initial doses of 80 mg at week 0 followed by 40 mg every other week starting at week 1) in adult patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 × ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been

post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumor Necrosis Factor alpha (TNFα) inhibitors. ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 0.1-0.2 nM).

Pharmacodynamic effects

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 rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration. Patients treated with adalimumab usually experienced improvement in hematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with adalimumab. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab-treated patients.

Clinical efficacy and safety

Rheumatoid arthritis

Adalimumab was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of adalimumab were assessed in five randomized, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration. Injection site pain of adalimumab was assessed in two randomized, active control, single-blind, two-period crossover studies.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti-rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of adalimumab or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of adalimumab were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomized to 40 mg of adalimumab or placebo every other week for 24 weeks.

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

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

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at week 52. RA studies III and

V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life. The primary endpoint in RA studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

ACR response

The percent of adalimumab-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarized in table 2.

Table 2. ACR responses in placebo-controlled trials (percent of patients)

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

[a] RA study I at 24 weeks, RA study II at 26 weeks, and RA study III at 24 and 52 weeks

[b] 40 mg adalimumab administered every other week

[c] MTX = methotrexate

** $p < 0.01$, adalimumab versus placebo

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dL) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

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

In RA study IV, the ACR 20 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 ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate-naïve, combination therapy with adalimumab and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and adalimumab monotherapy at week 52 and responses were sustained at week 104 (see table 3).

Table 3. ACR responses in RA study V (percent of patients)

Response	**MTX n = 257**	**Adalimumab n = 274**	**Adalimumab /MTX n = 268**	**p-value[a]**	**p-value[b]**	**p-value[c]**
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

[a] p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[b] p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[c] p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test

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

At week 52, 42.9% of patients who received adalimumab/methotrexate combination therapy achieved clinical remission (DAS28 (CRP) < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving adalimumab monotherapy. Adalimumab/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and adalimumab monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$). Of 342 subjects originally randomized to adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of adalimumab treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Radiographic response

In RA study III, where adalimumab-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. Adalimumab/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see table 4).

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

Table 4. Radiographic mean changes over 12 months in RA study III

	Placebo/ MTX[a]	**Adalimumab /MTX 40 mg every other week**	**Placebo/MTX-adalimumab /MTX (95% CI[b])**	**p-value**
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a] methotrexate

[b] 95% CIs for the differences in change scores between methotrexate and adalimumab

[c] Based on rank analysis

[d] Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see table 5).

Table 5. Radiographic mean changes at week 52 in RA study V

	MTX n = 257 (95% CI)	**Adalimumab n = 274 (95% CI)**	**Adalimumab/ MTX n = 268 (95% CI)**	**p-value[a]**	**p-value[b]**	**p-value[c]**
Total sharp score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

[a] p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[b] p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

[c] p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test

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

In the open-label extension of RA study V, the mean change from baseline at year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, 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.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at week 52 in RA study III. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to month 6 compared to placebo and in RA study III the same was seen at week 52. Results from the Short Form Health Survey (SF-36) for all doses/schedules of adalimumab in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week 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).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to week 156 (36 months) and improvement was maintained through that time.

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

Injection site pain

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

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Adalimumab 40 mg every other week was assessed in 393 patients in two randomized, 24 week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have 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 during which patients received adalimumab 40 mg every other week subcutaneously for up to an additional 28 weeks. 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 every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyzes.

In the larger AS study I with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with adalimumab compared to placebo. Significant response was first observed at week 2 and maintained through 24 weeks (table 6).

Table 6. Efficacy responses in placebo-controlled AS study – study I reduction of signs and symptoms

Response	**Placebo N = 107**	**Adalimumab N = 208**
ASAS[a] 20		
Week 2	16%	42%***
Week 12	21%	58%***
Week 24	19%	51%***
ASAS 50		
Week 2	3%	16%***
Week 12	10%	38%***
Week 24	11%	35%***
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%***
Week 24	8%	24%***
BASDAI[b] 50		
Week 2	4%	20%***
Week 12	16%	45%***
Week 24	15%	42%***

***, ** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between adalimumab and placebo at weeks 2, 12 and 24

[a] Assessments in Ankylosing Spondylitis

[b] Bath Ankylosing Spondylitis Disease Activity Index

Adalimumab-treated patients had significantly greater improvement at week 12 which was maintained through week 24 in both the SF-36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomized, double-blind, placebo controlled AS study II of 82 adult patients with active ankylosing spondylitis.

Axial spondyloarthritis without radiographic evidence of AS

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

Study nr-axSpA I

In Study nr-axSpA I, adalimumab 40 mg every other week was assessed in 185 patients in a randomized, 12 week double-blind, placebo-controlled study in patients with active nr-axSpA (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with adalimumab and 6.5 for those on placebo) who have had an inadequate response to or intolerance to ≥ 1 NSAIDs, or a contraindication for NSAIDs.

Thirty-three (18%) patients were treated concomitantly with disease-modifying anti-rheumatic drugs, and 146 (79%) patients with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients receive adalimumab 40 mg every other week subcutaneously for up to an additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active nr-axSpA in patients treated with adalimumab compared to placebo (table 7.

Table 7. Efficacy response in placebo-controlled Study nr-axSpA I

Double-Blind Response at week 12	**Placebo N = 94**	**Adalimumab N = 91**
ASAS[a] 40	15%	36%***
ASAS 20	31%	52%**
ASAS 5/6	6%	31%***
ASAS Partial Remission	5%	16%*
BASDAI[b] 50	15%	35%**
ASDAS[c,d,e]	-0.3	-1.0***
ASDAS Inactive Disease	4%	24%***
hs-CRP[d,f,g]	-0.3	-4.7***
SPARCC[h] MRI Sacroiliac Joints[d,i]	-0.6	-3.2**
SPARCC MRI Spine[d,j]	-0.2	-1.8**

[a] Assessment of SpondyloArthritis international Society

[b] Bath Ankylosing Spondylitis Disease Activity Index

[c] Ankylosing Spondylitis Disease Activity Score

[d] Mean change from baseline

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

[f] High sensitivity C-Reactive Protein (mg/L)

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

[h] Spondyloarthritis Research Consortium of Canada

[i] n = 84 placebo and adalimumab

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

***, **, * Statistically significant at $p < 0.001$, < 0.01, and < 0.05, respectively, for all comparisons between adalimumab and placebo

In the open-label extension, improvement in the signs and symptoms was maintained with adalimumab therapy through week 156.

Inhibition of inflammation

Significant improvement of signs of inflammation as measured by hs-CRP and MRI of both Sacroiliac Joints and the Spine was maintained in adalimumab-treated patients through week 156 and week 104, respectively.

Quality of life and physical function

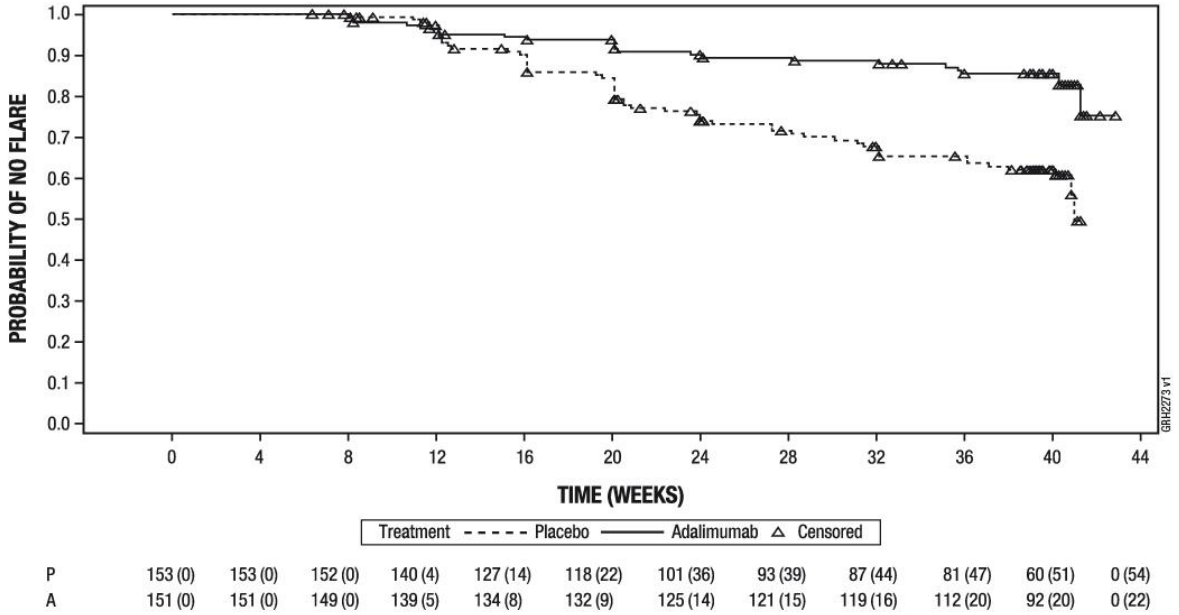
Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Adalimumab showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to week 12 compared to placebo. Improvement in health-related quality of life and physical function was maintained during the open-label extension through week 156.

Study nr-axSpA II

673 patients with active nr-axSpA (mean baseline disease activity [BASDAI] was 7.0) who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into the open-label period of Study nr-axSpA II during which they received adalimumab 40 mg eow for 28 weeks. These patients also had objective evidence of inflammation in the sacroiliac joints or spine on MRI or elevated hs-CRP. Patients who achieved sustained remission for at least 12 weeks (N = 305) (ASDAS < 1.3 at weeks 16, 20, 24, and 28) during the open-label period were then randomized to receive either continued treatment with adalimumab 40 mg eow (N = 152) or placebo (N = 153) for an additional 40 weeks in a double-blind, placebo-controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed adalimumab 40 mg eow rescue therapy for at least 12 weeks.

The primary efficacy endpoint was the proportion of patients with no flare by week 68 of the study. Flare was defined as ASDAS ≥ 2.1 at two consecutive visits four weeks apart. A greater proportion of patients on adalimumab had no disease flare during the double-blind period, when compared with those on placebo (70.4% vs. 47.1%, $p < 0.001$) (figure 1).

Figure 1: Kaplan-Meier curves summarizing time to flare in study nr-axSpA II



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

Among the 68 patients who flared in the group allocated to treatment withdrawal, 65 completed 12 weeks of rescue therapy with adalimumab, out of which 37 (56.9%) had regained remission (ASDAS < 1.3) after 12 weeks of restarting the open-label treatment.

By Week 68, patients receiving continuous adalimumab treatment showed statistically significant greater improvement of the signs and symptoms of active nr-axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study (table 8).

Table 8. Efficacy response in placebo-controlled period for study nr-axSpA II

Double-Blind **Response at Week 68**	**Placebo** **N=153**	**Adalimumab** **N=152**
ASAS[a,b] 20	47.1%	70.4%***
ASAS[a,b] 40	45.8%	65.8%***
ASAS[a] Partial Remission	26.8%	42.1%**
ASDAS[c] Inactive Disease	33.3%	57.2%***
Partial Flare[d]	64.1%	40.8%***

[a] Assessment of SpondyloArthritis international Society

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

[c] Ankylosing Spondylitis Disease Activity Score

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

***, ** Statistically significant at $p < 0.001$ and < 0.01, respectively, for all comparisons between adalimumab and placebo

Psoriatic arthritis

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

There is insufficient evidence of the efficacy of adalimumab in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

Table 9. ACR response in placebo-controlled psoriatic arthritis studies (percent of patients)

	PsA study I		**PsA study II**	
Response	**Placebo N = 162**	**Adalimumab N = 151**	**Placebo N = 49**	**Adalimumab N = 51**
ACR 20				
Week 12	14%	58%***	16%	39%*
Week 24	15%	57%***	N/A	N/A
ACR 50				
Week 12	4%	36%***	2%	25%***
Week 24	6%	39%***	N/A	N/A
ACR 70				
Week 12	1%	20%***	0%	14%*
Week 24	1%	23%***	N/A	N/A

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

* $p < 0.05$ for all comparisons between adalimumab and placebo

N/A not applicable

ACR responses in PsA study I were similar with and without concomitant methotrexate therapy. ACR responses were maintained in the open-label extension study for up to 136 weeks.

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

Adalimumab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS (mean ± SD) 0.8 ± 2.5 in the placebo group (at week 24) compared with 0.0 ± 1.9 ($p < 0.001$) in the adalimumab group (at week 48).

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.

Adalimumab-treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF-36) compared to placebo at week 24. Improved physical function continued during the open-label extension up to week 136.

Psoriasis

The safety and efficacy of adalimumab were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomized, double-blind studies. 73% of patients enrolled in psoriasis studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomized double-blind study (psoriasis study III).

Psoriasis study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg adalimumab every other week. Patients who maintained ≥ PASI 75 response at week 33 and were originally randomized to active therapy in period A, were re-randomized in period C to receive 40 mg adalimumab every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis study II (CHAMPION) compared the efficacy and safety of adalimumab versus methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to week 12, with a maximum dose of 25 mg or an initial dose of 80 mg adalimumab followed by 40 mg every other week (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%).

Patients participating in all phase 2 and phase 3 psoriasis studies were eligible to enroll into an open-label extension trial, where adalimumab was given for at least an additional 108 weeks.

In psoriasis studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at week 16 (see tables 10 and 12).

Table 10. Ps study I (REVEAL) - efficacy results at 16 weeks

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

[a] Percent of patients achieving PASI 75 response was calculated as center-adjusted rate

[b] $p < 0.001$, adalimumab versus placebo

Table 11. Ps study II (CHAMPION) efficacy results at 16 weeks

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

[a] $p < 0.001$ adalimumab versus placebo

[b] $p < 0.001$ adalimumab versus methotrexate

[c] $p < 0.01$ adalimumab versus placebo

[d] $p < 0.05$ adalimumab versus methotrexate

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

A total of 233 PASI 75 responders at week 16 and week 33 received continuous adalimumab therapy for 52 weeks in psoriasis study I, and continued adalimumab in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16

weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

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

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

Psoriasis study III (REACH) compared the efficacy and safety of adalimumab versus placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At week 16, a statistically significantly greater proportion of patients who received adalimumab achieved PGA of "clear" or "almost clear" for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [p = 0.014]).

Psoriasis study IV compared efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see table 12). Adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA ≥ 10% (60% of patients) and BSA < 10% and ≥ 5% (40% of patients)).

Table 12. Ps study IV efficacy results at 16, 26 and 52 weeks

Endpoint	**Week 16 Placebo-controlled**		**Week 26 Placebo-controlled**		**Week 52 Open-label**
	Placebo N = 108	Adalimumab 40 mg eow N = 109	Placebo N = 108	Adalimumab 40 mg eow N = 109	Adalimumab 40 mg eow N = 80
≥ mNAPSI 75 (%)	2.9	26.0[a]	3.4	46.6[a]	65.0
PGA-F clear/minimal and ≥ 2-grade improvement (%)	2.9	29.7[a]	6.9	48.9[a]	61.3
Percent change in total fingernail NAPSI (%)	-7.8	-44.2 [a]	-11.5	-56.2[a]	-72.2
[a] p < 0.001, adalimumab versus placebo					

Adalimumab-treated patients showed statistically significant improvements at week 26 compared with placebo in the DLQI.

Hidradenitis suppurativa

The safety and efficacy of adalimumab were assessed in randomized, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

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

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

Patients participating in Studies HS-I and HS-II were eligible to enroll into an open-label extension study in which adalimumab 40 mg was administered every week. Mean exposure in all adalimumab population was 762 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 a 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 13). Patients treated with adalimumab had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 13. Efficacy results at 12 weeks, HS studies I and II

	HS study I		**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 randomized 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

Treatment with adalimumab 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the adalimumab group experienced worsening of abscesses (23.0% versus 11.4%, respectively) and draining fistulas (30.0% versus 13.9%, respectively).

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

In patients with at least a partial response to adalimumab 40 mg weekly at week 12, the HiSCR rate at week 36 was higher in patients who continued weekly adalimumab than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see table 14).

Table 14. Proportion of patients[a] achieving HiSCR[b] at weeks 24 and 36 after treatment reassignment from weekly adalimumab at week 12

	Placebo (treatment withdrawal) **N = 73**	**Adalimumab 40 mg every other week** **N = 70**	**Adalimumab 40 mg weekly** **N = 70**
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[a] Patients with at least a partial response to adalimumab 40 mg weekly after 12 weeks of treatment

[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as non-responders

Among patients who were at least partial responders at week 12, and who received continuous weekly adalimumab therapy, the HiSCR rate at week 48 was 68.3% and at week 96 was 65.1%. Longer term treatment with adalimumab 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose adalimumab treatment was withdrawn at week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of adalimumab 40 mg weekly returned to levels similar to that observed before withdrawal (56.0%).

Crohn's disease

The safety and efficacy of adalimumab were assessed in over 1,500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomized, 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 (CLASSIC I) and CD study II (GAIN). In CD study I, 299 TNF-antagonist naïve patients were randomized to one of four treatment groups; placebo at weeks 0 and 2, 160 mg adalimumab at week 0 and 80 mg at week 2, 80 mg at week 0 and 40 mg at week 2, and 40 mg at week 0 and 20 mg at week 2. In CD study II, 325 patients who had lost response or were intolerant to infliximab were randomized to receive either 160 mg adalimumab at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD study III, 854 patients received open-label 80 mg at week 0 and 40 mg at week 2. At week 4 patients were randomized to 40 mg every other week, 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 analyzed separately from those not in clinical response at week 4. Corticosteroid taper was permitted after week 8.

CD study I and CD study II induction of remission and response rates are presented in table 15.

Table 15. Induction of clinical remission and response (percent of patients)

	CD study I: infliximab-naïve patients			**CD study II: infliximab experienced patients**	
	Placebo N = 74	**Adalimumab 80/40 mg N = 75**	**Adalimumab 160/80 mg N = 76**	**Placebo N = 166**	**Adalimumab 160/80 mg N = 159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for adalimumab versus placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD study III, at week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in table 16. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalizations and surgeries were statistically significantly reduced with adalimumab compared with placebo at week 56.

Table 16. Maintenance of clinical remission and response (percent of patients)

	Placebo	**40 mg adalimumab every other week**	**40 mg adalimumab every week**
Week 26	**N = 170**	**N = 172**	**N = 157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
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%*
Patients in steroid-free remission for > = 90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

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

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

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at week 4, 43% of adalimumab maintenance patients responded by week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by week 4 benefit from continued maintenance therapy through week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

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

Ulcerative colitis

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

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

In study UC-II, 248 patients received 160 mg of adalimumab at week 0, 80 mg at week 2 and 40 mg every other week 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.

Patients induced with 160/80 mg adalimumab achieved clinical remission versus placebo at week 8 in statistically significantly greater percentages in study UC-I (18% versus 9% respectively, p = 0.031) and study UC-II (17% versus 9% respectively, p = 0.019). In study UC-II, among those treated with adalimumab who were in remission at week 8, 21/41 (51%) were in remission at week 52.

Results from the overall UC-II study population are shown in table 17.

Table 17. Response, remission and mucosal healing in study UC-II (percent of patients)

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

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

Clinical response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30% plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1;

* $p < 0.05$ for adalimumab versus placebo pairwise comparison of proportions

** $p < 0.001$ for adalimumab versus placebo pairwise comparison of proportions

[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at week 52.

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

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score.

Hospitalization rates

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalizations and UC-related hospitalizations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalizations in the adalimumab treatment group was 0.18 per patient year versus 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalizations were 0.12 per patient year versus 0.22 per patient year.

Quality of life

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Intestinal Behcet's disease

Phase 3 Clinical study in Japan

In an open-label and uncontrolled study in 20 patients* with intestinal Behcet's disease who have had an inadequate response to conventional therapy (steroid or immunomodulator), marked improvement rate at week 24 (the proportion of the subjects whose global assessment of gastrointestinal symptoms and endoscopic improvement are both ≤ 1) was 45.0% (9/20).

Common adverse events (at week 52) were nasopharyngitis 9 cases (45.0%), diarrhea, Behcet's syndrome (exacerbation of original disease), contused wound and cough 3 cases (15.0%) each.

* The patients who were diagnosed to have the complete type, incomplete type or suspected according to the diagnostic criteria for Behcet's disease by the research division of the Ministry of Health, Labor and Welfare and were observed to have a typical ulcer of 1 cm or larger in longer diameter in the ileocecal region.

Uveitis

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

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

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

The primary efficacy endpoint in both studies was 'time to treatment failure'. 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).

Patients who completed Studies UV I and UV II were eligible to enroll in an uncontrolled long-term extension study with an originally planned duration of 78 weeks. Patients were allowed to continue on study medication beyond week 78 until they had access to adalimumab.

Clinical response

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 18). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see figure 2).

Table 18. Time to treatment failure in studies UV I and UV II

Analysis **Treatment**	**N**	**Failure** **N (%)**	**Median time to failure (months)**	**HR[a]**	**95% CI** **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

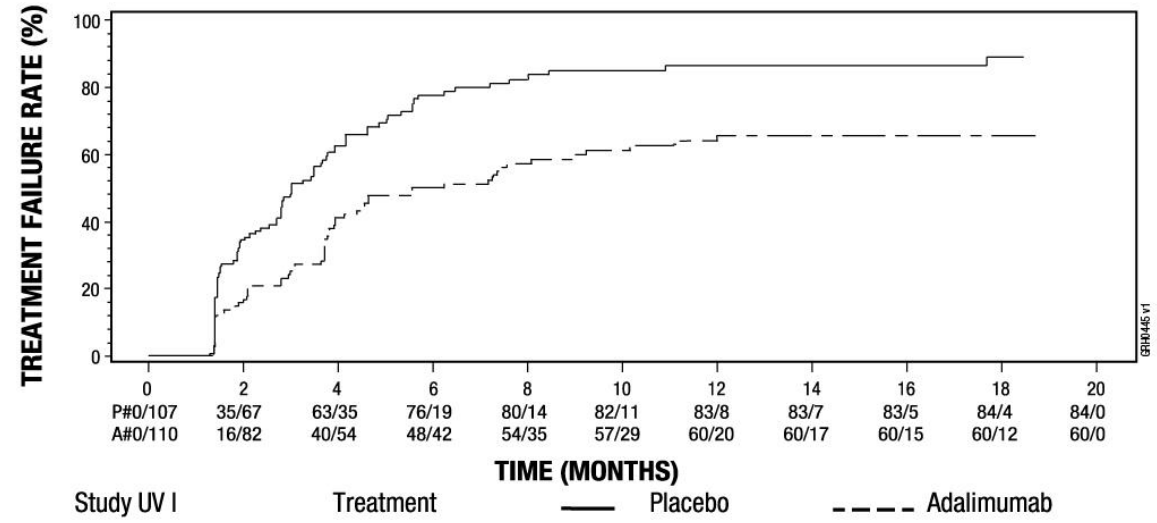
Note: Treatment failure at or after week 6 (study UV I), or at or after week 2 (study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out

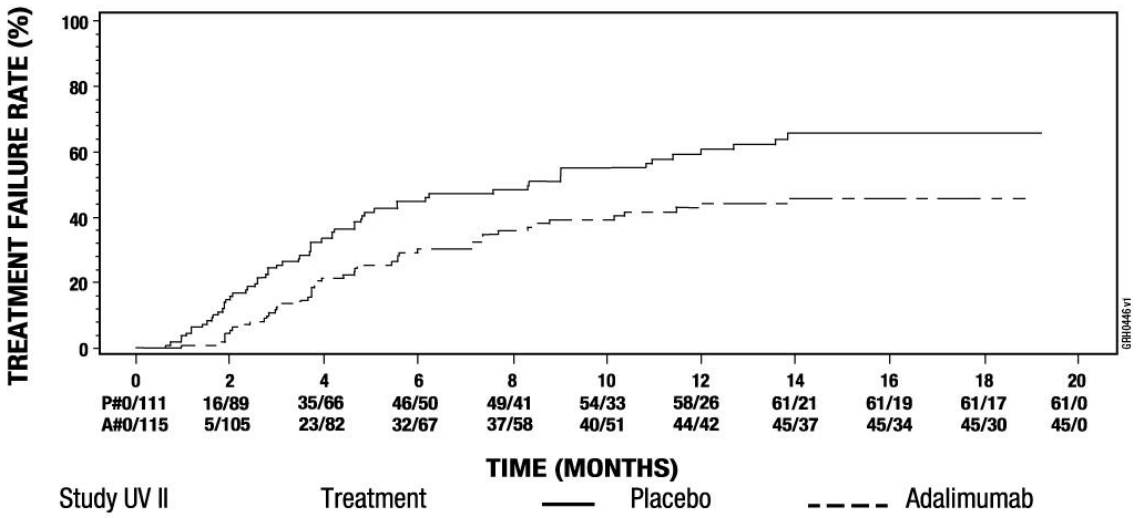
[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor

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

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

Figure 2: Kaplan-Meier curves summarizing time to treatment failure on or after week 6 (study UV I) or week 2 (study UV II)





Note: P# = Placebo (number of events/number at risk); A# = Adalimumab (number of events/number at risk).

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

Of the 424 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 60 subjects were regarded ineligible (e.g. due to deviations or due to complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 364 remaining patients, 269 evaluable patients (74%) reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 216 (80.3%) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 178 (66.2 %) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.6% of the eyes at week 78. Data beyond week 78 were generally consistent with these results but the number of enrolled subjects declined after this time. Overall, among the patients who discontinued the study, 18% discontinued due to adverse events, and 8% due to insufficient response to adalimumab treatment.

Quality of life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Adalimumab was numerically favored for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in study UV I, and for general vision and mental health in study UV II. Vision related effects were not numerically in favor of adalimumab for color vision in study UV I and for color vision, peripheral vision and near vision in study UV II.

Immunogenicity

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

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

In patients with psoriatic arthritis, anti-adalimumab antibodies were identified in 38/376 subjects (10%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.5 % (24/178 subjects), compared to 7 % (14 of 198 subjects) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis anti-adalimumab antibodies were identified in 17/204 subjects (8.3%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when adalimumab was used as add-on to methotrexate.

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

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

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In adult plaque psoriasis patients on long-term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

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

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

In Japanese patients with intestinal Behcet's disease, anti-adalimumab antibodies were identified in 5% (1/20) of patients treated with adalimumab.

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

5.2 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 mL/hour, the distribution volume (V_{ss}) ranged from 5 to 6 liters and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately 5 µg/mL (without concomitant methotrexate) and 8 to 9 µg/mL (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

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

In adult patients with psoriasis, the mean steady-state trough concentration was 5 µg/mL during adalimumab 40 mg every other week monotherapy treatment.

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

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 5.5 µg/mL during the induction period. 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 7 µg/mL were observed in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab every other week.

For patients who stayed on their randomized therapy, the mean (±SD) adalimumab trough concentrations at week 52 were 9.5 ± 5.6 µg/mL for the standard dose group and 3.5 ± 2.2 µg/mL for the low dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment every other week for 52 weeks. For patients who dose escalated from every other week 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).

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

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

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

In subjects with Behcet's disease, the mean steady-state trough adalimumab serum concentration was approximately 9 μg/mL during the treatment of 40 mg given every other week starting 4 week after an initial 160 mg dose on week 0 followed by 80 mg on week 2 as subcutaneous injections (Japanese Subjects).

Elimination

Population pharmacokinetic analyzes with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Adalimumab has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

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

An embryo-fetal developmental toxicity/perinatal developmental study has been performed in Cynomolgus monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the fetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralizing antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Sucrose

Polysorbate 80

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep AMGEVITA in the outer carton in order to protect from light.
The pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The pre-filled syringe or pre-filled pen must be protected from light, and discarded if not used within the 14-day period.

6.5 Nature and contents of container

AMGEVITA 20 mg solution for injection in pre-filled syringe
0.4 mL solution in pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a stainless steel needle with a needle shield (thermoplastic elastomer).
Pack size of one pre-filled syringe.

AMGEVITA 40 mg solution for injection in pre-filled syringe
0.8 mL solution in pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a stainless steel needle with a needle shield (thermoplastic elastomer).
Pack sizes of one, two, four or multipack of six (3 × 2) pre-filled syringes.

Not all pack sizes may be marketed.

AMGEVITA 40 mg solution for injection in pre-filled pen
0.8 mL solution for injection in pre-filled pen for patient use containing a pre-filled syringe (type I glass). The pen is a single use, disposable, handheld, mechanical injection device. The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex) (see section 4.4).
Pack sizes of one, two, four or multipack of six (3 × 2) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORIZATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. REGISTRATION HOLDER

Amgen Europe B.V.
P.O. BOX 53313
Tel - Aviv
Israel

9. LICENSE NUMBER

165-56-36181

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