**ABRILADA**

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## 1. NAME OF THE MEDICINAL PRODUCT

ABRILADA

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

ABRILADA 40 mg/0.8 mL 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 monoclonal antibody produced in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to very light brown solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

***ADULTS***

Rheumatoid arthritis (RA)

ABRILADA is indicated for reducing signs and symptoms and inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). ABRILADA can be used alone or in combination with methotrexate (MTX) or other DMARDs.

ABRILADA, in combination with MTX, can also be used in the treatment of patients with recently diagnosed moderate to severely active rheumatoid arthritis who have not received methotrexate.

Psoriatic arthritis (PsA)

ABRILADA is indicated for reducing signs and symptoms of active arthritis in adult patients with moderate to severe psoriatic arthritis when the response to previous DMARD therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of

peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

ABRILADA can be used alone or in combination with DMARDs.

Ankylosing spondylitis (AS)

ABRILADA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Crohn's disease (CD)

ABRILADA is indicated for the treatment of moderate to severe active Crohn's disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab. For induction treatment, ABRILADA should be given in combination with corticosteroids. ABRILADA can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inadequate.

Ulcerative colitis (UC)

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

Plaque psoriasis

ABRILADA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Hidradenitis suppurativa (HS)

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

Uveitis

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

***PAEDIATRICS***

Juvenile idiopathic arthritis

*Polyarticular juvenile idiopathic arthritis*

ABRILADA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA), in patients 2 years of age and older, who have had an inadequate response to one or more DMARDs. ABRILADA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

*Enthesitis-related arthritis*

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

Paediatric Crohn's disease

ABRILADA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in paediatric patients, 6 years of age and older, with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

Paediatric plaque psoriasis

ABRILADA is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Adolescent hidradenitis suppurativa

ABRILADA is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.

Paediatric uveitis

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

Paediatric ulcerative colitis

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

## 4.2. Posology and method of administration

Posology

***ADULTS***

***Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis***

The recommended dose of ABRILADA for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous (SC) injection. Methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with ABRILADA.

In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of ABRILADA to 40 mg every week or 80 mg every other week.

***Crohn's disease***

| | **Dose** | **Frequency** |
|---|---|---|
| Induction | 80 mg | Initial dose (Day 0) |
| | 40 mg | Second dose (Day 14) |
| Maintenance | 40 mg | Starting Day 28 and continuing fortnightly |

In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (given as 160 mg in one day or as 80 mg per day for two consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction.

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

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

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

***Ulcerative colitis***

The recommended ABRILADA induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (given as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with ABRILADA.

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

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

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

***Plaque psoriasis***

The recommended dose of ABRILADA for adult patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. Response should be periodically evaluated (for example, every 12 weeks). Patients with continued inadequate response should discontinue treatment. If adequate response is achieved with an increased dosage, the dose may subsequently be reduced to 40 mg fortnightly.

***Hidradenitis suppurativa***

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

Should treatment need to be interrupted, ABRILADA 40 mg every week may be re-introduced.

In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

***Uveitis***

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

The recommended dose of ABRILADA for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with ABRILADA alone. Treatment with ABRILADA can be initiated in combination with corticosteroids and/or with other

non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with ABRILADA.

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

***PAEDIATRICS***

***Juvenile idiopathic arthritis***

*Polyarticular juvenile idiopathic arthritis*

The recommended dose of ABRILADA for patients from 2 years of age with polyarticular juvenile idiopathic arthritis is based on body weight (Table 1). MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with ABRILADA. ABRILADA may be available in different strengths and/or presentations.

**Table 1. ABRILADA Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis**

| Patient Weight | Dosing Regimen |
|---|---|
| 10 kg to <30 kg | 20 mg every other week |
| ≥30 kg | 40 mg every other week |

Adalimumab has not been studied in patients with polyarticular juvenile idiopathic arthritis less than 2 years of age or in patients with a weight below 10 kg.

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

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

*Enthesitis-related arthritis*

The recommended dose of ABRILADA for patients from 6 years of age with enthesitis-related arthritis is based on body weight (Table 2). ABRILADA may be available in different strengths and/or presentations.

**Table 2. ABRILADA Dose for Patients with Enthesitis-Related Arthritis**

| Patient Weight | Dosing Regimen |
|---|---|
| 15 kg to <30 kg | 20 mg every other week |
| ≥30 kg | 40 mg every other week |

Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

***Paediatric Crohn's disease***

The recommended dose of ABRILADA for patients from 6 to 17 years of age with Crohn's disease is based on body weight (Table 3). ABRILADA is administered via subcutaneous injection. ABRILADA may be available in different strengths and/or presentations.

**Table 3. ABRILADA Dose for Paediatric Patients with Crohn's Disease**

| Patient Weight | Induction Dose | Maintenance Dose Starting at Week 4 |
|---|---|---|
| <40 kg | • 40 mg at Week 0 and 20 mg at Week 2<br><br>In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:<br>• 80 mg at Week 0 and 40 mg at Week 2 | 20 mg every other week |
| ≥40 kg | • 80 mg at Week 0 and 40 mg at Week 2<br><br>In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:<br>• 160 mg at Week 0 and 80 mg at Week 2 | 40 mg every other week |

Patients who experience insufficient response may benefit from an increase in dosage:
- <40 kg: 20 mg every week
- ≥40 kg: 40 mg every week or 80 mg every other week

Adalimumab has not been studied in children with Crohn's disease aged less than 6 years.

***Paediatric plaque psoriasis***

The recommended ABRILADA dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 4). ABRILADA is administered via subcutaneous injection. ABRILADA may be available in different strengths and/or presentations.

**Table 4. ABRILADA Dose for Paediatric Patients with Plaque Psoriasis**

| Patient Weight | Dosing Regimen |
|---|---|
| 15 kg to <30 kg | Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose |
| ≥30 kg | Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose |

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If re-treatment with ABRILADA is indicated, the above guidance on dose and treatment duration should be followed.

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

***Adolescent hidradenitis suppurativa***

There are no clinical trials with adalimumab in adolescent patients with HS. The posology of adalimumab in these patients has been determined from pharmacokinetic modelling and simulation.

The recommended ABRILADA dose in adolescent patients from 12 years of age weighing at least 30 kg with hidradenitis suppurativa is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

ABRILADA may be available in different strengths and/or presentations.

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

Antibiotics may be continued during treatment with ABRILADA if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with ABRILADA.

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

Should treatment be interrupted, ABRILADA may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated.

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

***Paediatric uveitis***

The recommended dose of ABRILADA for paediatric patients 2 years of age and older with chronic non-infectious anterior uveitis is based on body weight (Table 5). ABRILADA is administered via subcutaneous injection. ABRILADA may be available in different strengths and/or presentations.

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

**Table 5. ABRILADA Dose for Paediatric Patients with Uveitis**

| Patient Weight | Dosing Regimen |
|---|---|
| <30 kg | 20 mg every other week in combination with methotrexate |
| ≥30 kg | 40 mg every other week in combination with methotrexate |

When ABRILADA therapy is initiated, a loading dose of 40 mg for patients <30 kg or 80 mg for patients ≥30 kg may be administered one week prior to the start of maintenance therapy.

No clinical data are available on the use of an adalimumab loading dose in children <6 years of age (see section 5.2).

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

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

***Paediatric ulcerative colitis***

The recommended dose of ABRILADA for patients from 5 to 17 years of age with ulcerative colitis is based on body weight (Table 6). ABRILADA is administered via subcutaneous injection. ABRILADA may be available in different strengths and/or presentations.

**Table 6. ABRILADA Dose for Paediatric Ulcerative Colitis**

| Patient Weight | Induction Dose | Maintenance Dose Starting at Week 4* |
|---|---|---|
| <40 kg | • 80 mg at Week 0 and<br>• 40 mg at Week 2 | • 40 mg every other week or<br>• 20 mg every week |
| ≥40 kg | • 160 mg at Week 0 and<br>• 80 mg at Week 2 | • 80 mg every other week or<br>• 40 mg every week |

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

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

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

***Paediatric use***

Adalimumab has not been studied in children less than 2 years of age and there are limited data on adalimumab treatment in children with weight <10 kg. The safety and efficacy of adalimumab in paediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), paediatric Crohn's disease, paediatric plaque psoriasis, adolescent hidradenitis suppurativa and paediatric uveitis have not been established.

***Geriatric use***

Of the total number of subjects in clinical studies of adalimumab, 9.4% were 65 years and over, while approximately 2.0% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. No dose adjustment is needed for this population.

Method of administration

ABRILADA is administered by subcutaneous injection.

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

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

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

**4.3. Contraindications**

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

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

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

**4.4. Special warnings and precautions for use**

ABRILADA is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding its interchangeability.

Traceability

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

Infections

Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extra-pulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic or other opportunistic infections have been reported in patients receiving TNF-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, legionellosis and pneumocystis 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 ABRILADA 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 ABRILADA should be considered prior to initiating therapy (see *Other opportunistic infections*).

As with other TNF-antagonists, patients should be monitored closely for infections, including tuberculosis before, during and after treatment with ABRILADA.

Patients who develop a new infection while undergoing treatment with ABRILADA should be monitored closely and undergo a complete diagnostic evaluation. Administration of ABRILADA should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until infections are controlled.

Physicians should exercise caution when considering the use of ABRILADA in patients with a history of recurrent infection or with underlying conditions which may predispose patients.

*Tuberculosis*

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

Before initiation of therapy with ABRILADA, all patients should be evaluated for both active and inactive ("latent") tuberculosis infection. The 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., tuberculin skin test and chest X-ray) should be performed in accordance with local recommendations. Treatment of latent tuberculosis should be initiated prior to therapy with ABRILADA.

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, ABRILADA therapy must not be initiated.

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

Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of ABRILADA 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.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with ABRILADA. 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 ABRILADA 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, listlessness) occur during or after therapy with ABRILADA.

*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.

Hepatitis B reactivation

Use of TNF blockers 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 prior evidence of 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, ABRILADA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists, including adalimumab, have been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, optic neuritis and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of ABRILADA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of ABRILADA 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 ABRILADA therapy to assess for pre-existing central demyelinating disorders.

Allergic

Serious allergic reactions associated with adalimumab were rare during clinical trials. In post-marketing reports, cases of serious allergic reactions including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ABRILADA should be discontinued immediately and appropriate therapy initiated.

Malignancies

In the controlled portions of clinical trials of TNF-antagonist, including adalimumab, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. It should be noted that there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open-label trials with adalimumab, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

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

reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine used 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. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with ABRILADA cannot be excluded.

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

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

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

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

Haematologic events

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-blocking agents. Adverse events of the haematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been reported with adalimumab. 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 (e.g., persistent fever, bruising, bleeding, pallor) while on ABRILADA. Discontinuation of ABRILADA therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

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

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.

Patients on adalimumab may receive concurrent vaccinations, except for live vaccines.

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.

Congestive heart failure

Adalimumab has not been formally studied in patients with congestive heart failure (CHF) however, in clinical studies with another TNF-antagonist, a higher rate of serious CHF-related adverse events was observed. Cases of worsening CHF have also been reported in patients receiving adalimumab. Physicians should exercise caution when using ABRILADA in patients who have heart failure and monitor them carefully. ABRILADA should be used with caution in patients with mild heart failure (NYHA class I/II). ABRILADA is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with ABRILADA must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with ABRILADA 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 diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with ABRILADA, treatment should be discontinued (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

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

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

Immunosuppression

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

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

Geriatric use

The frequency of serious infection among adalimumab-treated subjects over 65 years of age was higher than for those under 65 years of age. Of the total number of subjects in clinical studies of adalimumab, 9.4% were 65 years and over, while approximately 2.0% were 75 and over. Because there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

## 4.5. Interaction with other medicinal products and other forms of interaction

When adalimumab was administered to 21 RA patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29% and 44% respectively. The data do not suggest the need for dose adjustment of either adalimumab or MTX.

Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with commonly used DMARDs (sulfasalazine, hydroxychloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs or analgesics.

Drug/laboratory test interaction

There is no known interference between adalimumab and laboratory tests.

## 4.6. Fertility, pregnancy and lactation

Pregnancy

An embryo-foetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (373 times human AUC when given 40 mg SC) and has revealed no evidence of harm to the foetuses due to adalimumab.

Limited clinical data on pregnant women exposed to adalimumab are available. In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled.

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

Although the registry has methodological limitations, including small sample size and non-randomised study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not treated with adalimumab. In addition, data from post-marketing surveillance does not establish the presence of a drug-associated risk. Even then, there are no adequate and well-controlled studies in pregnant women and therefore ABRILADA should only be used during pregnancy if clearly needed.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection.

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

Women of childbearing potential should be advised not to get pregnant during ABRILADA therapy.

Labour and delivery

There are no known effects of adalimumab on labour or delivery.

Nursing mothers

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

**4.7. Effects on ability to drive and use machines**

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

## 4.8. Undesirable effects

Clinical trials

Adalimumab was studied in 9,506 patients in pivotal controlled and open-label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long-term disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The controlled pivotal studies involved 6,089 patients receiving adalimumab and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking adalimumab and 5.4% for control-treated patients. Overall discontinuation rates in the RA trials were 12.7% for patients taking adalimumab and 16.8% for placebo-treated patients. The most common reasons in the RA trials for discontinuation with adalimumab were adverse events (6.6%), lack of efficacy (2.4%) and withdrawal of consent (1.9%). Approximately 13% of patients can be expected to experience injection site reactions, based on one of the most common adverse events with adalimumab in controlled clinical studies.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000) in Table 7 below. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

**Table 7. Adverse Reactions in Clinical Studies**

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| Infections and infestations* | Very common | Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral) |
| | Common | Systemic infections (including sepsis, candidiasis and influenza), Intestinal infections (including gastroenteritis viral), Skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), Ear infections, Oral infections (including herpes simplex, oral herpes and tooth infections), Reproductive tract infections (including vulvovaginal mycotic infection), Urinary tract infections |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | | (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 neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm), Melanoma** |
| Blood and the lymphatic system disorders* | Very common | Leukopenia (including neutropenia and agranulocytosis), Anaemia |
| | Common | Thrombocytopenia, Leucocytosis |
| | Uncommon | Idiopathic thrombocytopenic purpura |
| | Rare | Pancytopenia |
| Immune system disorders* | Common | Hypersensitivity*, Allergies (including seasonal allergy) |
| Metabolism and nutrition disorders | Very common | Lipids increased |
| | Common | Hypokalaemia, Uric acid increased, Blood sodium abnormal, Hypocalcaemia, Hyperglycaemia, Hypophosphatemia, Dehydration |
| Psychiatric disorders | Common | Mood alterations (including depression), Anxiety, Insomnia |
| Nervous system disorders* | Very common | Headache |
| | Common | Paraesthesias (including hypoesthesia), Migraine, Nerve root compression |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | | |
| | Uncommon | Tremor, Neuropathy |
| | Rare | Multiple sclerosis |
| Eye disorders | Common | Visual impairment, Conjunctivitis, Blepharitis, Eye swelling |
| | Uncommon | Diplopia |
| Ear and labyrinth disorders | Common | Vertigo |
| | Uncommon | Deafness, Tinnitus |
| Cardiac disorders* | Common | Tachycardia |
| | Uncommon | Arrhythmia, Congestive heart failure |
| | Rare | Cardiac arrest |
| Vascular disorders | Common | Hypertension, Flushing, Haematoma |
| | Uncommon | Vascular arterial occlusion, Thrombophlebitis, Aortic aneurysm |
| Respiratory, thoracic and mediastinal disorders* | Common | Cough, Asthma, Dyspnoea |
| | Uncommon | Chronic obstructive pulmonary disease, Interstitial lung disease, Pneumonitis |
| Gastrointestinal disorders | Very common | Abdominal pain, Nausea and vomiting |
| | Common | GI haemorrhage, Dyspepsia, Gastroesophageal reflux disease, Sicca syndrome |
| | Uncommon | Pancreatitis, Dysphagia, Face oedema |
| Hepatobiliary disorders* | Very common | Liver enzymes elevated |
| | Uncommon | Cholecystitis and cholelithiasis, Bilirubin increased, Hepatic steatosis |
| Skin and subcutaneous tissue disorders | Very common | Rash (including exfoliative rash) |

| System Organ Class | Frequency | Adverse Reaction |
|---|---|---|
| | Common | Pruritus, Urticaria, Bruising (including purpura), Dermatitis (including eczema), Onychoclasis, Hyperhidrosis |
| | Uncommon | Night sweats, Scar |
| Musculoskeletal and connective tissue disorders | Very common | Musculoskeletal pain |
| | Common | Muscle spasms (including blood creatine phosphokinase increased) |
| | Uncommon | Rhabdomyolysis, Systemic lupus erythematosus |
| Renal and urinary disorders | Common | Haematuria, Renal impairment |
| | Uncommon | Nocturia |
| Reproductive system and breast disorders | Uncommon | Erectile dysfunction |
| General disorders and administration site conditions* | Very common | Injection site reaction (including injection site erythema) |
| | Common | Chest pain, Oedema |
| | Uncommon | Inflammation |
| Investigations | Common | Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), Autoantibody tests positive (including double stranded DNA antibody), Blood lactate dehydrogenase increased |
| Injury, poisoning and procedural complications* | Common | Impaired healing |

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

** includes open-label extension studies

Hidradenitis suppurativa

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

Uveitis

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

Paediatric population

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

Description of selected adverse reactions

*Injection site reactions*

In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

*Infections*

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

In 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 extra-pulmonary locations) and invasive opportunistic infections (e.g., disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

*Malignancies and lymphoproliferative disorders*

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 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 498.1 patient-years during an adalimumab trial in paediatric patients with Crohn’s disease.

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

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

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

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non- radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 adalimumab-treated patients vs. a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients).

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

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

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1,000 patient-years in the controlled portion of clinical trials and in ongoing and completed open-label extension studies. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient-years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient-years. The median duration of these studies is approximately 3.3 years and included 6,427 patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 26,439.6 patient-years of therapy.

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

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

*Autoantibodies*

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I–V. In these 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 anti-nuclear antibody titres reported positive titres at Week 24.

Two patients out of 3,989 treated with adalimumab in all rheumatoid arthritis, 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 ABRILADA should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

*Liver enzyme elevations*

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

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

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

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

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

In controlled Phase 3 trials of adalimumab (40 mg every other week), 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.

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

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

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

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

No ALT elevations ≥3 x ULN occurred in the Phase 3 trial of adalimumab in paediatric patients with plaque psoriasis.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure 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.

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

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

**Table 8. Additional Adverse Reactions from Post-marketing Surveillance or Phase IV Clinical Trials**

| | |
|---|---|
| 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, Angioneurotic oedema, Sarcoidosis |
| Nervous system disorders* | Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), Cerebrovascular accident |
| Respiratory, thoracic and mediastinal disorders | Pulmonary embolism, Pleural effusion, Pulmonary fibrosis |
| Hepatobiliary disorders* | Reactivation of hepatitis B, Liver failure, Hepatitis, Autoimmune hepatitis |
| Gastrointestinal disorders* | Intestinal perforation |
| Skin and subcutaneous tissue disorders | Stevens-Johnson syndrome, Angioedema, New onset or worsening of psoriasis (including palmoplantar pustular psoriasis), Cutaneous vasculitis, Erythema multiforme, Alopecia, Lichenoid skin reaction** |
| Musculoskeletal and connective tissue disorders | Lupus-like syndrome |
| Cardiac disorders | Myocardial infarction |
| General disorders and administration site conditions | Pyrexia |
| Investigations | Weight increased‡ |

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

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

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

ABRILADA comparative clinical studies

The results of the ABRILADA clinical trial program support comparable safety profiles for ABRILADA and Humira (see section 5.1). The safety after transition from Humira to ABRILADA was similar to that with continuous treatment with either ABRILADA or Humira.

### 4.9. Overdose

The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with adalimumab. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of 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.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors.

General

Adalimumab binds specifically 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, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in hidradenitis suppurativa (HS) lesions. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

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

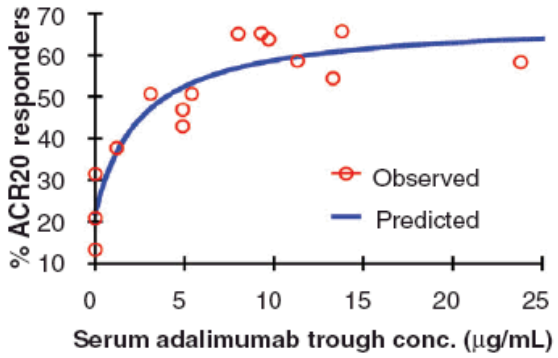
After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis.

A decrease in CRP levels was also observed in patients with juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa as well as a significant reduction in the expression of the TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease.

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 with RA, PsA and AS often experience mild to moderate anaemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with adalimumab usually experienced improvement in these haematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) 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 µg/mL were obtained through pharmacokinetic / pharmacodynamic modelling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.

ABRILADA biosimilarity (pharmacodynamic effects)

In Study B5381002, serum high sensitivity CRP (hs-CRP) was assessed as the PD biomarker and a component of the American College of Rheumatology (ACR) and disease activity score (DAS) assessments. Consistent with previous findings for TNFα inhibitors, mean serum hs-CRP concentrations decreased acutely in response to ABRILADA and Humira-EU (EU reference product) treatments, and remained suppressed through Week 26. In the ITT population, mean changes from baseline (standard deviation) in hs-CRP were -11.1 (21.92) and -13.6 (26.47) mg/L at Week 26 for the ABRILADA and Humira-EU treatments, respectively, and were similar between the treatment arms over time.

Clinical studies

***ADULTS***

***Rheumatoid arthritis clinical studies***

Adalimumab was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of adalimumab were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration. Injection site pain of adalimumab 40 mg/0.4 mL compared to adalimumab 40 mg/0.8 mL was assessed in two randomised, active control, single-blind, two period crossover studies.

RA Study I (DE009) evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥18 years old, had failed therapy with at least one but no more than four disease-modifying anti-rheumatic drugs (e.g., hydroxychloroquine, oral or injectable gold, azathioprine, D-penicillamine, sulfasalazine), 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 every other week for 24 weeks.

RA Study II (DE011) evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥18 years old and had failed therapy with at least one disease-modifying

anti-rheumatic drug (e.g., MTX, sulfasalazine, hydroxychloroquine, oral or injectable gold, D-penicillamine, azathioprine). Patients 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 every other week 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 rheumatoid arthritis 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 MTX dose remained constant at 12.5 to 25 mg every week. Unlike RA Study I, patients in RA Study III were not required to have failed therapy with any DMARDs other than MTX. 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 every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered every other week up to 10 years.

RA Study IV (DE031) assessed 636 patients with moderately to severely active rheumatoid arthritis 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 disease-modifying anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomised to 40 mg of adalimumab or placebo every other week for 24 weeks.

RA Study V (DE013) evaluated 799 methotrexate-naïve, adult patients with moderately to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of adalimumab 40 mg every other week/methotrexate combination therapy, adalimumab 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of adalimumab was administered every other week up to 10 years.

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

Results of all RA Study I-V were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary end point in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA Study V was the percent of patients who achieved an ACR 50 response at Week 52. RA Studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA Study III also had a primary endpoint of changes in quality of life. The

primary endpoint in RA Studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

*Clinical response*

*RA Studies I, II and III*

The percent of adalimumab-treated patients achieving ACR 20, 50 and 70 responses was consistent across all three trials. The results of the three trials are summarised in Table 9.

**Table 9. ACR Responses in Placebo-Controlled Trials (Percent of Patients)**

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

Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; RA=rheumatoid arthritis.

** p<0.01, adalimumab vs. placebo at all timepoints for ACR 20, 50, 70.

a. RA Study I at 24 weeks, RA Study II at 26 weeks, and RA Study III at 24 and 52 weeks.

b. 40 mg adalimumab administered every other week.

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

The results of the components of the ACR response criteria for RA Study III are shown in Table 10. The results depicted below are generally representative of each trial conducted.

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

**Table 10. Components of ACR Response in RA Study III**

| Parameter (median) | Placebo/MTX N=200 | | | Adalimumab[a]/MTX N=207 | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 24 | Week 52 | Baseline | Week 24 | Week 52 |
| Number of tender joints (0-68) | 26.0 | 15.0 | 15.0 | 24.0 | 8.0[*] | 6.0[*] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Number of swollen joints (0-66) | 17.0 | 11.0 | 11.0 | 18.0 | 5.0* | 4.0* |
| Physician global assessment disease activity[b] | 63.0 | 35.0 | 38.0 | 65.0 | 20.0* | 16.0* |
| Patient global assessment disease activity[b] | 53.5 | 39.0 | 43.0 | 52.0 | 20.0* | 18.0* |
| Pain[b] | 59.5 | 38.0 | 46.0 | 58.0 | 21.0* | 19.0* |
| Disability index (HAQ)[c] | 1.50 | 1.25 | 1.25 | 1.50 | 0.75* | 0.75* |
| CRP (mg/L) | 10.0 | 9.0 | 9.0 | 10.0 | 4.0* | 4.0* |

Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; RA=rheumatoid arthritis; HAQ=Health Assessment Questionnaire; CRP=C-reactive protein.

* $p<0.01$, adalimumab vs. placebo, based on mean change from baseline

a. 40 mg adalimumab administered every other week.

b. Visual analogue scale; 0 = best, 100 = worst.

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

In RA Study III, 84.7% of patients with ACR 20 responses at Week 24 maintained the response at 52 weeks. The following figures illustrate the durability of ACR 20 responses to adalimumab in RA Studies III and II.

**Figure 2. RA Study III ACR 20 Responses over 52 Weeks**

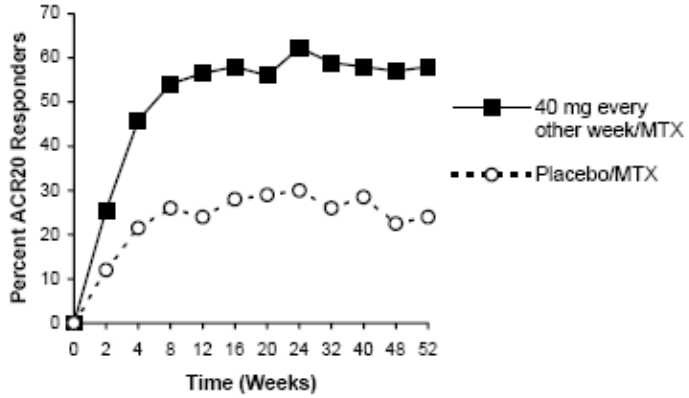
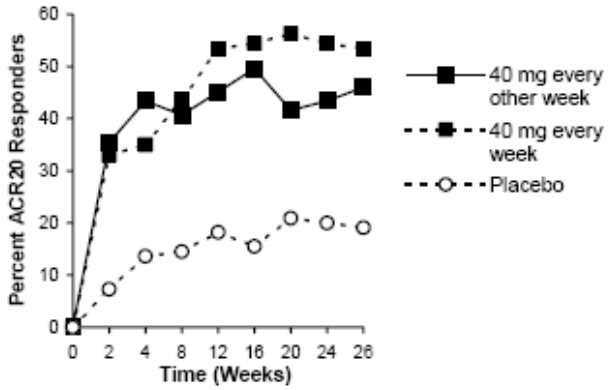



**Figure 3. RA Study II ACR 20 Responses over 26 Weeks**



*RA Study IV*

The ACR 20 response of patients treated with adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of adalimumab and other DMARDs were observed.

In RA Studies I-IV, adalimumab-treated patients achieved ACR 20, 50 and 70 responses faster and more often than placebo-treated patients. In RA Study I, there was a statistically significant difference in ACR 20 responses at week one (first study visit) between patients treated with adalimumab (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in RA Studies II, III and IV at week two (first study visit) between patients treated with adalimumab (36.4%, 29.1% and 33.7%, respectively) and placebo (7.3%, 13.0% and 8.6%, respectively). A similar pattern of the time to first ACR 50 and 70 responses was noted in all four studies.

Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week. This was confirmed in a long-term open-label study where patients with an incomplete response increased their dosing frequency from 40 mg every other week to 40 mg weekly.

*RA Study V*

In RA Study V with early rheumatoid arthritis patients who were methotrexate-naïve, combination therapy with adalimumab and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and adalimumab monotherapy at Week 52 and responses were sustained through Week 104 (see Table 11).

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% of patients who received adalimumab/methotrexate combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ($p<0.001$) and 24.5% of patients who received adalimumab monotherapy ($p<0.001$).

**Table 11. ACR Responses in RA Study V (Percent of Patients)**

| Response | MTX[b] N=257 | Adalimumab[c] N=274 | Adalimumab/MTX N=268 |
|---|---|---|---|
| ACR 20 | | | |
| Week 52 | 63% | 54% | 73% |
| Week 104 | 56% | 49% | 69% |
| ACR 50 | | | |
| Week 52 | 46% | 41% | 62% |
| Week 104 | 43% | 37% | 59% |
| ACR 70 | | | |
| Week 52 | 27% | 26% | 46% |
| Week 104 | 28% | 28% | 47% |
| Major Clinical Response[a] | | | |

| | | | |
|---|---|---|---|
| Week 104 | 28% | 25% | 49% |

Abbreviations: ACR=American College of Rheumatology; MTX=methotrexate; RA=rheumatoid arthritis.

a. Major clinical response is defined as achieving an ACR 70 response for a continuous six month period.

b. p<0.05, adalimumab/MTX vs. MTX for ACR 20
p<0.001, adalimumab/MTX vs. MTX for ACR 50 and 70, and Major Clinical Response.

c. p<0.001, adalimumab/MTX vs. adalimumab.

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

At Week 52, 42.9% of patients who received adalimumab/methotrexate combination therapy achieved clinical remission (Disease Activity Score (DAS28)-CRP <2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving adalimumab monotherapy. Adalimumab/methotrexate combination therapy was statistically and clinically superior to methotrexate (p<0.001) and adalimumab monotherapy (p<0.001) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis (see Table 12). Of 342 subjects originally randomised to adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of adalimumab treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

**Table 12. DAS28 Responses in RA Study V**

| DAS28 Response | MTX N=257 | Adalimumab N=274 | Adalimumab/MTX N=268 |
|---|---|---|---|
| Week 52 | | | |
| Baseline (Mean) | 6.3 | 6.4 | 6.3 |
| Mean Change from Baseline (Mean ± SD) | -2.8 ± 1.4[a] | -2.8 ± 1.5[b] | -3.6 ± 1.3 |
| Percent of Patients in Remission (DAS28<2.6) | 20.6%[a] | 23.4%[b] | 42.9%[*] |
| Week 104 | | | |
| Baseline (Mean) | 6.3 | 6.3 | 6.3 |
| Mean Change from Baseline (Mean ± SD) | -3.1 ± 1.4[a] | -3.2 ± 1.4[b] | -3.8 ± 1.3 |

Abbreviations: MTX=methotrexate; RA=rheumatoid arthritis.

a. p<0.001, adalimumab/methotrexate vs. methotrexate

b. p<0.001, adalimumab/methotrexate vs. adalimumab

*Radiographic response*

In RA Study III, where adalimumab-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were read at baseline, 6 months and 12 months. The 12-month results are shown in Table 13. A statistically significant difference for change in modified Total Sharp Score (TSS) and the erosion score was observed at 6 months and maintained at 12 months. Adalimumab/methotrexate-treated patients demonstrated less radiographic progression than

patients receiving methotrexate alone at 52 weeks. The inhibition of progression of structural damage was maintained through 104 weeks.

**Table 13. Radiographic Change Over 12 Months in RA Study III with Background MTX**

| | Placebo N=200 | Adalimumab[a] N=207 | Difference between Adalimumab[a] and Placebo | P-value |
|---|---|---|---|---|
| Change in Modified Total Sharp Score (mean) | 2.7 | 0.1 | -2.6 | <0.001[b] |
| Change in Erosions (mean) | 1.6 | 0.0 | -1.6 | <0.001 |
| No New Erosions (% of Patients) | 46.2 | 62.9 | 16.7 | <0.001 |
| Change in JSN Score (mean) | 1.0 | 0.1 | -0.9 | 0.002 |

Abbreviations: JSN=Joint Space Narrowing; MTX=methotrexate.

[a] 40 mg adalimumab administered every other week.

[b] Based on analysis of ranked ANCOVA.

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

In RA Study V, structural joint damage was assessed as in RA Study III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the adalimumab/MTX combination group as compared to either the MTX or adalimumab monotherapy group at Week 52 as well as at Week 104 (see Table 14).

**Table 14. 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 | <0.001 | 0.002 |
| Week 52 (mean) | 27.6 ± 24.6 | 21.8 ± 19.7 | 19.4 ± 19.9 | | |
| Change as Week 52 (mean ± SD) | 5.7 ± 12.7 | 3.0 ± 11.2 | 1.3 ± 6.5 | | |
| Week 104 | | | | | |
| Baseline (mean) | 21.8 ± 22.2 | 18.8 ± 19.0 | 18.1 ± 20.1 | <0.001 | <0.001 |
| 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 | | |

Abbreviations: MTX=methotrexate.

Note: Primary analysis imputation used for missing data.

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

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

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

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

*Quality of life and physical function*

Health-related quality of life was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in RA Study III. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo. In RA Study III, the mean (CI) improvement in HAQ from baseline at Week 52 was -0.60 (-0.65, -0.55) for adalimumab/MTX patients and -0.25 (-0.33, -0.17) for placebo/MTX (p<0.001) patients. Sixty-three percent of adalimumab/MTX-treated patients achieved a 0.5 or greater improvement in HAQ at Week 52 in the double-blind portion of the study. Most subjects who achieved improvement in physical function and continued treatment maintained improvement through Week 520 (10 years) of open-label treatment. Improvement in quality of life as measured by SF-36 was assessed up to Week 156 (36 months) and improvement was maintained through that time.

The Short Form Health Survey (SF-36) was also used to assess general health-related quality of life in all four adequate and well-controlled trials. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in SF-36 physical component summary scores from baseline to Month 6 compared to placebo, and this was maintained at Week 52 in RA Study III. Mean improvement in the SF-36 was also maintained through the end of measurement at Week 156 (36 months). The SF-36 mental component summary scores in RA Studies II and IV were also statistically significantly greater at Month 6 for adalimumab vs. placebo. The pain and vitality domain scores of the SF-36 showed statistically significantly greater improvement from baseline to Month 6 in all four studies for the 40 mg every other week dose of adalimumab compared to placebo. These findings were supported by functional assessment of chronic illness therapy (FACIT) scores that showed a statistically significant decrease in fatigue at Month 6 in all three studies analysed that was maintained at Week 52 in RA Study III.

In RA Study V, the improvement in the HAQ disability index and the physical component of the SF-36 was greater for the adalimumab/methotrexate combination therapy group versus both methotrexate and adalimumab monotherapy groups (p<0.001) at Week 52; this improvement was maintained through Week 104. Among the 250 subjects who completed the

open-label extension study, improvements in physical function were maintained through 10 years of treatment.

*Injection site pain*

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

***Psoriatic arthritis clinical studies***

The safety and efficacy of adalimumab was assessed in two randomised, double-blind, placebo-controlled studies in 413 patients with psoriatic arthritis. PsA study I (M02-518) enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrolment (stable dose of <30 mg/week for >1 month) could continue MTX at the same dose. Doses of adalimumab 40 mg or placebo every other week were administered during the 24-week double-blind period of the study. PsA study II (M02-570) with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg adalimumab was administered every other week.

*ACR and PASI response*

Compared to placebo, treatment with adalimumab resulted in improvements in the measures of disease activity (see Tables 15 and 16). Among patients with psoriatic arthritis who received adalimumab, the clinical responses were apparent in some patients at the time of the first visit (two weeks). Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the adalimumab group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

**Table 15. ACR Response in PsA Study I (Percent of Patients)**

| Response | Placebo N=162 | Adalimumab N=151 |
|---|---|---|
| ACR 20 | | |
| Week 12 | 14% | 58%* |
| Week 24 | 15% | 57%* |
| ACR 50 | | |
| Week 12 | 4% | 36%* |
| Week 24 | 6% | 39%* |
| ACR 70 | | |
| Week 12 | 1% | 20%* |
| Week 24 | 1% | 23%* |

Abbreviations: ACR=American College of Rheumatology; PsA=psoriatic arthritis.

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

**Table 16. Components of Disease Activity in PsA Study I**

| | Placebo N=162 | | Adalimumab* N=151 | |
|---|---|---|---|---|
| **Parameter: median** | **Baseline** | **24 Weeks** | **Baseline** | **24 Weeks** |
| Number of tender joints[a] | 23.0 | 17.0 | 20.0 | 5.0 |
| Number of swollen joints[b] | 11.0 | 9.0 | 11.0 | 3.0 |
| Physician global assessment[c] | 53.0 | 49.0 | 55.0 | 16.0 |
| Patient global assessment[c] | 49.5 | 49.0 | 48.0 | 20.0 |
| Pain[c] | 49.0 | 49.0 | 54.0 | 20.0 |
| Disability index (HAQ)[d] | 1.0 | 0.9 | 1.0 | 0.4 |
| CRP (mg/dL)[e] | 0.8 | 0.7 | 0.8 | 0.2 |

Abbreviations: PsA=psoriatic arthritis; HAQ=Health Assessment Questionnaire.

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

a. Scale 0-78

b. Scale 0-76

c. Visual analogue scale; 0=best, 100=worst

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

e. Normal range: 0-0.287 mg/dL

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by >3 tender joints and >3 swollen joints at enrolment.

*Radiographic response*

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

Adalimumab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS (mean ± SD) 0.8 ±

2.5 in the placebo group (at Week 24) compared with 0.0 ± 1.9 in the adalimumab group (at Week 48) ($p<0.001$).

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

*Quality of life and physical function*

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

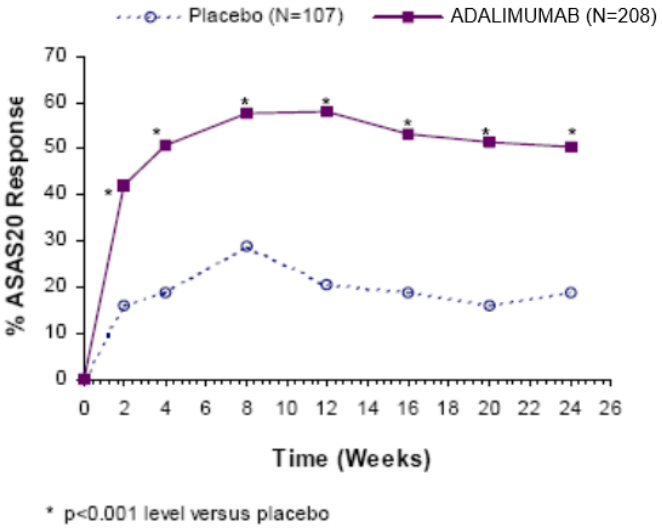
***Ankylosing spondylitis (AS) clinical studies***

The safety and efficacy of adalimumab 40 mg fortnightly was assessed in 393 adult patients in two randomised, 24-week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis. The larger study (AS Study I or M03-607) enrolled 315 adult patients with active AS (defined as fulfilling at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analogue scale (VAS) for total back pain ≥40 mm, (3) morning stiffness ≥1 hour, who had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease-modifying anti-rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open-label period during which patients received adalimumab every other week subcutaneously for up to an additional 236 weeks. Subjects (N=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg fortnightly subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

Results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with adalimumab compared to placebo. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 4 and Table 17.

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

**Figure 4. ASAS 20 Response By Visit**




* p<0.001 level versus placebo

**Table 17. Efficacy Responses in Placebo-Controlled AS Study I**

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

Abbreviations: AS=Ankylosing spondylitis; ASAS=Assessments in Ankylosing Spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index.

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

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

**Table 18. Components of Ankylosing Spondylitis Disease Activity**

| | Placebo N=107 | | Adalimumab N=208 | |
|---|---|---|---|---|
| | **Baseline mean** | **Week 24 mean** | **Baseline mean** | **Week 24 mean** |
| ASAS 20 Response Criteria[*] | | | | |
| Patient's Global Assessment of Disease Activity[a,*] | 65 | 60 | 63 | 38 |
| Total back pain[*] | 67 | 58 | 65 | 37 |
| Inflammation[b,*] | 6.7 | 5.6 | 6.7 | 3.6 |
| BASFI[c,*] | 56 | 51 | 52 | 34 |
| BASDAI[d] score[*] | 6.3 | 5.5 | 6.3 | 3.7 |
| BASMI[e] score[*] | 4.2 | 4.1 | 3.8 | 3.3 |
| Tragus to wall (cm) | 15.9 | 15.8 | 15.8 | 15.4 |
| Lumbar flexion (cm) | 4.1 | 4.0 | 4.2 | 4.4 |
| Cervical rotation (degrees) | 42.2 | 42.1 | 48.4 | 51.6 |
| Lumbar side flexion (cm) | 8.9 | 9.0 | 9.7 | 11.7 |
| Intermalleolar distance (cm) | 92.9 | 94.0 | 93.5 | 100.8 |
| CRP[f,*] | 2.2 | 2.0 | 1.8 | 0.6 |

a. Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analogue Scale (VAS) with 0="none" and 100="severe".
b. Mean of questions 5 and 6 of BASDAI (defined in 'd').
c. Bath Ankylosing Spondylitis Functional Index.
d. Bath Ankylosing Spondylitis Disease Activity Index.
e. Bath Ankylosing Spondylitis Metrology Index.
f. C-Reactive Protein (mg/dL).
* Statistically significant for comparisons between adalimumab and placebo at Week 24.

Similar trends (not all statistically significant) were seen in the smaller randomised, double-blind, placebo-controlled study (AS study II or M03-606) of 82 patients with active ankylosing spondylitis.

Patient reported outcomes were assessed in both ankylosing spondylitis studies using the generic health status questionnaire SF-36 and the disease specific Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL). The adalimumab-treated patients had significantly greater improvement in SF-36 physical component score (mean change: 6.93) compared to placebo-treated patients (mean change: 1.55; $p<0.001$) at Week 12, which was maintained through Week 24 (mean change 7.44 vs 1.85).

Results from the ASQoL support these findings demonstrating improvement in overall quality of life. The adalimumab-treated patients had statistically significant improvement (mean change: -3.15) compared to placebo-treated patients (mean change: -0.95; $p<0.001$) at Week 12, which was maintained through Week 24 (mean change -3.58 vs -1.06).

***Adult Crohn's disease clinical studies***

The safety and efficacy of multiple doses of adalimumab were assessed in over 1,400 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 and ≤450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI <150) was evaluated in two studies. In CD Study I (M02-403, CLASSIC I), 299 TNF-antagonist naïve patients were randomised to one of four treatment groups; the placebo group received placebo at Weeks 0 to 2, the 160/80 group received 160 mg adalimumab at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, CD Study II (M04-691, GAIN), 325 patients who had lost response or were intolerant to previous infliximab were randomised to receive either 160 mg adalimumab at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in CD Study III (M02-404, CHARM). In this study, 854 patients with active disease received open-label 80 mg adalimumab at Week 0 and 40 mg at Week 2. Patients were then randomised at Week 4 to 40 mg adalimumab every other week, 40 mg adalimumab every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (CR-70 = decrease in CDAI ≥70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

*Clinical results*

*Induction of clinical remission*

A statistically significantly greater percentage of the patients treated with 160/80 mg adalimumab achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF-antagonist naïve (CD Study I), or had been previously exposed to infliximab (CD Study II) (see Table 19).

**Table 19. Induction of Clinical Remission and Response (Percent of Patients)**

| | **CD Study I** | | **CD Study II** | |
|---|---|---|---|---|
| | **Placebo N=74** | **Adalimumab 160/80 mg N=76** | **Placebo N=166** | **Adalimumab 160/80 mg N=159** |
| Week 4 | | | | |
| Clinical remission | 12% | 36%* | 7% | 21%* |
| Clinical response (CR-100) | 24% | 49%** | 25% | 38%** |
| Clinical response (CR-70) | 34% | 58%** | 34% | 52%** |

Clinical remission is CDAI score <150; clinical response (CR-100) is decrease in CDAI ≥100 points; clinical response (CR-70) is decrease in CDAI ≥70 points. All p-values are pairwise comparisons of proportions for adalimumab vs. placebo.
Abbreviations: CD=Crohn's disease.
* p<0.001
** p<0.01

*Maintenance of clinical remission*

In CD Study III, at Week 4, 58% (499/854) patients were in clinical response (decrease in CDAI ≥70 points) and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other anti-TNF therapy. At Weeks 26 and 56, statistically significantly greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the adalimumab maintenance group compared to patients in the placebo maintenance group. Additionally, statistically significantly greater proportions of patients receiving concomitant corticosteroids at baseline were in clinical remission and were able to discontinue corticosteroid use for at least 90 days in the adalimumab maintenance groups compared to patients in the placebo maintenance group at Weeks 26 and 56 (see Table 20). The group that received adalimumab every week did not show significantly higher remission rates than the group that received adalimumab every other week. Clinical remission results presented in Table 20 remained relatively constant irrespective of previous TNF-antagonist exposure.

**Table 20. Maintenance of Clinical Remission and Response (Percent of Patients)**

| | **Placebo** | **40 mg Adalimumab every other week** | **40 mg Adalimumab every week** |
|---|---|---|---|
| **Week 26** | **N=170** | **N=172** | **N=157** |
| Clinical remission | 17% | 40%* | 47%* |
| Clinical response (CR-100) | 27% | 52%* | 52%* |
| Clinical response (CR-70) | 28% | 54%* | 56%* |
| Patients in steroid-free remission for ≥90 days[a] | 3% (2/66) | 19% (11/58)** | 15% (11/74)** |
| **Week 56** | **N=170** | **N=172** | **N=157** |
| Clinical remission | 12% | 36%* | 41%* |
| Clinical response (CR-100) | 17% | 41%* | 48%* |
| Clinical response (CR-70) | 18% | 43%* | 49%* |
| Patients in steroid-free remission for ≥90 days[a] | 5% (3/66) | 29% (17/58)* | 20% (15/74)** |

Clinical remission is CDAI score <150; clinical response (CR-100) is decrease in CDAI ≥100 points; clinical response (CR-70) is decrease in CDAI ≥70 points

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

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

a. Of those receiving corticosteroids at baseline.

Of those in response at Week 4 who attained remission during the study, patients in adalimumab maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group. Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

117/276 patients from CD Study I and 272/777 patients from CD Studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 (75.2%) and 189 (69.5%) patients, respectively, continued to be in clinical remission. Clinical response (CR-70) was maintained in 107 (91.5%) and 248 (91.2%) patients, respectively.

An endoscopy study (M05-769, EXTEND), which enrolled 135 patients, with moderate to severe Crohn's disease, indicated an effect of adalimumab on mucosal healing. 27.4% of patients treated with adalimumab had mucosal healing at Week 12 compared to 13.1% of patients given placebo (p=0.056), and 24.2% of patients treated with adalimumab had mucosal healing at Week 52 compared to 0% of patients given placebo (p<0.001).

*Quality of life*

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

***Ulcerative colitis clinical studies***

The safety and efficacy of multiple doses of adalimumab were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3 points) in two randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted.

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

In study UC-II, 248 patients received 160 mg of adalimumab at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

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

Results for both the overall UC-II study population and for patients who had responded at Week 8 of treatment per the full Mayo score are shown in Table 21.

**Table 21. Response, Remission and Mucosal Healing in Study UC-II (Percent of Patients)**

| | **Placebo** **N=246** | **Adalimumab 40 mg eow** **N=248** | **Adalimumab 160/80/40 mg Week 8 responders** **N=125** |
|---|---|---|---|
| Week 52 | | | |
| Clinical Response | 18% | 30%* | 47% |
| Clinical Remission | 9% | 17%* | 29% |
| Mucosal Healing | 15% | 25%* | 41% |
| Steroid-free remission for ≥90 days[a] | 6% (N=140) | 13%* (N=150) | 20% (N=90) |
| | | | |
| Week 8 and 52 | | | |
| Sustained Response | 12% | 24%** | - |
| Sustained Remission | 4% | 8%* | - |
| Sustained Mucosal Healing | 11% | 19%* | - |

Clinical remission is Mayo score ≤2 with no subscore >1.
Abbreviations: eow=every other week; UC=ulcerative colitis.
* p<0.05 for adalimumab vs. placebo pairwise comparison of proportions.
** p<0.001 for adalimumab vs. placebo pairwise comparison of proportions.
[a] Of those receiving corticosteroids at baseline.

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

The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers.

In the subgroup of patients in Study UC-II with prior TNF blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population. The subgroup of patients with prior TNF blocker use achieved induction of clinical remission at 9% (9/98) in the adalimumab group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the adalimumab group versus 1% (1/101) in the placebo group. In the subgroup of patients with prior TNF blocker use, 10% (10/98) were in clinical remission at Week 52 in the adalimumab group versus 3% (3/101) in the placebo group.

Patients from UC Studies I and II had the option to roll over into an open-label long-term extension study (UC-III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score, and of those who had received at least 4 years of adalimumab therapy, 77% (245/320) were in clinical remission per partial Mayo score. Patients, who lost response after one year of treatment or beyond, could benefit from an increase of dosing frequency to 40 mg weekly.

*Hospitalisation rates*

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

*Quality of life*

In study UC-II, improvement in the disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ) total score was achieved at Week 52 in patients randomised to adalimumab 160/80 mg compared to placebo (p=0.007).

***Plaque psoriasis clinical studies***

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

The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis Study IV).

Psoriasis Study I (M03-656, REVEAL) evaluated 1,212 patients with chronic plaque psoriasis with ≥10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, patients received placebo or adalimumab subcutaneously at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg adalimumab every other week. After 17 weeks of open-label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomised to active therapy in Period A were re-randomised in period C to receive 40 mg adalimumab every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (52.6%) to "severe" (41.3%) to "very severe" (6.1%).

Psoriasis Study II (M04-716, CHAMPION) compared the efficacy and safety of adalimumab versus methotrexate and placebo in 271 patients with 10% BSA involvement and PASI ≥10. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing adalimumab and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Ps Study III (M02-528) evaluated 148 patients with chronic plaque psoriasis with ≥5% BSA involvement for at least 1 year. Patients received placebo or adalimumab subcutaneously at a dose of 40 mg every other week starting at Week 1 after an initial dose of 80 mg at Week 0 or adalimumab at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg weekly.

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial (M03-658), where adalimumab was given for at least an additional 108 weeks.

*Clinical results*

In Psoriasis Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 for Studies I and II, and Week 12 for Study III. Other evaluated outcomes in Psoriasis Studies I, II, and III included the PGA and other PASI measures. Psoriasis Study I had an additional primary endpoint of loss of adequate response after Week 33 and on or before Week 52. Loss of adequate response is defined as a PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33.

In Psoriasis Studies I and II, more patients randomised to adalimumab than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16. Other relevant clinical parameters including PASI 100 (i.e., complete clearance of psoriasis skin signs) and PGA of "clear or minimal" were also improved over placebo. In Psoriasis Study II, superior results were achieved for PASI 75, PASI 100 and PGA of "clear or minimal" in patients randomised to the adalimumab treatment group versus those randomised to receive methotrexate (see Tables 22 and 23).

Improvements in signs and symptoms in patients with moderate to severe psoriasis were maintained for up to 1 year (pivotal study M03-656) and for up to 3 years.

**Table 22. Ps Study I (M03-656) - Efficacy Results at 16 Weeks (Percent of Patients)**

| | **Placebo N=398** | **Adalimumab 40 mg eow N=814** |
|---|---|---|
| ≥PASI 75 | 6.5 | 70.9[a] |
| PASI 100 | 0.8 | 20.0[a] |
| PGA: Clear/minimal | 4.3 | 62.2[a] |

Abbreviations: eow=every other week; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; Ps=psoriasis.

a. p< 0.001, adalimumab vs. placebo.

**Table 23. Ps Study II (M04-716) - Efficacy Results at 16 Weeks (Percent of Patients)**

| | Placebo N=53 | MTX N=110 | Adalimumab 40 mg eow N=108 |
|---|---|---|---|
| ≥PASI 75 | 18.9 | 35.5 | 79.6[a,b] |
| PASI 100 | 1.9 | 7.3 | 16.7[c,d] |
| PGA: Clear/minimal | 11.3 | 30.0 | 73.1[a,b] |

Abbreviations: eow=every other week; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; Ps=psoriasis.

[a] p<0.001, adalimumab vs. placebo.
[b] p<0.001, adalimumab vs. methotrexate.
[c] p<0.01, adalimumab vs. placebo.
[d] p<0.05, adalimumab vs. methotrexate.

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

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous adalimumab therapy for 52 weeks in Psoriasis Study I, and continued adalimumab in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 94 patients were randomised to adalimumab therapy in Psoriasis Study II, and continued adalimumab in the open-label extension trial. PASI 75 and PGA clear or minimal response rates in these patients were 58.1% and 46.2%, respectively, after an additional 108 weeks of open-label therapy (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and re-treatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the re-treatment period had a response of PGA "clear" or "minimal" after 16 weeks of re-treatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively).

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

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

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

Psoriasis Study IV compared efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. Nail psoriasis was assessed using the Modified Nail Psoriasis Severity Index (mNAPSI), and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A statistically significantly higher proportion of patients randomised to adalimumab achieved at least a 75% improvement in mNAPSI (mNAPSI 75) at Week 26, as compared with patients randomised to placebo (see Table 24). The percent improvement in NAPSI was statistically significantly greater in adalimumab patients compared with placebo at Week 16 (44.2% vs 7.8%) and at Week 26 (56.2% vs 11.5%).

A statistically significant higher proportion of patients in the adalimumab group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo. In this study, adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% and BSA<10% and ≥5%) and a statistically significant improvement in scalp psoriasis compared with placebo.

**Table 24. Efficacy Results at 26 Weeks**

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

Abbreviations: eow=every other week; mNAPSI=Modified Nail Psoriasis Severity Index; NAPSI=Nail Psoriasis Severity Index; PGA-F=Physician's Global Assessment of Fingernail Psoriasis.

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

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

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

Of those who continued to receive adalimumab treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response. Adalimumab-treated patients showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI (Dermatology Life Quality Index). The mean decrease (improvement) from baseline at Week 26 was 8.0 in the adalimumab group (N=94) and 1.9 in the placebo group (N=93).

*Results from Ps Study III supported the efficacy demonstrated in Ps Studies I and II*

In Psoriasis Study I, patients who were PASI 75 responders and were re-randomised to continue adalimumab therapy at Week 33 were less likely to experience a loss of adequate response on or before Week 52 than the PASI 75 responders who were re-randomised to placebo at Week 33 (4.9% versus 28.4%, $p<0.001$).

*Quality of life*

Patient Reported Outcomes (PRO) were evaluated by several measures. Quality of Life was assessed using the disease-specific Dermatology Life Quality Index (DLQI) in Psoriasis Study I and Psoriasis Study II. In Psoriasis Study I, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 & 16. The DLQI result was maintained at Week 52. In Psoriasis Study II, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, and pruritus compared to the placebo and methotrexate groups at Week 16, and clinically meaningful improvement in pain compared to the placebo group at Week 16.

The Short Form Health Survey (SF-36) was used to assess general health-related quality of life in Psoriasis Study I. The adalimumab-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

***Hidradenitis suppurativa clinical studies***

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

Study HS-I (M11-313) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive adalimumab 40 mg every week in Period B.

Study HS-II (M11-810) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at Week 0 and 80 mg at Week 2

and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomised in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

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

*Clinical response*

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

At Week 12, a significantly higher proportion of patients treated with adalimumab versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 25). Patients treated with adalimumab had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

**Table 25. Efficacy Results at 12 Weeks, HS Studies I and II**

| | **HS Study I** | | **HS Study II** | |
|---|---|---|---|---|
| **Endpoint** | **Placebo** | **Adalimumab 40 mg Weekly** | **Placebo** | **Adalimumab 40 mg Weekly** |
| Hidradenitis Suppurativa Clinical Response (HiSCR)[a] | N=154<br>40 (26.0%) | N=153<br>64 (41.8%)* | N=163<br>45 (27.6%) | N=163<br>96 (58.9%)*** |
| ≥30% Reduction in Skin Pain[b] | N=109<br>27 (24.8%) | N=122<br>34 (27.9%) | N=111<br>23 (20.7%) | N=105<br>48 (45.7%)*** |

Abbreviations: HS=hidradenitis suppurativa.

* p<0.05, *** p<0.001, adalimumab vs. placebo

[a] Among all randomised patients.

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

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

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

and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

***Uveitis clinical studies***

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis (also known as "non-infectious uveitis affecting the posterior segment"), excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV Study I (M10-877) and UV Study II (M10-880)). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of non-biologic immunosuppressants were permitted. The primary efficacy endpoint in both studies was 'time to treatment failure'. Following initial control of disease, a prolongation in time to treatment failure will result in reduced risk of disease flares, inflammation and vision loss.

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

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

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

*Clinical response*

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo (see Table 26). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see Figure 5).

**Table 26. Time to Treatment Failure in UV Studies I and II**

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

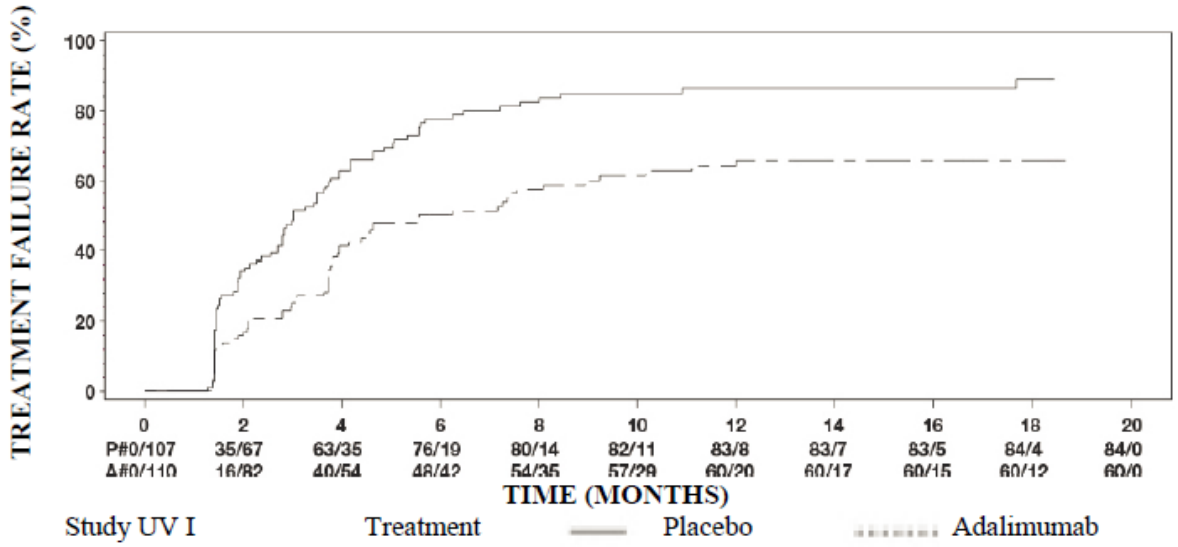
Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Dropouts due to reasons other than treatment failure were censored at the time of dropping out.
Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; UV=uveitis.

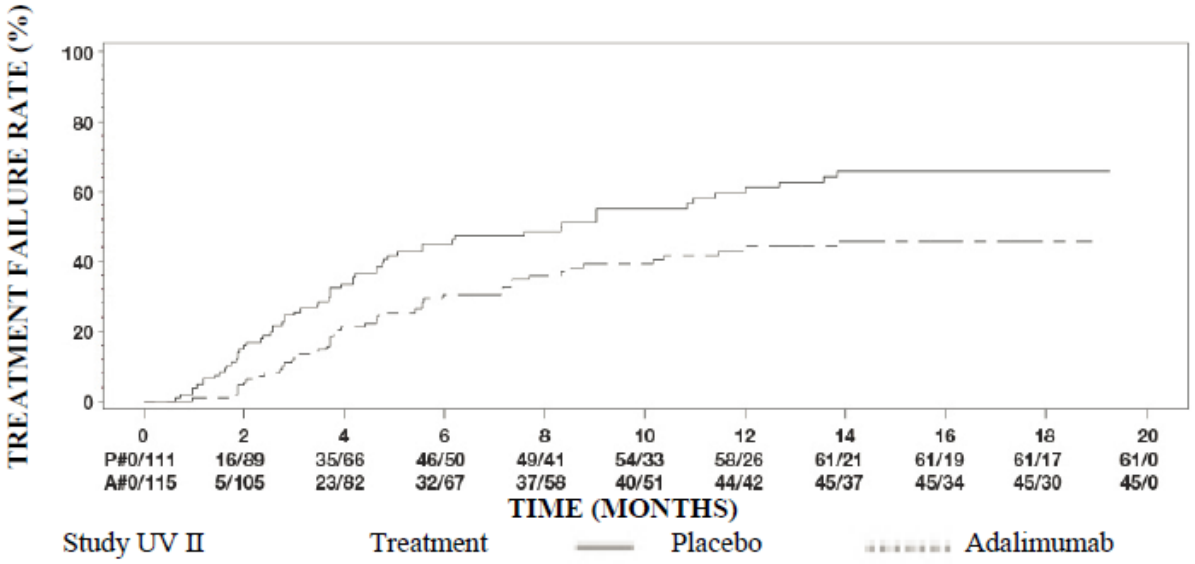
[a] HR of adalimumab vs. placebo from proportional hazards regression with treatment as factor.

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

[c] Fewer than half of at-risk subjects had an event.

**Figure 5. Kaplan-Meier Curves Summarising Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)**






Note: P#=Placebo (Number of Events/Number at Risk); A#=Adalimumab (Number of Events/Number at Risk).

In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups (Table 27).

**Table 27. Treatment Failure Components in UV Studies I and II**

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

Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Dropouts due to reasons other than treatment failure were censored at the time of dropping out.
Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; UV=uveitis.

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

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

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

Of the 417 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 46 subjects were regarded ineligible (e.g., developed complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 371 remaining patients, 276 evaluable patients reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 222 (80.4%) were in quiescence (no active inflammatory lesions, AC cell grade ≤0.5+, VH grade ≤0.5+) with a

concomitant steroid dose ≤7.5 mg per day, and 184 (66.7%) were in steroid-free quiescence. BCVA was either improved or maintained (<5 letters deterioration) in 88.4% of the eyes at Week 78. Among the patients who discontinued the study prior to Week 78, 11% discontinued due to adverse events, and 5% due to insufficient response to adalimumab treatment.

*Quality of life*

In UV Study 1, treatment with adalimumab resulted in maintenance of vision-related functioning and health-related quality of life, as measured by the NEI VFQ-25.

***PAEDIATRICS***

***Juvenile idiopathic arthritis (JIA) clinical studies***

*Polyarticular juvenile idiopathic arthritis (pJIA)*

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

*pJIA I*

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind, parallel-group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL-LI), patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum). In the OL-LI phase, all patients received 24 mg/m$^2$ up to a maximum of 40 mg adalimumab every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL-LI phase is presented in Table 28.

**Table 28. Distribution of Patients by Age and Adalimumab Dose Received During the OL-LI Phase**

| Age Group | Number of patients at Baseline n (%) | Minimum, median and maximum dose |
|---|---|---|
| 4 to 7 years | 31 (18.1) | 10, 20 and 25 mg |
| 8 to 12 years | 71 (41.5) | 20, 25 and 40 mg |
| 13 to 17 years | 69 (40.4) | 25, 40 and 40 mg |

Abbreviation: OL-LI=open-label lead in.

Patients demonstrating a Paediatric ACR 30 response at Week 16 were eligible to be randomised into the double-blind phase and received either adalimumab 24 mg/m$^2$ up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria was defined as a worsening of ≥30% from baseline in ≥3 of 6 Paediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1

of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open-label extension phase.

**Table 29. Ped ACR Responses in the JIA Study**

| **Stratum** | **MTX** | | **Without MTX** | |
|---|---|---|---|---|
| **Phase** | | | | |
| OL-LI 16 weeks | | | | |
| Ped ACR 30 response (n/N) | 94.1% (80/85) | | 74.4% (64/86) | |
| **Double-Blind** | **Adalimumab (N=38)** | **Placebo (N=37)** | **Adalimumab (N=30)** | **Placebo (N=28)** |
| Disease flares at the end of 32 weeks[a] (n/N) | 36.8% (14/38) | 64.9% (24/37)[b] | 43.3% (13/30) | 71.4% (20/28)[c] |
| Median time to disease flare | >32 weeks | 20 weeks | >32 weeks | 14 weeks |

Abbreviations: ACR=American College of Rheumatology; JIA=juvenile idiopathic arthritis; MTX=methotrexate; OL-LI=open-label lead in.

[a] Ped ACR 30/50/70 responses Week 48 significantly greater than those of placebo treated patients.

[b] p=0.015.

[c] p=0.031.

Among those who responded at Week 16 (n=144), the Paediatric ACR 30/50/90 responses were maintained for up to two years in the open-label extension (OLE) phase in patients who received adalimumab throughout the study.

Overall responses were generally better and fewer patients developed antibodies when treated with the combination of adalimumab and MTX compared to adalimumab alone. Taking these results into consideration, adalimumab is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate.

*pJIA II*

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

At Week 12 and Week 24, Paediatric ACR 30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with Paediatric ACR 50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Paediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Paediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

*Enthesitis-related arthritis*

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m$^2$ body surface area (BSA) of adalimumab up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label period during which patients received 24 mg/m$^2$ BSA of adalimumab up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved (p=0.039) with mean percent decrease of -62.6% in patients in the adalimumab group compared to -11.6% in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the open-label period through Week 156. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Paediatric ACR 30 response, Paediatric ACR 50 response, and Paediatric ACR 70 response and maintained these improvements during the open-label period through Week 156 of the study.

***Paediatric Crohn's disease clinical study***

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

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥40 kg, and 80 mg and 40 mg, respectively, for subjects <40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 30.

**Table 30. Maintenance Regimen**

| Patient Weight | Low Dose | Standard Dose |
|---|---|---|
| <40 kg | 10 mg eow | 20 mg eow |
| ≥40 kg | 20 mg eow | 40 mg eow |

Abbreviation: eow=every other week

*Efficacy results*

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 31. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 32.

**Table 31. Paediatric CD Study – PCDAI Clinical Remission and Response**

| | Standard Dose 40/20 mg eow N=93 | Low Dose 20/10 mg eow N=95 | P-value* |
|---|---|---|---|
| **Week 26** | | | |
| Clinical remission | 38.7% | 28.4% | 0.075 |
| Clinical response | 59.1% | 48.4% | 0.073 |
| **Week 52** | | | |
| Clinical remission | 33.3% | 23.2% | 0.100 |
| Clinical response | 41.9% | 28.4% | 0.038 |

Abbreviations: CD=Crohn's disease; eow=every other week.

* P-value for Standard Dose vs. Low Dose comparison.

**Table 32. Paediatric CD Study – Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission**

| | Standard Dose 40/20 mg eow | Low Dose 20/10 mg eow | P-value[1] |
|---|---|---|---|
| **Discontinued corticosteroids** | **N=33** | **N=38** | |
| Week 26 | 84.8% | 65.8% | 0.066 |
| Week 52 | 69.7% | 60.5% | 0.420 |
| **Discontinuation of Immunomodulators[2]** | **N=60** | **N=57** | |
| Week 52 | 30.0% | 29.8% | 0.983 |
| **Fistula remission[3]** | **N=15** | **N=21** | |
| Week 26 | 46.7% | 38.1% | 0.608 |
| Week 52 | 40.0% | 23.8% | 0.303 |

Abbreviations: CD=Crohn's disease; eow=every other week.

1 P-value for Standard Dose vs. Low Dose comparison.

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

3 Defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits.

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

***Paediatric plaque psoriasis clinical study***

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

Patients received adalimumab 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At Week 16, more patients randomised

to adalimumab 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to MTX.

**Table 33. Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks**

| | **MTX N=37** | **Adalimumab 0.8 mg/kg eow N=38** |
|---|---|---|
| PASI 75[a] | 12 (32.4%) | 22 (57.9%) |
| PGA: Clear/minimal[b] | 15 (40.5%) | 23 (60.5%) |

Abbreviations: eow=every other week; MTX=methotrexate; PASI= Psoriasis Area and Severity Index; PGA=Physician's Global Assessment.

[a] p=0.027, adalimumab 0.8 mg/kg vs. MTX.

[b] p=0.083, adalimumab 0.8 mg/kg vs. MTX.

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (loss of PGA response). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and responses observed during re-treatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

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

***Adolescent hidradenitis suppurativa***

There are no clinical trials with adalimumab in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. The recommended adolescent HS dosing schedule of 40 mg every other week is predicted to provide similar efficacy to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses.

***Paediatric uveitis clinical study***

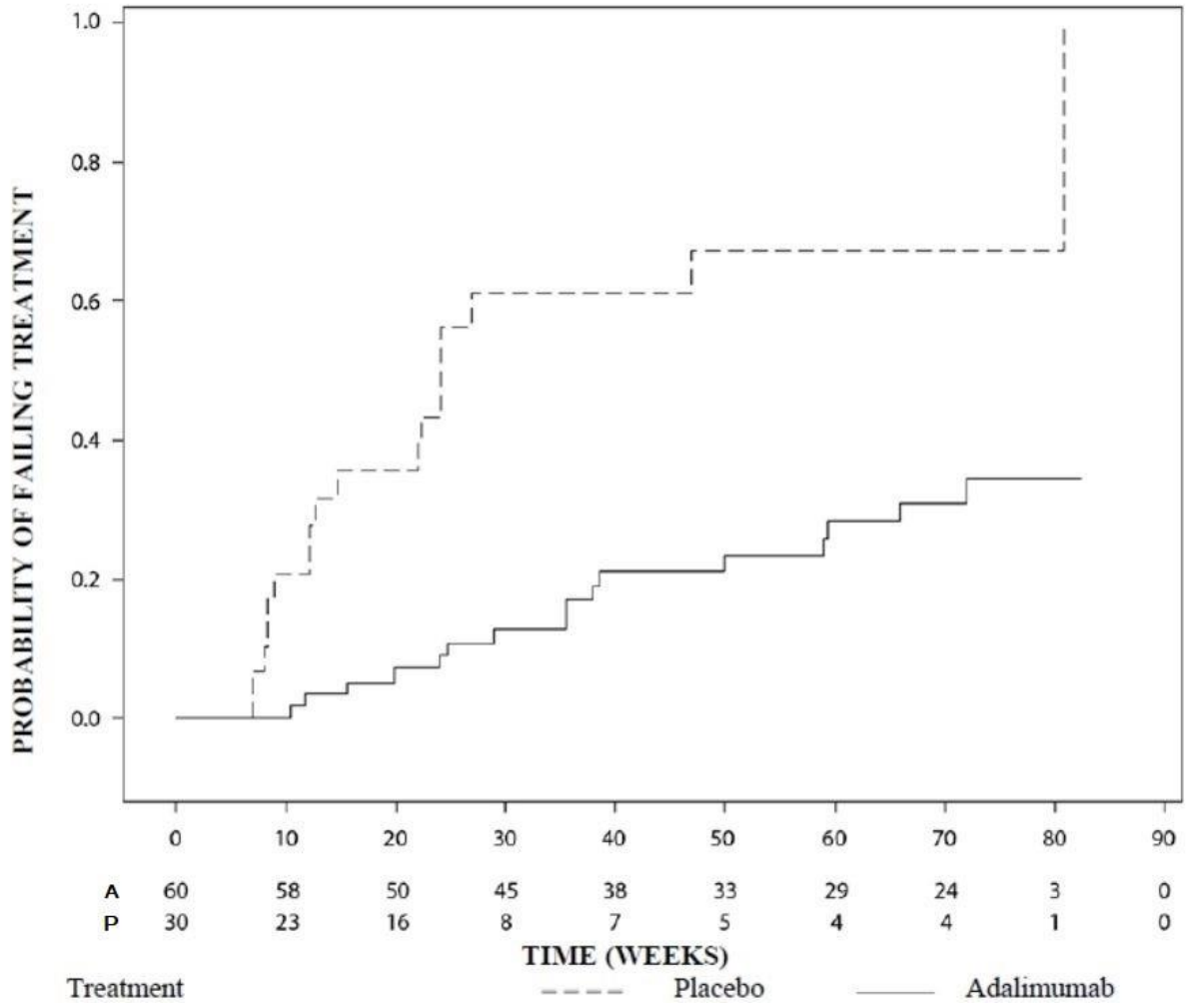
The safety and efficacy of adalimumab was assessed in a randomised, double-masked, controlled study of 90 paediatric patients from 2 to <18 years of age with active JIA-associated non-infectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either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

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

*Clinical response*

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (see Figure 6, P<0.0001 from log rank test). The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR=0.25 [95% CI: 0.12, 0.49]).

**Figure 6. Kaplan-Meier Curves Summarising Time to Treatment Failure in the Paediatric Uveitis Study**




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

***Paediatric ulcerative colitis***

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

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

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

Disease flare was defined as an increase in PMS of at least 3 points (for patients with PMS of 0 to 2 at Week 8), at least 2 points (for patients with PMS of 3 to 4 at Week 8), or at least 1 point (for patients with PMS of 5 to 6 at Week 8).

Patients who met criteria for disease flare at or after Week 12 were randomised to receive a re-induction dose of 2.4 mg/kg (maximum of 160 mg) or a dose of 0.6 mg/kg (maximum of 40 mg) and continued to receive their respective maintenance dose regimen afterwards.

*Efficacy results*

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

Clinical remission rates per PMS at Week 8 for patients in each of the adalimumab double-blind induction groups are presented in Table 34.

**Table 34. Clinical Remission per PMS at 8 Weeks**

| | **Adalimumab[a] Maximum of 160 mg at Week 0/Placebo at Week 1 N = 30** | **Adalimumab[b,c] Maximum of 160 mg at Week 0 and Week 1 N = 47** |
|---|---|---|
| Clinical remission | 13/30 (43.3%) | 28/47 (59.6%) |

[a] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2

[b] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2

[c] Not including open-label Induction dose of adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2

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

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

At Week 52, clinical remission per FMS in Week 8 responders, clinical response per FMS (defined as a decrease in Mayo score ≥3 points and ≥30% from Baseline) in Week 8 responders, mucosal healing (defined as Mayo endoscopy subscore ≤1) in Week 8 responders, clinical remission per FMS in Week 8 remitters, and the proportion of subjects in corticosteroid-free remission per FMS in Week 8 responders were assessed in patients who received adalimumab at the double-blind maximum 40 mg eow (0.6 mg/kg) and maximum 40 mg ew (0.6 mg/kg) maintenance doses (Table 35).

**Table 35. Efficacy Results at 52 Weeks**

| | **Placebo[a] N = 12** | **Adalimumab[b] Maximum of 40 mg eow N = 31** | **Adalimumab[c,d] Maximum of 40 mg ew N = 31** |
|---|---|---|---|
| Clinical remission in Week 8 PMS responders | 4/12 (33%) | 9/31 (29.0%) | 14/31 (45.2%) |
| Clinical response in Week 8 PMS responders | 4/12 (33%) | 19/31 (61.3%) | 21/31 (67.7%) |
| Mucosal healing in Week 8 PMS responders[e] | 4/12 (33%) | 12/31 (38.7%) | 16/31 (51.6%) |
| Clinical remission in Week 8 PMS remitters | 3/8 (38%) | 9/21 (42.9%) | 10/22 (45.5%) |
| Corticosteroid-free remission in Week 8 PMS responders[f] | N/A | 4/13 (30.8%) | 5/16 (31.3%) |

[a] Twelve patients who demonstrated clinical response per PMS at Week 8 were randomised to receive placebo. There are limitations to the interpretability of the placebo data due to the small sample size.

[b] Adalimumab 0.6 mg/kg (maximum of 40 mg) every other week

[c] Adalimumab 0.6 mg/kg (maximum of 40 mg) every week

[d] There are no anticipated clinically relevant differences in efficacy between the studied higher dosage administered during the 52-week paediatric UC trial and the recommended dosage of adalimumab

[e] Mucosal healing = endoscopic improvement

[f] In patients receiving concomitant corticosteroids at baseline

Note: Patients with missing values at Week 52 or who were randomised to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints

N/A = not available

Additional exploratory efficacy endpoints included clinical response per the Paediatric Ulcerative Colitis Activity Index (PUCAI) (defined as a decrease in PUCAI ≥20 points from Baseline) and clinical remission per PUCAI (defined as PUCAI <10) at Week 8 and Week 52 (Table 36).

**Table 36. Exploratory Endpoints Results per PUCAI**

| | **Week 8** | |
|---|---|---|
| | **Adalimumab[a] Maximum of 160 mg at Week 0/Placebo at Week 1 N = 30** | **Adalimumab[b,c] Maximum of 160 mg at Week 0 and Week 1 N = 47** |
| Clinical remission per PUCAI | 10/30 (33.3%) | 22/47 (46.8%) |
| Clinical response per PUCAI | 15/30 (50.0%) | 32/47 (68.1%) |
| | **Week 52** | |
| | **Adalimumab[d] Maximum of 40 mg eow N = 31** | **Adalimumab[e] Maximum of 40 mg ew N = 31** |
| Clinical remission per PUCAI in Week 8 PMS responders | 14/31 (45.2%) | 18/31 (58.1%) |
| Clinical response per PUCAI in Week 8 PMS responders | 18/31 (58.1%) | 16/31 (51.6%) |

[a] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2
[b] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2
[c] Not including open-label Induction dose of adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2
[d] Adalimumab 0.6 mg/kg (maximum of 40 mg) every other week
[e] Adalimumab 0.6 mg/kg (maximum of 40 mg) every week
Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6
Note 2: Patients with missing values at Week 8 were considered as not having met the endpoints
Note 3: Patients with missing values at Week 52 or who were randomised to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints

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

*Quality of life*

Improvements from Baseline were observed in IMPACT III and the caregiver Work Productivity and Activity Impairment (WPAI) scores for the groups treated with adalimumab.

Increases (improvement) from Baseline in height velocity were observed for the groups treated with adalimumab, and increases (improvement) from Baseline in Body Mass Index were observed for subjects on the high maintenance dose of maximum 40 mg (0.6 mg/kg) ew.

Immunogenicity

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

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

***Adults***

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

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

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

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

In patients with moderately to severely active ulcerative colitis, the rate of anti-adalimumab antibody development in patients treated with adalimumab was 5.0%.

In patients with psoriasis, anti-adalimumab antibodies were identified in 8.4% (77/920) of patients treated with adalimumab without concomitant methotrexate. 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 2.3%, and was similar to the rate observed prior to withdrawal 1.9%.

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

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

***Paediatrics***

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 16.0% (27/171) of patients treated with

adalimumab. In patients not given concomitant methotrexate, the incidence was 26.0% (22/86), compared to 6.0% (5/85) when adalimumab was used as add-on to methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years old or aged 4 and above weighing <15 kg, anti-adalimumab antibodies were identified in 7.0% (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 moderately to severely active paediatrics Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3% (6/182).

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

ABRILADA clinical study – rheumatoid arthritis

The biosimilar clinical development program for ABRILADA included a randomised, double-blind, active-controlled trial in subjects with moderately to severely active RA and an inadequate response to background MTX.

Study B5381002 was a multi-national, double-blind, randomised, comparative efficacy and safety study of 597 subjects designed to demonstrate the absence of clinically meaningful differences in the efficacy, safety and immunogenicity of ABRILADA and Humira-EU (EU reference product), and to evaluate the safety and immunogenicity of ABRILADA after treatment transition from Humira-EU to ABRILADA. The dose regimen was 40 mg injected subcutaneously every other week. The primary efficacy endpoint was ACR20 response rate at Week 12. Secondary endpoints included the ACR20 time course to Week 26, ACR50/70, DAS28-CRP, European League Against Rheumatism (EULAR) response, and ACR/EULAR remission evaluations. At Week 26, 50% of the Humira-EU arm was blindly re-randomised to the ABRILADA arm. At Week 52, all patients received open-label ABRILADA for an additional 24 weeks.

For the ACR20 primary endpoint at Week 12, observed response rates were 68.7% for ABRILADA and 72.7% for Humira-EU. The primary analysis for ACR20 at Week 12 was performed with non-response imputation (NRI) for subjects who discontinued treatment earlier than Week 12 or had a missing Week 12 assessment; the Week 12 ACR20 response rates (ITT; NRI) were 68.4% and 71.1%. In both ITT and PP populations, the 2-sided 95% CIs and 90% CIs of the treatment difference in Week 12 ACR20 response rates between the 2 groups were entirely contained within a symmetric equivalence margin of (-14.0% to 14.0%) and an asymmetric equivalence margin of (-12.0% to 15.0%), demonstrating therapeutic equivalence (similarity) between ABRILADA and HUMIRA-EU treatments.

Similar responses between ABRILADA and Humira-EU treatments were observed at each study visit up to Week 26 as measured by ACR20, ACR50, ACR70, individual ACR parameters (including HAQ-DI), DAS28-CRP, EULAR response, DAS remission and ACR/EULAR remission. No clinically meaningful differences in safety or immunogenicity were found between ABRILADA and Humira-EU.

In line with the findings from the first treatment period, dosing up to Week 52 continued to show the absence of clinically meaningful differences in efficacy, PD, immunogenicity and safety among subjects receiving ABRILADA, Humira-EU, and subjects who transitioned from Humira-EU to ABRILADA.

Based on the comparative clinical efficacy and safety results obtained in Study B5381002 in subjects with RA, it is concluded that biosimilarity was demonstrated between ABRILADA and Humira-EU. The totality of evidence supports that ABRILADA is biosimilar to Humira.

## 5.2. Pharmacokinetic properties

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was slow, with mean peak serum concentration being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%.

Distribution and elimination

The single dose pharmacokinetics of adalimumab 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 litres, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. 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. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 µg/mL (without concomitant methotrexate (MTX)) and 8 to 9 µg/mL (with concomitant MTX), respectively. The serum adalimumab trough levels at steady-state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with psoriasis, the mean steady-state trough concentration was 5 µg/mL during adalimumab 40 mg every other week without concomitant MTX treatment.

In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 µg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12

through Week 36 were approximately 8 to 10 μg/mL during adalimumab 40 mg every week treatment.

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

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

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The systemic clearance of adalimumab is approximately 12 mL/h. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time in RA patients.

Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab on Week 2 achieves serum adalimumab trough levels of approximately 5.5 μg/mL during the induction period. A loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough levels of approximately 12 μg/mL during the induction period. Mean steady-state trough levels of approximately 7 μg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg adalimumab every other week.

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

Special populations

Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

***Geriatrics***

A lower clearance with increasing age was observed in patients with RA aged 40 to >75 years.

***Paediatrics***

Following the administration of 24 mg/m$^2$ (maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/mL (102% CV) for adalimumab without concomitant MTX and 10.9 ± 5.2 μg/mL (47.7% CV) with concomitant MTX. The mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant MTX or with concomitant MTX were 6.8 μg/mL and 10.9 μg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week without concomitant MTX or with concomitant MTX were 6.6 μg/mL and 8.1 μg/mL, respectively.

In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/m$^2$, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 μg/mL (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/mL (71.2% CV) with concomitant methotrexate.

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

In paediatric patients with moderately to severely active CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 μg/mL for patients ≥40 kg (160/80 mg) and 10.6 ± 6.1 μg/mL for patients <40 kg (80/40 mg).

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

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

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

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

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

***Male and female patients***

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy subjects and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

***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 rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

Anti-drug antibody (ADA) effects on pharmacokinetics

***Rheumatoid arthritis***

The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA. A trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies was identified.

***Paediatric ulcerative colitis***

Antibodies to adalimumab by ECL assay were associated with reduced serum adalimumab concentrations in paediatric patients with moderately to severely active ulcerative colitis.

***Hidradenitis suppurativa***

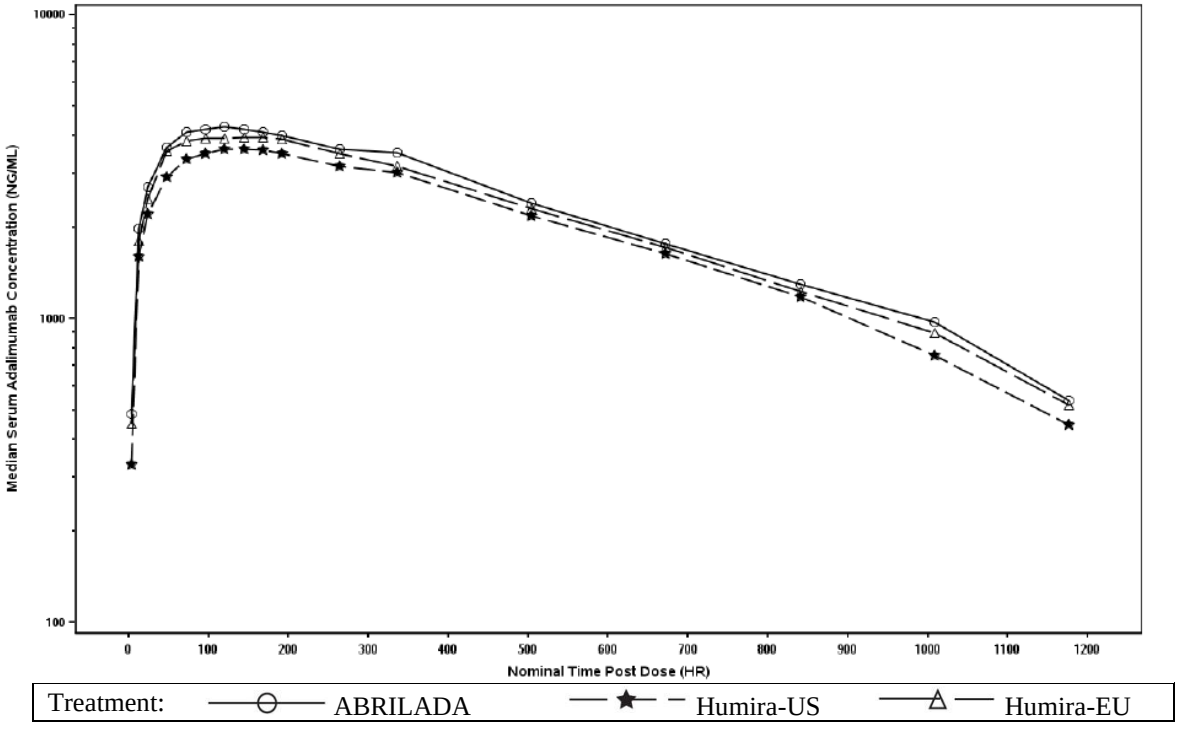
In subjects with moderate to severe HS, antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titres of antibodies to adalimumab.

ABRILADA pharmacokinetic similarity study

The pharmacokinetic (PK) similarity of ABRILADA and Humira was evaluated in the clinical development program. Study B5381007 was a three-arm, parallel-group, double-blind, randomised (1:1:1), single dose pivotal PK similarity study that compared the PK of ABRILADA, Humira-EU (EU reference product) and Humira-US (reference product) following subcutaneous administration of 40 mg to healthy adult subjects.

The 3 study drugs exhibited similar median PK profiles, which were characterised by an increase in serum drug concentrations to $C_{max}$ at approximately 5-6 days, after which the concentrations exhibited a steady decline to Day 50.

**Figure 7. Median Serum Concentration-Time Profiles of ABRILADA, Humira-US and Humira-EU Following a Single 40 mg Subcutaneous Dose to Healthy Subjects**




Consistent with the median concentration-time profiles, the mean $C_{max}$, $AUC_{0\text{-}2wk}$, $AUC_t$ and $AUC_{inf}$ estimates were similar among the 3 study treatments. The inter-subject variability for each of the PK parameters, though considerable, was similar across the 3 study drugs, with CV values of 28-29%, 26-29%, 29-33%, and 33-40% for $C_{max}$, $AUC_{0\text{-}2wk}$, $AUC_t$ and $AUC_{inf,}$ respectively.

**Table 37. Mean (±SD) Pharmacokinetic Parameter Estimates of ABRILADA, Humira-US and Humira-EU (Study B5381007)**

| Parameters (Units) | ABRILADA | Humira-US | Humira-EU |
|---|---|---|---|
| Subjects, n | N=106 | N=101 | N=104 |
| $C_{max}$ (µg/mL) | 4.53 ± 1.27 | 4.04 ± 1.18 | 4.09 ± 1.17 |
| $T_{max}$ (h)* | 120 (48, 362) | 144 (48, 363) | 132 (24, 336) |
| $AUC_{0\text{-}2wk}$ (µg•h/mL) | 1254 ± 348.01 | 1101 ± 289.57 | 1130 ± 332.50 |
| $AUC_t$ (µg•h/mL) | 2586 ± 858.85 | 2281 ± 705.92 | 2392 ± 697.93 |
| $AUC_{inf}$ (µg•h/mL)† | 3113 ± 1254.0 | 2748 ± 1078.8 | 2886 ± 965.4 |
| CL/F (mL/h)† | 15.27 ± 6.91 | 16.80 ± 6.29 | 15.76 ± 6.45 |
| $V_z$/F (mL)† | 6422 ± 2131.0 | 7095 ± 2347.4 | 7244 ± 3295.9 |
| $t_{½}$ (h)† | 351.5 ± 188.78 | 346.2 ± 204.61 | 362.4 ± 200.83 |

Abbreviations: EU=European Union; n=total number of subjects in the treatment group in the indicated population; $r^2$=coefficient of determination; SD=standard deviation; US=United States.

* Median (range) values are reported for $T_{max}$.

† Number of subjects with a well-defined disposition terminal phase (containing a minimal of 3 concentration-time data points and with $r^2 \geq 0.9$), permitting reliable estimation of the slope of the terminal phase (λ) and therefore estimations of $AUC_{inf}$, CL/F, $V_z$/F and $t_{½}$, was 103, 102 and 99 in the ABRILADA, Humira-EU and Humira-US groups, respectively.

Table 38 summarises the ratio of adjusted geometric means and the 90% CIs for the primary PK parameter comparisons. For the PK similarity comparisons of ABRILADA to each of the comparator products (Humira-EU and Humira-US), the 90% CIs for the test-to-reference ratios of $C_{max}$, $AUC_{0\text{-}2wk}$, $AUC_t$, and $AUC_{inf}$ were all contained within the pre-specified acceptance criteria of 80.00% to 125.00%.

In addition, for the PK similarity comparison of Humira-EU to Humira-US, the 90% CIs for the test-to-reference ratios of $C_{max}$, $AUC_{0\text{-}2wk}$, $AUC_t$, and $AUC_{inf}$ were all contained within the pre-specified acceptance criteria of 80.00% to 125.00%.

**Table 38. Summary of Statistical Comparisons of PK Exposure Parameters ($C_{max}$, $AUC_{0-2wk}$, $AUC_t$, and $AUC_{inf}$) between Test and Comparator Products (Study B5381007)**

| Parameter (units) | Adjusted Geometric Means | | Ratio (Test/Comparator) of Adjusted Means[a] | 90% CI for Ratio[a] |
|---|---|---|---|---|
| | Test | Comparator | | |
| **ABRILADA (Test) vs. Humira-EU(Comparator)** | | | | |
| $C_{max}$ (µg/mL) | 4.34 | 3.90 | 111.36 | 103.97 – 119.27 |
| $AUC_{0-2wk}$ (µg•h/mL) | 1199 | 1072 | 111.88 | 104.19 – 120.15 |
| $AUC_t$ (µg•h/mL) | 2430 | 2275 | 106.80 | 98.76 – 115.49 |
| $AUC_{inf}$ (µg•h/mL) | 2866 | 2718 | 105.44 | 96.43 – 115.29 |
| **ABRILADA (Test) vs. Humira-US (Comparator)** | | | | |
| $C_{max}$ (µg/mL) | 4.34 | 3.89 | 111.64 | 104.18 – 119.64 |
| $AUC_{0-2wk}$ (µg•h/mL) | 1199 | 1064 | 112.73 | 104.92 – 121.12 |
| $AUC_t$ (µg•h/mL) | 2430 | 2172 | 111.87 | 103.39 – 121.05 |
| $AUC_{inf}$ (µg•h/mL) | 2866 | 2556 | 112.12 | 102.47 – 122.68 |
| **Humira-EU (Test) vs. Humira-US (Comparator)** | | | | |
| $C_{max}$ (µg/mL) | 3.90 | 3.89 | 100.25 | 93.52 – 107.47 |
| $AUC_{0-2wk}$ (µg•h/mL) | 1072 | 1064 | 100.76 | 93.74 – 108.30 |
| $AUC_t$ (µg•h/mL) | 2275 | 2172 | 104.75 | 96.77 – 113.38 |
| $AUC_{inf}$ (µg•h/mL) | 2718 | 2556 | 106.34 | 97.17 – 116.37 |

Abbreviations: CI=confidence interval; EU=European Union; US=United States; vs=versus.

[a] The ratios (and 90% CIs) are expressed as percentages.

In conclusion, Study B5381007 demonstrated PK similarity of ABRILADA to both Humira-US and Humira-EU. PK similarity was also demonstrated for Humira-EU to Humira-US, thus, establishing a bridge for the use of the Humira-EU product in a subsequent clinical comparability Study B5381002.

Study B5381005 was an open-label, randomised (1:1), parallel-group, 2-arm, single dose PK comparability study to assess the PK of ABRILADA following subcutaneous administration in the lower abdomen or upper anterior thigh using a pre-filled syringe or a pre-filled pen in healthy adult subjects.

The 2 treatment arms exhibited comparable PK profiles, which were characterised by an increase in serum drug concentrations to $C_{max}$ at approximately 6-7 days, after which the concentrations exhibited a steady decline to Week 6.

Consistent with the mean concentration-time profiles, the mean $C_{max}$, $AUC_{0-2wk}$, $AUC_t$ and $AUC_{0-inf}$ estimates were similar between the 2 study arms (Table 39). The inter-subject variability for each of the PK parameters was similar across the 2 study arms, with CV values of 29-30%, 28-30%, 31-35%, and 32-36% for $C_{max}$, $AUC_{0-2wk}$, $AUC_t$ and $AUC_{0-inf}$, respectively.

**Table 39. Arithmetic Mean (±SD) ABRILADA Pharmacokinetic Parameter Estimates**

| Parameters (units) | PFS | PFP |
|---|---|---|
| Subjects, n | 80 | 83 |
| $C_{max}$ (µg/mL) | 4.34 ± 1.28 | 4.65 ± 1.34 |
| $T_{max}$ (h)[a] | 166 (47.7, 674) | 142 (45.4, 336) |
| $AUC_{0\text{-}2wk}$ (µg•h/mL) | 1155 ± 342.28 | 1211 ± 333.32 |
| $AUC_{last}$ (µg•h/mL) | 2227 ± 696.19 | 2241 ± 792.06 |
| $AUC_{inf}$ (µg•h/mL)[b] | 2291 ± 823.86 | 2336 ± 757.19 |
| CL/F (mL/h)[b] | 19.73 ± 6.99 | 19.42 ± 7.78 |
| $V_z$/F (mL)[b] | 5472 ± 2043.4 | 5282 ± 2010.2 |
| $t_{½}$ (h)[b] | 210.1 ± 84.55 | 209.2 ± 96.73 |

Abbreviations: h=hour(s); CL/F=apparent clearance; n=number of subjects; PFP=pre-filled pen; PFS=pre-filled syringe; $r^2$=the goodness-of-fit statistic from the regression; SD=standard deviation; $V_z$/F=apparent volume of distribution.

[a] Median (range) values were reported for $T_{max}$.

[b] Number of subjects with a well-defined terminal phase (containing a minimal of 3 concentration-time data points and with $r^2 \geq 0.9$), permitting reliable estimation of $AUC_{0\text{-}inf}$, CL/F, $V_z$/F and $t_{½}$, was 48 and 58 for the PFS and PFP treatment arms, respectively.

Table 40 summarises the ratio of adjusted geometric means and the 90% confidence intervals (CIs) for the comparisons of primary ($C_{max}$ and $AUC_{0\text{-}2wk}$) and secondary ($AUC_t$ and $AUC_{0\text{-}inf}$) endpoints. For the PK comparisons between the 2 device study arms, the 90% CIs for the test-to-reference ratios of all primary and secondary PK endpoints were within the pre-specified acceptance window of 80.00% to 125.00%.

**Table 40. Summary of Statistical Comparisons of PK Exposure Parameters ($C_{max}$, $AUC_{0\text{-}2wk}$, $AUC_t$, and $AUC_{0\text{-}inf}$) for ABRILADA by Pre-filled Pen or Pre-filled Syringe Treatment Arms (B5381005)**

| Parameter (units) | Adjusted Geometric Means | | Ratio (Test/Comparator) of Adjusted Means[a] | 90% CI for Ratio[a] |
|---|---|---|---|---|
| | Test (PFP) | Comparator (PFS) | | |
| $C_{max}$ (µg/mL) | 4.45 | 4.13 | 107.74 | 99.16 – 117.06 |
| $AUC_{0\text{-}2wk}$ (µg•h/mL) | 1150 | 1097 | 104.89 | 95.76 – 114.89 |
| $AUC_{last}$ (µg•h/mL) | 2042 | 2101 | 97.23 | 86.75 – 108.98 |
| $AUC_{inf}$ (µg•h/mL) | 2203 | 2154 | 102.27 | 91.12 – 114.78 |

Abbreviations: CI=confidence interval; PFP=pre-filled pen; PFS=pre-filled syringe.

[a] The ratios (and 90% CIs) were expressed as percentages.

In conclusion, the 90% CIs of the test-to-reference ratios for the primary PK parameters ($C_{max}$ and $AUC_{0\text{-}2wk}$) were within the pre-specified acceptance window of 80.00-125.00%, thus, PK comparability was demonstrated for ABRILADA following subcutaneous administration using either a pre-filled syringe or a pre-filled pen.

In Study B5381002 in Treatment Period 1, the mean and median serum drug concentrations were numerically higher for the ABRILADA arm compared to the Humira-EU arm; however, considerable overlap and high variability were observed for both treatment arms.

The concentrations of serum ABRILADA and Humira-EU were lower in ADA positive subjects compared to ADA negative subjects, and the impact of ADA on serum concentrations in ADA positive subjects was similar between treatment arms.

In Treatment Period 2, the mean and median serum drug concentrations were numerically slightly higher for the ABRILADA/ABRILADA and Humira-EU/ABRILADA groups as compared to the Humira-EU/Humira-EU group; however, given the considerable overlap in serum drug concentrations between the 3 treatment groups and the high variability observed in the data, these numerical differences are not considered to be clinically meaningful.

The impact of ADA on serum concentrations in ADA positive subjects was comparable among the 3 treatment groups. As expected, the serum drug trough concentrations were lower in ADA positive subjects compared to ADA negative subjects.

In conclusion, although the systemic exposures of ABRILADA were observed to be slightly higher compared to either Humira-EU or Humira-US, these differences are not considered to be clinically meaningful. Thus, the totality of the PK data provides clinical evidence of PK similarity between ABRILADA and Humira.

## 5.3. Preclinical safety data

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

Carcinogenesis, mutagenesis, and impairment of fertility

Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

ABRILADA preclinical safety data summary

ABRILADA was evaluated in comparison to Humira-EU (EU reference product) and Humira-US (reference product) in a series of *in vitro* pharmacology studies, as well as in comparison to Humira-EU in an *in vivo*, repeat-dose 1 month toxicity study in cynomolgus monkeys, a species that the originator showed was pharmacologically relevant. The physicochemical and functional data demonstrated that ABRILADA was identical to Humira-US and Humira-EU with respect to amino acid sequence, and similar to Humira-US and Humira-EU with respect to physicochemical properties, and response in *in vitro* assays that evaluated Fab-based biological activity and Fc-based functionality.

ABRILADA and Humira-EU were tolerated when administered by subcutaneous injection at a dose of 157 mg/kg, once weekly, for 1 month (total of 5 doses), and anti-drug antibody (ADA) response and toxicokinetics (TK) of ABRILADA were similar to that of Humira-EU. There were no adverse effects in any parameter evaluated, so the no observed adverse effect level (NOAEL) was 157 mg/kg/dose, the only dose tested. There were no relevant differences in the incidence or severity of microscopic findings between ABRILADA and Humira-EU groups, and responses between the groups appeared similar.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

The inactive ingredients in ABRILADA solution for injection in pre-filled syringe and pre-filled pen are L-Histidine, L-Histidine HCl monohydrate, Edetate Disodium Dihydrate, Sucrose, L-Methionine, Polysorbate 80 and Water for Injection.

### 6.2. Incompatibilities

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

### 6.3. Shelf life

Refer to outer carton.

### 6.4. Special precautions for storage

Pre-filled syringe

Store in a refrigerator (2°C–8°C). Do not freeze. Keep the pre-filled syringe in its outer carton in order to protect from light. Do not use if frozen even if it has been thawed.

A single ABRILADA pre-filled syringe may be stored at temperatures up to a maximum of 30°C for a period of up to 30 days. The syringe must be protected from light, and discarded if not used within the 30-day period.

Pre-filled pen

Store in a refrigerator (2°C–8°C). Do not freeze. Keep the pre-filled pen in its outer carton in order to protect from light. Do not use if frozen even if it has been thawed.

A single ABRILADA pre-filled pen may be stored at temperatures up to a maximum of 30°C for a period of up to 30 days. The syringe or pen must be protected from light, and discarded if not used within the 30-day period.

### 6.5. Nature and contents of container

Pre-filled syringe (PFS)

Solution for injection in pre-filled syringe (Type I glass) having a (staked) needle, a thermoplastic elastomer needle shield with a polypropylene rigid cover, and a fluoropolymer coated elastomeric plunger stopper.

PFS is a single-dose syringe supplied in three different dose strengths, with each PFS containing 40 mg/0.8 mL or 20 mg/0.4 mL of solution for injection.

*ABRILADA 20 mg/0.4 mL solution for injection in pre-filled syringe:*

Pack size of two pre-filled syringe.

*ABRILADA 40 mg/0.8 mL solution for injection in pre-filled syringe:*
Pack size of one pre-filled syringe;
Pack size of two pre-filled syringes.

Pre-filled pen (PFP)

Solution for injection in pre-filled syringe enclosed in pre-filled pen made up of two subassemblies (front subassembly and power pack subassembly), a syringe clip and a label.

The front subassembly consists of a transparent outer housing with a white cap that forms the body of the pre-filled pen, rigid needle shield perforated bracket, rigid needle shield remover, needle guard, syringe holder, button blocker and needle guard spring. The power pack subassembly consist of the power pack housing, bezel, activation button, end click bracket, spring guide rod, drive spring, and plunger rod.

*ABRILADA 40 mg/0.8 mL solution for injection in pre-filled pen:*
Pack size of two pre-filled pen.

Not all strengths may be marketed.

### 6.6. Special precautions for disposal and other handling

ABRILADA does not contain preservatives; therefore, unused portions should be discarded.

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

## 7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017, USA

ABR-SIN-0922/1
Date of last revision: May 2023

**INSTRUCTIONS FOR USE**

ABRILADA (adalimumab)

20 mg/0.4 mL Solution for Injection in Pre-filled Syringe

Single-dose, for subcutaneous injection

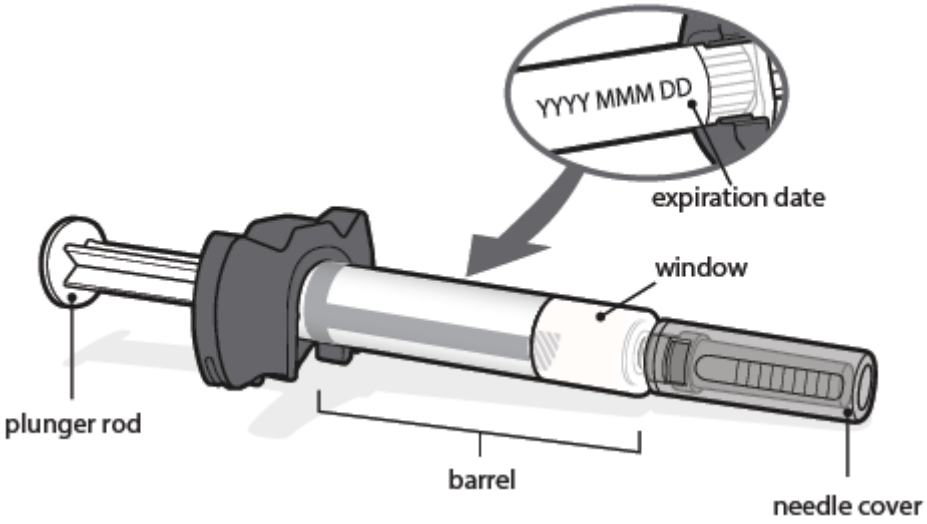
**Keep this leaflet. These instructions show step-by-step how to prepare and give an injection.**
**Store ABRILADA pre-filled syringe in the refrigerator between 2°C to 8°C.**
**Store ABRILADA pre-filled syringe in the original carton until use to protect from direct sunlight.**
**Do not use if frozen even if it has been thawed.**
**If needed, for example when you and your child are traveling, you may store ABRILADA pre-filled syringe at room temperature up to 30°C for up to 30 days.**
**Keep ABRILADA, injection supplies, and all other medicines out of the reach of children.**

ABRILADA solution for injection comes in a disposable single use pre-filled syringe that contains a single dose of medicine.
**Do not** try to inject ABRILADA to your child until you have read and understood the Instructions for Use. If your child's doctor, nurse or pharmacist decides that you may be able to give injections of ABRILADA to your child at home, you should receive training on the correct way to prepare and inject ABRILADA.
It is also important to talk to your child's doctor, nurse or pharmacist to be sure you understand your child's ABRILADA dosing instructions. To help you remember when to inject ABRILADA, you can mark your calendar ahead of time. Talk to your child's doctor, nurse or pharmacist if you have any questions about the correct way to inject ABRILADA.
After proper training, the ABRILADA solution for injection can be given by your child or given by another person, for example, a family member or friend.

## 1. Supplies you need

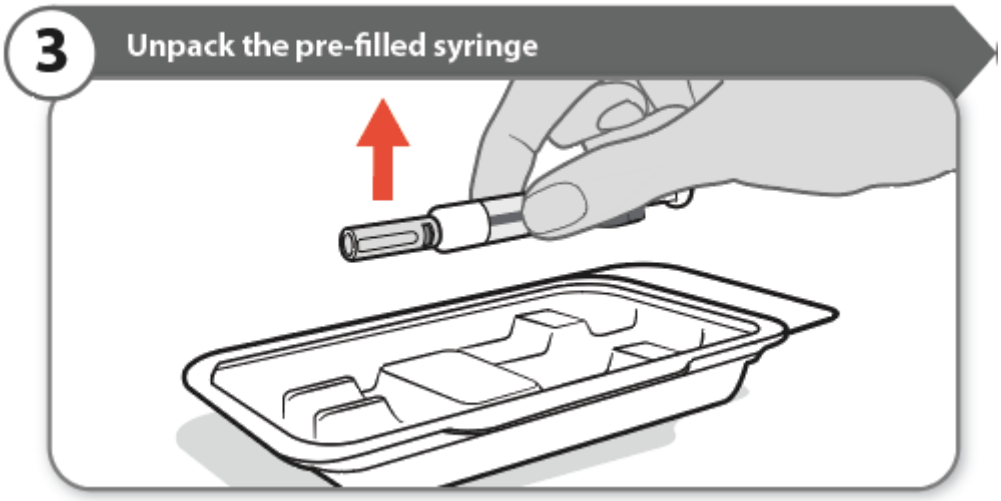
- You will need the following supplies for each injection of ABRILADA. Find a clean, flat surface to place the supplies on.
  - 1 ABRILADA pre-filled syringe in a tray, inside the carton
  - 1 alcohol swab, inside the carton
  - 1 cotton ball or gauze pad (not included in the ABRILADA carton)
  - A suitable sharps container (not included in the ABRILADA carton).

  **Important:** If you have any questions about your child's ABRILADA pre-filled syringe or medicine, talk to your child's doctor, nurse or pharmacist.

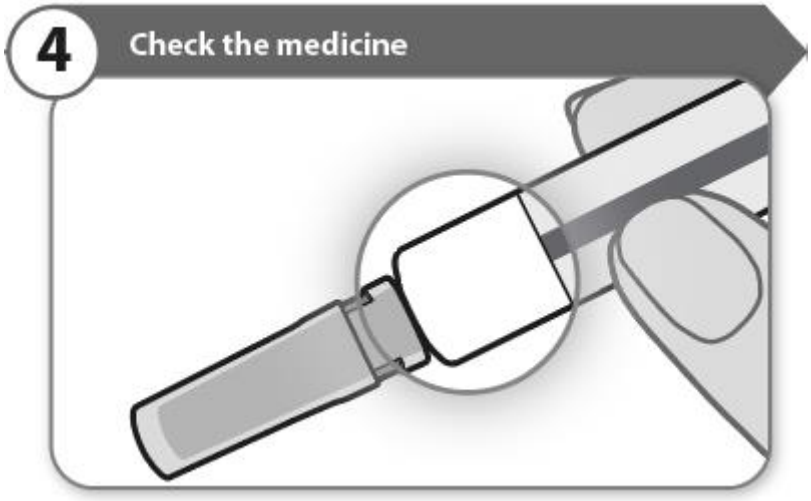



## 2. Getting ready

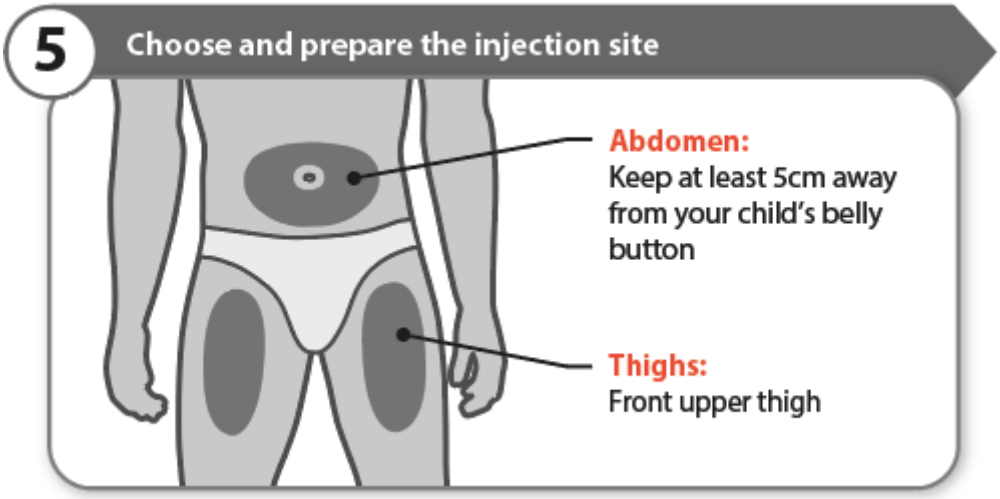
- Remove ABRILADA carton from the refrigerator.
- Open the carton and take out the tray containing the pre-filled syringe.
- Check the carton and tray; **do not** use if:
  - the expiration date has passed
  - it has been frozen or thawed
  - it has been dropped, even if it looks undamaged
  - it has been out of the refrigerator for more than 30 days
  - it appears to be damaged
  - the seals on a new carton are broken.
- If any of the above apply, dispose of the pre-filled syringe in the same way as a used syringe. You will need a new pre-filled syringe to give your child's injection.
- Wash your hands with soap and water, and dry completely.
  If you have any questions about your child's medicine, please talk to your child's doctor, nurse or pharmacist.



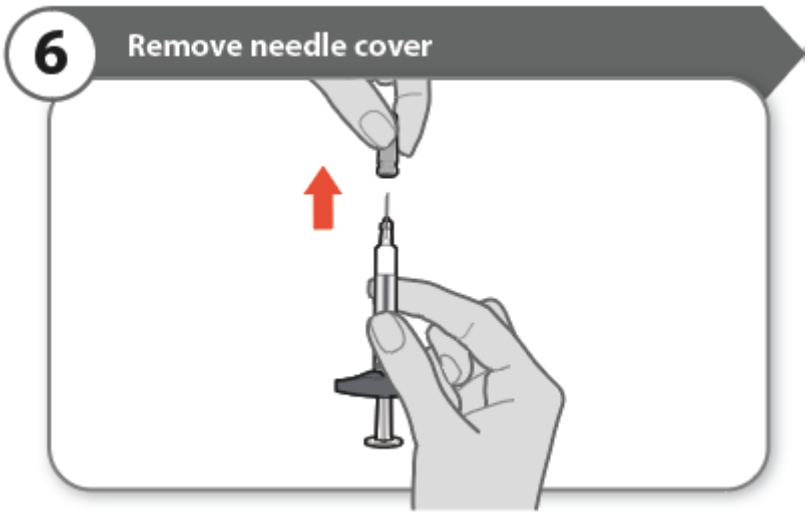
- Peel back the paper seal on the tray.
- Remove 1 pre-filled syringe from the tray and put the original carton with any unused pre-filled syringes back in the refrigerator.
- **Do not** use the syringe if it appears to be damaged.
- The pre-filled syringe may be used straight from the refrigerator.
- You may find that using the pre-filled syringe at room temperature reduces stinging or discomfort. Leave the pre-filled syringe at room temperature away from direct sunlight for 15 to 30 minutes before your child's injection.
- **Do not** remove the needle cover from the pre-filled syringe until you are ready to inject. **Always hold the pre-filled syringe by the barrel to prevent damage.**



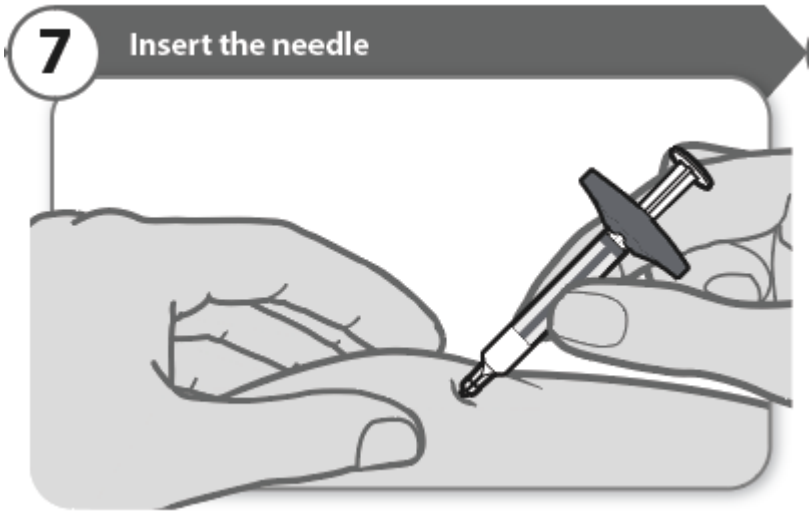

- Look carefully at your child's medicine in the window.
- Gently tilt the pre-filled syringe back and forth to check the medicine.
- **Do not** shake the pre-filled syringe. Shaking can damage your child's medicine.
- Make sure the medicine in the pre-filled syringe is clear and colourless to very light brown and free from flakes or particles. It is normal to see one or more air bubbles in the window. **Do not** attempt to remove air bubbles.
  If you have any questions about your child's medicine, please talk to your child's doctor, nurse or pharmacist.



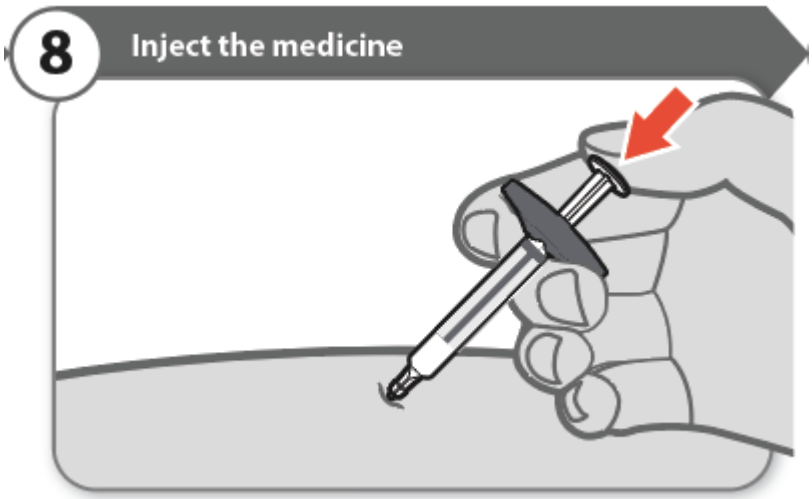

- Choose a different site each time you give your child an injection.
- **Do not** inject into bony areas or areas on your child's skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
    - If your child has psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions on your child's skin.
- **Do not** inject through your child's clothes.
- Wipe the injection site with the alcohol swab.
- Allow the injection site to dry.



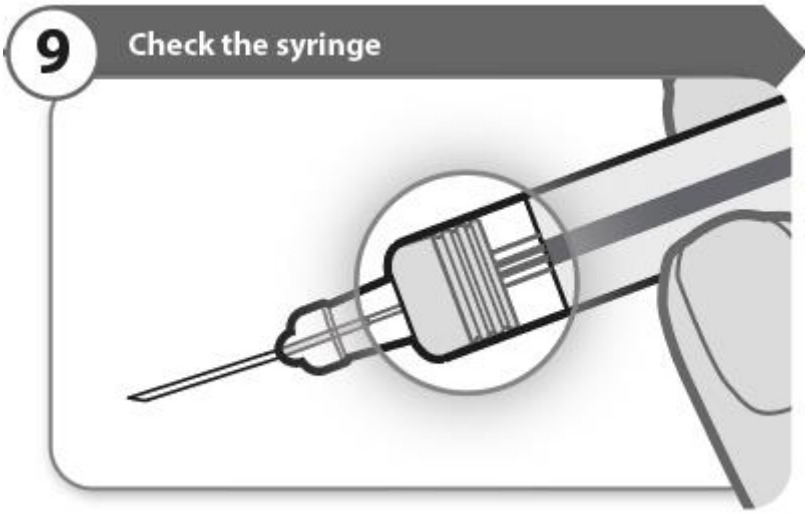

- Hold the pre-filled syringe by the syringe barrel. Carefully pull the needle cover straight off and away from your body when you are ready to inject.
- It is normal to see a few drops of medicine at the needle tip when you remove the needle cover.
- Throw the needle cover away into a sharps disposal container.
  **Note:** Be careful when you handle the pre-filled syringe to avoid an accidental needle stick injury.



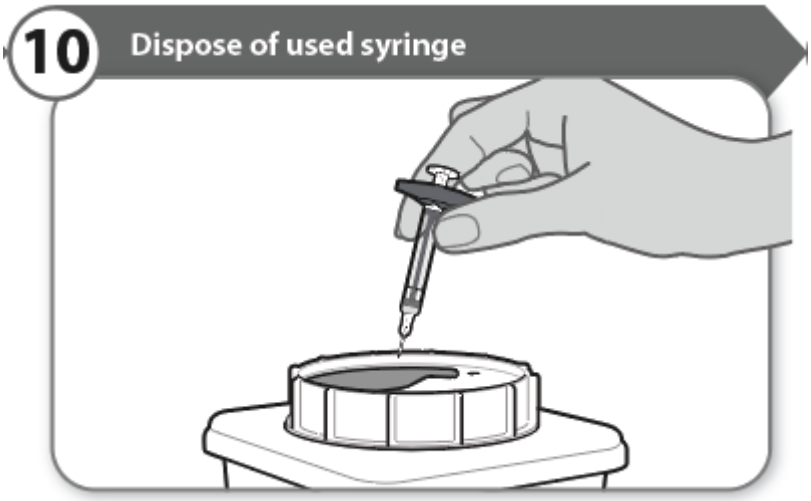

- Gently pinch up a fold of skin in the cleaned injection site area.
- Insert the needle to its full depth into the skin, at a 45 degree angle, as shown.
- After the needle is inserted, release the pinched skin.
  **Important: Do not** re-insert the needle into your child's skin. If the needle has already been inserted into the skin and you change your mind about where to inject, you will need a replacement pre-filled syringe.



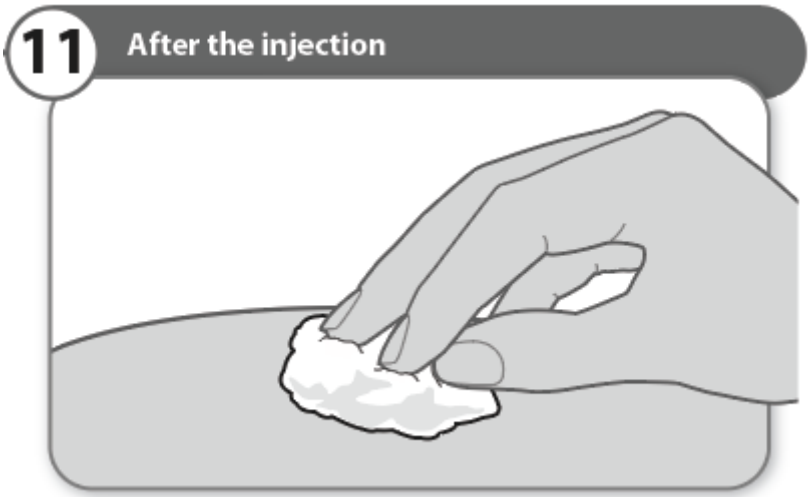

- Using slow and constant pressure, push the plunger rod all the way down until the barrel is empty. It usually takes 2 to 5 seconds to deliver the dose.
  **Note:** It is recommended to hold the pre-filled syringe in the skin for an additional 5 seconds after the plunger has been pressed down completely.
- Pull the needle out of the skin at the same angle at which it entered.




- Check that your child's medicine has completely emptied from the pre-filled syringe.
- **Never re-insert the needle.**
- **Never re-cap the needle.**
  **Note:** If the grey stopper is not in the position shown, you may not have injected all of your child's medicine. Talk to your child's doctor, nurse or pharmacist right away.




- Dispose of the syringe straight away as instructed by your child's doctor, nurse or pharmacist and in accordance with local health and safety laws.




- Look closely at your child’s injection site. If there is blood, use a clean cotton ball or gauze pad to press lightly on the injection area for a few seconds.
- **Do not** rub the site.
  **Note:** Store any unused syringes in the refrigerator in the original carton.

**INSTRUCTIONS FOR USE**

ABRILADA (adalimumab)

40 mg/0.8 mL Solution for Injection in Pre-filled Syringe

Single-dose, for subcutaneous injection

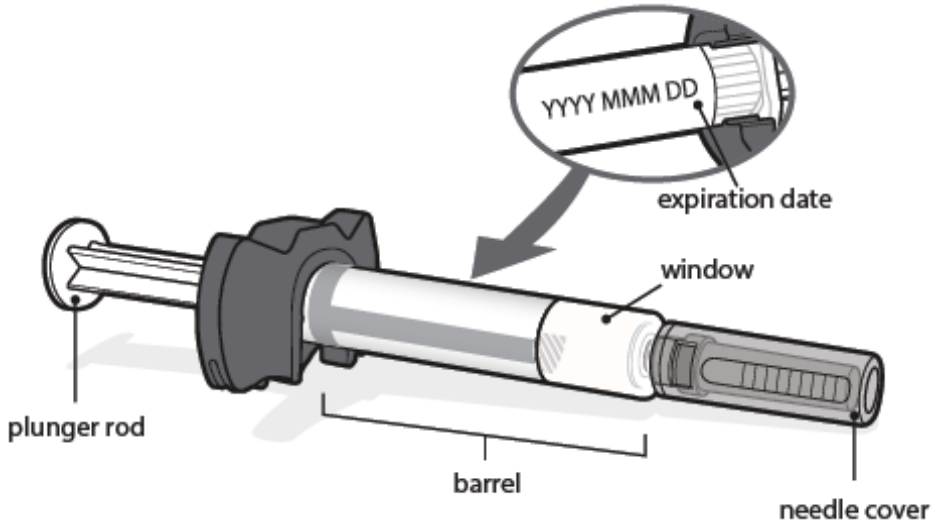
**Keep this leaflet. These instructions show step-by-step how to prepare and give an injection.**
**Store ABRILADA pre-filled syringe in the refrigerator between 2°C to 8°C.**
**Store ABRILADA pre-filled syringe in the original carton until use to protect from direct sunlight.**
**Do not use if frozen even if it has been thawed.**
**If needed, for example when you are traveling, you may store ABRILADA pre-filled syringe at room temperature up to 30°C for up to 30 days.**
**Keep ABRILADA, injection supplies, and all other medicines out of the reach of children.**

ABRILADA solution for injection comes in a disposable single use pre-filled syringe that contains a single dose of medicine.
**Do not** try to inject ABRILADA yourself until you have read and understood the Instructions for Use. If your doctor, nurse or pharmacist decides that you or a caregiver may be able to give your injections of ABRILADA at home, you should receive training on the correct way to prepare and inject ABRILADA.
It is also important to talk to your doctor, nurse or pharmacist to be sure you understand your ABRILADA dosing instructions. To help you remember when to inject ABRILADA, you can mark your calendar ahead of time. Talk to your doctor, nurse or pharmacist if you or your caregiver have any questions about the correct way to inject ABRILADA.
After proper training, ABRILADA solution for injection can be self-administered or given by a caregiver.

## 1. Supplies you need

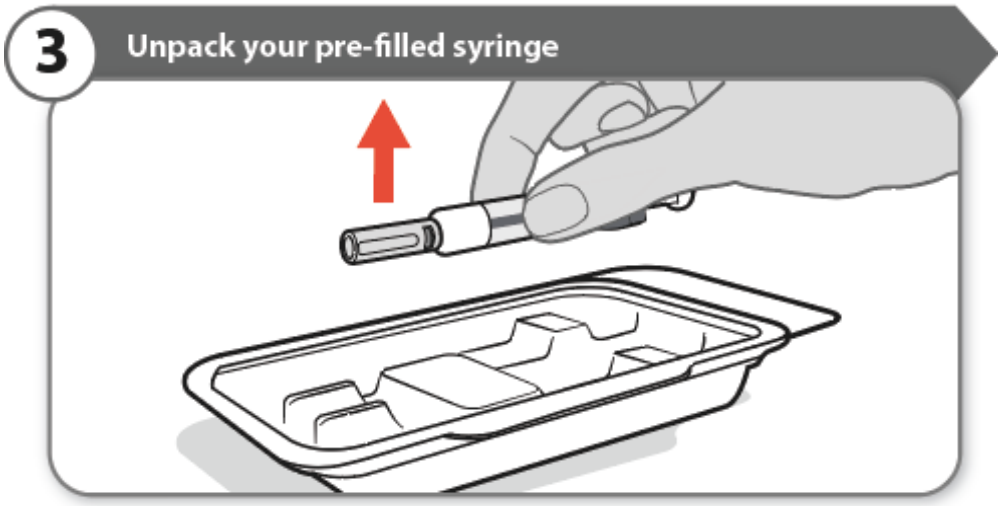
- You will need the following supplies for each injection of ABRILADA. Find a clean, flat surface to place the supplies on.
  - 1 ABRILADA pre-filled syringe in a tray, inside the carton
  - 1 alcohol swab, inside the carton
  - 1 cotton ball or gauze pad (not included in your ABRILADA carton)
  - A suitable sharps container (not included in your ABRILADA carton).

  **Important:** If you have any questions about your ABRILADA pre-filled syringe or medicine, talk to your doctor, nurse or pharmacist.

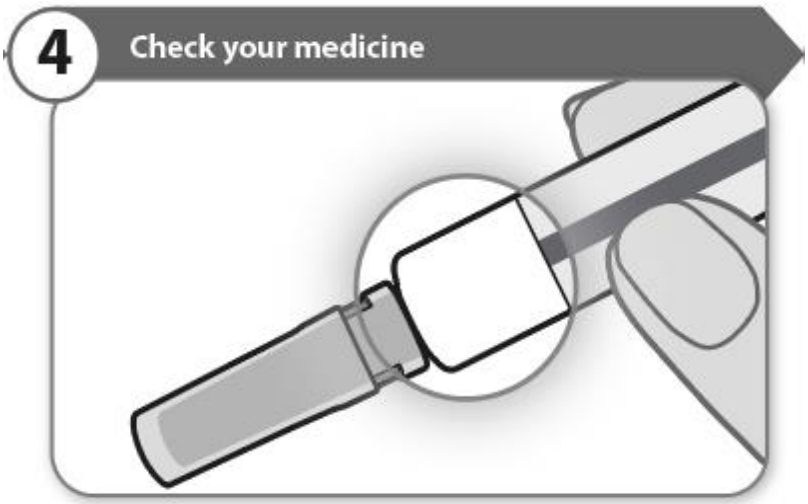



## 2. Getting ready

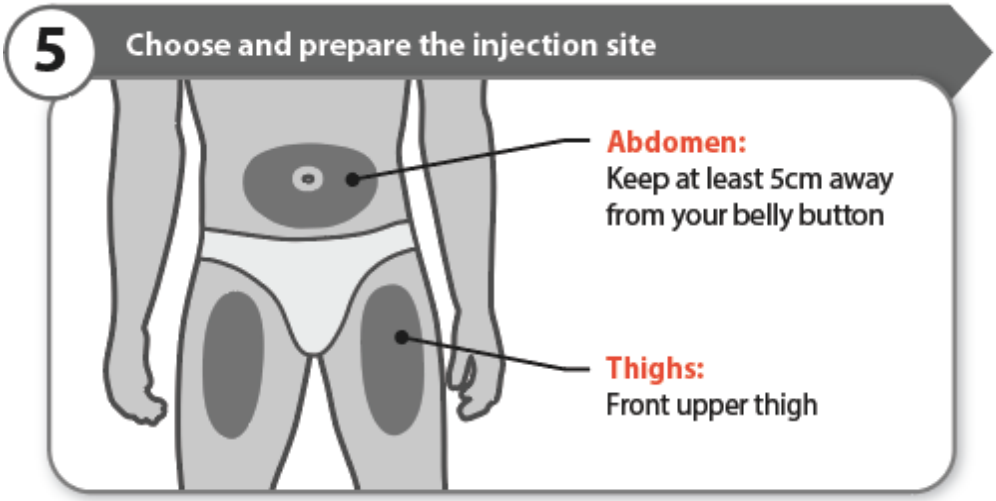
- Remove ABRILADA carton from the refrigerator.
- Open the carton and take out the tray containing your pre-filled syringe.
- Check your carton and tray; **do not** use if:
  - the expiration date has passed
  - it has been frozen or thawed
  - it has been dropped, even if it looks undamaged
  - it has been out of the refrigerator for more than 30 days
  - it appears to be damaged
  - the seals on a new carton are broken.
- If any of the above apply, dispose of your pre-filled syringe in the same way as a used syringe. You will need a new pre-filled syringe to give your injection.
- Wash your hands with soap and water, and dry completely.
  If you have any questions about your medicine, please talk to your doctor, nurse or pharmacist.



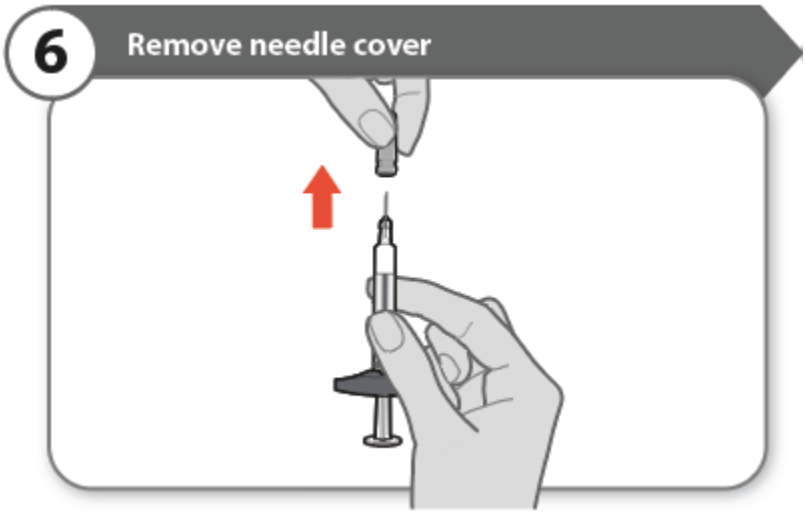
- Peel back the paper seal on the tray.
- Remove 1 pre-filled syringe from the tray and put the original carton with any unused pre-filled syringes back in the refrigerator.
- **Do not** use your syringe if it appears to be damaged.
- Your pre-filled syringe may be used straight from the refrigerator.
- You may find that using your pre-filled syringe at room temperature reduces stinging or discomfort. Leave your pre-filled syringe at room temperature away from direct sunlight for 15 to 30 minutes before your injection.
- **Do not** remove the needle cover from your pre-filled syringe until you are ready to inject.
  **Always hold the pre-filled syringe by the syringe barrel to prevent damage.**



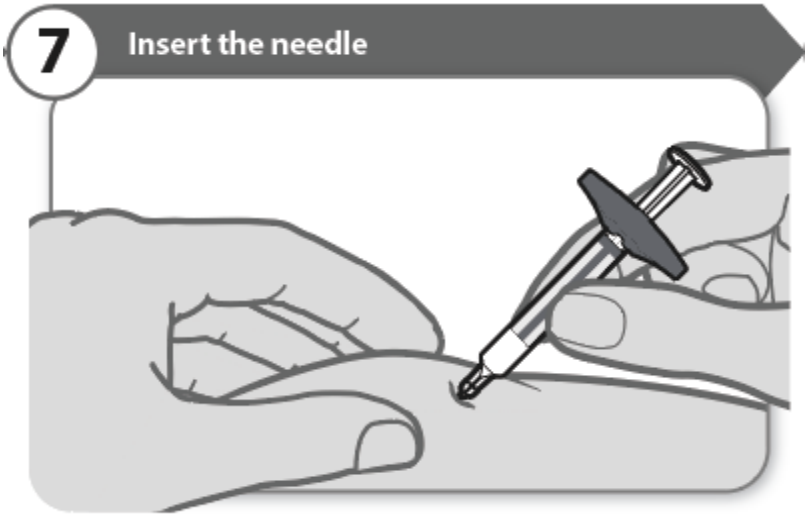

- Look carefully at your medicine in the window.
- Gently tilt your pre-filled syringe back and forth to check the medicine.
- **Do not** shake your pre-filled syringe. Shaking can damage your medicine.
- Make sure the medicine in the pre-filled syringe is clear and colourless to very light brown and free from flakes or particles. It is normal to see one or more air bubbles in the window. **Do not** attempt to remove air bubbles.
  If you have any questions about your medicine, please talk to your doctor, nurse or pharmacist.



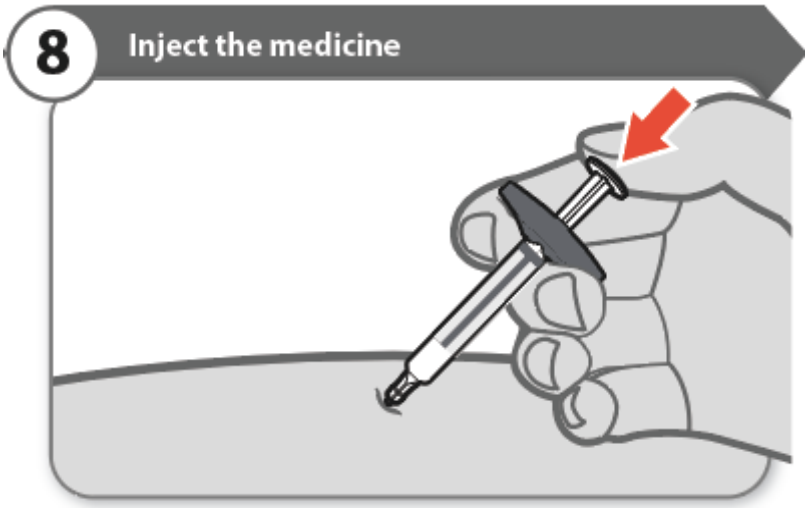

- Choose a different site each time you give yourself an injection.
- **Do not** inject into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
    - If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions on your skin.
- **Do not** inject through your clothes.
- Wipe the injection site with the alcohol swab.
- Allow the injection site to dry.



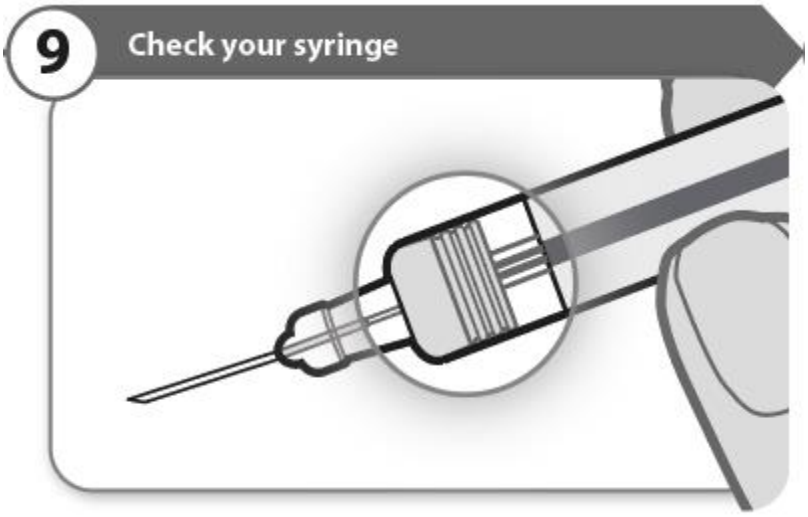

- Hold the pre-filled syringe by the syringe barrel. Carefully pull the needle cover straight off and away from your body when you are ready to inject.
- It is normal to see a few drops of medicine at the needle tip when you remove the needle cover.
- Throw the needle cover away into a sharps disposal container.
  **Note:** Be careful when you handle your pre-filled syringe to avoid an accidental needle stick injury.



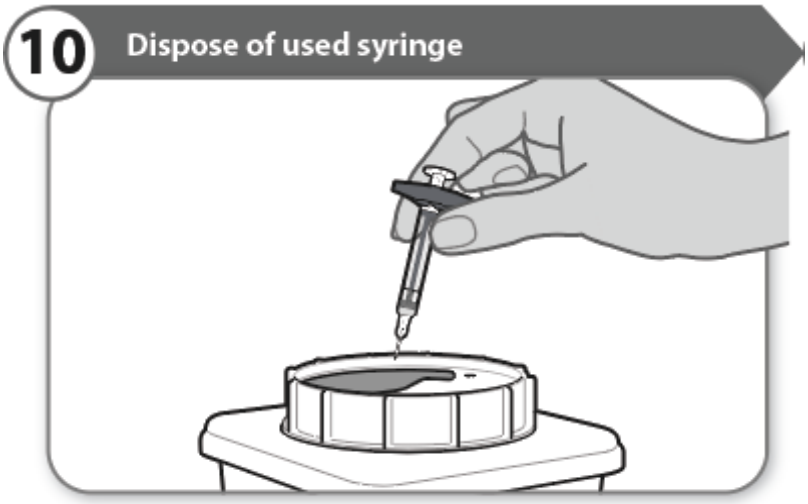

- Gently pinch up a fold of skin in the cleaned injection site area.
- Insert the needle to its full depth into the skin, at a 45 degree angle, as shown.
- After the needle is inserted, release the pinched skin.
  **Important: Do not** re-insert the needle into your skin. If the needle has already been inserted into the skin and you change your mind about where to inject, you will need a replacement pre-filled syringe.



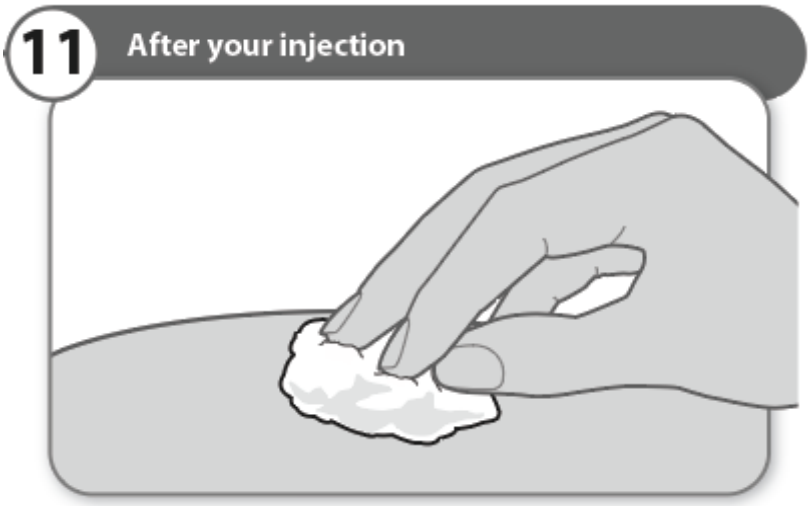

- Using slow and constant pressure, push the plunger rod all the way down until the barrel is empty. It usually takes 2 to 5 seconds to deliver the dose.
  **Note:** It is recommended to hold your pre-filled syringe in the skin for an additional 5 seconds after the plunger has been pressed down completely.
- Pull the needle out of the skin at the same angle at which it entered.




- Check that your medicine has completely emptied from your pre-filled syringe.
- **Never re-insert the needle.**
- **Never re-cap the needle.**
  **Note:** If the grey stopper is not in the position shown, you may not have injected all of your medicine. Talk to your doctor, nurse or pharmacist right away.




- Dispose of the syringe straight away as instructed by your doctor, nurse or pharmacist and in accordance with local health and safety laws.




- Look closely at your injection site. If there is blood, use a clean cotton ball or gauze pad to press lightly on the injection area for a few seconds.
- **Do not** rub the site.
  **Note:** Store any unused syringes in the refrigerator in the original carton.

**INSTRUCTIONS FOR USE**

ABRILADA (adalimumab)
40 mg/0.8 mL Solution for Injection in Pre-filled Pen
Single-dose, for subcutaneous injection

**Keep this leaflet. These instructions show step-by-step how to prepare and give an injection.**
**Store ABRILADA pen in the refrigerator between 2°C to 8°C.**
**Store ABRILADA pen in the original carton until use to protect from direct sunlight.**
**Do not use if frozen even if it has been thawed.**
**If needed, for example when you are traveling, you may store ABRILADA pen at room temperature up to 30°C for up to 30 days.**
**Keep ABRILADA, injection supplies, and all other medicines out of the reach of children.**

ABRILADA solution for injection comes in a disposable single use pen that contains a single dose of medicine.
**Do not** try to inject ABRILADA yourself until you have read and understood the Instructions for Use. If your doctor, nurse or pharmacist decides that you or a caregiver may be able to give your injections of ABRILADA at home, you should receive training on the correct way to prepare and inject ABRILADA.
It is also important to talk to your doctor, nurse or pharmacist to be sure you understand your ABRILADA dosing instructions. To help you remember when to inject ABRILADA, you can mark your calendar ahead of time. Talk to your doctor, nurse or pharmacist if you or your caregiver have any questions about the correct way to inject ABRILADA.
After proper training, ABRILADA solution for injection can be self-administered or given by a caregiver.

## 1. Supplies you need

- You will need the following supplies for each injection of ABRILADA. Find a clean, flat surface to place the supplies on.
  - 1 ABRILADA pen, inside the carton
  - 1 alcohol swab, inside the carton
  - 1 cotton ball or gauze pad (not included in your ABRILADA carton)
  - A suitable sharps container (not included in your ABRILADA carton).

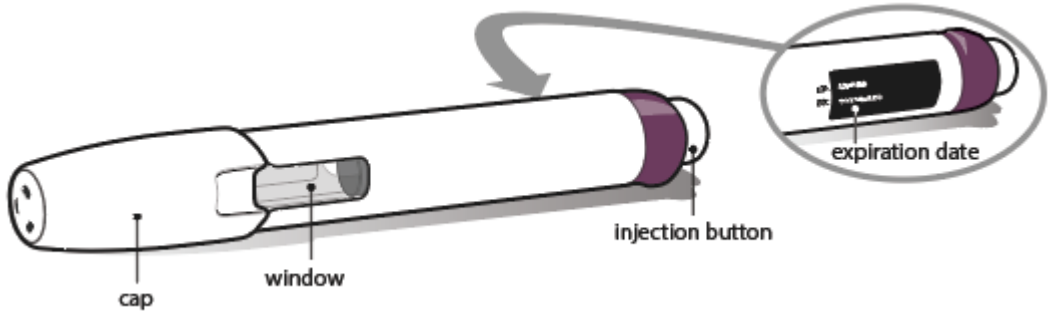
  **Important:** If you have any questions about your ABRILADA pen or medicine, talk to your doctor, nurse or pharmacist.

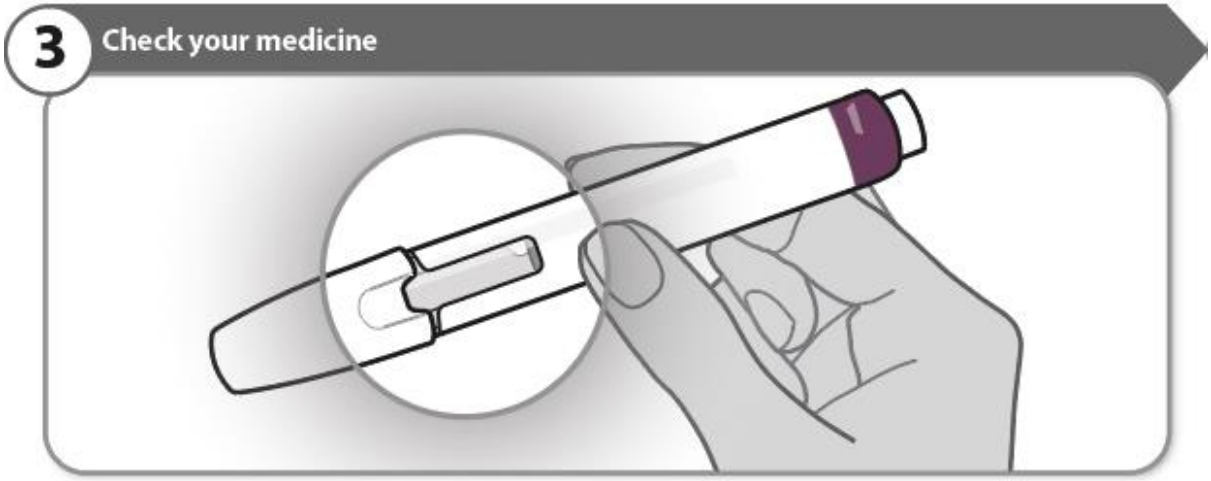
## 2. Getting ready

- Remove the ABRILADA carton from the refrigerator.
- Take out 1 ABRILADA pen and the alcohol swab. Keep your pen out of direct sunlight. Put the original carton with any unused pens back in the refrigerator.
- **Do not** use your pen if:
  - your pen or the carton containing the pen has been dropped, even if it looks undamaged
  - it has been frozen or thawed

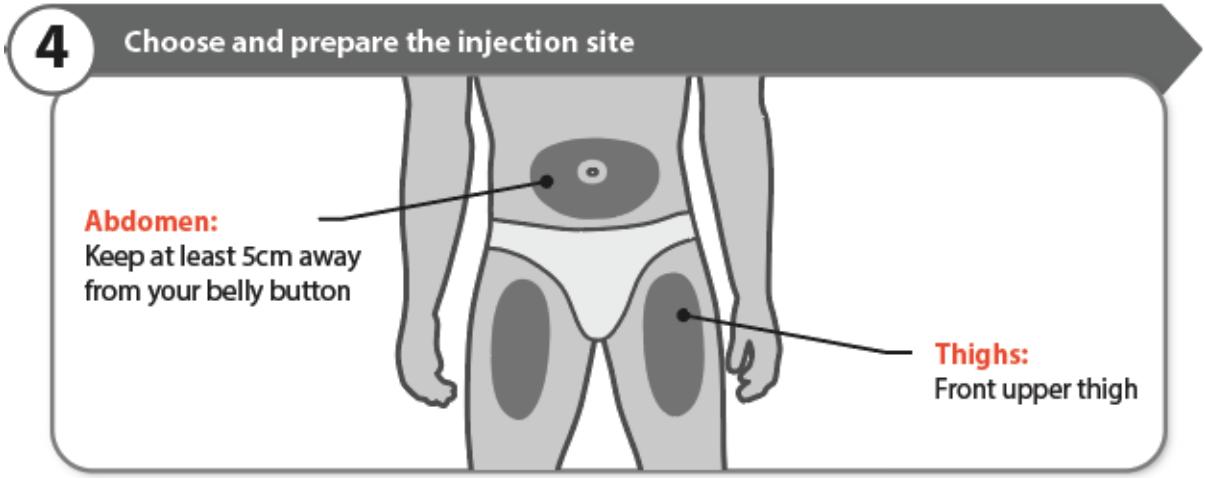
- it appears to be damaged
- the seals on a new carton are broken
- it has been out of the refrigerator for more than 30 days
- the expiration date has passed.

- If any of the above apply, dispose of your pen in the same way as a used pen. You will need a new pen to give your injection.
- Your pen may be used straight from the refrigerator.
- You may find that using your pen at room temperature reduces stinging or discomfort. Leave your pen at room temperature away from direct sunlight for 15 to 30 minutes before your injection.
- Wash your hands with soap and water, and dry completely.
- **Do not** remove the cap until you are ready to inject.

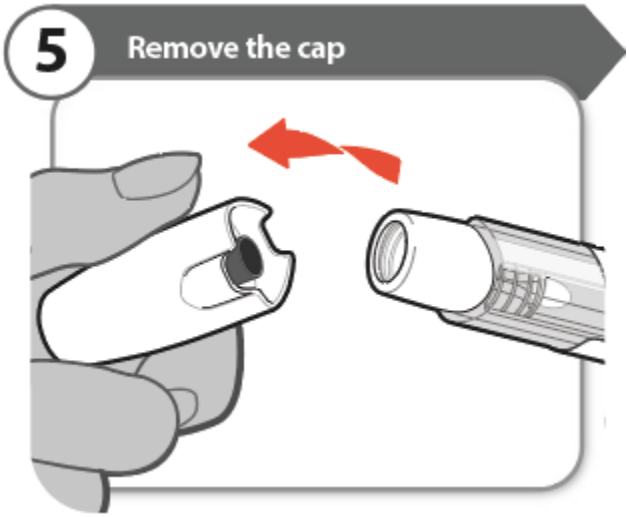


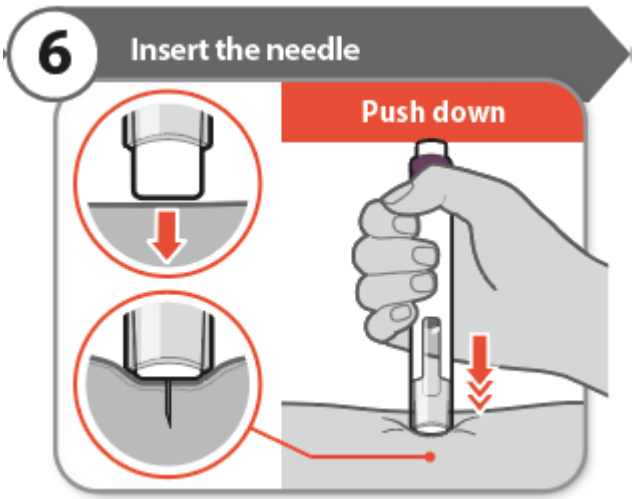

- Look carefully at your medicine in the window.
- Gently tilt your pen back and forth to check the medicine.
- **Do not** shake your pen. Shaking can damage your medicine.
- Make sure the medicine in the pen is clear and colourless to very light brown and free from flakes or particles. It is normal to see one or more air bubbles in the window. **Do not** attempt to remove air bubbles.
  If you have any questions about your medicine, please talk to your doctor, nurse or pharmacist.



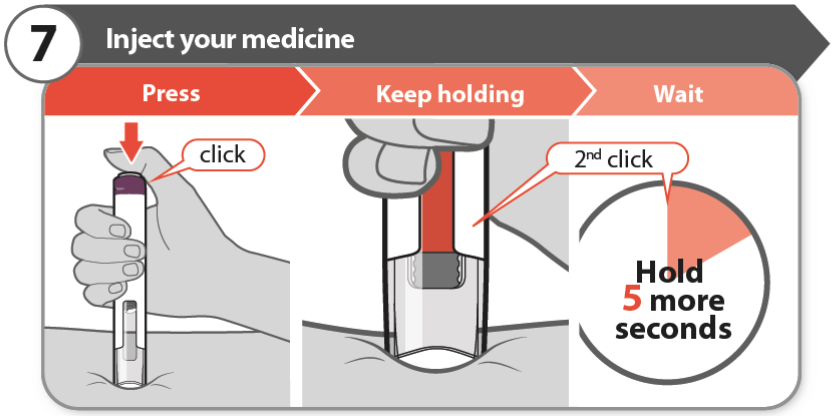

- Choose a different site each time you give yourself an injection.
- **Do not** inject into bony areas or areas on your skin that are bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
    - If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions on your skin.
- **Do not** inject through your clothes.
- Wipe the injection site with the alcohol swab.
- Allow the injection site to dry.




- Twist and pull off the cap.
- Throw the cap away into a sharps disposal container; it is not needed again.
- It is normal to see a few drops of medicine at the needle tip when you remove the cap.
  **Caution:** Handle your pen with care to avoid an accidental needle stick injury.
  **Note:** The needle cover stays inside the cap after removal.

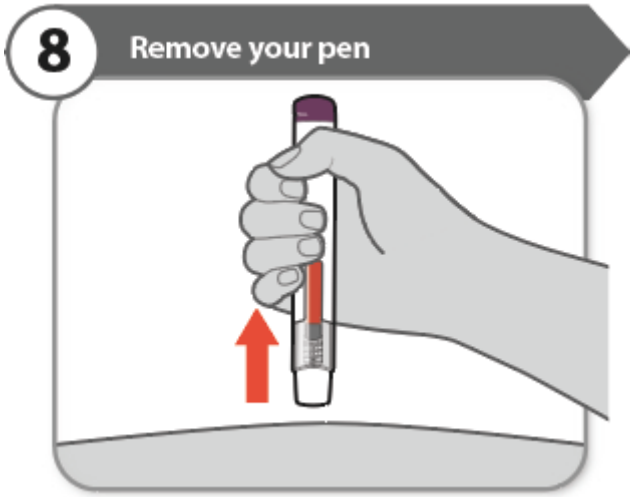



- **Push** your pen firmly against the skin at 90 degrees, as shown.
  **Note:** The needle goes into the skin as you push your pen down. The injection button will unlock when you are pushing the pen down firmly enough.
- **Keep your pen pushed against the skin until Step 8.**
  **Note: Do not** re-insert the needle into your skin if you change your mind about where to inject. You will need a replacement pen if the needle has already been inserted into the skin.

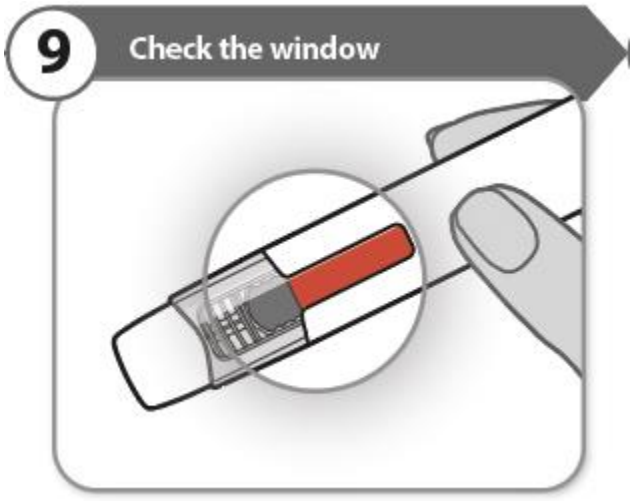



- **Press** the injection button all the way down and you will hear a click. You may take your finger off the injection button when the injection has started.
- **Keep holding** your pen firmly against the skin while the orange bar moves across the window. This usually takes 3 to 10 seconds to deliver the dose.
- **Wait** for at least 5 more seconds after the 2nd click to allow the medicine to be absorbed.
  **Note:** If you cannot press down the injection button, it is because you are not pushing the pen down firmly enough. Take your finger off the injection button and push your pen down more firmly against the skin. Then try pushing the button again. If this does

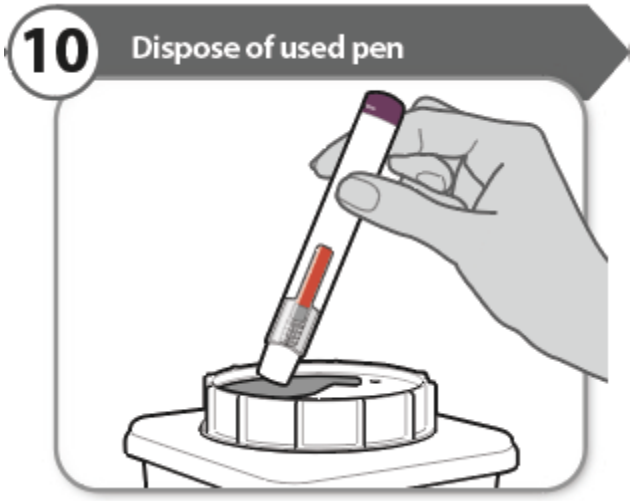
not work, stretching or pinching the skin may make the injection site firmer, making pressing the injection button easier.



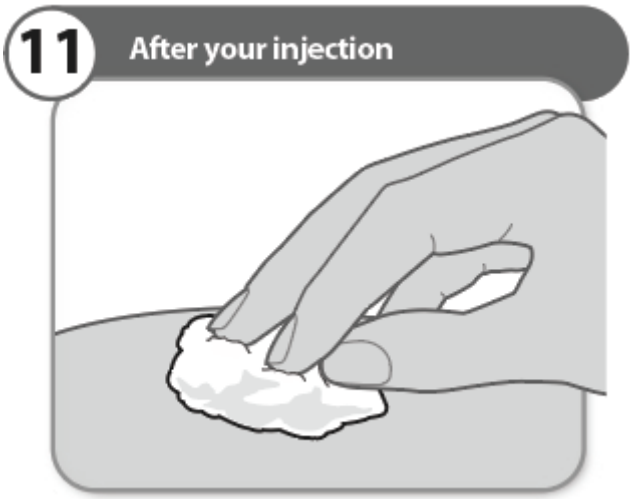

- **Do not remove your pen until you have waited at least 5 seconds after the 2nd click.**
- Remove your pen from the skin.
  **Note:** After you remove your pen from the skin, the needle will be automatically covered.
- If you see more than a small drop of medicine on the skin after your injection, next time you inject wait a little longer to remove the pen from the skin.




- You should see an orange bar in the window.
- If the window has not turned orange, or if it looks like the medicine is still injecting, this means you have not received a full dose. Talk to your doctor, nurse or pharmacist right away.
- **Do not inject another dose.**




- Dispose of the pen straight away as instructed by your doctor, nurse or pharmacist and in accordance with local health and safety laws.




- Look closely at your injection site. If there is blood, use a clean cotton ball or gauze pad to press lightly on the injection area for a few seconds.
- **Do not** rub the injection site.
  **Note:** Store any unused pens in the refrigerator in the original carton.