AUSTRALIAN PRODUCT INFORMATION

HADLIMA® (adalimumab) Solution for Injection

1 NAME OF THE MEDICINE

Hadlima® (adalimumab) 40 mg solution for injection in pre-filled syringe

Hadlima® (adalimumab) 40 mg solution for injection in PushTouch™ auto-injector

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences.

Excipient(s) with known effect

This medicine contains sorbates.
For the full list of excipients, see Section **6.1 - LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rheumatoid Arthritis

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

Hadlima can be used alone or in combination with methotrexate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Hadlima is indicated in adult patients with moderate to severely active rheumatoid arthritis only and is not indicated for use in other conditions (see Section **4.1 - THERAPEUTIC INDICATIONS**).

Hadlima is administered by subcutaneous injection.

This product is for one dose in one patient only.

Hadlima is only available as 40 mg pre-filled syringe and 40 mg PushTouch™ auto-injector.

Rheumatoid Arthritis

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

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

Preparation of Hadlima

Hadlima is intended for use under the guidance and supervision of a physician. Patients may self-inject Hadlima if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

Sites for self-injection include thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Hadlima should not be mixed in the same syringe with any other medicine. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Hadlima contains no antimicrobial agent. Hadlima is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

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

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

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hadlima is indicated in adult patients with moderate to severely active rheumatoid arthritis only and is not indicated for use in other conditions (see Section **4.1 - THERAPEUTIC INDICATIONS**). This section also summarises information about adalimumab in other conditions.

Traceability

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

Infections

Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving TNF-blocking agents, including adalimumab. Sepsis, rare cases of tuberculosis and candidiasis have also been reported with the use of TNF antagonists, including adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections.

Treatment with adalimumab should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with adalimumab should be considered prior to initiating therapy (see Section **4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Other Opportunistic Infections**).

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

Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying

conditions, which may predispose patients to infections.

Hepatitis B Virus

Use of TNF blockers, including adalimumab, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for evidence of prior HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, Hadlima should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Tuberculosis

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

Before initiation of therapy with adalimumab, all patients should be evaluated for both active and inactive (latent) tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (e.g., chest X-ray and tuberculin skin test) should be performed in accordance with local recommendations. Treatment of latent tuberculosis infections should be initiated prior to therapy with Hadlima. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG).

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or travelled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.

If active tuberculosis is diagnosed, Hadlima therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of Hadlima in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of Hadlima in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate

course of treatment cannot be confirmed. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis. The benefit/risk balance of therapy with adalimumab should be very carefully considered.

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

Patients receiving Hadlima should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised.

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

Other Opportunistic Infections

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

Patients taking TNF blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Patients who develop a severe fungal infection are also advised to stop the TNF blocker until infections are

controlled.

Neurologic Events

Adalimumab has been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and optic neuritis, and peripheral demyelinating disease, including Guillain Barré syndrome. Prescribers should exercise caution in considering the use of Hadlima in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Hadlima should be considered if any of these disorders develop.

There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Hypersensitivity Reactions

Serious allergic reactions associated with adalimumab were rare during clinical trials. Allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed-drug reaction, non-specific drug reaction, urticaria) have been observed in approximately 1% of patients. Reports of serious allergic reactions including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Hadlima should be discontinued immediately and appropriate therapy initiated.

Haematologic Event

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

Immunosuppression

The possibility exists for TNF blocking agents, including adalimumab, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with adalimumab on the development and

course of malignancies, as well as active and/or chronic infections is not fully understood. The safety and efficacy of adalimumab in patients with immunosuppression have not been evaluated. (See Section **4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Infections** and Section **4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Description of Selected Adverse Reactions - Infections - Malignancies**).

Vaccinations

In a randomised, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with adalimumab, antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86% of patients in the adalimumab group compared to 82% in the placebo group. A total of 37% of adalimumab-treated subjects and 40% of placebo-treated subjects achieved at least a 2-fold increase in at least 3 out of 5 pneumococcal antigens. In the same study 98% of patients in the adalimumab group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of adalimumab-treated subjects and 63% of placebo-treated subjects achieved at least a 4-fold increase in at least 2 out of 3 influenza antigens.

Patients on adalimumab may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy.

Congestive Heart Failure

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

Malignancies

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist, including adalimumab compared with control patients (see Section **4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS)- Description of Selected Adverse Reactions - Malignancies**). However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk in rheumatoid

arthritis patients with long-standing, highly active inflammatory disease, which complicates the risk estimation.

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

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

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

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving adalimumab. Thus, additional caution should be exercised in considering Hadlima treatment for these patients.

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

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

Cases of acute and chronic leukaemia have been reported in association with postmarketing TNF blocker use in rheumatoid arthritis and other conditions. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukaemia, even in the absence of TNF-blocking therapy.

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

Autoimmune Processes

Treatment with adalimumab may result in the formation of autoantibodies and rarely in the development of a lupus-like syndrome. The impact of long-term treatment with adalimumab on the development of autoimmune disease is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Hadlima, treatment should be discontinued (see Section **4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Description of Selected Adverse Reactions - Autoantibodies**).

Concurrent Administration of biologic DMARDS or TNF-antagonists

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

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

Use in Psoriasis

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

Use in Hepatic Impariment

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

Use in Renal Impariment

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

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

Paediatric Use

Hadlima is not indicated for use in children less than 18 years of age.

Information about the paediatric population from other adalimumab products is summarised below.

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

Use in the Elderly

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

Effects on Laboratory Tests

There is no known interference between adalimumab and laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Adalimumab has been studied in RA patients taking concomitant methotrexate (see Section **5.1 - PHARMACODYNAMIC PROPERTIES – Clinical Trials for Rheumatoid Arthritis** and Section **5.2 - PHARMACOKINETIC PROPERTIES - Pharmacokinetics Steady-State**). The data do not suggest the need for dose adjustment of either adalimumab or methotrexate. Interactions between adalimumab and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. Concurrent administration of TNF-alpha inhibitors with anakinra or abatacept has been associated with an increased risk of serious infections (see Section **4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE** above).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effect of adalimumab on fertility has not been investigated.

Use in Pregnancy (Category C)

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

Limited clinical data on pregnant women exposed to adalimumab are available.

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

Because animal studies are not always predictive of human responses, the use of adalimumab during pregnancy is not recommended. Women of child bearing potential should be advised to use adequate contraception during adalimumab therapy. The long half-life of adalimumab should also be considered when discontinuing therapy.

Use in Lactation

It is not known whether adalimumab is excreted in animal or human milk or whether it would be absorbed by neonates after ingestion.

However, because many drugs and human immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions, breast feeding is not recommended for at least 5 months after the last Hadlima treatment. A decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother. The long half-life of adalimumab should also be considered when discontinuing therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hadlima is indicated in adult patients with moderate to severely active rheumatoid arthritis only and is not indicated for use in other conditions (see Section **4.1 - THERAPEUTIC INDICATIONS**). This section also summarises information about adalimumab in other conditions.

Clinical Trials

Adalimumab was studied in 9316 patients in controlled and open label trials. These trials included rheumatoid arthritis patients with short term and long standing disease and other conditions not approved for Hadlima - juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 5994 patients receiving adalimumab and 3704 patients receiving placebo or active comparator during the controlled period.

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

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

Adverse events at least possibly causally-related to adalimumab for clinical studies, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1000 to < 1/100); and rare ≥ 1/10000 to < 1000 in Table 1 below.

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

Table 1: Adverse Drug Reactions in Clinical Studies

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
Infections and infestations	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, 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	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	lymphoma* solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma*
Blood and the lymphatic system disorders	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	thrombocytopenia, leukocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders	Common	hypersensitivity, allergies (including seasonal allergy)

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
Metabolism and nutrition disorders	Very common Common	lipids increased hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia hyperglycaemia, hypophosphotemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders	Very common Common Uncommon Rare	headache paraesthesias (including hypoaesthesia), migraine, nerve root compression tremor, neuropathy multiple sclerosis
Eye disorders	Common Uncommon	visual impairment, conjunctivitis, blepharitis, eye swelling, diplopia
Ear and labyrinth disorders	Common Uncommon	vertigo deafness, tinnitus
Cardiac disorders	Common Uncommon Rare	tachycardia arrhythmia, congestive heart failure cardiac arrest
Vascular disorders	Common Uncommon	hypertension, flushing, haematoma vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	Common Uncommon	cough, asthma, dyspnea chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
Gastrointestinal disorders	Very common Common Uncommon	abdominal pain, nausea and vomiting GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome pancreatitis, dysphagia, face oedema
Hepato-biliary disorders	Very common Uncommon	liver enzymes elevated cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very common Common Uncommon	rash (including exfoliative rash) pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis (e.g. nail disorders), hyperhydrosis night sweats, scar
Musculoskeletal and connective tissue disorders	Very common Common Uncommon	musculoskeletal pain muscle spasms (including blood creatine phosphokinase increased) rhabdomyolysis systemic lupus erythematosus
Renal and urinary disorders	Common Uncommon	haematuria, renal impairment nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions	Very common Common Uncommon	injection site reaction (including injection site erythema) chest pain, oedema 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

System Organ Class[a)]	Frequency	Adverse Reaction[a)]
Injury, poisoning and procedural complications	Common	impaired healing

* includes open label extension studies
a) MedDRA

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

Rheumatoid Arthritis

Table 2 contains adverse reactions reported in at least 1% of RA patients with higher incidence (≥ 1%) in patients treated with adalimumab compared to control in 4 placebo-controlled RA trials (RA study I-IV).

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

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

System Organ Class[a)]	Adverse Reaction[a)]	Adalimumab (N = 1380) (%)	Control (N =690) (%)
Gastrointestinal disorders	nausea and vomiting	12	11
	abdominal pain	10	6
	sicca syndrome	3	2
	GI haemorrhage	2	1
Hepato-biliary disorders	liver enzymes elevated	12	8
Skin and subcutaneous tissue disorders	rash (including exfoliative rash)	14	7
	pruritus	5	1
	dermatitis (including eczema)	3	1
	bruising (including purpura)	2	0
Musculoskeletal, connective tissue and bone disorders	musculoskeletal pain	14	9
	muscle spasms (including blood creatine phosphokinase increased)	5	4
Renal and urinary disorders	haematuria	9	4
	renal impairment	8	4
General disorders and administration site conditions	injection site reaction (including injection site erythema)	20	13
	oedema	5	4
Investigations	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged)	9	4
	blood lactate dehydrogenase increased	2	1

[a)] MedDRA

Polyarticular Juvenile Idiopathic Arthritis

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

Hidradenitis Suppurativa

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

Uveitis

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

Description of Selected Adverse Reactions

Injection Site Reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.3% of patients receiving control treatments. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections

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

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

Malignancies

During the controlled portions of pivotal adalimumab trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, and hidradenitis suppurativa and uveitis malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.9 (4.4, 10.6) per 1000 patients years among 5196 adalimumab-treated patients versus a rate of 6.4 (3.5, 11.9) per 1000 patient years among 3347 control patients (median duration of treatment was 4.0 months for adalimumab and 3.9 months for control-treated patients).

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

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

When combining controlled portions of these trials and ongoing open label extension studies with a median duration of approximately 3.3 years including 6279 patients and over 26045 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.6 per 1000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.8 per 1000 patient years and the observed rate of lymphomas is approximately 1.3 per 1000 patient years.

No malignancies were observed in 217 paediatric patients with an exposure of 610.4

patient years during adalimumab trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

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

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

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

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

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I–V. In these adequate and well-controlled trials, 11.9% of patients treated with adalimumab and 8.1% of placebo and active control treated patients that had negative baseline antinuclear antibody titres reported positive titres at Week 24. Two patients out of 3989 treated with adalimumab in all rheumatoid, psoriatic arthritis, and ankylosing spondylitis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown.

Psoriasis: New-Onset and Worsening

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

Liver Enzyme Elevations

Rheumatoid Arthritis and Psoriatic Arthritis (PsA) Clinical Trials: In controlled Phase 3 trials of adalimumab (40 mg fortnightly), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme

elevations (e.g., NSAIDS, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear.

Juvenile Idiopathic Arthritis Clinical Trials: In a controlled Phase 3 trial of adalimumab in patients with polyarticular JIA who were 4 to 17 years and Enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of adalimumab-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular JIA who were 2 to <4 years or aged 4 years and above weighing <15 kg.

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

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

Crohn's Disease Clinical Trials: In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg fortnightly), in patients with Crohn's disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of control-treated patients.

Paediatric Crohn's Disease Clinical Trials: In the Phase 3 trial of adalimumab in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

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

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

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

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

In these studies, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare postmarketing reports of severe hepatic reactions including liver failure in patients receiving TNF blockers, including adalimumab. The causal relationship to adalimumab treatment remains unclear.

Concurrent Treatment with Azathioprine/6-Mercaptopurine

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

Polyarticular Juvenile Idiopathic Arthritis Clinical Trials

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

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

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

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

discontinuation of adalimumab treatment.

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

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

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

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

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

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

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

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

Body System	Adverse Reaction
Infections and infestations	Diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Hepatosplenic T-cell lymphoma, leukaemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)
Immune system disorders	Anaphylaxis, sarcoidosis
Nervous System Disorders	Cerebrovascular accident, Demyelinating disorders,(e.g. optic neuritis, Guillain-Barré syndrome)
Cardiac disorders	Myocardial infarction
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, pulmonary fibrosis, pleural effusion
Gastrointestinal Disorders	Intestinal perforation
Hepato-biliary disorders	Reactivation of hepatitis B, liver failure, hepatitis
Skin and subcutaneous tissue disorders	Alopecia, angioedema, cutaneous vasculitis, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), erythema multiforme, Stevens Johnson Syndrome
Musculoskeletal and connective tissue disorders	Lupus-like syndrome
General disorders and administration site conditions	Pyrexia

Comparability of Hadlima with Humira® - Adverse Effects

During clinical studies with Hadlima, 63 healthy subjects were exposed to a single dose of Hadlima, and 268 patients with RA were exposed to Hadlima every other week (EOW) up to Week 50 via subcutaneous injection (a total of 26 administrations of investigational product (IP)).

The incidence of treatement-emergent adverse events (TEAEs) up to Week 24 were 35.8% and 40.7% in the Hadlima treatment group and Humira® treatment group, respectively.

Any TEAEs that occurred in at least 1% of all patients who received Hadlima or Humira® up to Week 24 in Study SB5-G31-RA are outlined in Table 4.

Table 4: Number (%) of Patients with Treatment-Emergent Adverse Events by Preferred Term That Occurred in ≥ 1% of Patients up to Week 24 in Any Treatment Group (Safety Set 1) (Study SB5-G31-RA)

System Organ Class	Preferred Term	Hadlima 40 mg N=268		Humira® 40 mg N=273	
		n	%	n	%
Blood and Lymphatic System Disorders	Idiopathic neutropenia	3	1.1	0	0.0
Gastrointestinal Disorders	Nausea	5	1.9	6	2.2
	Diarrhoea	4	1.5	3	1.1
	Abdominal Pain	1	0.4	4	1.5
General Disorders and Administration Site Conditions	Asthenia	3	1.1	2	0.7
	Injection Site Erythema	1	0.4	4	1.5
	Injection Site Reaction	0	0.0	4	1.5
Hepatobiliary Disorders	Hepatic Steatosis	0	0.0	3	1.1
Infections and Infestations	Nasopharyngitis	13	4.9	25	9.2
	Bronchitis	7	2.6	7	2.6
	Upper Respiratory Tract Infection	5	1.9	4	1.5
	Oral Herpes	4	1.5	1	0.4
	Urinary Tract Infection	4	1.5	4	1.5
	Herpes Zoster	3	1.1	1	0.4
	Pharyngitis	2	0.7	3	1.1
Investigations	Alanine Aminotransferase Increased	6	2.2	8	2.9
	Aspartate Aminotransferase Increased	3	1.1	4	1.5
Musculoskeletal and Connective Tissue Disorders	Spinal Pain	6	2.2	7	2.6
	Arthralgia	4	1.5	1	0.4
	Back Pain	4	1.5	1	0.4
Nervous System Disorders	Headache	9	3.4	7	2.6
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1	0.4	3	1.1
Skin and Subcutaneous Tissue Disorders	Dermatitis Allergic	1	0.4	3	1.1
	Erythema	0	0.0	3	1.1
Vascular Disorders	Hypertension	1	0.4	5	1.8

N = number of patient in the Safety Set 1; n = number of patient with TEAEs.
Percentages were based on the number of patient in the Safety Set 1.
Adverse events were coded by system organ class and preferred term using the MedDRA Version 17.0 coding dictionary.

At Week 24, of the 254 subjects receiving Humira®, 125 patients were randomised to transition to Hadlima 40 mg (Humira®/Hadlima) and 129 patients were randomised to continue on Humira® 40 mg (Humira®/Humira®). The incidence of treatement-emergent adverse events (TEAEs) up to Week 52 were 52.2%, 56.4%, and 54.3% in the Hadlima, Humira® overall, and Humira®/Humira® treatment groups, respectively. Up to Week 52, 3.4% of patients reported SAEs in the Hadlima group, and 5.9% and 4.7% of patients reported SAEs each in the Humira® overall and the Humira®/Humira® treatment group among a total of 29 SAEs from 25 (4.6%) patients. After 24 weeks, the overall incidence of TEAEs reported were Hadlima/Hadlima (32.3%), Humira®/Hadlima (37.6%) and Humira®/Humira® (33.1%). After Week 24 for SAF2,

2.4%, 3.2%, and 3.1% of patients reported SAEs accordingly in the Hadlima/Hadlima treatment group, in the Humira®/Hadlima treatment group, and in the Humira®/Humira® treatment group.

Any TEAEs that occurred in at least 2% of all patients who received Hadlima or Humira® up to Week 52 and after Week 24 in Study SB5-G31-RA are outlined in Table 5 and Table 6, respectively.

Table 5: Number (%) of Patients with Treatment-Emergent Adverse Events by Preferred Term That Occurred in ≥ 2% of Patients up to Week 52 in Any Treatment Group (Safety Set 1) (Study SB5-G31-RA)

System Organ Class	Preferred Term	Hadlima 40 mg N=268		Humira® 40 mg			
				Overall N=273		Humira 40 mg N=127[a]	
		n	%	n	%	n	%
Gastrointestinal Disorders	Nausea	8	3.0	6	2.2	4	3.1
Infections and Infestations	Nasopharyngitis	24	9.0	30	11.0	16	12.6
	Bronchitis	11	4.1	11	4.0	5	3.9
	Latent Tuberculosis	11	4.1	8	2.9	7	5.5
	Upper Respiratory Tract Infection	10	3.7	8	2.9	1	0.8
	Urinary Tract Infection	8	3.0	7	2.6	2	1.6
Investigations	Increased Alanine Aminotransferase I	9	3.4	12	4.4	7	5.5
	Increased Aspartate Aminotransferase	3	1.1	6	2.2	3	2.4
Musculoskeletal and Connective Tissue Disorders	Spinal Pain	8	3.0	9	3.3	6	4.7
	Arthralgia	7	2.6	2	0.7	0	0.0
	Back Pain	7	2.6	4	1.5	3	2.4
	Rheumatoid Arthritis	4	1.5	7	2.6	4	3.1
Nervous System Disorders	Headache	11	4.1	14	5.1	6	4.7

N = number of patient in the Safety Set 1; n = number of patient with TEAEs
Percentages were based on the number of patient in the Safety Set 1.
[a] based on the patients in the Safety Set 2
Adverse events were coded by system organ class and preferred term using the MedDRA Version 17.0 coding dictionary.
Humira® Overall = consisted of results from all patients who were randomised to Humira® at Week 0, regardless of whether they were re-randomised to Hadlima or Humira® at Week 24

Table 6: Number (%) of Patient with Treatment-Emergent Adverse Events by Preferred Term Newly Occurred after Week 24 in ≥ 2% of Patients in Any Treatment Group (Safety Set 2) (Study SB5-G31-RA)

System Organ Class	Preferred Term	Hadlilma / Hadlima 40 mg N=254		Humira®/Hadlima 40 mg N=125						Humira ®/ Humira ® 40 mg N=127	
				Hadlima		Undeter-mined		Overall			
		n	%	n	%	n	%	n	%	n	%
Infections and Infestations	Upper Respiratory Tract Infection	4	1.6	1	0.8	5	4.0	5	4.0	0	0.0
	Urinary Tract Infection	5	2.0	1	0.8	2	1.6	3	2.4	0	0.0
	Bronchitis	5	2.0	0	0.0	2	1.6	2	1.6	2	1.6
	Latent Tuberculosis	8	3.1	0	0.0	1	0.8	1	0.8	7	5.5
	Nasopharyngitis	11	4.3	0	0.0	4	3.2	4	3.2	3	2.4
Investigations	Increased Alanine Aminotransferase	3	1.2	1	0.8	0	0.0	1	0.8	3	2.4
	Mycobacterium Tuberculosis Complex Test Positive	2	0.8	1	0.8	3	2.4	4	3.2	1	0.8
Musculoskeletal and Connective Tissue Disorders	Rheumatoid Arthritis	4	1.6	1	0.8	2	1.6	3	2.4	4	3.1
	Spinal Pain	5	2.0	0	0.0	3	2.4	3	2.4	2	1.6
Nervous System Disorders	Headache	2	0.8	0	0.0	3	2.4	3	2.4	4	3.1

N = number of patient in the Safety Set 2; n = number of patient with TEAEs
E = frequency of the adverse events; TEAE = treatment-emergent adverse event
Adverse events were coded by system organ class and preferred term using the MedDRA Version 17.0 coding dictionary.
For Humira®/Hadlima treatment group, if a lag time window overlapped with pre-transition IP (Humira®) exposure time period (28 days), then the AE was considered to be undetermined. Otherwise, the AE was considered to be attributed to post-transition IP (Hadlima).
Percentages were based on the number of subjects in the Safety Set 2.

Abnormalities in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for Hadlima observed in Study SB5-G31-RA are included in Table 4, Table 5 and Table 6.

Blood samples for determination of immunogenicity were collected at baseline and Weeks 4, 8, 16, 24, 32, 40 and 52.

The incidence of ADAs and NAbs to adalimumab for the safety set is presented in Table 7.

Table 7. Incidence of Anti-Drug Antibodies and Neutralizing Antibodies to Adalimumab (Safety Set 1 and Safety Set 2, Study SB5-G31-RA)

Timepoint	Parameter	Result	Hadlima 40 mg	Humira® 40 mg			Total
				Overall	Hadlima 40 mg	Humira® 40 mg	
			N=268	N=273	N=125[a]	N=127[a]	N=541
			n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Week 0	ADA	Positive	19/267 (7.1)	8/271 (3.0)	3/125 (2.4)	3/126 (2.4)	27/538 (5.0)
	NAb	Positive	1/19 (5.3)	0/8 (0.0)	0/3 (0.0)	0/3 (0.0)	1/27 (3.7)
Week24	ADA	Positive	67/256 (26.2)	67/257 (26.1)	35/125 (28.0)	31/127 (24.4)	134/513 (26.1)
	NAb	Positive	32/67 (47.8)	32/67 (47.8)	15/35 (42.9)	17/31 (54.8)	64/134 (47.8)
Week 24 overall[b]	ADA	Positive	79/246 (32.1)	81/260 (31.2)	42/122 (34.4)	35/123 (28.5)	160/506 (31.6)
Week 52	ADA	Positive	62/247 (25.9)	75/242 (31.0)	35/118 (29.7)	40/124 (32.3)	139/489 (28.4)
	NAb	Positive	32/64 (50.0)	41/75 (54.7)	18/35 (51.4)	23/40 (57.5)	73/139 (52.5)
Week 52 overall[b]	ADA	Positive	88/246 (35.8)	97/260 (37.3)	47/122 (38.5)	46/123 (37.4)	185/506 (36.6)
After Week 24 overall[c,d]	ADA	Positive	9/160 (5.6)	16/167 (9.6)	5/80 (6.3)	11/87 (12.6)	25/327 (7.6)
Week 52 overall[b,c]	ADA	Positive	85/236 (36.0)	93/245 (38.0)	47/122 (38.5)	46/123 (37.4)	178/481 (37.0)

N = number of patients in the Safety Set 1 (all patients who received at least 1 dose of IP during the study);
n = number of patients with event of interest, n' = number of patients with available assessment result against Hadlima at each timepoint
ADA = anti-drug antibody, NAb = neutralizing antibody
[a] Based on the patients in the Safety Set 2 (all SAF1 patients who received at least 1 dose of IP after re-randomization at Week 24); Humira®/ Hadlima and Humira®/Humira® may not add up to Humira® overall.
[b] Overall ADA results were determined as 'Positive' if patient had at least 1 ADA-positive until the relevant timepoint among the patients with ADA-negative result at Week 0 and 'Negative' if patient had no ADA-positive until the relevant timepoint.
[c] Values were from the Safety Set 2.
[d] After transition overall were determined as 'Positive' if patient had at least one ADA-positive from Week 32 to Week 52 among patients with the overall ADA-negative at Week 24 and 'Negative' if patient had no ADA-positive from Week 32 to Week 52 among patients with the overall ADA-negative at Week 24.
Percentages were based on n'.
Safety Set 1 (SAF1): this set consisted of all patients who received at least 1 dose of IP during the study. Patients who received the wrong IP were analyzed according to the actual treatment received.
Safety Set 2 (SAF2): this set consisted of all SAF1 patients who received at least 1 dose of IP after re-randomization at Week 24. This set was analyzed for the data after the re-randomization.

4.9 OVERDOSE

The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with Hadlima. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

General

Adalimumab binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis (RA) and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.

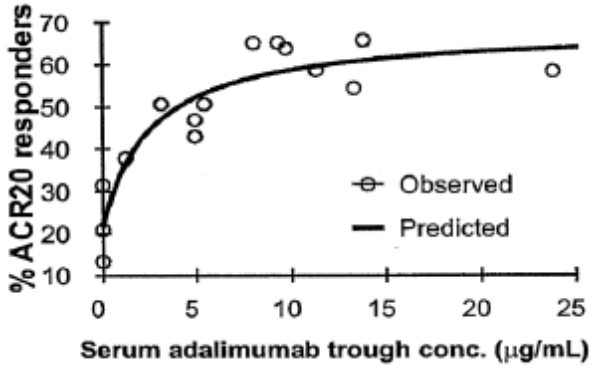
Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

Pharmacodynamics

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with RA. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients treated with adalimumab usually experienced improvement in haematological signs of chronic inflammation.

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

Figure 1: Concentration-Efficacy Relationship



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

Comparability of Hadlima with Humira® - Pharmacodynamic Properties

The comparability assessments of pharmacodynamic *in vitro* studies including binding- and cell-based assays, as well as an *in vivo* efficacy study using a Tg197 transgenic mouse model of arthritis demonstrated similar pharmacological activity between Hadlima and Humira®.

Results from *in vitro* assays including binding assays on TNF-α, C1q and Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa and FcRn), and other cell-based assays such as apoptosis, Antibody Dependent Cell-mediated Cytotoxicity (ADCC) and Complement Dependent Cytotoxicity (CDC) assays demonstrated similarity between Hadlima and Humira®.

An *in vivo* study using a Tg197 transgenic mouse model of arthritis was performed to assess drug efficacy in animals. The *in vivo* study results showed a similar inhibition level of arthritic and histopathologic scores between Hadlima, and US Humira®, which demonstrated a similar *in vivo* behaviour, especially in relation to the mechanism of action of adalimumab. A repeated dose toxicity study was performed to evaluate and demonstrate similarity in toxicological profiles between Hadlima and US Humira® in cynomolgus monkeys. The results showed that Hadlima and US Humira® were similarly well tolerated.

Clinical Trials with Humira®

Clinical Trials for Rheumatoid Arthritis

Description of Clinical Trials

Adalimumab was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for greater than 60 months duration. The efficacy and safety of adalimumab were assessed in five randomised, double-blind and well-controlled studies.

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

RA Study I (DE009) evaluated 271 patients with moderately to severely active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying anti-rheumatic drugs (DMARDs) and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Patients had ≥ 6 swollen joints and ≥ 9 tender joints and RA diagnosed according to ACR criteria. Doses of 20, 40 or 80 mg of adalimumab or placebo were given fortnightly for 24 weeks.

RA Study II (DE011) evaluated 544 patients with moderately to severely active RA who were ≥ 18 years old and had failed therapy with at least one DMARD. Patients, who were not permitted methotrexate or other DMARDs during the study, had ≥ 10 swollen joints and ≥ 12 tender joints and were also diagnosed according to ACR criteria. Doses of 20 or 40 mg of adalimumab were given by subcutaneous injection fortnightly with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration.

RA Study III (DE019) evaluated 619 patients with moderately to severely active RA who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. Patients had 6 swollen joints and ≥ 9 tender joints and RA diagnosed according to ACR criteria. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab fortnightly with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered fortnightly, for up to 5 years. The objectives of this open-label extension were to evaluate the long-term safety and maintenance of efficacy of adalimumab in subjects with RA receiving concurrent MTX. The maintenance of efficacy was assessed by evaluating the effect of adalimumab on the signs and symptoms of RA, physical function, structural damage, rates of clinical remission and patient-reported outcomes. Of the 457 patients who entered the open-label extension, 53/457 (11.6%) subjects discontinued the study due to adverse events, and 16/457 (3.5%) subjects discontinued because of a lack of efficacy/disease progression.

RA Study IV (DE031) primarily assessed safety in 636 patients with moderately to severely active RA who were ≥ 18 years old. These patients met the ACR criteria for diagnosis of RA for at least three months and had at least 6 swollen joints and 9 tender joints. Patients were permitted to be either DMARD naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomised to 40 mg of adalimumab or placebo fortnightly for 24 weeks.

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

Results of all five trials were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary endpoint in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR20 response at Week 24 or 26. The primary endpoint in RA Study V was the percent of patients who achieved an ACR50 response at Week 52. RA Studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA Study III also had a primary endpoint of changes in quality of life.

Clinical Response

RA Studies I, II and III

The percent of adalimumab-treated patients achieving ACR20, 50 and 70 responses was consistent across all three trials. The results for the 40 mg fortnightly dose are summarised in Table 8.

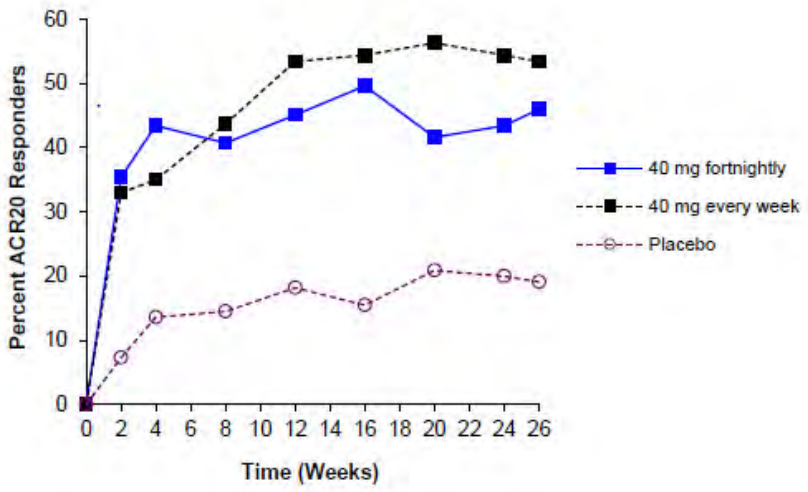
Table 8: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a*]		RA Study II[a*]		RA Study III[a, c *]	
	Placebo /MTX N=60	Adalimumab[b] /MTX N=63	Placebo N=110	Adalimumab[b] *N=113	Placebo /MTX N=200	Adalimumab[b] /MTX N=207
ACR20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] RA Study I at 24 weeks, RA Study II at 26 weeks, and RA Study III at 24 and 52 weeks
[b] 40 mg adalimumab administered fortnightly
[c] The 12 months placebo-controlled phase of RA Study III was followed by 12 months of open-label treatment with ACR responses at 24 months of 48.8% (ACR20), 36.2% (ACR50) and 22.7% (ACR70).
* $p<0.01$, Adalimumab vs. placebo at all timepoints for ACR20, 50, 70
MTX Methotrexate

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

Figure 2: RA Study II ACR20 Responses over 26 Weeks



The results of the components of the ACR response criteria for RA Study III are shown in Table 9. ACR response rates and improvement in all ACR response criteria were maintained to Week 104. Over the 2 years in RA Study III, 20% of adalimumab patients achieved a major clinical response, defined as maintenance of an ACR70 response over a > 6 month period.

Table 9: Components of ACR Response in RA Study lll

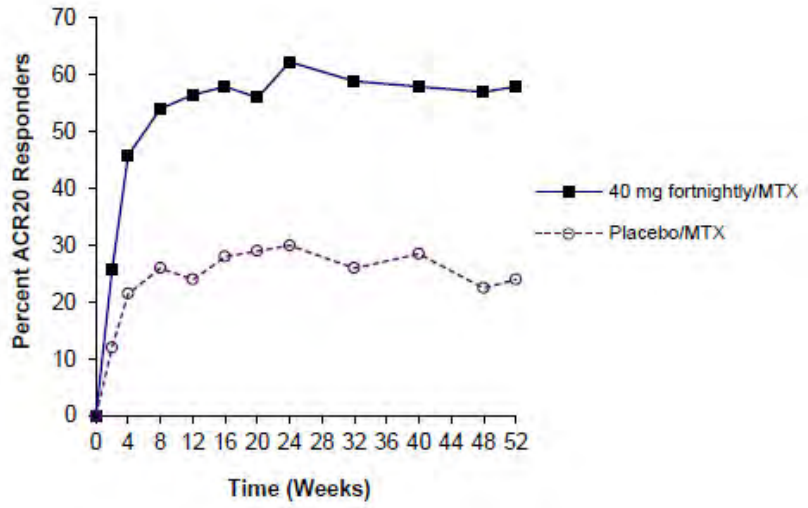
Parameter (median)	Placebo/MTX (N=200)			Adalimumab[a]/MTX (N=207)		
	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Number of tender joints (0-68)	26.0	15.0	15.0	24.0	8.0*	6.0*
Number of swollen joints (0-66)	17.0	11.0	11.0	18.0	5.0*	4.0*
Physician global assessment disease activity[b]	63.0	35.0	38.0	65.0	20.0*	16.0*
Patient global assessment disease activity[b]	53.5	39.0	43.0	52.0	20.0*	18.0*
Pain[b]	59.5	38.0	46.0	58.0	21.0*	19.0*
Disability index (HAQ)[c]	1.50	1.25	1.25	1.50	0.75*	0.75*
CRP (mg/L)	10.0	9.0	9.0	10.0	4.0*	4.0*

[a] 40 mg adalimumab administered fortnightly
[b] Visual analogue scale; 0 = best, 100 = worst
[c] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to erform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* p<0.001, Adalimumab vs. placebo, based on mean change from baseline

In RA Study III, 84.7% of patients with ACR20 responses at Week 24 maintained the response at 52 weeks. Clinical responses were maintained for up to 5 years in the

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

Figure 3: RA Study III ACR20 Responses over 52 Weeks



RA Study IV

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

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

RA Study V

In RA Study V for early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with adalimumab plus methotrexate led to significantly greater ACR responses than methotrexate monotherapy at Week 52 and responses were sustained at Week 104 (see Table 10).

At Week 52, all individual components of the ACR response criteria improved with adalimumab/methotrexate therapy and improvements were maintained to Week 104.

Over the two-year study, 48.5% patients who received adalimumab/methotrexate combination therapy achieved a major clinical response (ACR70 for > six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ($p<0.001$).

Table 10: ACR20/50/70 Response at Weeks 26, 52, 76 and 104 (All Randomised Subjects) in RA Study V

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

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

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

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

In RA Study V, adalimumab/methotrexate combination therapy was superior to methotrexate monotherapy in achieving clinical remission defined as Disease Activity Score (DAS28) < 2.6 at Week 52 (see Table 11).

Table 11: Subjects in Remission as Defined by DAS28 < 2.6 at Week 52 (All Randomised Subjects) in RA Study V

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

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

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

MTX Methotrexate

Radiographic Response

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

In the open-label extension of RA Study III, 77% of the original patients treated with any dose of adalimumab were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS; 54% had no progression of structural damage as defined by a change in the TSS of zero or less.

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

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

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

[a] 40 mg administered fortnightly
[b] Based on rank analysis
MTX Methotrexate
* 95% confidence intervals for the differences in change scores between MTX and adalimumab

In RA Study V, adalimumab-treated patients had a mean duration of rheumatoid arthritis of less than 9 months and had not previously received methotrexate. Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score. The Week 52 results are shown in Table 13. A statistically significant difference for change in modified Total Sharp Score and the erosion score was observed at Week 52 and maintained at Week 104.

Table 13: Change in Modified Total Sharp Score from Baseline at Weeks 52 and 104 (All Randomised Subjects) in RA Study V

	MTX N=257	Adalimumab N=274	Adalimumab + MTX N=268	p-value[a]	p-value[b]
Week 52					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 52 (mean)	27.6 ± 24.6	21.8 ± 19.7	19.4 ± 19.9		
Change at Week 52 (mean ± SD)	5.7 ± 12.7	3.0 ± 11.2	1.3 ± 6.5	< 0.001	0.002
Week 104					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 104 (mean)	32.3 ± 30.0	24.3 ± 23.2	20.0 ± 20.5		
Change at Week 104 (mean ± SD)	10.4 ± 21.7	5.5 ± 15.8	1.9 ± 8.3	< 0.001	< 0.001

Note: Primary analysis imputation used for missing data.

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

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

Physical Function

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

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

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

Results

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

Table 14: Percentage of Patients Achieving Improvement in Physical Function After One and Two Years of Treatment In RA Study III

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

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

Quality of Life

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

In RA Study V, the active-comparator controlled study in early rheumatoid arthritis, the improvement in the HAQ disability index and the physical component of the SF-36 showed greater improvement ($p<0.001$) for adalimumab/methotrexate combination therapy versus methotrexate monotherapy at Week 52, which was maintained through Week 104.

Comparability of Hadlima with Humira® - Clinical Trials

The comparability of Hadlima and EU Humira® was assessed in a randomised, double-blind, parallel group, multicentre, clinical Phase III study in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (Study SB5-G31-RA).

This study evaluated 544 patients who were 18-75 years old with moderate to severe active disease despite MTX therapy. At Week 0, 544 patients were randomised in 1:1 ratio to receive either Hadlima 40 mg or Humira® 40 mg every other week via subcutaneous injection. Up to Week 24, 271 patients and 273 patients were exposed to at least one dose of Hadlima and Humira®, respectively. In addition to adalimumab, each patient also took a stable dose of oral or parenteral MTX (10-25 mg weekly) and was required to take folic acid (5-15 mg weekly) while taking MTX.

The primary objective of the study was to demonstrate therapeutic equivalence of Hadlima to EU Humira® at Week 24, in terms of ACR20 response. The two treatment groups were considered equivalent if the 95% CI of the difference of the two proportions was entirely contained within the pre-justified margin of [−15%, 15%]. Other efficacy endpoints included the ACR50 response, the ACR70 response, individual components of the ACR improvement criteria, DAS28, major clinical response, and the European League Against Rheumatism (EULAR) response (good response, moderate or no response).

The demographic characteristics were comparable between the Hadlima and EU Humira® treatment groups, however, there was a statistically significant difference in age between the groups (49.8 vs. 52.5 years, p-value = 0.010).The proportion of patients aged at least 65 years was 10.7% in the SB5 treatment group, and 14.7% in the EU Humira® treatment group. The majority of patients were female (81.1%) and white (99.3%).

The baseline disease characteristics were comparable, with no statistically significant differences between the Hadlima treatment group and the EU Humira® treatment group. The mean disease duration of RA at baseline was 5.44 years in the Hadlima treatment group and 5.46 years in the EU Humira® treatment group. Furthermore, the overall mTSS score at baseline in the Hadlima treatment group and the EU Humira® treatment group were 29.51 and 31.39, respectively. The mean weekly dose of MTX at Baseline was 15.13 mg in the Hadlima treatment group and 15.35 mg in the EU Humira® treatment group.

The primary efficacy endpoint, ACR20 response rate at Week 24 was equivalent in Hadlima treatment group and Humira® treatment group in the per-protocol set 1 (PPS1) (see Table 15). The proportion of patients achieving ACR20 response at Week 24 was 72.4% (173/239) and 72.2% (171/237) in the Hadlima and EU Humira® treatment groups, respectively. The adjusted treatment difference in ACR20 response rate at Week 24 was 0.1% and the 95% confidence interval (CI) of the adjusted treatment difference was [−7.83%, 8.13%] which was completely contained within the pre-defined equivalence margin of [−15%, 15%]. Furthermore, with non-responder imputation, the ACR20 response rates of Hadlima and EU Humira® were

equivalent at Week 24 for the full analysis set; 68.0% of the Hadlima patients and 67.4% of the EU Humira® patients achieved the ACR20 response rates at Week 24.

The secondary efficacy endpoints of ACR50, ACR70, DAS28, EULAR response at Week 24 were comparable between Hadlima and EU Humira®.

The analysis of ACR 20, ACR50, ACR70 response rate at Week 24 are shown in Table 15.

Table 15: Primary Analysis of ACR20, ACR50 and ACR70 Response Rate at Week 24 Per protocol Set, Study SB5-G31-RA)

ACR Response	Time Point	Treatment	n/n'	(%)	Estimated Difference in Proportions	95% CI (%)
ACR20[a]	Week 24	Hadlima (N=239)	173/239	(72.4)	0.1%	[−7.83%, 8.13%]
		EU Humira® (N=237)	171/237	(72.2)		
ACR50[a]	Week 24	Hadlima (N=239)	91/239	(38.1)	−2.0%	[−10.69%, 6.75%]
		EU Humira® (N=237)	94/237	(39.7)		
ACR70 [a]	Week 24	Hadlima (N=239)	46/239	(19.2)	−1.3%	[−8.41%, 5.80%]
		EU Humira® (N=237)	48/237	(20.3)		

N = number of patients in the per-protocol Set; n = number of responders; n' = number of patients with an assessment; ACR20 = American College of Rheumatology 20% response criteria; ACR50 =American College of Rheumatology 50% response criteria; ACR70 =American College of Rheumatology 70% response criteria; CI = confidence interval

Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline C-reactive protein (CRP) value as a covariate.

[a] Per-protocol set 1 (PPS1) = this set consisted of all full analysis set (FAS) patients who completed the Week 24 visit and had an adherence (through Week 24) within the range of 80-120% of both the expected number of investigational product (IP) administrations and the expected sum of MTX doses without any major protocol deviations (PDs) that had an impact on the efficacy assessment. The PPS1 is the primary analysis set. Major PDs that led to exclusion from this set were pre-specified prior to unblinding the treatment codes

At Week 24, 254 patients receiving Humira® were randomised again to either continue on Humira® 40 mg (Humira®/Humira®) or be transitioned to Hadlima 40 mg (Humira®/Hadlima) every other week up to Week 50. Patients receiving Hadlima 40 mg continued to receive Hadlima 40 mg (Hadlima/Hadlima) up to Week 50. 129 patients were continued to be exposed to at least one dose of Humira® and 125 patients were exposed to at least one dose of Hadlima following the transition from Humira® treatment.

The analysis of ACR 20, ACR50, ACR70 response rate at Week 52 are shown in the Table 16.

Table 16. Primary Analysis of ACR20, ACR50 and ACR70 Response Rate at Week 52 Per protocol Set, Study SB5-G31-RA)

ACR Response	Time Point	Treatment	n/n'	(%)
ACR20[a]	Week 52	Hadlima (N=212)	163/212	(76.9)
		Humira®/Humira® (N=111)	79/111	(71.2)
		Humira®/Hadlima (N=106)	86/106	(81.1)
		Humira® overall (N=217)	165/217	(76.0)
ACR50[a]	Week 52	Hadlima (N=212)	104/212	(49.1)
		Humira®/Humira® (N=111)	57/111	(51.4)
		Humira®/Hadlima (N=106)	57/106	(53.8)
		Humira® overall (N=217)	114/217	(52.5)
ACR70 [a]	Week 52	Hadlima (N=212)	66/212	(31.1)
		Humira®/Humira® (N=111)	34/111	(30.6)
		Humira®/Hadlima (N=106)	28/106	(26.4)
		Humira® overall (N=217)	62/217	(28.6)

N = number of patients in the per-protocol Set; n = number of responders; n' = number of patients with an assessment; ACR20 = American College of Rheumatology 20% response criteria; ACR50 =American College of Rheumatology 50% response criteria; ACR70 =American College of Rheumatology 70% response criteria; CI = confidence interval
Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline C-reactive protein (CRP) value as a covariate.
[a] Per-protocol set 2 (PPS2) = this set consisted of all FAS patients who completed the Week 52 visit and had an adherence (through Week 52) within the range of 80-120% of both the expected number of IP administrations and the expected sum of MTX doses without any major PDs that had an impact on the efficacy assessment including deviation from inclusion/exclusion criteria and having taken prohibited concomitant medication and not in the assigned treatment group.

During the study, the efficacy by anti-drug antibody (ADA) status was assessed as a subgroup analysis. In ADA positive patients, the ACR20 response rate at Week 24 was lower in the Hadlima treatment group than in the Humira® treatment group (57.5% and 71.2%, respectively), while the ACR50 response rates were 28.8% and 35.6%, and the ACR 70 response rates were 19.2% and 16.4% in the Hadlima and the Humira® treatement groups, respectively. The ACR20 response rates at Week 52 in ADA positive patients were 67.1%, 82.1%, and 76.2% in the Hadlima, Humira®/Hadlima, and Humira®/Humira® treatment groups, respectively. Due to the small subgroup analyses, these results have a limitation to draw a definite conclusion.

Immunogenicity of Humira®

Hadlima is indicated in adult patients with moderate to severely active rheumatoid arthritis only and is not indicated for use in other conditions (see Section **4.1 - THERAPEUTIC INDICATIONS**). This section also summarises information about adalimumab in other conditions.

Patients in rheumatoid arthritis studies I, II, and III were tested at multiple time points for anti-adalimumab antibodies during the 6- to 12-month period. Approximately 5.5% (58 of 1,062) of adult rheumatoid arthritis patients receiving

adalimumab developed low-titer antibodies to adalimumab at least once during treatment, which were neutralising *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg fortnightly as monotherapy, the ACR20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

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

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

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 11% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 14% (3/22), compared to 8% (2/24) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis, the rate of development of anti-adalimumab antibodies in adalimumab-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving adalimumab monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. The immunogenicity rate was 8% for psoriasis patients who were treated with adalimumab monotherapy.

In adult patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab. In paediatric patients with moderately to severely active Crohn's disease, the rate of antibody development in patients receiving adalimumab was 3.3%.

In patients with ulcerative colitis, anti-adalimumab antibodies were identified in 3.9% (19/487) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were <2 micrograms/mL. Among the patients whose serum adalimumab levels were < 2 micrograms/mL (approximately 25% of total patients studied), the immunogenicity rate was 20. 7%.

In plaque psoriasis patients on long term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was similar to the rate observed prior to withdrawal.

In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 13% (5/38) of subjects treated with 0.8 mg/kg adalimumab monotherapy.37 of the 38 subjects completed the initial double blind period (16 weeks) of Study M04-717, and one subject entered the long term follow up period after Week 4.

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

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

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

Immunogenicity of Hadlima

Refer to Section **4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Comparability of Hadlima with Humira® - Adverse Effects,** and to Section **5.1 - PHARMACODYNAMIC PROPERTIES - Comparability of Hadlima with Humira® - Clinical Trials** for information on the immunogenicity of Hadlima.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics

Absorption

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

Distribution and Elimination

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

Steady-State

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab fortnightly to patients with RA, with mean steady-state trough concentrations of approximately 5 micrograms/mL (without concomitant methotrexate (MTX)) and 8 to 9 micrograms/mL (with concomitant MTX), respectively. These trough concentration levels are well above the EC_{50} estimates of 0.8 to 1.4 micrograms/mL and consistent with those at which ACR20 responses appear to reach a maximum (Figure 1). The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg fortnightly and every week SC dosing. In long-term studies with dosing for more than two years, there was no evidence of changes in clearance over time.

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

Minor increases in apparent clearance were predicted in RA patients receiving doses lower than the recommended dose, and in RA patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

Special Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Geriatrics

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

Gender

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

Race

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

Hepatic and Renal Insufficiency

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

Disease States

Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Drug Interactions, Methotrexate

When adalimumab was administered to 21 RA patients on stable methotrexate therapy, there were no statistically significant changes in the serum methotrexate concentration profiles. In contrast, after single and multiple dosing, methotrexate reduced adalimumab's apparent clearances by 29% and 44% respectively (see Section **4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE**, Section **4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). This is consistent with the higher trough concentrations of adalimumab found in patients treated with concomitant methotrexate (see Section **5.2 - PHARMACOKINETIC PROPERTIES - Pharmacokinetics - Steady-State**).

Comparability of Hadlima with Humira® - Pharmacokinetic Properties

The pharmacokinetic profiles of Hadlima and Humira® were comparable in a randomised, single-blind, three-arm, parallel group clinical Phase I study in healthy subjects following a single SC injection of either Hadlima, EU Humira® or US Humira® (40 mg) (Study SB5-G11-NHV). The PK parameters, AUC_{inf}, AUC_{last} and C_{max}, were compared between Hadlima and Humira®. The summary of the pharmacokinetic profiles of Hadlima and EU Humira® in healthy volunteers are listed in Table 17.

Table 17: Statistical Comparison of PK Parameters (Hadlima vs. EU Humira®) (Study SB5-G11-NHV)

PK Parameter	Treatment	N	n	Geometric LS Mean	LS Mean Ratio	90% CI of Ratio
AUC_{inf}	Hadlima	62	53	2262.1	0.990	0.885 - 1.108

PK Parameter	Treatment	N	n	Geometric LS Mean	LS Mean Ratio	90% CI of Ratio
(µg·h/mL)	EU Humira®	63	61	2284.3		
AUC_{last} (µg·h/mL)	Hadlima	62	53	2007.0	1.027	0.915 - 1.153
	EU Humira®	63	61	1954.0		
C_{max} (µg/mL)	Hadlima	62	53	3.229	0.957	0.870 - 1.054
	EU Humira®	63	61	3.373		

AUC_{last} : area under the concentration-time curve from time zero to the last quantifiable concentration;
AUC_{inf} : area under the concentration-time curve from time zero to infinity;
CI : confidence interval;
C_{max} : maximum concentration; LS Means: least squares means; N: number of subjects in PK population; n: number of subjects who contributed to analysis.

In addition, to provide supportive evidence of PK similarity between Hadlima and EU Humira® in patients with RA, pharmacokinetic profiles were evaluated in a subset of RA patients receiving either 40 mg of Hadlima (n=178) or 40 mg of EU Humira® (n=178) in a randomised, double-blind, parallel group clinical Phase III study (Study SB5-G31-RA). The levels of C_{trough} from Week 4 to Week 24 were comparable between Hadlima and EU Humira®, ranging from 3.850 to 6.761 µg/mL for Hadlima and 3.892 to 6.773 µg/mL for EU Humira®.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

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

Genotoxicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hadlima 40 mg: Inactive ingredients include: 1.6 mg sodium citrate dihydrate, 0.544 mg citric acid monohydrate, 0.96 mg L-histidine, 8.64 mg L-histidine hydrochloride monohydrate, 20.0 mg sorbitol, 0.64 mg polysorbate 20 and water for injections.

6.2 INCOMPATIBILITIES

Hadlima should not be mixed in the same syringe with any other medicine.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (in a refrigerator) and store the syringe and PushTouch™ auto-injector in the outer carton to protect from light. Do not freeze.

Do not use beyond the expiration date.

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

Hadlima is a prescription only medicine.

6.5 NATURE AND CONTENTS OF CONTAINER

Hadlima (adalimumab) solution for injection is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 mL sterile solution for subcutaneous administration in the following packaging configurations:

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

  - 0.8 mL solution for injection in single-use pre-filled syringe (type I glass) with a stainless steel needle, a rigid needle shield, a rubber plunger (bromobutyl), a plunger rod, a safe-shield body and a finger flange

  - Carton containing 2 inner cartons, each containing 1 pre-filled syringe

- Hadlima 40 mg solution for injection in single-use PushTouch™ auto-injector (for **patient use**):

  - 0.8 mL solution for injection in single-use pre-filled pen for patient use containing

a pre-filled syringe. The syringe inside the pen is made from type I glass with a stainless steel needle, a rigid needle shield, a rubber plunger (bromobutyl).

- Carton containing 2 inner cartons, each containing 1 PushTouch™ auto-injector

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

Hadlima contains no antimicrobial agent. Hadlima is for single use in one patient only. Discard any residue.

6.7 PHYSICOCHEMICAL PROPERTIES

Hadlima (adalimumab) is a biosimilar medicine to Humira® (adalimumab). The comparability of Hadlima with Humira has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see Section **5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials with Humira®** and Section **4.8 - ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). The evidence for comparability supports the use of Hadlima for the listed indication.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human tumour necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble tumour necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

Hadlima is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The solution of Hadlima is clear to opalescent and colourless to pale brown solution with a pH of 5.2 ± 0.3. The drug product is supplied as either a single-use, pre-filled syringe, or as a single use, auto-injector (Hadlima PushTouch™).

The adult presentations contain 40 mg adalimumab per 0.8 mL (50 mg/mL).

CAS number: 331731-18-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Sponsor:
SAMSUNG BIOEPIS AU PTY LTD
Level 16, 201 Elizabeth Street,
Sydney NSW 2000, AUSTRALIA
sb5.global@samsung.com

Distributor:
Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A,
26 Talavera Road
Macquarie Park NSW 2113, AUSTRALIA

9 DATE OF FIRST APPROVAL

N/A

10 DATE OF REVISION

Jan 2018