

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

PrSimlandi™

Adalimumab injection

40 mg in 0.4 mL sterile solution (100 mg/mL) subcutaneous injection

80 mg in 0.8 mL sterile solution (100 mg/mL) subcutaneous injection

Biological Response Modifier

Manufacturer's Standard

**Simlandi (adalimumab) treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, adult ulcerative colitis, adult and adolescent (12 to 17 years of age weighing  $\geq$  30 kg) hidradenitis suppurativa, psoriasis or adult and pediatric uveitis, and familiar with the adalimumab efficacy and safety profile.**

Jamp Pharma Corporation  
1310 Nobel Street  
Boucherville, Quebec  
J4B 5H3  
1-866-399-9091  
<https://www.jamppharma.ca/en/>

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Indications have been granted on the basis of similarity between Simlandi™ (adalimumab injection) and the reference biologic drug HUMIRA®.

**Simlandi treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), adult ulcerative colitis (UC), adult and adolescent (12 to 17 years of age weighing  $\geq$  30 kg) hidradenitis suppurativa (HS), psoriasis (Ps) or adult and pediatric uveitis, and familiar with the adalimumab efficacy and safety profile.**

Simlandi indicated for:

#### **Rheumatoid Arthritis**

- reducing the signs and symptoms, inducing major clinical response and clinical remission, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. Simlandi can be used alone or in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs).

When used as first-line treatment in recently diagnosed patients who have not been previously treated with methotrexate, Simlandi should be given in combination with methotrexate. Simlandi can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is contraindicated.

#### **Polyarticular Juvenile Idiopathic Arthritis**

- in combination with methotrexate, reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients, 2 years of age and older, weighing  $\geq$  30 kg, who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Simlandi can be used as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is not appropriate (see **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Pediatric, Polyarticular Juvenile Idiopathic Arthritis, Study Results**). Adalimumab

has not been studied in pediatric patients with polyarticular juvenile idiopathic arthritis aged less than 2 years.

### **Psoriatic Arthritis**

- reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult psoriatic arthritis patients. Simlandi can be used in combination with methotrexate (MTX) in patients who do not respond adequately to methotrexate alone.

### **Ankylosing Spondylitis**

- reducing the signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy.

### **Adult Crohn's Disease**

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

### **Adult Ulcerative Colitis**

- treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids and/or azathioprine or 6-mercaptopurine (6-MP) or who are intolerant to such therapies. The efficacy of Simlandi in patients who have lost response to or were intolerant to TNF blockers has not been established.

### **Hidradenitis Suppurativa**

- treatment of active moderate to severe hidradenitis suppurativa in adult and adolescent patients (12 to 17 years of age weighing  $\geq 30$  kg) who have not responded to conventional therapy (including systemic antibiotics).

### **Plaque Psoriasis**

- treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Simlandi should be used after phototherapy has been shown to be ineffective or inappropriate.

### **Adult Uveitis**

- treatment of non-infectious uveitis (intermediate, posterior and panuveitis) in adult patients with inadequate response to corticosteroids or as corticosteroid sparing treatment in corticosteroid-dependent patients.

### **Pediatric Uveitis**

- treatment of chronic non-infectious anterior uveitis in pediatric patients from 2 years of age, weighing  $\geq 30$  kg, who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

## 1.1 Pediatrics (<18 years of age)

### **Polyarticular JIA**

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

Simlandi is available for pediatric polyarticular juvenile patients who require the full 40 mg dose based on body weight (See DOSAGE AND ADMINISTRATION).

The auto-injector and pre-filled syringe are not designed to deliver a portion of the full 40 mg dose and must not be used in pediatric patients who require < 40 mg dose.

### **Adolescent Hidradenitis Suppurativa**

There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa (HS). The dosage of Simlandi in these patients has been determined based on pharmacokinetic/pharmacodynamic modeling and simulation (see **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Pediatric, Adolescent Hidradenitis Suppurativa**).

### **Pediatric Uveitis**

Adalimumab has not been studied in pediatric patients with uveitis less than 2 years of age. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

## 1.2 Geriatrics (>65 years of age)

Evidence from clinical studies and experience suggests that use of adalimumab in the geriatric population is not associated with differences in effectiveness. (A brief discussion can be found under **7 WARNINGS AND PRECAUTIONS, 7.1 SPECIAL POPULATIONS, 7.1.4 Geriatrics (>65 years of age)**).

## 2 CONTRAINDICATIONS

- Patients with known hypersensitivity to adalimumab or any of its components. For a complete listing, (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).
- Patients with severe infections such as sepsis, tuberculosis and opportunistic infections. See (**3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Infections** and **7 WARNINGS AND PRECAUTIONS**).
- Patients with moderate to severe heart failure (NYHA class III/IV). See (**7 WARNINGS AND PRECAUTIONS, Cardiovascular, Patients with Congestive Heart Failure**).

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

### Serious Warnings and Precautions

#### **Hepatosplenic T-cell Lymphoma**

Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for Crohn's 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.

#### **Infections**

Serious infections due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidiomycosis), viral, parasitic, or other

opportunistic infections have been reported in patients receiving tumor necrosis factor (TNF)-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, legionellosis and pneumocystis have also been reported with the use of TNF-blocking agents, including adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization 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 Simlandi should not be initiated in patients with active infections, including chronic or localized infections, until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Simlandi should be considered prior to initiating therapy. See (**7 WARNINGS AND PRECAUTIONS, Infections, Tuberculosis, Other Opportunistic Infections**).

As with other TNF-blockers, patients should be monitored closely for infections (including tuberculosis) before, during and after treatment with Simlandi.

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

Physicians should exercise caution when considering the use of Simlandi in patients with a history of recurrent infection or with underlying conditions which may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. See (**7 WARNINGS AND PRECAUTIONS, Infections, Tuberculosis**) and (**8 ADVERSE REACTIONS, Adverse Drug Reaction Overview, Infections**). The benefits and risks of treatment with Simlandi should be carefully considered before initiating therapy.

### **Pediatric Malignancy**

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including adalimumab. See **7 WARNINGS AND PRECAUTIONS, Malignancies, Malignancies in Pediatric Patients and Young Adults**).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

#### **Pediatrics**

##### Polyarticular JIA

See **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dosage and Dosage Adjustment, Pediatrics, Polyarticular Juvenile Idiopathic Arthritis.**

Safety and effectiveness in pediatric patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg have not been established.

##### Adolescent Hidradenitis Suppurativa

See **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dosage and Dosage Adjustment, Pediatrics, Adolescent Hidradenitis Suppurativa.**

There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa (HS). The dosage of adalimumab in these patients has been determined based on pharmacokinetic/ pharmacodynamic modeling and simulation.

##### Pediatric Uveitis

See **4 DOSAGE AND ADMINISTRATION, Recommended Dosage and Dosage Adjustment, Pediatrics, Pediatric Uveitis.**

Safety and effectiveness in pediatric patients with uveitis less than 2 years of age have not been established. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

#### **Geriatrics**

Evidence from clinical studies and experience suggests that use of adalimumab in the geriatric population is not associated with differences in effectiveness. No dose adjustment is needed for this population. A brief discussion can be found under (**7 WARNINGS AND PRECAUTIONS, General 7.1 SPECIAL POPULATIONS, 7.1.4 Geriatrics (>65 years of age).**)

#### **Gender**

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers 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. Dosage adjustment is not required.

### **Hepatic Insufficiency**

No pharmacokinetic data are available in patients with hepatic impairment. No dose recommendation can be made.

### **Renal Insufficiency**

No pharmacokinetic data are available in patients with renal impairment. No dose recommendation can be made.

### **Disease States**

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. (See **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Disease States**).

### **Concomitant Medications**

Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with Simlandi. When treated with Simlandi as monotherapy, some rheumatoid arthritis patients who experience a decrease in their response to Simlandi 40 mg every other week may benefit from an increase in dose intensity to Simlandi 40 mg every week.

## [4.2 Recommended Dose and Dosage Adjustment](#)

**Note:** See Table 3 at the end of this section for available presentations of Simlandi for each indication in pediatrics and adults.

## Pediatrics

### Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of Simlandi for patients with polyarticular JIA from 2 years of age is based on body weight (Table 1). Simlandi is administered every other week via subcutaneous injection only in patients who require the full 40 mg dose.

A 40 mg autoinjector and a 40 mg pre-filled syringe of Simlandi are available for patients to administer a full 40 mg dose. The 40 mg autoinjector and 40 mg pre-filled syringe are not designed to deliver a portion of the full 40 mg dose and must not be used in pediatric patients requiring less than the full 40 mg dose.

Simlandi can be used in combination with methotrexate or as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is not appropriate.

**Table 1. Simlandi Dose for Patients with Polyarticular JIA**

Patient Weight	Dosing Regimen
≥ 30 kg	40 mg every other week

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Efficacy and safety in patients who do not respond by Week 16 have not been established.

There is no relevant use of Simlandi in children aged <2 years in this indication.

### Adolescent Hidradenitis Suppurativa

The recommended Simlandi dose regimen for adolescent patients with HS (12 to 17 years of age weighing ≥ 30 kg) is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Simlandi 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Pediatric, Adolescent Hidradenitis Suppurativa**).

Antibiotics may be continued during treatment with Simlandi if necessary.

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

### Pediatric Uveitis

The recommended dose of Simlandi in combination with methotrexate for pediatric patients with chronic non-infectious anterior uveitis 2 years of age and older is based on body weight (Table 2). Simlandi is administered every other week via subcutaneous injection only in patients who require the full 40 mg dose.

A 40 mg autoinjector and a 40 mg pre-filled syringe of SIMLANDI are available for patients to administer a full 40 mg dose. The 40 mg autoinjector and 40 mg pre-filled syringe are not designed to deliver a portion of the full 40 mg dose and must not be used in pediatric patients requiring less than the full 40 mg dose.

In pediatric uveitis, there is no experience in the treatment with Simlandi without concomitant treatment with methotrexate.

**Table 2. Simlandi Dose for Pediatric Patients with Uveitis**

Patient Weight	Dosage Regimen
≥30 kg	40 mg every other week in combination with methotrexate

When Simlandi is initiated in patients ≥ 6 years of age, an optional loading dose 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 a loading dose for Simlandi in children < 6 years of age.

There are no data on the use of Simlandi in children aged less than 2 years for this indication.

## **Adults**

### Rheumatoid Arthritis

The recommended dose of Simlandi for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection.

### Psoriatic Arthritis

The recommended dose of Simlandi for adult patients with psoriatic arthritis is 40 mg administered every other week as a subcutaneous injection.

For the rheumatoid arthritis and psoriatic arthritis indications, available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

### Ankylosing Spondylitis

The recommended dose of Simlandi for patients with ankylosing spondylitis is 40 mg administered every other week via subcutaneous injection. Glucocorticoids, salicylates,

nonsteroidal anti-inflammatory drugs, analgesics or disease modifying anti-rheumatic drugs can be continued during treatment with Simlandi.

### Crohn's Disease

The recommended Simlandi induction dose regimen for adult patients with Crohn's disease is 160 mg at Week 0, followed by 80 mg at Week 2 administered by subcutaneous injection. The first dose of 160 mg can be given in one day (four 40 mg injections or two 80 mg injections) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day). The second dose of 80 mg at Week 2 is given as two 40 mg injections or one 80 mg injection in one day.

The recommended Simlandi maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week beginning at Week 4.

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

For patients who experience a disease flare, dose escalation may be considered. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Crohn's Disease**).

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

The use of adalimumab in Crohn's disease has been evaluated up to one year in controlled clinical studies. In open-label studies, 510/1,594 patients were evaluated for three years, and 118/1,594 patients for at least five years (see **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Crohn's Disease**).

### Ulcerative Colitis

The recommended Simlandi induction dose regimen for adult patients with ulcerative colitis is 160 mg at Week 0, followed by 80 mg at Week 2 administered by subcutaneous injection. The first dose of 160 mg can be given in one day (four 40 mg injections or two 80 mg injections) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day). The second dose of 80 mg at Week 2 is given as two 40 mg injections or one 80 mg injection in one day. Beginning at Week 4, continue with a dose of 40 mg every other week. Simlandi should only be continued in patients who have responded during the first 8 weeks of therapy.

Aminosalicylates and/or corticosteroids may be continued during treatment with Simlandi. Azathioprine and 6-mercaptopurine (6-MP) may be continued during treatment with Simlandi if

necessary (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatosplenic T-cell Lymphoma**)

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

#### Hidradenitis Suppurativa

The recommended Simlandi initial dose for adult patients with hidradenitis suppurativa is 160 mg, followed by 80 mg two weeks later administered by subcutaneous injection. The first dose of 160 mg at Week 0 can be given in one day (four 40 mg injections or two 80 mg injections) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day). The second dose of 80 mg at Week 2 is given as two 40 mg injections or one 80 mg injection in one day.

The recommended Simlandi maintenance dose regimen for adult patients with hidradenitis suppurativa is 40 mg every week beginning four weeks after the initial dose.

Antibiotics may be continued during treatment with Simlandi if necessary.

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

#### Plaque Psoriasis

The recommended dose of Simlandi for adult patients with psoriasis is an initial dose of 80 mg administered subcutaneously (two 40 mg injections or one 80 mg injection), followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

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

#### Uveitis

The recommended dose of Simlandi for adult patients with non-infectious uveitis is an initial dose of 80 mg administered subcutaneously (two 40 mg injections or one 80 mg injection), followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Simlandi can be initiated in combination with corticosteroids and/or other non-biologic immunomodulatory agents. Corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Simlandi. There is limited experience with the initiation of treatment with Simlandi alone.

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

**Table 3. Available Presentations for Each Adult and Pediatric Indication**

Indication	40 mg/0.4 mL		80 mg/0.8 mL
	Pre-filled Syringe with needle guard	Autoinjector	Pre-filled Syringe with needle guard
Rheumatoid Arthritis	X	X	N/A
Polyarticular Juvenile Idiopathic Arthritis	X	X	N/A
Psoriatic Arthritis	X	X	N/A
Ankylosing Spondylitis	X	X	N/A
Adult Crohn's Disease	X	X	X
Adult Ulcerative Colitis	X	X	X
Adult Hidradenitis Suppurativa	X	X	X
Adolescent Hidradenitis Suppurativa	X	X	X
Psoriasis	X	X	X
Adult Uveitis	X	X	X
Pediatric Uveitis	X	X	X
N/A= Not applicable			

### 4.3 Administration

Simlandi is intended for use under the guidance and supervision of a physician. Patients

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

See Patient Medication Information in Part III of this Product Monograph.

Illustrated Instructions for Use are available in the cartons for both the pre-filled syringe with needle guard and the Autoinjector.

#### 4.4 Missed Dose

Patients who miss a dose of Simlandi should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

## 5 OVERDOSAGE

For management of a suspected drug overdose. Contact your regional Poison Control Centre.
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The maximum tolerated dose of adalimumab has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

### 6.1 Physical Characteristics

Simlandi is supplied as a sterile solution for subcutaneous administration in the following packaging configurations:

#### **Pre-filled Syringe with Needle Guard**

This consists of a single-use pre-filled syringe fitted with a plunger rod, finger flanges and a needle guard. It is available as 40 mg/0.4 mL and 80 mg/0.8 mL dose presentations.

In addition to the active ingredient, adalimumab, the 40 mg/0.4 mL strength (100 mg/mL) and 80 mg/0.8 mL strength (100 mg/mL) also contains the following non-medicinal ingredients: sodium chloride, sucrose, polysorbate 80 and water for injection.

The pre-filled syringe with needle guard is packaged in a carton containing either 1 or 2 pre-filled syringes, along with the Patient Medication Information document, an illustrated Directions for Use and a Quick Reference Guide for injecting.

### **Autoinjector**

This consists of a main functional component, together with two housing covers, and a cap remover sleeve that encloses the pre-filled syringe. It is available in the 40 mg/0.4 mL dose presentation.

In addition to the active ingredient, adalimumab, the 40 mg/0.4 mL strength (100 mg/mL) also contains the following non-medicinal ingredients: sodium chloride, sucrose, polysorbate 80 and water for injection.

The Autoinjector is packaged in a carton containing: 1 or 2 Autoinjectors, along with the Patient Medication Information document, an illustrated Directions for Use and a Quick Reference Guide for injecting.

### **Description**

Simlandi is a recombinant fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) that specifically binds to tumor necrosis factor- $\alpha$  (TNF) and blocks its interaction with the p55 (TNFR1) and p75 (TNFR2) cell surface TNF receptors, thereby neutralizing the effect of TNF in inflammatory conditions. Simlandi is approved as a biosimilar to Humira (adalimumab).

## 7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**

### **General**

#### Concurrent Administration of Biologic DMARDs or TNF-Antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, etanercept, with no added benefit compared to etanercept alone. Because of the nature of the adverse events seen with the

combination etanercept and anakinra, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of Simlandi and anakinra is not recommended. See (**9 DRUG INTERACTIONS, Drug-Drug Interactions**).

Concomitant administration of Simlandi with other biologic DMARDs (e.g., anakinra and abatacept) or other TNF antagonists is not recommended based upon the increased risk for infections and other potential pharmacological interactions. See (**9 DRUG INTERACTIONS, Drug-Drug Interactions**)

#### Switching Between Biological DMARDS

When switching from one biologic to another, patients should continue to be monitored for signs of infection.

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

#### **Cardiovascular: Patients with Cardiovascular Heart Failure**

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers. Cases of worsening CHF have also been observed with adalimumab. Adalimumab has not been formally studied in patients with CHF; however, in clinical trials of another TNF-blocker, a higher rate of serious CHF-related adverse events was observed. Physicians should exercise caution when using Simlandi in patients who have heart failure and monitor them carefully. Simlandi is contraindicated in moderate to severe heart failure (see **2 CONTRAINDICATIONS**).

#### **Gastrointestinal: Small Bowel Obstruction**

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

#### **Hematologic**

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF-blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently 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 Simlandi. Discontinuation of Simlandi therapy should be considered in patients with confirmed significant hematologic abnormalities.

## Immune

### Autoimmunity

Treatment with Simlandi may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Simlandi, treatment should be discontinued. See (**8 ADVERSE REACTIONS, 8.1 Adverse Drug Reaction Overview, Autoantibodies**).

### Immunosuppression

The possibility exists for TNF-blocking agents, including adalimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis who 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. The impact of treatment with adalimumab on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood. (See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Infections and Pediatric Malignancy**) and **8 ADVERSE REACTIONS, 8.1 Adverse Drug Reaction Overview, Infections and Malignancies**).

### Immunizations

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

placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of adalimumab-treated patients and 63% of placebo-treated patients achieved at least a 4-fold increase in antibody titer to at least two out of three influenza antigens.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Simlandi therapy.

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

Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for five months following the mother's last Simlandi injection during pregnancy. See (**7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

## **Infections**

### Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Before initiation, during and after treatment with adalimumab, patients should be evaluated for active and inactive ("latent") tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infections should be initiated prior to therapy with Simlandi. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guérin (BCG).

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

The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis. If latent infection is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment, in accordance with the Canadian Tuberculosis Standards and Centers for Disease Control and Prevention guidelines, before the initiation of Simlandi. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of Simlandi 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.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients receiving 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 active tuberculosis while being treated with TNF-blocking agents.

Patients receiving Simlandi 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 Simlandi, and physicians should monitor for signs and symptoms of active tuberculosis, including patients who are tuberculosis skin test negative.

#### Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. These infections are not consistently recognized 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, dyspnea, 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 Virus (HBV) Reactivation

Very rare cases of hepatitis B virus (HBV) reactivation have been associated with anti-TNF therapy. Clinically active HBV infection occurred following a latency period ranging from 3 to 20 months after initiation of therapy. In the majority of cases, patients were also taking other immunosuppressive drugs, including methotrexate, azathioprine, and/or corticosteroids. Hence, establishing a causal relationship to anti-TNF agents is confounded by the presence of these other medications. Where outcome information was provided, most patients were reported to have improved after antiviral treatment and/or discontinuation of the anti-TNF agent. However, fatal outcomes have also occurred in reported cases. Patients at risk of HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy. Those identified as chronic carriers (i.e., surface antigen positive) should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation of therapy. Reactivation of HBV is not unique to anti-TNF-alpha agents and has been reported with other immunosuppressive drugs.

### **Malignancies**

In the controlled portions of clinical trials of some TNF-blocking agents, including adalimumab, more cases of malignancies have been observed among patients receiving those TNF-blockers compared to control patients.

In the controlled and uncontrolled open-label portions of clinical trials of adalimumab, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma.

Cases of acute and chronic leukemia 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 leukemia, even in the absence of TNF-blocking therapy.

### Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents and young adults

who received treatment with TNF -blocking agents (i.e., including adalimumab). 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 and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). 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.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF -blockers including adalimumab. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF-blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6-MP) concomitantly with a TNF-blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF-blocker or a TNF-blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and adalimumab should be carefully considered.

No malignancies were observed in the indicated pediatric patient population with Crohn's disease treated with adalimumab (n=102) for 52 weeks in a clinical trial.

No malignancies were observed in pediatric patients aged 3 to 17 years with active JIA- associated chronic non-infectious anterior uveitis who were treated with adalimumab (n=90, randomized 2:1 to adalimumab: placebo) for up to 18 months in a clinical trial.

Treatment-emergent malignancies occurred in 2/480 adalimumab-treated UC patients in the double-blind controlled portion of two clinical trials (range of treatment duration from Weeks 0 to 52). The malignancies were squamous cell carcinoma and gastric cancer. Gastric cancer was considered serious and the patient discontinued as a result.

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 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.

## Lymphoma

In the controlled portions of clinical trials of all the TNF -blocking agents, more cases of lymphoma have been observed among patients receiving TNF-blockers compared to control patients.

However, for adalimumab, the occurrence of lymphoma was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF -antagonist therapy. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation.

In combining the controlled and uncontrolled open-label portions of the 23 clinical trials in adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis, and uveitis, with a median duration of approximately 2.4 years, including 8764 patients and 27,196 patient-years of therapy, the observed rate of lymphomas (95% CI) is 1.2 [0.9, 1.7] per 1000 patient-years. This is approximately 3-fold higher than expected in the general population.

During the controlled and open-label periods of 14 trials with adalimumab, the overall standard incidence ratio (SIR) of malignancies was 0.99 [95% confidence interval (CI), 0.81 to 1.20]. With current knowledge in this area, a possible risk for development of lymphomas or other malignancies in patients treated with a TNF -antagonist 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. Additional caution should be exercised when considering adalimumab treatment in these patients.

## Non-Lymphoma Malignancy

During the controlled portions of 21 adalimumab trials in adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, 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% CI) of 6.9 (4.4, 10.6) per 1,000 patient-years among 5196 adalimumab-treated patients versus a rate of 6.4 (3.5, 11.9) per 1,000 patient-years among 3347 control patients (median duration of treatment of 4.0 months for HUMIRA-

treated patients and 3.9 months for control-treated patients). (See **14.5 CLINICAL TRIALS - REFERENCE BIOLOGIC DRUG**).

During the controlled portions of 21 adalimumab rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis, and uveitis trials, the rate (95% CI) of non-melanoma skin cancers was 8.9 (6.1, 13.1) per 1,000 patient-years among adalimumab-treated patients and 3.2 (1.3, 7.7) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% CI) of 2.7 (1.4, 5.5) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1,000 patient-years among control patients. The rate (95% CI) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1,000 patient-years among control patients. (See **14.5 CLINICAL TRIALS-REFERENCE BIOLOGIC DRUG**).

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately (95% CI) 8.5 (7.4, 9.7) 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 (95% CI) approximately 9.6 (8.5, 10.9) per 1,000 patient years, and the observed rate of lymphomas is (95% CI) approximately 1.3 (0.9, 1.8) per 1,000 patient years. The median duration of these studies is approximately 3.3 years and included 6276 adult patients who were on adalimumab for at least one year or who developed a malignancy within a year of starting therapy, representing over 26,044 patient years of therapy. (See **14.5 CLINICAL TRIALS-REFERENCE BIOLOGIC DRUG**).

All patients, and in particular psoriasis patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of Psoralen Ultra-Violet A (PUVA) treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab.

## **Monitoring and Laboratory Tests**

There is no known interference between adalimumab and laboratory tests.

## **Neurologic**

Use of TNF-blocking agents, including adalimumab, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis, and optic neuritis, and peripheral

demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent onset central nervous system demyelinating disorders; discontinuation of adalimumab 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 Simlandi therapy to assess for pre-existing central demyelinating disorders.

### **Sensitivity: Hypersensitivity Reactions**

Allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients receiving adalimumab in clinical trials. See (**8 ADVERSE REACTIONS, 8.2 Clinical trial Adverse Reactions**). Reports of serious allergic reactions, including anaphylaxis, have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reactions occur, administration of Simlandi should be discontinued immediately and appropriate therapy initiated.

The Simlandi Pre-filled Syringe with needle guard is a single use glass 1 mL syringe with a fixed needle and rigid rubber needle shield made of a polypropylene shell and a bromobutyl plunger with a fluoropolymer coating.

The Autoinjector is a single use, disposable, needle-based injection system with automated functions (see **6 DOSAGE FORMS, COMPOSITION AND PACKAGING**).

## 7.1 Special Populations

### 7.1.1 Pregnant Women

The extent of exposure in pregnancy during clinical trials is very limited, consisting only of individual cases.

An embryo-fetal perinatal developmental toxicity study has been performed in *cynomolgus* monkeys at dosages up to 100 mg/kg (266 times human area under the curve (AUC) when given 40 mg adalimumab subcutaneously with methotrexate every week, or 373 times human AUC when given 40 mg adalimumab subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, adalimumab should be

used during pregnancy only if clearly needed.

In a prospective cohort pregnancy exposure registry, conducted by the Organization of Teratology Information Specialists (OTIS)/MotherToBaby in the U.S. and Canada between 2004 and 2016, the risk of major birth defects in live-born infants was compared in 69 women with RA and 152 women with CD treated with adalimumab at least during the first trimester with 74 women with RA and 32 women with CD not treated with adalimumab during pregnancy. The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively.

No pattern of major birth defects was observed. This study cannot reliably establish whether there is an association between adalimumab and the risk for major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

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 five months following the mother's last adalimumab injection during pregnancy.

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

#### 7.1.2 Breast-feeding

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

#### 7.1.3 Pediatrics (<18 years of age)

##### Polyarticular JIA

The efficacy and safety of adalimumab have been studied in pediatric patients aged 4 to 17 years (n=171) and 2 to 4 years (n=32). No overall differences were observed in the efficacy

and safety between the two age groups. Adalimumab has not been studied in pediatric patients with polyarticular JIA less than 2 years of age or in pediatric patients with a weight below 10 kg.

### Pediatric Uveitis

The efficacy and safety of adalimumab have been studied in pediatric patients with uveitis aged 2 to 17 years (n=90, randomized 2:1 to adalimumab : placebo). Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age. Serious adverse events were more frequent in children 4 years of age and younger.

#### 7.1.4 Geriatrics (>65 years of age)

A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years and older, received adalimumab in clinical Studies DE009, DE011, DE019 and DE031. No overall differences in effectiveness were observed between these patients and younger patients. The frequency of serious infection and malignancy among adalimumab-treated patients over age 65 was higher than for those under the age of 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Rheumatoid Arthritis**).

## 8 ADVERSE REACTIONS

*The adverse reaction profiles reported in clinical studies that compared Simlandi to Humira were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.*

### 8.1 Adverse Reaction Overview

The most serious adverse reactions were (see **7 WARNINGS AND PRECAUTIONS**):

- serious infections
- neurologic events
- malignancies

The most common adverse reaction in rheumatoid arthritis patients treated with adalimumab during clinical trials was injection site reactions. In controlled trials for rheumatoid arthritis, polyarticular JIA, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, adult hidradenitis suppurativa, psoriasis, and adult uveitis, 13% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of rheumatoid arthritis patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of rheumatoid arthritis Studies DE009, DE011, DE019 and DE031 was 7.0% for patients taking adalimumab, and 4.0% for placebo-treated patients. The most common adverse events leading to discontinuation of adalimumab were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%). (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**)

Among patients with rheumatoid arthritis in placebo-controlled studies, deaths occurred in 8 of 1,380 (0.58%) adalimumab-treated patients compared to 1 of 690 (0.14%) placebo-treated patients. The rate of deaths in both treatment arms is less than expected in the normal population with a standard mortality ratio (SMR) of 0.87 (95% CI, 0.38, 1.72) in the adalimumab group and 0.25 (95% CI, 0.00, 1.37) in the placebo group. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**)

In Study DE019, 553 patients were exposed to at least one dose of adalimumab and 202 patients completed 10 years of study. A total of 24 patients died during the 10-year exposure period to adalimumab (4 during the double-blind phase, 14 during the open-label extension phase and an additional 6 after study drug termination). Among the treatment-emergent deaths, the most common reasons were: 4 sepsis, 3 cancers and 3 respiratory system events. However, the total number of deaths was not higher than that calculated according to age-adjusted Standardized Mortality Rates. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**)

Of the 553 patients, 23.0% discontinued due to an adverse event. The most common adverse events associated with discontinuation of study drug were pneumonia and breast cancer (n = 5 each). Fatigue, pneumonia, cellulitis, and histoplasmosis (n = 3 each) were the most common treatment-related adverse events leading to discontinuation of study drug.

In total, 49% of patients treated with adalimumab experienced a serious adverse event; 15.7% were considered at least possibly related to study drug. The most common serious

adverse events were rheumatoid arthritis disease flare (n = 35, 6.3%), pneumonia (n = 26, 4.7%) and myocardial infarction (n = 10, 1.8%); of these, only pneumonia was considered to be at least possibly related to study drug.

The most frequently reported treatment-emergent adverse events were infections (total n = 448, 81%; serious n = 85, 15.4%) and injection site reactions (n = 115, 20.8%).

Adverse events of special interest among the 553 patients included 35 patients with malignancies other than non-melanoma skin cancer (including 5 cases of lymphoma); and 3 patients with tuberculosis. Serious adverse events of special interest included 5 patients each with pulmonary embolism and diverticulitis; 2 patients with multiple sclerosis; and 1 patient with hypersensitivity reaction.

Adalimumab has also been studied in 542 patients with early rheumatoid arthritis (disease duration less than three years) who were methotrexate naïve (Study DE013). No new safety signals were seen in this patient population compared to the safety profile seen in HUMIRA Studies DE009, DE011, DE019 and DE031. In this study, deaths occurred in 5 of 542 (0.92%) HUMIRA-treated patients compared to 1 of 257 (0.39%) methotrexate-treated patients. The rate of deaths in both treatment arms is less than expected in the normal population with a standard mortality ratio (SMR) of 0.57 (95% CI, 0.18, 1.32) in the adalimumab group and 0.22 (95% CI, 0.00, 1.23) in the methotrexate group. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**)

Adalimumab has also been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study, in 393 patients with ankylosing spondylitis in two placebo-controlled studies and in over 1,500 patients with Crohn's disease in five placebo-controlled and two open-label extension studies. The safety profile for patients with psoriatic arthritis treated with adalimumab 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, adalimumab Studies DE009, DE011, DE019, DE031 and DE013. During the controlled period of the psoriatic arthritis studies, no deaths occurred in the adalimumab-treated or placebo-treated patients. During the psoriatic arthritis open-label study, two deaths occurred in 382 patients with 795.7 patient-years of exposure. The rate of deaths is less than expected in the normal population with a standard mortality ratio (SMR) of 0.39 (95% CI, 0.04, 1.43). Among patients enrolled in the psoriasis open-label study, 5 deaths occurred in 1,468 patients with 4,068.6 patient-years of exposure. (See **14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**)

Adalimumab has also been studied in 1,010 patients with ulcerative colitis (UC) in two randomized, double-blind, placebo-controlled studies (M06-826, 8 weeks and M06-827, 52 weeks) and an open-label extension study. No new safety signals were seen in the ulcerative colitis patient population. During the controlled period of the ulcerative colitis studies, no deaths occurred in the adalimumab-treated or placebo-treated patients. In the overall

adalimumab ulcerative colitis development program of 1,010 patients with 2007.4 patient years of exposure (622 patients were treated for >1 year), 2 treatment-emergent deaths occurred during the long-term open-label extension study (cardio-respiratory arrest and right ventricular failure). There were no new safety signals compared to the known safety profile of adalimumab in the double-blind controlled portion of ulcerative colitis studies.

Adalimumab has also been studied in 727 adult patients with hidradenitis suppurativa (HS) in three randomized, double-blind, placebo-controlled studies and an open-label extension study. No deaths were reported during the placebo-control periods. In the overall adalimumab hidradenitis suppurativa development program of 727 patients with 635.7 patient years of exposure (281 patients were treated for >1 year), 2 treatment-emergent deaths occurred (cardio-respiratory arrest and autoimmune pancreatitis). No new safety signals were seen in the hidradenitis suppurativa adult patient population.

Adalimumab has also been studied in 464 adult patients with uveitis in two randomized, double-masked, placebo-controlled studies (M10-877 and M10-880) and an open-label extension study (M11-327). No new safety signals for adalimumab were identified in the uveitis adult patient population. In the overall adalimumab adult uveitis development program of 464 adalimumab adult patients with 1308.2 patient-years of exposure, 6 treatment-emergent deaths were reported (chronic renal failure, aortic dissection/acute tamponade, B-cell lymphoma, brain abscess, pancreatic carcinoma, and accident). Two deaths occurred during the controlled period of the adult uveitis studies and 4 during the open-label extension study.

The Humira 40 mg/0.4 mL formulation was evaluated and compared to the Humira 40 mg/0.8 mL formulation in patients with active rheumatoid arthritis in Study M13-390 (Phase 2b randomized, double-blind study) and Study M13-692 (open-label extension of Study M13-390). All patients who received at least one dose of study drug (n=100) were included in the safety analyses. The adverse events that were most frequently reported were nasopharyngitis and upper respiratory tract infection. No deaths or serious infections were reported in both studies. Humira was generally safe and well tolerated with no obvious trends in adverse events. The safety profile of the Humira 40 mg/0.4 mL formulation is similar to that of the 40 mg/0.8 mL formulation.

## **Autoantibodies**

Patients had serum samples tested for autoantibodies at multiple time points in Studies DE009, DE011, DE019, DE031 and DE013. In those rheumatoid arthritis controlled trials, 11.9% of patients treated with adalimumab and 8.1% of placebo- or active control-treated patients who had negative baseline antinuclear antibody (ANA) titers, developed positive

titers at Week 24. Two patients out of 3441 treated with adalimumab 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.

### **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.

#### Pediatric

In clinical trials with adalimumab therapy for polyarticular JIA, the proportion of patients achieving PedACR response was lower in anti-adalimumab antibody (AAA)-positive patients compared with AAA-negative patients.

In patients with polyarticular JIA who were 4 to 17 years (Study DE038), anti-adalimumab antibodies were identified in 27/171 subjects (15.8%) treated with HUMIRA. In patients not given concomitant MTX, the incidence was 22/86 (25.6%), compared to 5/85 (5.9%) when HUMIRA was used as add-on to MTX. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg (Study M10-444), anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant MTX.

In patients 13 to 17 years of age with severely active Crohn's disease, anti-adalimumab antibodies were identified in 3.5% (4/114) of patients receiving adalimumab.

#### Adult

Rheumatoid arthritis patients in Studies DE009, DE011, and DE019 were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58/1062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing in vitro. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%). With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the American College of Rheumatology (ACR 20) response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

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

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

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

In patients with ulcerative colitis, anti-adalimumab antibodies were identified in 5.0% (19/379) of patients receiving adalimumab. The clinical significance of this is unknown.

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

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

In patients with plaque psoriasis, the rate of antibody development with adalimumab monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among these patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In patients with plaque psoriasis on long-term adalimumab monotherapy who participated in a withdrawal and retreatment study and whose serum adalimumab levels were < 2 mcg/mL (approximately 12% of total patients studied), the immunogenicity rate was 16%; the overall rate of antibody development prior to withdrawal was 1.9%, and 2.3% after retreatment.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%.

The data reflect the percentage of patients whose test results were considered positive for

antibodies to adalimumab in an enzyme-linked immunosorbent assay (ELISA), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

## Infections

### Adults

In 23 controlled trials for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis, and uveitis the rate of infection was

147.4 per 100 patient-years in 5630 adalimumab-treated patients and 142.7 per 100 patient-years in 3587 control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

The incidence of serious infections was 3.4 per 100 patient-years in adalimumab-treated patients and 3.2 per 100 patient-years in placebo and active control-treated patients.

In controlled and open-label studies with adalimumab, serious infections such as legionellosis (0.02 per 100 patient-years) have been reported. No cases of listeriosis have been reported and therefore, an estimated rate of 0.01 per 100 patient-years was calculated. Both infections have been reported spontaneously during the post-marketing period. (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions**)

In controlled and open-label 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, and aspergillosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

In the double-blind controlled portion of two clinical trials with adalimumab in patients with UC, serious infections occurred in 4/480 patients treated with adalimumab; they were appendicitis (n=1), anal abscess (n=1), catheter sepsis (n=1) and salmonellosis (n=1). Serious infections occurred in 8 placebo patients. Opportunistic infections occurred in 7/480 patients treated with adalimumab; they were candidiasis (n=3), oesophageal candidiasis (n=1) and oral candidiasis

(n=3). Opportunistic infections occurred in 3 placebo patients.

In the double-blind controlled portion of three clinical trials with adalimumab in patients with HS, serious infections occurred in 4/419 patients treated with adalimumab; they were Escherichia infection (n=1), genital infection bacterial (n=1), infection (n=1), pilonidal cyst (n=1) and pyelonephritis (n=1). Serious infections occurred in 2/366 placebo patients.

In the double-masked controlled portion of two clinical trials with adalimumab in patients with uveitis, serious infections occurred in 7/250 (2.8%) patients treated with adalimumab; they were pneumonia (n = 2), and 1 each of bronchitis, pilonidal cyst, pneumonia Legionella, tuberculosis, upper respiratory tract infection and urinary tract infection. Serious infections occurred in 4/250 (1.6%) placebo patients. Opportunistic infections occurred in 7/250 patients treated with adalimumab; they were active tuberculosis (n = 1), latent tuberculosis (n = 4) and oral candidiasis (n = 2). Latent tuberculosis occurred in 1 placebo-treated patient. In the open-label extension study (M11-327), the exposure-adjusted incidence rate of serious infections was increased in patients who received concomitant systemic corticosteroids and immunosuppressants in addition to treatment with adalimumab.

### Pediatrics

In a controlled trial for polyarticular JIA (Study DE038), the rate of adverse events of infections was 238.5 per 100 patient-years in the adalimumab-treated JIA patients compared to 269.5 per 100 patient-years in control (placebo) treated patients, and the rate of serious infections was 6.1 per 100 patient-years in the adalimumab-treated JIA patients compared to 0 events in control (placebo) treated patients.

In an open-label trial for polyarticular JIA (Study M10-444), the rate of adverse events of infections was 206.2 per 100 patient-years while receiving adalimumab and the rate of serious infections was 6.7 per 100 patient-years while receiving adalimumab.

In a randomized double-blind trial (M06-806) for the indicated pediatric patient population with Crohn's disease, the rate of infections was 161.4 per 100 patient-years for the High-Dose group and 225.9 per 100 patient-years for the Low-Dose group. The rates of serious infections were 9.5 per 100 patient-years for the High-Dose group and 3.7 per 100 patient-years for the Low-Dose group. The rates of infections were 55.8% (29/52) and 52.0% (26/50) for High-Dose and Low-Dose groups, respectively. The rates of serious infections were 5.8% (3/52) and 2.0% (1/50) for High-Dose and Low-Dose groups, respectively and included anal abscess, gastroenteritis, and histoplasmosis disseminated in the High-Dose group and Bartholin's abscess in the Low-Dose group.

In a randomized controlled trial (SYCAMORE) for pediatric patients with active JIA-associated chronic non-infectious anterior uveitis, the rate of adverse events of infections was 236.4 per 100 patient-years (77%) for the adalimumab-treated group compared to 164.5 per 100 patient-years (40%) for the control (placebo) group. The rate of serious infections was 17.1 per 100 patient-years (13%) in the adalimumab-treated uveitis patients compared to 0 events in control (placebo) treated patients.

### **Injection Site Reactions**

In controlled trials in adults and children, 13% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Based on two Phase II clinical studies (n=60 and n=62), injection site pain immediately after dosing of adalimumab 40 mg/0.4 mL was reduced by a median of 84% in comparison with adalimumab 40 mg/0.8 mL, based on mean score of visual analogue scale (VAS), in patients with moderately to severely active rheumatoid arthritis who were either biologic-naïve or current users of adalimumab 40 mg/0.8 mL that rated their average injection site pain as at least 3 cm (on a 0-10 cm VAS).

### **Malignancies**

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials. (See **7 WARNINGS AND PRECAUTIONS**), **Malignancies**).

### **Neurologic Events**

In 21 controlled trials for adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, and psoriasis the rate of new onset or exacerbation of central nervous system demyelinating disease (including multiple sclerosis and optic neuritis) and peripheral demyelinating disease (including Guillain-Barre syndrome) was less than 0.4 per 1000 patient-years in 5,380 adalimumab-treated patients and 0.7 per 1000 patient-years in 3,337 control-treated patients. In controlled and open-label studies for adult patients treated with adalimumab, the rate (95% CI) of demyelinating diseases was 0.7 (0.4, 1.1) per 1000 patient-years. Demyelinating diseases were reported spontaneously during the post-marketing period.

In the double-masked controlled portion of two clinical trials with adalimumab in adult patients

with uveitis, 1 (0.4%) case of multiple sclerosis was reported in 250 patients treated with adalimumab. In the adult uveitis development program including the open-label study, the rate (95% CI) of demyelinating diseases (i.e., multiple sclerosis and optic neuritis) was 5.4 (2.2, 11.0) per 1000 patient-years. (See **7 WARNINGS AND PRECAUTIONS, Neurologic Events**).

### **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., methotrexate, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker.

Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of adalimumab should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

### **Liver Enzyme Elevations**

In controlled Phase 3 trials of adalimumab (40 mg subcutaneous every other week), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, alanine aminotransferase (ALT) elevations  $\geq 3 \times$  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 adult patients with Crohn's disease with a control period duration ranging from 4 to 52 weeks, ALT elevations  $\geq 3 \times$  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), in patients with UC with a control period duration ranging from 1 to 52 weeks, ALT elevations  $\geq 3 \times$  ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. The incidence of ALT elevations  $\geq 5 \times$  ULN was 0.5% in adalimumab-treated patients and 0.2% in 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  $\geq 3 \times$  ULN occurred in 1.8% of adalimumab-treated patients and 1.8% 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  $\geq 3 \times$  ULN occurred in 2.4% of adalimumab-treated patients and 0.7% 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 adult patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations  $\geq 3 \times$  ULN occurred in 0.3% of adalimumab-treated patients and 0.6% of control-treated patients.

In controlled Phase 3 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 adult uveitis with an exposure of 165.4 patient-years and 119.8 patient-years in adalimumab-treated and control-treated patients, respectively, ALT elevations  $\geq 3 \times$  ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

Across all adult indications in clinical trials, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis, in patients receiving TNF blockers, including adalimumab. 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. (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatosplenic T-cell Lymphoma**)

## 8.2 Clinical Trial Adverse Reactions

*Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.*

The following adverse reaction information is sourced from the Humira Product Monograph, Approved on June 25, 2019.

#### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

## Polyarticular Juvenile Idiopathic Arthritis

**Table 4. Number and Percentage of Subjects with  $\geq 1\%$  Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Double Blind Placebo-Controlled Phase in the Polyarticular JIA Trial (Study DE038)**

System Organ Class MedDRA 12.1 Preferred Term	MTX		Non-MTX		Overall	
	Placebo N = 37 n (%)	HUMIRA N = 38 n (%)	Placebo N = 28 n (%)	HUMIRA N = 30 n (%)	Placebo N = 65 n (%)	HUMIRA N = 68 n (%)
<b>Any at least possibly related adverse event</b>	17 (45.9)	22 (57.9)	9 (32.1)	16 (53.3)	26 (40.0)	38 (55.9)
<b>Blood and Lymphatic System Disorders</b>	0	2 (5.3)	0	1 (3.3)	0	3 (4.4)
Leukopenia	0	1 (2.6)	0	0	0	1 (1.5)
Neutropenia	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
<b>Ear and Labyrinth Disorders</b>	0	0	0	1 (3.3)	0	1 (1.5)
Ear pain	0	0	0	1 (3.3)	0	1 (1.5)
<b>Gastrointestinal Disorders</b>	1 (2.7)	1 (2.6)	0	0	1 (1.5)	1 (1.5)
Gastroduodenitis	1 (2.7)	0	0	0	1 (1.5)	0
Vomiting	0	1 (2.6)	0	0	0	1 (1.5)
<b>General Disorders and Administration Site Conditions</b>	10 (27.0)	15 (39.5)	6 (21.4)	11 (36.7)	16 (24.6)	26 (38.2)
Application site reaction	1 (2.7)	1 (2.6)	0	0	1 (1.5)	1 (1.5)
Fatigue	0	0	0	1 (3.3)	0	1 (1.5)
Influenza like illness	1 (2.7)	0	0	0	1 (1.5)	0
Injection site erythema	1 (2.7)	2 (5.3)	0	1 (3.3)	1 (1.5)	3 (4.4)
Injection site haematoma	0	1 (2.6)	0	0	0	1 (1.5)
Injection site hypersensitivity	1 (2.7)	0	0	0	1 (1.5)	0
Injection site pain	7 (18.9)	7 (18.4)	3 (10.7)	9 (30.0)	10	16 (23.5)

					(15.4)	
Injection site pruritus	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
Injection site reaction	1 (2.7)	7 (18.4)	1 (3.6)	3 (10.0)	2 (3.1)	10 (14.7)
Pain	0	1 (2.6)	2 (7.1)	2 (6.7)	2 (3.1)	3 (4.4)
Pyrexia	0	2 (5.3)	0	0	0	2 (2.9)
<b>Immune System Disorder</b>	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
Hypersensitivity	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
<b>Infections and Infestations</b>	7 (18.9)	10 (26.3)	3 (10.7)	6 (20.0)	10 (15.4)	16 (23.5)
Acute tonsillitis	1 (2.7)	1 (2.6)	0	0	1 (1.5)	1 (1.5)
Bronchitis	1 (2.7)	0	0	1 (3.3)	1 (1.5)	1 (1.5)
Ear infection	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
Folliculitis	1 (2.7)	0	0	0	1 (1.5)	0
Fungal infection	0	0	1 (3.6)	0	1 (1.5)	0
Herpes simplex	0	0	0	1 (3.3)	0	1 (1.5)
Herpes virus infection	0	0	0	1 (3.3)	0	1 (1.5)
Impetigo	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
Influenza	0	1 (2.6)	1 (3.6)	1 (3.3)	1 (1.5)	2 (2.9)
Molluscum contagiosum	1 (2.7)	0	0	0	1 (1.5)	0
Oral herpes	1 (2.7)	1 (2.6)	0	0	1 (1.5)	1 (1.5)
Paronychia	0	1 (2.6)	0	0	0	1 (1.5)
Pharyngotonsillitis	1 (2.7)	0	0	1 (3.3)	1 (1.5)	1 (1.5)
Rhinitis	0	2 (5.3)	0	1 (3.3)	0	3 (4.4)
Sinusitis	0	1 (2.6)	0	0	0	1 (1.5)
Staphylococcal skin infection	0	0	1 (3.6)	0	1 (1.5)	0

Upper respiratory tract infection	2 (5.4)	3 (7.9)	0	2 (6.7)	2 (3.1)	5 (7.4)
Urinary tract infection	0	1 (2.6)	0	0	0	1 (1.5)
Viral infection	1 (2.7)	3 (7.9)	0	0	1 (1.5)	3 (4.4)
Viral upper respiratory tract infection	0	0	0	1 (3.3)	0	1 (1.5)
<b>Injury, Poisoning and Procedural Complications</b>	1 (2.7)*	0*	1 (3.6) *	0*	2 (3.1) *	0*
Excoriation <sup>†</sup>	1 (2.7)	4 (10.5)	1 (3.6)	3 (10.0)	2 (3.1)	7 (10.3)
Injury	0	0	1 (3.6)	0	1 (1.5)	0
Scratch	1 (2.7)	0	0	0	1 (1.5)	0
<b>Investigations</b>	0	1 (2.6)	0	0	0	1 (1.5)
Lymphocyte count increased	0	1 (2.6)	0	0	0	1 (1.5)
Neutrophil count decreased	0	1 (2.6)	0	0	0	1 (1.5)
<b>Metabolism and Nutrition Disorders</b>	1 (2.7)	0	0	0	1 (1.5)	0
Enzyme abnormality	1 (2.7)	0	0	0	1 (1.5)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	3 (8.1)	1 (2.6)	0	1 (3.3)	3 (4.6)	2 (2.9)
Arthralgia	0	0	0	1 (3.3)	0	1 (1.5)
Groin pain	1 (2.7)	0	0	0	1 (1.5)	0
Juvenile arthritis	1 (2.7)	1 (2.6)	0	0	1 (1.5)	1 (1.5)
Rheumatoid arthritis	1 (2.7)	0	0	0	1 (1.5)	0
<b>Nervous System Disorders</b>	1 (2.7)	0	0	1 (3.3)	1 (1.5)	1 (1.5)
Headache	1 (2.7)	0	0	1 (3.3)	1 (1.5)	1 (1.5)
<b>Renal and Urinary Disorders</b>	0	0	2 (7.1)	0	2 (3.1)	0
Dysuria	0	0	1 (3.6)	0	1 (1.5)	0
Proteinuria	0	0	1 (3.6)	0	1 (1.5)	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	0	2 (5.3)	0	1 (3.3)	0	3 (4.4)
Asthma	0	1 (2.6)	0	0	0	1 (1.5)

Cough	0	0	0	1 (3.3)	0	1 (1.5)
Epistaxis	0	1 (2.6)	0	0	0	1 (1.5)
<b>Skin and Subcutaneous Tissue Disorders</b>	1 (2.7)*	1 (2.6)*	0	1 (3.3)*	1 (1.5)*	2 (2.9)*
Acne	0	0	0	1 (3.3)	0	1 (1.5)
Dermatitis	1 (2.7)	0	0	0	1 (1.5)	0
Rash <sup>†</sup>	0	1 (2.6)	0	2 (6.7)	0	3 (4.4)
Rash papular	0	0	0	1 (3.3)	0	1 (1.5)
Skin lesion	0	1 (2.6)	0	0	0	(1.5)

\*Total only includes values for the terms considered possibly or probably related by the investigator

† Term was not considered possibly or probably related as assessed by the investigator, however, these terms were considered more common in patients treated with HUMORA vs placebo in the clinical trial

In Study DE038, Humira was studied in 171 patients aged 4 to 17 years with polyarticular JIA. Serious adverse events were observed in 28% of patients treated with HUMIRA and included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia and appendicitis. Serious infections were observed in 6.4% of patients treated with Humira and included cases of herpes zoster, appendicitis, pneumonia, urinary tract infection, streptococcal pharyngitis, viral infection and cervicitis. A total of 45% of patients experienced an infection while receiving Humira with or without concomitant MTX in the first 16 weeks of treatment (see **7 WARNINGS AND PRECAUTIONS, Infections**). Granuloma annulare was reported in two patients (see **7 WARNINGS AND PRECAUTIONS, Malignancies**).

During the double-blind phase of Study DE038, the most common (≥ 5%) adverse reactions occurring in the JIA population treated with Humira were viral infection (18%), injection site pain (18%), upper respiratory tract infection (16%), injection site reaction (15%), contusion (13%), excoriation (10%), rhinitis (7%), vomiting (6%) and drug hypersensitivity (6%).

Throughout Study DE038, 6% of patients had mild to moderate allergic reaction adverse events primarily localized allergic hypersensitivity reactions and urticaria (see **7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**).

In the JIA trial, 10% of patients treated with Humira who were negative at baseline for anti-double-stranded DNA antibodies developed positive titers after 48 weeks of treatment (see **8 ADVERSE REACTIONS, Adverse Drug Reaction Overview, Immunogenicity, Pediatric**).

In Study M10-444, Humira was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in Study DE038.

In Study M10-444, 78% of patients experienced an infection while receiving Humira. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving Humira in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study M10-444, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

### Hidradenitis Suppurativa

There are no clinical trials conducted to evaluate the safety of Humira in adolescents with hidradenitis suppurativa (HS).

### Pediatric Uveitis

Table 5 summarizes adverse drug reactions reported in the SYCAMORE study at a rate of at least 1% in the indicated pediatric patient population with active JIA-associated chronic non-infectious anterior uveitis treated with Humira in combination with methotrexate.

**Table 5. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug in the SYCAMORE Pediatric Uveitis Study**

<b>System Organ Class (SOC)</b>	<b>HUMIRA N=60 n (%)</b>	<b>Placebo N=30 n (%)</b>
<b>Blood and Lymphatic System Disorders</b>	4 (6.7)	0
Lymphadenopathy	3 (5.0)	0
Neutropenia	1 (1.7)	0
<b>Eye Disorders</b>	4 (6.7)	4 (13.3)
Anterior chamber flare	0	1 (3.3)
Dry eye	1 (1.7)	0
Eye inflammation	1 (1.7)	0
Eye pain	1 (1.7)	0
Uveitis	0	3 (10.0)
Visual impairment	1 (1.7)	0
<b>Gastrointestinal Disorders</b>	10 (16.7)	2 (6.7)
Abdominal pain	1 (1.7)	0
Diarrhoea	4 (6.7)	0
Food poisoning	1 (1.7)	0
Nausea	2 (3.3)	0
Vomiting	7 (11.7)	2 (6.7)
<b>General Disorders and Administration Site Conditions</b>	23 (38.3)	5 (16.7)
Chest discomfort	1 (1.7)	0
Fatigue	0	1 (3.3)
Influenza like illness	1 (1.7)	0

Injection site erythema	3 (5.0)	1 (3.3)
Injection site mass	2 (3.3)	0
Injection site pain	5 (8.3)	2 (6.7)
Injection site pruritus	3 (5.0)	0
Injection site reaction	6 (10.0)	0
Injection site swelling	3 (5.0)	1 (3.3)
Injection site vesicles	1 (1.7)	0
Malaise	1 (1.7)	0
Pyrexia	8 (13.3)	1 (3.3)
Swelling	1 (1.7)	0

<b>System Organ Class (SOC)</b>	<b>HUMIRA N=60 n (%)</b>	<b>Placebo N=30 n (%)</b>
<b>Infections and Infestations</b>	<b>32 (53.3)</b>	<b>8 (26.7)</b>
Candida infection	1 (1.7)	0
Cellulitis	1 (1.7)	0
Conjunctivitis viral	1 (1.7)	0
Ear infection	3 (5.0)	2 (6.7)
Eye infection	1 (1.7)	0
Herpes simplex	1 (1.7)	0
Herpes zoster	0	1 (3.3)
Impetigo	3 (5.0)	1 (3.3)
Infected bites	1 (1.7)	0
Infection	1 (1.7)	0
Localised infection	0	1 (3.3)
Lower respiratory tract infection	8 (13.3)	2 (6.7)
Molluscum contagiosum	2 (3.3)	0
Nasopharyngitis	6 (10.0)	2 (6.7)
Oral herpes	2 (3.3)	1 (3.3)
Paronychia	2 (3.3)	1 (3.3)
Pharyngitis	2 (3.3)	0
Pneumonia	1 (1.7)	0
Rhinitis	1 (1.7)	0
Scarlet fever	1 (1.7)	0
Skin infection	2 (3.3)	0
Staphylococcal infection	1 (1.7)	0

Streptococcal infection	1 (1.7)	0
Tonsillitis	10 (16.7)	0
Upper respiratory tract infection	3 (5.0)	1 (3.3)
Urethritis	0	1 (3.3)
Urinary tract infection	6 (10.0)	2 (6.7)
Varicella	1 (1.7)	0
Viral infection	8 (13.3)	1 (3.3)
<b>Injury, Poisoning and Procedural Complications</b>	1 (1.7)	0
Contusion	1 (1.7)	0
<b>Investigations</b>	6 (10.0)	1 (3.3)
Alanine aminotransferase increased	3 (5.0)	0
Aspartate aminotransferase increased	2 (3.3)	0
Blood alkaline phosphatase increased	1 (1.7)	0
Liver function test abnormal	1 (1.7)	0
Neutrophil count decreased	0	1 (3.3)
Red blood cell sedimentation rate abnormal	1 (1.7)	0
Rubulavirus test positive	1 (1.7)	0
<b>Metabolism and Nutrition Disorders</b>	3 (5.0)	0
Decreased appetite	2 (3.3)	0
Dehydration	1 (1.7)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	5 (8.3)	1 (3.3)
Arthralgia	3 (5.0)	1 (3.3)
Arthritis	1 (1.7)	0
Joint stiffness	1 (1.7)	0
Pain in extremity	1 (1.7)	0
<b>Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)</b>	4 (6.7)	0
Skin papilloma	4 (6.7)	0
<b>Nervous System Disorders</b>	5 (8.3)	1 (3.3)
Headache	5 (8.3)	1 (3.3)
<b>Reproductive System and Breast Disorders</b>	1 (1.7)	0
Pruritus genital	1 (1.7)	0

<b>Respiratory, Thoracic and Mediastinal Disorders</b>	12 (20.0)	2 (6.7)
Cough	9 (15.0)	2 (6.7)
Nasal discomfort	2 (3.3)	0
Oropharyngeal pain	8 (13.3)	0
Productive cough	1 (1.7)	0
Snoring	1 (1.7)	0
Tonsillar hypertrophy	1 (1.7)	0
<b>Skin and Subcutaneous Tissue Disorders</b>	3 (5.0)	2 (6.7)
Dermatitis	0	1 (3.3)
Erythema	1 (1.7)	0
Ingrowing nail	1 (1.7)	0
Rash	1 (1.7)	1 (3.3)

In the SYCAMORE study, Humira was studied in 90 pediatric patients (randomized 2:1 to Humira: placebo) with active JIA-associated chronic non-infectious anterior uveitis. Overall, serious adverse events were observed in 22% of patients treated with HUMIRA in combination with MTX and included varicella, streptococcal infections, viral infection, diarrhea, syncope, scarlet fever, cellulitis, infected bites, lower respiratory tract infection, cataract, testes exploration, antiviral prophylaxis, food poisoning, and tonsillar hypertrophy. Serious infections were observed in 13% of patients with HUMIRA. Serious adverse events were more frequent in children 4 years of age and younger.

## 8.2.2 Clinical trial Adverse reaction - Adults

### Rheumatoid Arthritis

#### **Description of Data Sources**

The data described below reflect exposure to Humira in 3,046 patients, including more than 2,000 patients exposed for six months, and more than 1,500 exposed for more than one year (Studies DE009, DE011, DE019, DE031 and DE013). Humira was studied in placebo-controlled trials and in long-term follow-up studies for up to 60 months duration in patients with moderately to severely active rheumatoid arthritis who had failed previous DMARD therapy; the mean age was 54 years, 77% were female and 91% Caucasian (Studies DE009, DE011, DE019, DE031). A further study (Study DE013) was in patients with recently

diagnosed rheumatoid arthritis who had not previously been treated with methotrexate. Most patients received Humira 40 mg every other week.

### **Relative Frequency of Adverse Drug Reactions**

Table 6 summarizes adverse drug reactions reported at a rate of at least 1% in patients treated with Humira 40 mg every other week, as well as all doses of Humira tested, compared to placebo or methotrexate (Study DE013). Adverse reaction rates in patients treated with Humira 40 mg weekly were similar to rates in patients treated with Humira every other week. In Study DE019, the types and frequencies of adverse drug reactions in the 10-year open-label extension were similar to those observed in the one-year double-blind portion.

**Table 6. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Rheumatoid Arthritis Studies (Studies DE009, DE011, DE019, DE031, DE013)**

<b>System Organ Class (SOC)</b>	<b>HUMIRA 40 mg s.c. eow N = 1247 n (%)</b>	<b>HUMIRA (all adalimumab) N = 1922 n (%)</b>	<b>Placebo (not Study DE013) N = 690 n (%)</b>	<b>MTX (Study DE013) N = 257 n (%)</b>
<b>Gastrointestinal Disorders</b>				
Nausea	80 (6.4)	112 (5.8)	12 (1.7)	33 (12.8)
Diarrhea	47 (3.8)	60 (3.1)	17 (2.5)	18 (7.0)
Abdominal pain	22 (1.8)	29 (1.5)	5 (0.7)	3 (1.2)
Abdominal pain upper	20 (1.6)	25 (1.3)	0 (0.0)	13 (5.1)
Mouth ulceration	17 (1.4)	24 (1.2)	5 (0.7)	12 (4.7)
Dyspepsia	14 (1.1)	21 (1.1)	4 (0.6)	7 (2.7)
Vomiting	16 (1.3)	20 (1.0)	5 (0.7)	6 (2.3)
<b>General Disorders and Administration Site Conditions</b>				
Injection site irritation	74 (5.9)	122 (6.3)	61 (8.8)	3 (1.2)
Injection site reaction	49 (3.9)	67 (3.5)	3 (0.4)	2 (0.8)
Injection site pain	36 (2.9)	63 (3.3)	24 (3.5)	6 (2.3)
Injection site erythema	36 (2.9)	60 (3.1)	2 (0.3)	1 (0.4)
Fatigue	37 (3.0)	58 (3.0)	7 (1.0)	9 (3.5)
Injection site rash	17 (1.4)	22 (1.1)	2 (0.3)	0 (0.0)
Influenza-like illness	15 (1.2)	21 (1.1)	2 (0.3)	8 (3.1)
Pyrexia	13 (1.0)	20 (1.0)	1 (0.1)	6 (2.3)
<b>Infections and Infestations</b>				

Nasopharyngitis	61 (4.9)	95 (4.9)	10 (1.5)	28 (10.9)
Upper respiratory infection	72 (5.8)	93 (4.8)	15 (2.2)	17 (6.6)
Sinusitis	46 (3.7)	55 (2.9)	17 (2.5)	4 (1.6)
Herpes simplex	33 (2.6)	48 (2.5)	6 (0.9)	5 (1.9)
Urinary tract infection	31 (2.5)	44 (2.3)	6 (0.9)	7 (2.7)
Bronchitis	19 (1.5)	29 (1.5)	8 (1.2)	9 (3.5)
Herpes zoster	17 (1.4)	23 (1.2)	8 (1.2)	2 (0.8)
Influenza	16 (1.3)	21 (1.1)	7 (1.0)	5 (1.9)
Pneumonia	17 (1.4)	21 (1.1)	3 (0.4)	1 (0.4)
<b>Investigations</b>				
Lymphocyte count decreased	11 (0.9)	38 (2.0)	11 (1.6)	1 (0.4)
Alanine aminotransferase increased	27 (2.2)	33 (1.7)	4 (0.6)	9 (3.5)
Liver function test abnormal	19 (1.5)	22 (1.1)	4 (0.6)	7 (2.7)
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Rheumatoid arthritis	11 (0.9)	28 (1.5)	7 (1.0)	2 (0.8)
<b>Nervous System Disorders</b>				
Headache	75 (6.0)	124 (6.5)	14 (2.0)	14 (5.4)
Dizziness	23 (1.8)	32 (1.7)	6 (0.9)	3 (1.2)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	44 (3.5)	66 (3.4)	9 (1.3)	8 (3.1)
Pruritus	28 (2.2)	43 (2.2)	4 (0.6)	5 (1.9)
Alopecia	22 (1.8)	28 (1.5)	2 (0.3)	6 (2.3)
Rash pruritic	14 (1.1)	22 (1.1)	0 (0.0)	3 (1.2)

Definitions: s.c. = subcutaneous; o.w. = every other week

## Psoriatic Arthritis

Table 7 summarizes adverse drug reactions reported in placebo-controlled and open-label studies at a rate of at least 1% in psoriatic arthritis patients treated with Humira 40 mg every other week.

**Table 7. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control and Open-Label Periods in Psoriatic Arthritis Studies (Studies M02-518, M02-570, and M02-537)**

	Double-Blind Study	Open-Label Study
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System Organ Class (SOC)	Placebo N = 211 n (%)	HUMIRA 40 mg s.c. eow N = 202 n (%)	HUMIRA 40 mg s.c. eow N = 382 n (%)
<b>Gastrointestinal Disorders</b>			
Nausea	2 (0.9)	2 (1.0)	3 (0.8)
<b>General Disorders and Administration Site Conditions</b>			
Injection site reaction	5 (2.4)	11 (5.4)	21 (5.5)
Injection site pain	8 (3.8)	8 (4.0)	2 (0.5)
Injection site erythema	0 (0.0)	4 (2.0)	2 (0.5)
Injection site burning	4 (1.9)	4 (2.0)	4 (1.0)
Fatigue	5 (2.4)	0 (0.0)	4 (1.0)
<b>Infections and Infestations</b>			
Upper respiratory infection	7 (3.3)	8 (4.0)	17 (4.5)
Herpes simplex	3 (1.4)	6 (3.0)	7 (1.8)
Skin fungal infection NOS	0 (0.0)	3 (1.5)	-
Pharyngitis	1 (0.5)	2 (1.0)	4 (1.0)
Sinusitis	4 (1.9)	2 (1.0)	12 (3.1)
Urinary tract infection	0 (0.0)	2 (1.0)	6 (1.6)
Bronchitis	1 (0.5)	1 (0.5)	5 (1.3)
Nasopharyngitis	2 (0.9)	1 (0.5)	8 (2.1)
Influenza	2 (0.9)	0 (0.0)	5 (1.3)
<b>Investigations</b>			
Liver function tests abnormal	1 (0.5)	2 (1.0)	5 (1.3)
<b>Nervous System Disorders</b>			
Headache	5 (2.4)	5 (2.5)	5 (1.3)
Paresthesia	1 (0.5)	3 (1.5)	2 (0.5)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Rhinitis NOS	0 (0.0)	3 (1.5)	3 (0.8)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Erythema	0 (0.0)	3 (1.5)	-

Definitions: s.c. = subcutaneous eow = every other week

### Ankylosing Spondylitis

Humira has been studied in 393 patients with ankylosing spondylitis in two placebo-controlled studies. The safety profile for patients with ankylosing spondylitis treated with Humira 40 mg every other week was similar to the safety profile seen in patients with

rheumatoid arthritis, Humira Studies DE009, DE011, DE019, and DE031. Table 8 summarizes adverse drug reactions reported at a rate of at least 1% in ankylosing spondylitis patients treated with Humira 40 mg every other week compared to placebo.

**Table 8. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Ankylosing Spondylitis Studies (Studies M03-607 and M03-606)**

System Organ Class (SOC)	HUMIRA 40 mg s.c. eow N = 246 n (%)	Placebo N = 151 n (%)
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	5 (2.0)	3 (2.0)
Injection site erythema	5 (2.0)	1 (0.7)
Injection site irritation	4 (1.6)	2 (1.3)
Injection site pain	6 (2.4)	3 (2.0)
Injection site reaction	8 (3.3)	1 (0.7)
<b>Infections and Infestations</b>		
Nasopharyngitis	8 (3.3)	0 (0.0)
Upper respiratory tract infection	5 (2.0)	2 (1.3)
<b>Nervous System Disorders</b>		
Dizziness	3 (1.2)	3 (2.0)
Headache	11 (4.5)	4 (2.6)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Eczema	3 (1.2)	1 (0.7)
Pruritus	4 (1.6)	1 (0.7)
Pruritus generalized	3 (1.2)	0 (0.0)
Rash	4 (1.6)	1 (0.7)
Urticaria	3 (1.2)	0 (0.0)

Definitions: s.c. = subcutaneous eow = every other week

### Crohn's Disease

Humira has been studied in over 1,500 patients with Crohn's disease in five placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with Humira was similar to the safety profile seen in patients with rheumatoid arthritis including the safety profile for patients in placebo-controlled Study M05-769. No new safety signals occurred during the open-label long-term studies with Humira exposure up to five years. The safety profile of Humira in Crohn's disease remains unaltered.

Table 9 and Table 10 summarize adverse drug reactions reported at a rate of at least 1% in Crohn's disease patients treated with Humira in induction and maintenance studies, respectively.

**Table 9. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Induction Study Medications in Crohn's Disease Studies (Studies M02-403 and M04-691)**

System Organ Class (SOC)	HUMIRA 160/80 mg N = 235 n (%)	HUMIRA 80/40 mg N = 75 n (%)	Placebo N = 240 n (%)
<b>Eye Disorders</b>			
Corneal pigmentation	0 (0.0)	1 (1.3)	0 (0.0)
Visual disturbance	0 (0.0)	1 (1.3)	0 (0.0)
<b>Gastrointestinal Disorders</b>			
Abdominal pain	5 (2.1)	0 (0.0)	2 (0.8)
Abdominal pain lower	3 (1.3)	0 (0.0)	0 (0.0)
Change of bowel habit	0 (0.0)	1 (1.3)	0 (0.0)
Cheilitis	0 (0.0)	1 (1.3)	1 (0.4)
Constipation	2 (0.9)	1 (1.3)	3 (1.3)
Crohn's disease	2 (0.9)	1 (1.3)	3 (1.3)
Flatulence	3 (1.3)	0 (0.0)	0 (0.0)
Nausea	6 (2.6)	0 (0.0)	4 (1.7)
Vomiting	1 (0.4)	1 (1.3)	3 (1.3)
<b>General Disorders and Administration Site Conditions</b>			
Asthenia	0 (0.0)	1 (1.3)	1 (0.4)
Chills	0 (0.0)	2 (2.7)	1 (0.4)
Fatigue	2 (0.9)	1 (1.3)	10 (4.2)
Influenza like illness	0 (0.0)	2 (2.7)	2 (0.8)
Injection site bruising	5 (2.1)	1 (1.3)	1 (0.4)
Injection site erythema	4 (1.7)	0 (0.0)	0 (0.0)
Injection site irritation	19 (8.1)	8 (10.7)	14 (5.8)
Injection site pain	6 (2.6)	4 (5.3)	9 (3.8)
Injection site pruritus	3 (1.3)	0 (0.0)	0 (0.0)
Injection site reaction	11 (4.7)	5 (6.7)	6 (2.5)
Pain	2 (0.9)	1 (1.3)	3 (1.3)
Pyrexia	3 (1.3)	3 (1.3)	3 (1.3)
<b>Infections and Infestations</b>			

Staphylococcal infection	0 (0.0)	1 (1.3)	0 (0.0)
<b>Investigations</b>			
Double stranded DNA antibody	0 (0.0)	1 (1.3)	0 (0.0)
White blood cell count increased	0 (0.0)	1 (1.3)	0 (0.0)
<b>Metabolism and Nutrition Disorders</b>			
Hypokalemia	0 (0.0)	1 (1.3)	0 (0.0)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	3 (1.3)	1 (1.3)	2 (0.8)
Back pain	0 (0.0)	1 (1.3)	0 (0.0)
Muscle spasms	0 (0.0)	1 (1.3)	1 (0.4)
Pain in extremity	0 (0.0)	1 (1.3)	0 (0.0)
<b>Nervous System Disorders</b>			
Dizziness	3 (1.3)	0 (0.0)	2 (0.8)
Headache	8 (3.4)	2 (2.7)	7 (2.9)
Restless legs syndrome	0 (0.0)	1 (1.3)	0 (0.0)
<b>Reproductive System and Breast Disorders</b>			
Genital pruritus female	0 (0.0)	1 (1.3)	0 (0.0)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Eczema	1 (0.4)	1 (1.3)	0 (0.0)
Erythema	1 (0.4)	1 (1.3)	1 (0.4)
Hyperhidrosis	0 (0.0)	1 (1.3)	0 (0.0)
Onychorrhexis	0 (0.0)	1 (1.3)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)	4 (1.7)
Rash	2 (0.9)	2 (2.7)	1 (0.4)
Rash maculo-papular	1 (0.4)	1 (1.3)	0 (0.0)
Rash pruritic	0 (0.0)	1 (1.3)	1 (0.4)

**Table 10. Number and Percentage of Patients with  $\geq$  1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Blinded Study Maintenance Medications in Crohn's Disease Studies (Studies M02-404 and M02-433)**

System Organ Class (SOC)	HUMIRA 40 mg s.c. eow, 40 mg ew N = 554 n (%)	Placebo N = 279 n (%)
<b>Gastrointestinal Disorders</b>		
Abdominal pain	7 (1.3)	4 (1.4)
Crohn's disease	9 (1.6)	9 (3.2)
Diarrhea	7 (1.3)	1 (0.4)

Nausea	9 (1.6)	5 (1.8)
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	10 (1.8)	1 (0.4)
Injection site bruising	6 (1.1)	1 (0.4)
Injection site erythema	10 (1.8)	0 (0.0)
Injection site irritation	18 (3.2)	2 (0.7)
Injection site pain	8 (1.4)	2 (0.7)
Injection site reaction	26 (4.7)	1 (0.4)
Pyrexia	7 (1.3)	5 (1.8)
<b>Herpes simplex</b>		
Herpes simplex	6 (1.1)	4 (1.4)
<b>Nasopharyngitis</b>		
Nasopharyngitis	8 (1.4)	2 (0.7)
<b>Rhinitis</b>		
Rhinitis	7 (1.3)	1 (0.4)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	9 (1.6)	2 (0.7)
<b>Nervous System Disorders</b>		
Headache	19 (3.4)	6 (2.2)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	11 (2.0)	5 (1.8)

Definitions: s.c. = subcutaneous      ew = every week      eow = every other week

### Ulcerative Colitis

Humira has been studied in 1,010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with Humira was similar to the safety profile observed in patients with Crohn's Disease.

Table 11 and Table 12 summarize adverse drug reactions reported at a rate of at least 1% in ulcerative colitis disease patients treated with Humira during induction and maintenance periods, respectively.

**Table 11. Number and Percentage of Subjects ≥ 1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Induction Study Medications in Ulcerative Colitis Studies (Studies M06-826 and M06-827)**

<b>System Organ Class (SOC)</b>	<b>HUMIRA 160/80 mg</b> N = 480 n (%)	<b>HUMIRA 80/40 mg</b> N = 130 n (%)	<b>Placebo</b> N = 483 n (%)
<b>Gastrointestinal Disorders</b>	17 (3.5)	7 (5.4)	27 (5.6)
Abdominal pain	0 (0.0)	2 (1.5)	2 (0.4)
Colitis Ulcerative	7 (1.5)	2 (1.5)	8 (1.7)
Nausea	6 (1.3)	1 (0.8)	7 (1.4)
<b>General Disorders and Administration Site Conditions</b>	44 (9.2)	8 (6.2)	34 (7.0)
Fatigue	9 (1.9)	1 (0.8)	7 (1.4)
Influenza like illness	1 (0.2)	1 (0.8)	5 (1.0)
Injection site erythema	8 (1.7)	1 (0.8)	2 (0.4)
Injection site haematoma	2 (0.4)	2 (1.5)	0 (0.0)
Injection site pain	11 (2.3)	2 (1.5)	11 (2.3)
Injection site pruritus	6 (1.3)	1 (0.8)	1 (0.2)
Injection site reaction	5 (1.0)	1 (0.8)	2 (0.4)
Pyrexia	3 (0.6)	1 (0.8)	7 (1.4)
<b>Infections and Infestations</b>	19 (4.0)	7 (5.4)	24 (5.0)
Herpes simplex	0 (0.0)	2 (1.5)	0 (0.0)
Nasopharyngitis	5 (1.0)	1 (0.8)	4 (0.8)
Oral herpes	2 (0.4)	2 (1.5)	2 (0.4)
<b>Nervous System Disorders</b>	14 (2.9)	2 (1.5)	25 (5.2)
Headache	7 (1.5)	2 (1.5)	20 (4.1)
<b>Psychiatric Disorders</b>	1 (0.2)	2 (1.5)	4 (0.8)
Anxiety	0 (0.0)	2 (1.5)	0 (0.0)
<b>Skin and Subcutaneous Tissue Disorders</b>	19 (4.0)	8 (6.2)	17 (3.5)
Erythema	5 (1.0)	2 (1.5)	1 (0.2)
Rash	2 (0.4)	2 (3.1)	1 (0.2)

**Table 12. Number and Percentage of Subjects  $\geq$  1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Double-blind Induction and Maintenance Periods of Ulcerative Colitis Studies (Studies M06-826 and M06-827)**

<b>System Organ Class (SOC)</b>	<b>HUMIRA 160/80 mg</b> N = 480 n (%)	<b>Placebo</b> N = 483 n (%)
<b>Gastrointestinal Disorders</b>	31 (6.5)	36 (7.5)

Colitis ulcerative	12 (2.5)	14 (2.9)
Nausea	9 (1.9)	9 (1.9)
<b>General Disorders and Administration Site Conditions</b>	<b>64 (13.3)</b>	<b>38 (7.9)</b>
Fatigue	10 (2.1)	8 (1.7)
Influenza like illness	3 (0.6)	5 (1.0)
Injection site erythema	15 (3.1)	3 (0.6)
Injection site pain	11 (2.3)	12 (2.5)
Injection site pruritus	9 (1.9)	2 (0.4)
Injection site reaction	11 (2.3)	2 (0.4)
Injection site swelling	5 (1.0)	0 (0.0)
Malaise	5 (1.0)	2 (0.4)
Oedema peripheral	5 (1.0)	1 (0.2)
Pyrexia	3 (0.6)	9 (1.9)
<b>Infections and Infestations</b>	<b>40 (8.3)</b>	<b>42 (8.7)</b>
Influenza	0 (0.0)	5 (1.0)
Nasopharyngitis	9 (1.9)	7 (1.4)
Upper respiratory tract infection	5 (1.0)	7 (1.4)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>12 (2.5)</b>	<b>12 (2.5)</b>
Arthralgia	5 (1.0)	4 (0.8)
<b>Nervous System Disorders</b>	<b>19 (4.0)</b>	<b>28 (5.8)</b>
Headache	10 (2.1)	22 (4.6)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>38 (7.9)</b>	<b>29 (6.0)</b>
Erythema	6 (1.3)	2 (0.4)
Pruritus	5 (1.0)	5 (1.0)
Rash	7 (1.5)	5 (1.0)

Serious adverse events resulting in hospitalizations were reported by 18% (67/379) in the Humira-treated patients compared to 26% (56/214) in the placebo group adjusted for patient years at risk.

During the double-blind controlled clinical trials, the most common ( $\geq 5\%$ ) adverse drug reactions in subjects receiving Humira 160/80 during induction were ulcerative colitis (n=35, 7.3%) and nasopharyngitis (n=26, 5.4%), and during maintenance were ulcerative colitis (n=38, 16.2%), nasopharyngitis (n=26, 11.1%), abdominal pain (n=17, 7.3%), and arthralgia (n=17, 7.3%). There were 2/480 Humira-treated patients who experienced severe leukopenia of which one

case was serious. The patient with serious leukopenia, which was considered secondary to 6-MP, had an associated viral infection.

During the double-blind controlled clinical trials, the most common serious adverse event occurring in >1 patient more often in the Humira-treated patients compared to placebo when adjusted for exposure was deep vein thrombosis reported in 2 patients (4%, 1.12 events/100 patient-years).

During the double-blind controlled clinical trials, severe adverse events reported in >1 patient occurring more often in the Humira-treated patients compared to placebo when adjusted for exposure were deep vein thrombosis reported in 3 patients (0.6%, 1.68 events/100 patient-years), and constipation, leukopenia and fatigue, which were reported in 2 patients (0.4%, 1.12 events/100 patients-years).

The most common adverse event associated with discontinuation reported in >1 subject during induction and maintenance was ulcerative colitis [n=18 (3.8%) and n=8 (3.4%), respectively].

### Hidradenitis Suppurativa

Humira has been studied in 727 adult patients with hidradenitis suppurativa in three placebo-controlled studies and one open-label extension study.

Table 13 summarizes adverse drug reactions reported at a rate of at least 1% in hidradenitis suppurativa patients treated with Humira during the placebo-controlled portion of the studies.

**Table 13. Number and Percentage of Patients  $\geq$  1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug in Controlled Hidradenitis Suppurativa Studies (Studies M10-467, M11-313 and M11-810)**

System Organ Class (SOC)	HUMIRA 40 mg Every other week N = 52 n (%)	HUMIRA 40 mg weekly N = 367 n (%)	Placebo N = 366 n (%)
<b>Eye Disorders</b>			
Cataract	1 (1.9)	0 (0.0)	0 (0.0)
Conjunctivitis	1 (1.9)	0 (0.0)	0 (0.0)
Vision blurred	1 (1.9)	1 (0.3)	0 (0.0)
<b>Gastrointestinal Disorders</b>			
Abdominal pain	1 (1.9)	1 (0.3)	0 (0.0)

Diarrhoea	1 (1.9)	8 (2.2)	3 (0.8)
Nausea	1 (1.9)	6 (1.6)	8 (2.2)
Vomiting	1 (1.9)	3 (0.8)	3 (0.8)
<b>General Disorders and Administration Site Conditions</b>			
Asthenia	0 (0.0)	1 (0.3)	5 (1.4)
Chills	1 (1.9)	0 (0.0)	1 (0.3)
Fatigue	1 (1.9)	4 (1.1)	4 (1.1)
Injection site erythema	0 (0.0)	5 (1.4)	0 (0.0)
Injection site pain	0 (0.0)	6 (1.6)	6 (1.6)
Injection site pruritus	0 (0.0)	5 (1.4)	0 (0.0)
Injection site reaction	1 (1.9)	3 (0.8)	1 (0.3)
Oedema	1 (1.9)	0 (0.0)	0 (0.0)
Pain	1 (1.9)	0 (0.0)	0 (0.0)
Pyrexia	1 (1.9)	1 (0.3)	1 (0.3)
<b>Infections and Infestations</b>			
Bronchitis	0 (0.0)	2 (0.5)	5 (1.4)
Cellulitis	0 (0.0)	0 (0.0)	4 (1.1)
Gastroenteritis	1 (1.9)	2 (0.5)	0 (0.0)
Herpes simplex	2 (3.8)	0 (0.0)	1 (0.3)
Localised infection	1 (1.9)	1 (0.3)	0 (0.0)
Nasopharyngitis	3 (5.8)	11 (3.0)	9 (2.5)
Pneumonia	1 (1.9)	0 (0.0)	3 (0.8)
Skin bacterial infection	1 (1.9)	0 (0.0)	0 (0.0)
Tooth abscess	1 (1.9)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	3 (5.8)	7 (1.9)	6 (1.6)
Urinary tract infection	0 (0.0)	3 (0.8)	4 (1.1)
Vaginal infection	1 (1.9)	0 (0.0)	0 (0.0)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	0 (0.0)	5 (1.4)	0 (0.0)
Pain in extremity	1 (1.9)	0 (0.0)	0 (0.0)
<b>Nervous System Disorders</b>			
Dizziness	1 (1.9)	6 (1.6)	1 (0.3)
Dysgeusia	1 (1.9)	2 (0.5)	0 (0.0)
Headache	4 (7.7)	17 (4.6)	11 (3.0)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			

Cough	0 (0.0)	4 (1.1)	2 (0.5)
Dyspnea	1 (1.9)	1 (0.3)	1 (0.3)
Interstitial lung disease	1 (1.9)	0 (0.0)	0 (0.0)
Nasal congestion	1 (1.9)	0 (0.0)	0 (0.0)
Oropharyngeal pain	1 (1.9)	1 (0.3)	0 (0.0)
Sneezing	1 (1.9)	0 (0.0)	0 (0.0)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Hidradenitis	2 (3.8)	11 (3.0)	16 (4.4)
Pruritus	2 (3.8)	2 (0.5)	1 (0.3)
Pruritus generalised	1 (1.9)	0 (0.0)	0 (0.0)

### Psoriasis

Humira has been studied in 1,696 patients with psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with psoriasis treated with Humira was similar to the safety profile seen in patients with rheumatoid arthritis. Safety results of the long-term open-label study are consistent with the known safety profile of Humira in other psoriasis studies. Table 14 summarizes adverse drug reactions reported at a rate of at least 1% in psoriasis patients treated with an initial dose of Humira 80 mg followed by Humira 40 mg every other week compared to placebo or methotrexate.

**Table 14. Number and Percentage of Patients  $\geq$  1% Reporting Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug in Controlled Psoriasis Studies (Studies M03-656, M04-716 and M02-528)**

<b>System Organ Class (SOC)</b>	<b>HUMIRA 80 mg x 1, then 40 mg s.c. eow N = 966 n (%)</b>	<b>Placebo + MTX N = 613 n (%)</b>
<b>Gastrointestinal Disorders</b>		
Nausea	10 (1.0)	11 (1.8)
<b>General Disorders and administration Site Conditions</b>		
Injection site reaction	29 (3.0)	9 (1.5)
Injection site irritation	16 (1.7)	6 (1.0)
Injection site pain	14 (1.5)	9 (1.5)
Fatigue	10 (1.0)	5 (0.8)
<b>Infections and Infestations</b>		
Upper respiratory infection	12 (1.2)	3 (0.5)

### Musculoskeletal and Connective Tissue Disorders

Arthralgia	10 (1.0)	3 (0.5)
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### Nervous System Disorders

Headache	19 (2.0)	14 (2.3)
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Definitions: s.c.=subcutaneous eow= every other week MTX= methotrexate

### Uveitis

Humira has been studied in 500 adult patients with uveitis in two placebo-controlled studies and one open-label extension study. The safety profile for adult patients with uveitis treated with Humira was consistent with the known safety profile of Humira. Safety results of the long-term open-label study are generally consistent with the known safety profile of Humira in the controlled uveitis studies; the exposure-adjusted incidence rates of severe and serious adverse events (including serious infections) were higher in patients who received concomitant systemic corticosteroids and immunosuppressants. Table 15 summarizes adverse drug reactions reported at a rate of at least 1% in adult patients with uveitis treated with an initial dose of Humira 80 mg followed by Humira 40 mg every other week compared to placebo.

**Table 15. Number and Percentage of Patients  $\geq$  1% Reporting Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug in Controlled Adult Uveitis Studies (Studies M10-877 and M10-880)**

System Organ Class (SOC)	HUMIRA 80 mg x 1, then 40 mg s.c. eow N = 250; n (%)	Placebo N = 250; n (%)
<b>Cardiac Disorders</b>	6 (2.4)	1 (0.4)
Palpitations	4 (1.6)	1 (0.4)
<b>Ear and Labyrinth Disorders</b>	2 (0.8)	4 (1.6)
Tinnitus	1 (0.4)	3 (1.2)
<b>Endocrine Disorders</b>	5 (2.0)	4 (1.6)
Cushingoid	3 (1.2)	3 (1.2)
<b>Eye Disorders</b>	20 (8.0)	20 (8.0)
Cataract	3 (1.2)	4 (1.6)
Cataract subcapsular	3 (1.2)	1 (0.4)
Cystoid Macular Oedema	3 (1.2)	1 (0.4)
Uveitis	3 (1.2)	6 (2.4)
<b>Gastrointestinal Disorders</b>	26 (10.4)	17 (6.8)
Abdominal discomfort	3 (1.2)	1 (0.4)
Abdominal pain upper	4 (1.6)	2 (0.8)
Dry mouth	4 (1.6)	0

Dyspepsia	3 (1.2)	2 (0.8)
Nausea	5 (2.0)	7 (2.8)
<b>General Disorders and Administration Site Conditions</b>	<b>50 (20.0)</b>	<b>38 (15.2)</b>
Fatigue	13 (5.2)	11 (4.4)
Injection site bruising	2 (0.8)	3 (1.2)
Injection site erythema	4 (1.6)	1 (0.4)
Injection site pain	10 (4.0)	12 (4.8)
Injection site rash	6 (2.4)	1 (0.4)
Injection site swelling	4 (1.6)	0
Malaise	2 (0.8)	4 (1.6)
Oedema peripheral	5 (2.0)	3 (1.2)
Peripheral swelling	3 (1.2)	0
Pyrexia	4 (1.6)	2 (0.8)
<b>Infections and Infestations</b>	<b>51 (20.4)</b>	<b>29 (11.6)</b>
Bronchitis	4 (1.6)	3 (1.2)
Influenza	1 (0.4)	3 (1.2)
Nasopharyngitis	14 (5.6)	7 (2.8)
Rash pustular	4 (1.6)	0
Upper respiratory tract infection	7 (2.8)	3 (1.2)
Urinary tract infection	7 (2.8)	5 (2.0)
<b>Investigations</b>	<b>32 (12.8)</b>	<b>18 (7.2)</b>
Alanine aminotransferase increased	8 (3.2)	1 (0.4)
Aspartate aminotransferase increased	7 (2.8)	0
Blood creatinine increased	3 (1.2)	2 (0.8)
Blood pressure increased	4 (1.6)	0
Intraocular pressure increased	5 (2.0)	3 (1.2)
Weight increased	5 (2.0)	2 (0.8)
White blood cell count increased	3 (1.2)	1 (0.4)
<b>Metabolism and Nutrition Disorders</b>	<b>12 (4.8)</b>	<b>8 (3.2)</b>
Diabetes mellitus	0	4 (1.6)
Increased appetite	1 (0.4)	4 (1.6)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>39 (15.6)</b>	<b>30 (12.0)</b>
Arthralgia	14 (5.6)	12 (4.8)
Back pain	3 (1.2)	1 (0.4)
Joint swelling	2 (0.8)	3 (1.2)

Muscle spasms	5 (2.0)	2 (0.8)
Musculoskeletal stiffness	3 (1.2)	2 (0.8)
Myalgia	4 (1.6)	3 (1.2)
Pain in extremity	8 (3.2)	1 (0.4)
<b>Nervous System Disorders</b>	29 (11.6)	16 (6.4)
Dizziness	2 (0.8)	4 (1.6)
Headache	12 (4.8)	12 (4.8)
Paraesthesia	7 (2.8)	1 (0.4)
Tremor	4 (1.6)	1 (0.4)
Psychiatric Disorders	24 (9.6)	10 (4.0)
Anxiety	4 (1.6)	0
Insomnia	13 (5.2)	7 (2.8)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	18 (7.2)	8 (3.2)
Cough	5 (2.0)	3 (1.2)
Dyspnoea	2 (0.8)	3 (1.2)
<b>Skin and Subcutaneous Tissue Disorders</b>	40 (16.0)	36 (14.4)
Acne	5 (2.0)	7 (2.8)
Alopecia	3 (1.2)	6 (2.4)
Dermatitis allergic	3 (1.2)	2 (0.8)
Eczema	3 (1.2)	1 (0.4)
Erythema	4 (1.6)	3 (1.2)
Hyperhidrosis	6 (2.4)	3 (1.2)
Pruritus	5 (2.0)	1 (0.4)
Rash	3 (1.2)	4 (1.6)
<b>Vascular Disorders</b>	12 (4.8)	10 (4.0)
Hot flush	4 (1.6)	2 (0.8)
Hypertension	4 (1.6)	3 (1.2)

Definitions: s.c. = subcutaneous eow = every other week

During the double-masked controlled clinical trials, the most common ( $\geq 5\%$ ) adverse drug reactions in adult subjects receiving Humira were nasopharyngitis (n = 44, 17.6%), arthralgia (n = 38, 15.2%), headache (n = 30, 12.0%), fatigue (n = 26, 10.4%), urinary tract infection (n = 21, 8.4%), uveitis (n = 20, 8.0%), back pain (n = 19, 7.6%), insomnia (n = 18, 7.2%), cough (n = 18, 7.2%), eye pain (n = 18, 7.2%), and upper respiratory tract infection (n = 15, 6.0%).

During the double-masked controlled clinical trials, the most common serious adverse event

occurring in >1 patient more often in the Humira-treated patients compared to placebo was pneumonia (n = 2). During the overall Humira uveitis development program, including the double-masked controlled, and open-label extension trials, the most frequently reported serious adverse event was cataract (n = 7 patients).

During the double-masked controlled clinical trials, severe adverse events reported in >1 patient occurring more often in the Humira-treated patients compared to placebo were diarrhea (n = 2) and pneumonia (n = 2). During the overall Humira uveitis development program, including the double-masked controlled, and open-label extension trials, the most common severe adverse events reported were hypertension (n = 5 patients), pneumonia, urinary tract infection, reduced visual acuity and severe vision loss (n = 4 patients each).

### **Other Common Clinical Trial Adverse Drug Reactions**

Other clinical trial adverse reactions occurring at an incidence of  $\geq 1\%$  that were observed among the various indications include:

Eye Disorders: conjunctivitis, visual impairment  
Renal and Urinary Disorders: hematuria, renal impairment

### 8.3 Less Common Clinical Trial Adverse Reactions

Infrequent serious adverse drug reactions occurring at an incidence of less than 1% in patients treated with Humira in RA Studies DE009, DE011, DE019, DE031 and DE013, JIA Study DE038, PsA Studies M02-518 and M02-570, AS Studies M03-607 and M03-606, CD Maintenance Studies M02-404 and M02-433, UC Studies M06-826 and M06-827, HS Studies M10-467, M11-313 and M11-810, Ps Studies M03-656, M04-716, and M02-528, and adult uveitis Studies M10-877 and M10-880:

Blood and Lymphatic System Disorders: agranulocytosis, anemia, eosinophilia, leukopenia, lymphadenopathy, lymphocytosis, neutropenia, pancytopenia  
Cardiac Disorders: arrhythmia supraventricular, cardiac arrest, chest pain, palpitations  
Eye Disorders: blepharitis, diplopia, eye swelling  
Gastrointestinal Disorders: abdominal pain, anal fistula, Crohn's disease, frequent bowel movements, hematochezia, hemorrhoidal hemorrhage, pancreatitis, rectal hemorrhage, small intestine obstruction

General Disorders and Administration Site Conditions:	death, non-cardiac chest pain, pyrexia
Hepatobiliary Disorders:	hepatic necrosis
Immune System Disorders:	hypersensitivity
Infections and Infestations:	abscess, abscess limb, arthritis bacterial, bronchitis, bronchopneumonia, cellulitis, cystitis, device-related infection, diverticulitis, erysipelas, escherichia sepsis, gastroenteritis, genital herpes, herpes virus infection, herpes zoster, histoplasmosis, infected skin ulcer, infection, lobar pneumonia, lower respiratory tract infection, meningitis viral, mycobacterium avium complex infection, necrotizing fasciitis, perianal abscess, pharyngitis, pneumonia, pneumonia pneumococcal, pyelonephritis, respiratory tract infection, sepsis, septic shock, sinusitis, tuberculosis, urinary tract infection, urosepsis, viral infection, wound infection
Injury, Poisoning and Procedural Complications:	postoperative wound complication
Investigations:	double-stranded DNA antibody, hepatic enzyme increased
Metabolism and Nutrition Disorders:	hyperglycemia*
Musculoskeletal and Connective Tissue Disorders:	arthritis, arthropathy, back pain, muscular weakness, musculoskeletal chest pain, osteitis, rheumatoid arthritis, systemic lupus erythematosus
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps):	basal cell carcinoma, B-cell lymphoma, breast cancer, malignant melanoma <i>in situ</i> , metastases to liver, ovarian cancer, squamous cell carcinoma, testicular seminoma (pure)
Nervous System Disorders:	clonus, hyperreflexia, hydrocephalus, hypertensive encephalopathy, intention tremor, multiple sclerosis, paresthesia, tremor, neuropathy
Pregnancy, Puerperium and Perinatal Conditions:	abortion spontaneous
Psychiatric Disorders:	confusional state
Renal and Urinary	nocturia

Disorders:

	cervical dysplasia, endometrial hyperplasia	
Reproductive System and Breast Disorders:	bronchospasm, lung infiltration, pleural effusion, pleurisy, pneumonitis, respiratory failure	cervical dyspl
Respiratory, Thoracic and Mediastinal Disorders:	psoriasis, pustular psoriasis, rash	bronchospas pneumonitis,
Skin and Subcutaneous Tissue Disorders:	arthrodesis	psoriasis, pus
Surgical and Medical Procedures:	circulatory collapse, rheumatoid vasculitis	arthrodesis
Vascular Disorders:		circulatory co
*Hyperglycemia ADR in trials were nonserious		

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#### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.

##### **Pediatric**

In the polyarticular juvenile idiopathic arthritis trial (Study DE038), 10/171 (5.8%) and 5/171 (2.9%) of patients treated with Humira developed severe elevations of ALT and aspartate aminotransferase (AST) (exceeding > 3 times the upper limit of normal [ULN] of ALT and AST, respectively). Forty-two (42)/171 (25%) developed elevations of creatine phosphokinase (CPK); with 10/171 (5.8%) patients with severe elevations.

Liver enzyme elevations were more frequent among those treated with the combination of HUMIRA and MTX than treated with Humira alone (ALT: 9.5% vs. 2.3%; AST: 5.9% vs. 0%).

No ALT or AST elevations  $\geq 3 \times$  ULN occurred in the open-label study of Humira in patients with polyarticular JIA who were 2 to <4 years of age (Study M10-444).

##### **Adult**

In controlled rheumatoid arthritis clinical trials (Studies DE009, DE011, DE019, and DE031), elevations of alanine aminotransferase (ALT) were similar in patients receiving Humira or placebo. In patients with early rheumatoid arthritis (disease duration of less than three years) (Study DE013), elevations of ALT were more common in the combination arm (Humira + methotrexate) compared to the methotrexate monotherapy arm or the Humira monotherapy arm.

In psoriatic arthritis clinical trials, elevations in ALT were more common in psoriatic arthritis patients compared with patients in rheumatoid arthritis clinical studies.

In controlled Crohn's disease clinical trials and ulcerative colitis, elevations of ALT were similar in patients receiving Humira or placebo.

In all indications, patients with raised ALT were asymptomatic and, in most cases, elevations were transient and resolved on continued treatment.

## 8.5 Post-Market Adverse Reactions

Cardiac Disorders:	myocardial infarction
Gastrointestinal Disorders:	diverticulitis, intestinal perforation, pancreatitis
General disorders and administration site conditions:	pyrexia
Hematologic Events:	thrombocytopenia <sup>†</sup>
Hepatobiliary Disorders:	liver failure, hepatitis, autoimmune hepatitis
Hypersensitivity Reactions:	anaphylaxis <sup>†</sup> , angioedema, angioneurotic edema
Immune System Disorders:	sarcoidosis
Infections:	infections in infants exposed in utero, legionellosis, listeriosis, reactivation of hepatitis B virus (HBV) <sup>†</sup>
Musculoskeletal and Connective Tissue Disorders:	lupus-like syndrome <sup>†*</sup>
Neoplasia:	hepatosplenic T-cell lymphoma (HSTCL) <sup>†</sup> , leukemia <sup>†</sup> , Merkel cell carcinoma (neuroendocrine carcinoma of the skin)

Nervous System Disorders:	cerebrovascular accident, demyelinating disorders (e.g., Guillain- Barré syndrome, optic neuritis)
Skin Reactions:	alopecia, cutaneous vasculitis, erythema multiforme, lichenoid skin reaction**, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis)*, Stevens-Johnson syndrome
Respiratory, Thoracic and Mediastinal Disorders:	interstitial lung disease (including pulmonary fibrosis), pulmonary embolism
Vascular Disorders:	deep vein thrombosis, systemic vasculitis

† See (3 SERIOUS WARNINGS AND PRECAUTIONS)

\* See (8 ADVERSE REACTIONS, 8.1 Adverse Drug Reaction Overview)

\*\* occurring in patients receiving a TNF-antagonist including HUMIRA

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

#### Serious Drug Interactions

Serious infections and sepsis, including fatalities, have been reported with the use of TNF - blocking agents, including adalimumab. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis, could predispose them to infections.

Tuberculosis and invasive opportunistic fungal infections have been observed in patients treated with TNF-blocking agents, including adalimumab.

### 9.2 Drug Interactions Overview

Population pharmacokinetic analyses with data from over 1,200 rheumatoid arthritis patients revealed that co-administration of methotrexate had an intrinsic effect on the apparent clearance of adalimumab (CL/F). See (9 DRUG INTERACTIONS, 9.3 Drug-Drug Interactions). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

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

Adalimumab has been studied in rheumatoid arthritis patients taking concomitant methotrexate. See (14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Rheumatoid Arthritis). The data do not suggest the need for dose adjustment of either adalimumab or methotrexate.

### 9.3 Drug-Drug Interactions

**Table 16. Established or Potential Drug-Drug Interactions**

Concomitant Drug Name	Clinical Comment
Abatacept	Concurrent administration of TNF-blockers and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-blockers alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of TNF-blockers and abatacept is not recommended.
Anakinra	Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent have been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including adalimumab, may also result in similar toxicities. See (7 WARNINGS AND PRECAUTIONS, General, Concurrent Administration of Biologic DMARDS or TNF-antagonists).
Cytochrome P450 (CYP450) Substrates	The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ , IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of adalimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.
Methotrexate (MTX)	When adalimumab was administered to 21 rheumatoid arthritis 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, in patients with rheumatoid arthritis. See (14.5 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG).
Other	Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In rheumatoid arthritis clinical trials where adalimumab was co-administered with commonly-used DMARDS (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics, no safety signals were seen.  There are no data on other DMARDS, and patients with prior treatment with alkylating agents (e.g., cyclophosphamide) were excluded.

Definitions: DMARDS = disease-modifying anti-rheumatic drugs; MTX = methotrexate; TNF = tumor necrosis factor

## 9.4 Drug-Food Interactions

Simlandi is administered as a subcutaneous injection. Interactions with food are therefore not applicable.

## 9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

## 9.6 Drug-Laboratory Test Interactions

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.

## 9.7 Drug-Lifestyle Interactions

Simlandi may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of Simlandi.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Adalimumab binds specifically to TNF- $\alpha$  and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF-expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF- $\beta$ ). 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 polyarticular JIA, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both pathologic inflammation and joint destruction that are hallmarks of these diseases.

Increased levels of TNF are also found in psoriasis plaques, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease. Increased levels of TNF are also found in hidradenitis suppurativa lesions.

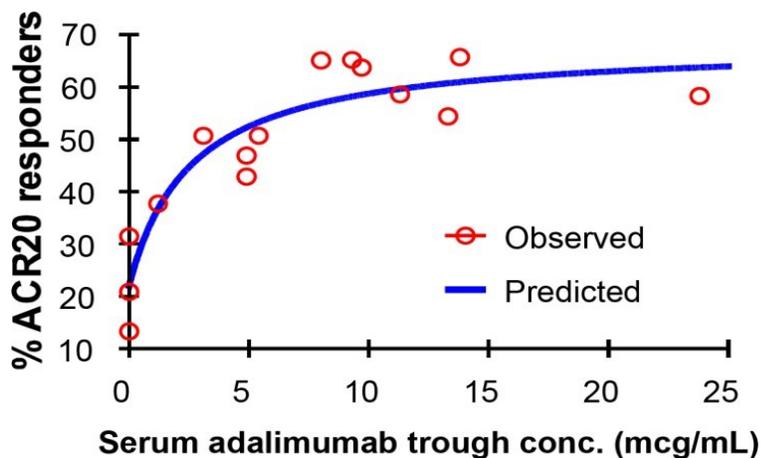
Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration [ELAM-1, VCAM-1, and ICAM-1 with a half maximal inhibitory concentration (IC50) of 1 to 2 x 10<sup>-10</sup>M].

## 10.2 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 rapid decrease in CRP levels was also observed in patients with Crohn's disease ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after Humira administration.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill Emax equation as shown in Figure 1.

**Figure 1. Adalimumab Concentration-Efficacy Relationship as Measured by the American College of Rheumatology Response Criteria (ACR 20)**



The half maximal effective concentration (EC<sub>50</sub>) estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic / pharmacodynamic modelling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase 2 and 3 trials.

### 10.3 Pharmacokinetics

#### Pediatric

Following the administration of 24 mg/m<sup>2</sup> (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular JIA who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.5 ± 5.6 mcg/mL (102% CV) Humira monotherapy and 10.9 ± 5.2 mcg/mL (47.7% CV) with concomitant MTX. In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with Humira 24 mg/m<sup>2</sup>, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 mcg/mL (101% CV) Humira monotherapy and 7.9 ± 5.6 mcg/mL (71.2% CV) with concomitant MTX.

In pediatric patients 13 to 17 years of age weighing ≥ 40 kg with severely active Crohn's disease and/or who have had an inadequate response or were intolerant to conventional therapy, the mean ± SD serum adalimumab trough concentration achieved at Week 4 was 15.7 ± 6.64 mcg/mL following administration of 160 mg Humira at Week 0 and 80 mg Humira at Week 2.

The mean ± SD adalimumab trough concentrations at Week 4 were 17.2 ± 6.67 mcg/mL (n=45)

for patients who were naïve to infliximab. The mean  $\pm$  SD adalimumab trough concentrations at Week 4 were  $14.4 \pm 6.40$  mcg/mL (n=51) for patients who were infliximab-experienced.

For patients who stayed on their randomized double-blind therapy, the mean  $\pm$  SD adalimumab trough concentration at Week 52 was  $9.43 \pm 4.98$  mcg/mL following administration of 40 mg Humira every other week and  $3.59 \pm 2.91$  mcg/mL following administration of 20 mg Humira every other week. For patients who stayed on their randomized double-blind therapy and were naïve to infliximab, the mean  $\pm$  SD adalimumab trough concentrations at Week 52 were  $12.0 \pm 3.89$  mcg/mL (n=11) and  $3.06 \pm 2.02$  mcg/mL (n=10) for the High-Dose and Low-Dose groups, respectively. For patients who stayed on their randomized double-blind therapy and were infliximab-experienced, the mean  $\pm$  SD adalimumab trough concentrations at Week 52 were  $6.85 \pm 4.72$  mcg/mL (n=11) and  $4.27 \pm 2.82$  mcg/mL (n=8) for the High-Dose and Low-Dose groups, respectively.

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, and enthesitis-related arthritis). Serum adalimumab concentrations in adolescent patients with HS receiving the recommended dosage regimen are predicted to be similar to those observed in adult subjects with HS (steady-state trough concentration of approximately 8 to 10 mcg/mL).

Adalimumab exposure in pediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other pediatric patients (N = 524) (pediatric psoriasis [age 5 to 18 years, n = 109], juvenile idiopathic arthritis [age 2 to 17 years, n = 181], and enthesitis-related arthritis [age 6 to 18 years, n = 45]). 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.

## **Adult**

The single-dose pharmacokinetics of adalimumab in rheumatoid arthritis patients were determined in several studies with intravenous doses ranging from 0.25 to 10.0 mg/kg. The distribution volume (V<sub>ss</sub>) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/h. The mean terminal half-life was approximately two weeks, ranging from 10 to 20 days across studies. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

Adalimumab mean steady-state trough concentrations of approximately 5 mcg/mL and 8 to 9 mcg/mL, were observed in rheumatoid arthritis patients without and with methotrexate, 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 subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies.

In patients with psoriatic arthritis, adalimumab mean steady-state trough concentrations of 8.5 to 12 mcg/mL and 6 to 10 mcg/mL were observed in patients with and without methotrexate, respectively.

In patients with Crohn's disease, the loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves mean serum adalimumab trough concentrations of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients who received a maintenance dose of Humira 40 mg every other week.

Population pharmacokinetic analysis in patients with Crohn's disease revealed a lower apparent clearance of adalimumab as compared to patients with rheumatoid arthritis.

In patients with ulcerative colitis, a loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieved serum adalimumab trough concentrations of  $11.8 \pm 4.0$  mcg/mL at Week 2 (n=167) and  $12.3 \pm 5.4$  mcg/mL at Week 4 (n=160). At Week 52, trough levels of  $8.0 \pm 6.1$  mcg/mL were observed in UC patients who received a maintenance dose of 40 mg Humira every other week (n=101). Trough levels at Week 52 were  $10.8 \pm 7.5$  mcg/mL in UC patients achieving remission (n=39) and  $6.2 \pm 4.2$  mcg/mL in UC patients not achieving remission (n=62).

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

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

## Absorption

The maximum serum concentration ( $C_{max}$ ) and the time to reach the maximum concentration ( $T_{max}$ ) were  $4.7 \pm 1.6$  mcg/mL and  $131 \pm 56$  hours respectively, following a single 40 mg subcutaneous administration of adalimumab to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

## Distribution

Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

## Metabolism

No formal studies have been conducted to evaluate the metabolism of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its metabolism would follow the course of other IgG molecules.

## Excretion

No formal studies have been conducted to evaluate the excretion of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its excretion would follow the course of other IgG molecules.

## 10.4 Special Populations and Conditions

### Pediatrics

Adalimumab has not been studied in pediatric patients with polyarticular JIA less than 2 years of age or in patients with a weight <10 kg. The majority (102/192) of pediatric patients with Crohn's disease studied were 13 to 17 years of age weighing  $\geq 40$  kg.

There are no clinical trials with adalimumab in adolescent patients (12 to 17 years of age) with hidradenitis suppurativa (HS). Use of adalimumab in adolescent patients is supported by evidence from adequate and well-controlled studies of Humira in adult HS patients with supplemental pharmacokinetic modeling and simulation. The use of adalimumab has not been established in patients younger than 12 years of age with HS.

Adalimumab has not been studied in pediatric patients with uveitis less than 2 years of age. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

### **Geriatrics**

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward lower clearance with increasing age in patients aged 40 to > 75 years of age.

### **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 Insufficiency**

No pharmacokinetic data are available in patients with hepatic impairment.

### **Renal Insufficiency**

No pharmacokinetic data are available in patients with renal impairment.

### **Disease States**

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. Population pharmacokinetic analyses predicted minor increases in apparent clearance in patients receiving doses lower than the recommended dose and in patients with high rheumatoid factor or C-reactive protein (CRP) concentrations. These increases are not likely to be clinically important. See (**4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, Disease States**).

## 11 STORAGE, STABILITY AND DISPOSAL

Simlandi must be refrigerated between 2 and 8°C. Store in original carton until time of administration. **DO NOT FREEZE**. Protect from light. Do not use beyond the expiration date.

Once removed from the refrigerator, Simlandi in either the SD Syringe or the Autoinjector must be used within 14 days or must be discarded.

## 12 SPECIAL HANDLING INSTRUCTIONS

Simlandi does not contain preservatives in either the needle guard Syringe or the Autoinjector.

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

A puncture-resistant container for the disposal of needles, syringes and the Autoinjector should be used. Patients or caregivers should be instructed in the handling technique as well as proper syringe and needle disposal and be cautioned against reuse of any of these items.

A healthcare professional (e.g., doctor, nurse or pharmacist) should be consulted for instructions as to how to properly dispose of used items. Special provincial or local laws regarding the proper disposal of needles, syringes and the Autoinjector and should be followed and **NEVER** be thrown in the household trash or recycling bin.

- Used needles, syringes and the Autoinjector should be placed in a container made especially for this purpose (sharps container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labelled "Used Syringes". Glass or clear plastic containers should not be used.
- The container should always be kept out of the reach of children.
- When the container is about two-thirds full, the cap or lid should be taped down so that it does not come off. The container should be disposed of as instructed by a healthcare professional. **CONTAINERS SHOULD NEVER BE THROWN IN THE HOUSEHOLD TRASH OR RECYCLING BIN.**
- Unless otherwise instructed by a healthcare professional, used alcohol pads (not included in the Simlandi carton) may be placed in the trash. Dose trays and covers may be recycled.

## PART II: SCIENTIFIC INFORMATION

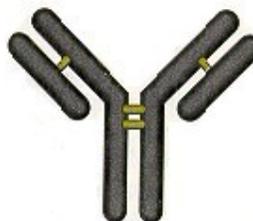
### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper Name: adalimumab

Chemical Name: Not applicable. Adalimumab is not a chemical. It is an immunoglobulin (recombinant human IgG1 monoclonal antibody).

Molecular formula and Molecular Mass:  $C_{6428}H_{9912}O_{987}N_{1694}S_{46}$   
Total apparent molecular weight of 148 kilodaltons (kDa), as determined by Q-TOF and SDS-PAGE analysis



Structural formula:

Physicochemical Properties:

Adalimumab (AVT02) is an IgG antibody composed of two kappa light chains, each with a molecular weight of approximately 23 kDa and two IgG1 heavy chains, each with a molecular weight of approximately 51 kDa for a total apparent molecular weight of 148 kDa, as determined by LC-MS.

The solution of adalimumab is clear and colourless, with a pH of 5.2.

Product characteristics:

Adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF).

Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

One comparative bioavailability study and one comparative clinical study were conducted to support the similarity between Simlandi (AVT02) and the reference biologic drug, Humira:

- A randomized, double-blind, comparative bioavailability study (Study # AVT02-GL-101) in healthy subjects
- A controlled efficacy and safety study (Study # AVT02-GL-301) in patients with psoriasis (PsO).

The AVT02-GL-301 study is a multi-center, randomized, double blind study that includes 412 patients with moderate to severe plaque psoriasis randomized 1:1 to AVT02 and Humira. The study was designed to rule out any clinically meaningful differences between AVT02 and Humira.

The patient population studied in AVT02-GL-301 trial consisted of adult male and female patients with moderate-to-severe plaque psoriasis involving a body surface area (BSA) of at least 10%, a minimal PASI of 12 and an investigator global assessment (IGA) of at least moderate severity (score 3). Eligible patients had to have previously received at least one phototherapy or systemic therapy for psoriasis and is a candidate to receive systemic therapy in the opinion of the investigator. Randomization at baseline was stratified by presence or absence of PsA and prior use of biologic therapy for the treatment of PsO or PsA.

The primary efficacy endpoint was percent improvement in PASI from baseline to Week 16.

The 95% CI of the adjusted treatment difference remained within the predefined equivalence margin of [-10%, 10%].

The study has been completed and the last patient last visit has been achieved on 20<sup>th</sup> July 2020.

**NOTE:** The research designation for Simlandi is AVT02, which will be used throughout this section to denote the proposed biosimilar drug.

**Table 17. Summary of Trial Design and Patient Demographics**

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (N)	Mean age in yrs. (Range)	Sex
AVT02-GL-101 (Safety Population)	Multi-centre, randomized, double-blind, 3 arm, parallel study to compare the PK of AVT02 with EU-Humira and US-Humira	40 mg s.c. Single dose AVT02 EU Humira US Humira	Overall: 390 AVT02: 130 EU Humira: 129 US Humira: 131	Overall: 27.8 (18 – 53)  AVT02: 27.1 (18 – 53)  EU Humira: 28.5 (18 – 53)  US Humira: 27.8 (18 – 52)	Overall: Male: 175 (44.9) Female: 215 (55.1)  AVT02: Male: 57 (43.8) Female: 73 (56.2)

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (N)	Mean age in yrs. (Range)	Sex
					EU Humira: Male: 55 (42.6) Female: 74 (57.4)  US Humira: Male: 63 (48.1) Female: 68 (51.9)

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (N)	Mean age in yrs. (Range)	Sex
AVT02-GL-301 Safety and efficacy study and measure of steady state serum trough levels and immunogenicity	<p><u>Stage 1:</u> Multi-centre, double-blind, randomized parallel group, active control (vs. Humira)</p> <p><u>Stage 2:</u> Double-blind, Long-term Efficacy and Safety</p> <p><u>Stage 3:</u> Safety follow-up to Week 54 (the EOS)</p>	<p>Group 1: <u>Initial:</u> Simlandi loading dose of 80 mg s.c. x 1 week <u>Week 2-Week 14:</u> 40 mg s.c. EOW</p> <p><u>Group 2:</u> <u>Initial:</u> loading dose of Humira 80 mg s.c. x 1 week <u>Week 2-Week 14:</u> 40 mg s.c. EOW</p> <p><u>Week 16 – Week 54:</u> Group 1: AVT02 40 mg s.c. EOW</p> <p>Group 2: 2A: AVT02 40 mg EOW 2B: Humira 40 mg EOW</p> <p>Week 50-Week 54</p>	<p>Overall: 412</p> <p>AVT02: 205</p> <p>EU- Humira: 207</p> <p>AVT02/AVT02: 197</p> <p>Humira/AVT02: 97</p> <p>Humira/Humira: 98</p>	<p>Overall: 42.8(18-71)</p> <p>AVT02: 42.5 (20-71)</p> <p>EU- Humira: 43.2 (18-70)</p> <p>AVT02/AVT02: 42.4 (20-71)</p> <p>Humira/AVT02: 43.6 (22-69)</p> <p>Humira/Humira: 42.3 (18-70)</p>	<p>Male: 254 Female: 158</p>
<p>Definitions: s.c. = subcutaneous      EOW = every other week      PsO = psoriasis      EU = European Union</p> <p>PASI = Psoriasis Area and Severity Index      EOS = End of Study</p>					

Similar efficacy and safety of AVT02 to HUMIRA were confirmed in a multi-center, randomized, double blind study that included 412 patients with moderate to severe chronic plaque psoriasis.

## 14.2 Study Results

The percent improvement scores over time was similar for both AVT02 and the reference biologic.

**Table 18. Percent Improvement in PASI from BL to Week 16 in PsO Patients (Study AVT02-GL-301)**

Parameter	AVT02	Humira
N	205	207
LS Mean (SE)	89.2 (1.61)	86.9 (1.65)
LS Mean Difference (SE) (AVT02 vs. Humira)	2.3 (1.84)	
95% CI	-1.31, 5.91	
Definitions: PASI = Psoriasis Area and Severity Index LS = least squares SE = standard error BL = baseline CI = confidence interval <ul style="list-style-type: none"> <li>The primary endpoint analysis is based on Full Analysis Set. The LS means, difference in LS means between treatment groups together with two-sided 95% CI are from the ANCOVA model using treatment, presence or absence of psoriatic arthritis, and prior biologic treatment of psoriasis or psoriatic arthritis as factors, and baseline PASI score as covariate. Missing data is imputed using LOCF method for subjects with post-BL assessment. A predefined equivalence margin of (-10%, 10%) is used for demonstrating the therapeutic equivalence of AVT02 and Humira.</li> </ul>		

### 14.3 Comparative Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologics drug

### 14.4 Comparative Bioavailability Studies

**Table 19. Summary of PK Similarity Assessment of AVT02 and EU-Humira (Study AVT02-GL-101)**

<b>Adalimumab</b> <b>(1 x 40 mg)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV%)</b>
---

<b>Parameter (Units)</b>	<b>Test: AVT02</b>	<b>Reference: EU-Humira†</b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>last</sub> (hr*ug/mL)	2010 2208 (41.9%)	1809 2021 (44.9%)	111.1	100.8 – 122.6
AUC <sub>inf</sub> (hr*ug/mL)	2149 2413 (47.4%)	1977 2216 (47.7%)	108.7	98.0 – 120.5
C <sub>max</sub> (ug/mL)	3.34 3.59 (36.1%)	3.24 3.46 (37.9%)	103.1	95.3 – 111.6
T <sub>max</sub> (h)	192 (46.7%)	168 (44.6%)		
T <sub>1/2</sub> (h)	251.0 (85.9%)	221.1 (81.3%)		

1. Analysis of variance of log-transformed PK parameter with treatment only as fixed effect is used in the analysis.
2. Median (CV%) presented for T<sub>max</sub>.
3. For AVT02: n = 129 for C<sub>max</sub>, AUC<sub>last</sub> and T<sub>max</sub>. n = 128 for AUC<sub>inf</sub> and T<sub>1/2</sub>.
4. For EU-Humira: n = 128 for C<sub>max</sub>, AUC<sub>last</sub> and T<sub>max</sub>. n = 124 for AUC<sub>inf</sub> and T<sub>1/2</sub>.

†: Reference product was purchased in Germany from the Manufacturer of Abbvie Deutschland GmbH&Co.KG, Knollstrasse, 67061, Ludwigshafen, Germany

## 14.5 Immunogenicity

As part of Study AVT02-GL-101, anti-drug antibodies (ADA's) and neutralizing antibodies (nAb) to adalimumab were detected over time in >95% and in >80% of healthy subjects, respectively, during the 64-day study period. The time of onset and frequencies of ADA and nAb development were similar in all three treatment groups and progressively increased over the duration of the study. On day 64, the frequency of ADA and nAb was comparable for AVT02, EU-Humira and US-Humira. As expected, there appeared to be a lag time between positive detection of ADAs and formation of nAbs in all three treatment groups.

Immunogenicity was also measured in the pivotal comparative study (Study AVT02-GL-301) in randomized PsO patients who had at least 1 evaluable post-dose immunogenicity result. ADAs and nAbs were detected in the majority of patients (>90%) during the course of treatment with both AVT02 and EU-Humira. The time of onset and frequencies were similar. As expected, adalimumab C<sub>trough</sub> levels with both AV02 and EU-Humira were higher in patients who were ADA-negative than in the overall population.

## 14.6 Clinical Trials – Reference Biologic Drug

### 14.6.1 Rheumatoid Arthritis

#### Study Demographics and Trial Design

The efficacy and safety of HUMIRA (adalimumab) were assessed in five randomized, double-blind studies in patients ≥ 18 years of age with active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had at least six swollen and nine tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (12.5 to 25 mg, Studies DE009, DE019 and DE013), or as monotherapy (Studies DE011 and DE013), or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study DE031).

Table 20 summarizes the controlled clinical trials that were done in patients with active rheumatoid arthritis.

**Table 20. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Rheumatoid Arthritis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
DE009 (RA I)	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA 20 mg, 40 mg, or 80 mg; eow	200	54.8 ± 11.9	75.5
		Placebo Subcutaneous 24 weeks	60	55.2 ± 10.9	83.3
DE011 (RA II)	Multicenter, double-blind, randomized,	HUMIRA 20 mg or 40 mg; ew or eow	434	53.0 ± 12.3	77.4
		Placebo	110	53.5 ± 13.2	77.3

	placebo-controlled	Subcutaneous 26 weeks			
DE019 (RA III)	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA 20 mg ew or 40 mg eow	419	56.2 ± 12.1	75.9
		Placebo	200	55.6 ± 12.0	73.0
	Open-label extension	Subcutaneous 52 weeks HUMIRA 40 mg eow up to 10 years	457	55.7 ± 12.02	74.7
DE031 (RA IV)	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA 40 mg eow	315	55.2 ± 12.7	80.0
		Placebo Subcutaneous	315	55.7 ± 12.4	79.7
		24 weeks			
DE009, DE011, DE019, DE031 Combined	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA	1368	54.7 ± 12.3	77.3
		Placebo	685	55.3 ± 12.3	77.7
DE013	Phase 3,	HUMIRA 40 mg eow	274	52.1 ± 13.5	77.4
(RA V)	multicenter, double-blind, active comparator- controlled, parallel-group	HUMIRA 40 mg eow + MTX ew	268	51.9 ± 14.0	72.0
		MTX ew	257	52.0 ± 13.1	73.9
		Subcutaneous and oral, 104 weeks			

Definitions: ew = every week; eow = every other week; MTX = methotrexate

Mean ages across the four studies ranged from 53.0 years (HUMIRA group, Study DE011) to 56.2 years (HUMIRA group, Study DE019). The mean age in Study DE013 was 51.9 years (HUMIRA + methotrexate group) to 52.0 years (methotrexate group). Mean weight ranged from 68.5 kg (HUMIRA group, Study DE011) to 80.3 kg (placebo group, Study DE019). The mean weight in Study DE013 was 74.4 kg (HUMIRA group) to 76.8 kg (HUMIRA + methotrexate group). As expected, based on the demographics of the disease, patients were predominantly female, with the percentage of female patients ranging from 73.0% (placebo group, Study DE019) to 83.3% (placebo group, Study DE009). Similarly, the percentage of females in Study DE013 ranged from 72.0% (HUMIRA + methotrexate group) to 77.4% (HUMIRA group). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 75.0% (placebo group, Study DE009) to 99.1% (placebo group, Study DE011). The

percentage of Caucasian patients in Study DE013 ranged from 93.3% (HUMIRA + methotrexate group) to 94.2% (methotrexate group). The high percentage of Caucasian patients in Study DE011 was consistent with the populations of the geographic regions in which this study was conducted (i.e., Europe, Canada, and Australia). Overall, the demographic characteristics of the study patients were fairly representative of rheumatoid arthritis in the general population. There were no notable differences between the studies in any of the demographic characteristics analyzed.

## **Description of Clinical Studies**

HUMIRA was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for up to 10 years. The efficacy and safety of HUMIRA were assessed in five randomized, double-blind, well-controlled studies.

Study DE009 evaluated 271 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one but no more than four DMARDs and had inadequate response to methotrexate.

Study DE011 evaluated 544 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given by subcutaneous injection as monotherapy every other week or weekly for 26 weeks.

Study DE019 evaluated 619 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to Week 52. Study DE019 had an additional primary endpoint at Week 52 of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to ten years. 202 patients completed 10 years of the study; the efficacy demonstrated at 5 years (reduction in signs and symptoms of RA, improvement in physical function, inhibition of structural joint damage, and rates of clinical response including remission) was maintained through 10 years with continued HUMIRA in these patients. For efficacy results in these patients, see **14 CLINICAL TRIALS-REFERENCE BIOLOGIC DRUG**. For a description of safety in these patients, see **8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview**).

Study DE031 assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were either DMARD-naïve or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study DE013 evaluated 799 patients with moderate to severely active early rheumatoid arthritis (disease duration less than three years) who were  $\geq 18$  years old and methotrexate naïve. This study compared the efficacy of HUMIRA + methotrexate combination therapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis. Patients were randomized to receive HUMIRA 40 mg every other week + methotrexate combination therapy, HUMIRA 40 mg every other week monotherapy, or methotrexate given weekly, for 104 weeks.

## Study Results

### Clinical response: Studies DE009, DE011 and DE019

The percent of HUMIRA-treated patients achieving ACR 20/50/70 responses was consistent across all three trials. The results of the three trials are summarized in Table 21.

**Table 21. ACR Responses in Placebo-Controlled Trials (Percent of Patients)**

Response		Study DE009*		Study DE011*			Study DE019*	
		Placebo + MTX N = 60	HUMIRA 40 mg eow + MTX N = 63	Placebo N = 110	HUMIRA 40 mg eow N = 113	HUMIRA 40 mg ew N = 103	Placebo + MTX N = 200	HUMIRA 40 mg eow + MTX N = 207
ACR 20	6 months	13.3%	65.1%**	19.1%	46.0%**	53.4%**	29.5%	63.3%**
	12 months	NA	NA	NA	NA	NA	24.0%	58.9%**
ACR 50	6 months	6.7%	52.4%**	8.2%	22.1%**	35.0%**	9.5%	39.1%**
	12 months	NA	NA	NA	NA	NA	9.5%	41.5%**
ACR 70	6 months	3.3%	23.8%**	1.8%	12.4%**	18.4%**	2.5%	20.8%**
	12 months	NA	NA	NA	NA	NA	4.5%	23.2%**

\*Study DE009 at Week 24, Study DE011 at Week 26 and Study DE019 at Weeks 24 and 52

\*\* p<0.01 for Humira vs. placebo

Definitions: MTX = methotrexate; ACR = American College of Rheumatology

The results of the components of the ACR response criteria for Studies DE011 and DE019 are shown in Table 22. ACR response rates and improvement in all components of ACR response were maintained to Week 104. Over the two years in Study DE019, 24% of HUMIRA patients receiving 40 mg every other week achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to five years with continuous HUMIRA treatment in the open-label

portion of Study DE019.

**Table 22. Components of ACR Response in Studies DE011 and DE0019**

Parameter (median)	Study DE011				Study DE019					
	Placebo N = 110		HUMIRA 40 mg eow N = 103		Placebo + MTX N = 200			HUMIRA 40 mg eow + MTX N = 207		
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Number of tender joints (Scale 0 to 68)	35	26	31	16*	26	15	15	24	8.0*	6.0*
Number of swollen joints (Scale 0 to 66)	19	16	18	10*	17	11	11	18	5.0*	4.0*
Physician global assessment disease activity <sup>†</sup>	7	6.1	6.6	3.7*	6.3	3.5	3.8	6.5	2.0*	1.6*
Patient global assessments disease activity <sup>†</sup>	7.5	6.3	7.5	4.5*	5.4	3.9	4.3	5.2	2.0*	1.8*
Pain <sup>†</sup>	7.3	6.1	7.3	4.1*	6	3.8	4.6	5.8	2.1*	1.9*
Disability index(HAQ) <sup>‡</sup>	2	1.9	1.9	1.5*	1.5	1.25	1.25	1.5	0.75*	0.75*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1	0.9	0.9	1	0.40*	0.40*

<sup>†</sup> Visual analogue scale; 0 = best; 10 = worst

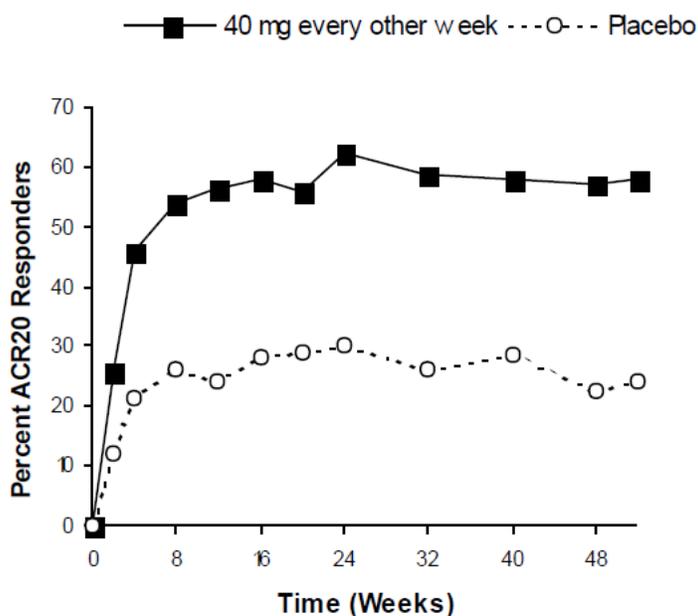
<sup>‡</sup> Disability index of the Health Assessment Questionnaire (HAQ); 0 = best; 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

\*p<0.001 for HUMIRRA versus placebo, based on mean change from baseline

Definitions: MTX = methotrexate; CRP = C-reactive protein

The time course of ACR 20 response for Study DE019 is shown in Figure 2. In Study DE019, 85% of patients with ACR 20 responses at Week 24 maintained the response at Week 52. The time course of ACR 20 response for Studies DE009 and DE011 were similar.

**Figure 2. Study DE019 ACR 20 Responses Over 52 Weeks**



In the open-label extension for Study DE019, durable and sustained ACR 20, 50 and 70 responses have been observed through 5 and 10 years. Of 207 patients, 114 patients continued on HUMIRA 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 HUMIRA 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.

### Study DE031

In Study DE031, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at Week 24 compared to 35% on placebo plus standard of care ( $p < 0.001$ ). No unique adverse reactions related to the combination of HUMIRA and other DMARDs were observed.

In all four studies, HUMIRA-treated patients achieved ACR 20/50/70 responses faster and more

often than placebo-treated patients. In Study DE009, there was a statistically significant difference in ACR 20 responses at Week 1 (first study visit) between patients treated with HUMIRA (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in Studies DE011, DE019 and DE031 at Week 2 (first study visit) between patients treated with HUMIRA (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.

### Study DE013

In Study DE013, for early rheumatoid arthritis patients who were methotrexate naïve, the combination therapy with HUMIRA + methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy at Week 52, and responses were sustained at Week 104. The clinical responses for Study DE013 are presented in Table 23.

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

Over the two-year study, 48.5% of patients who received HUMIRA + methotrexate combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ( $p < 0.001$ ).

**Table 23. Clinical Responses in Study DE013 (All Randomized Subjects)**

Response		MTX <sup>a</sup> N = 257 (%)	HUMIRA <sup>b</sup> N = 274 (%)	HUMIRA + MTX N = 268 (%)
ACR 20	Week 52	62.6	54.4	72.8
	Week 104	56.0	49.3	69.4
ACR 50	Week 52	45.9	41.2	61.6
	Week 104	42.8	36.9	59.0
ACR 70	Week 52	27.2	25.9	45.5
	Week 104	28.4	28.1	46.6
Major Clinical Response <sup>c</sup>		27.2	24.5	48.5

- a.  $p < 0.05$  for HUMIRA + MTX versus MTX for ACR 20  
 $p < 0.001$  for HUMIRA + MTX versus MTX for ACR 50 and 70 and Major Clinical Response
- b.  $p < 0.001$  for HUMIRA + MTX versus HUMIRA
- c. Major Clinical response is achieving ACR 70 response for a continuous six-month period  
Definitions: MTX = methotrexate; ACR = American College of Rheumatology

At Week 52 and Week 104 of treatment in Study DE013, HUMIRA + methotrexate combination

therapy was superior to methotrexate monotherapy in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis, as demonstrated by the number of patients who achieved clinical remission [disease activity score (DAS28) < 2.6] at Week 52 and change from baseline in DAS28 at Week 52 and Week 104.

DAS28 responses for Study DE013 are presented in Table 24.

**Table 24. Change in DAS28 from Baseline at Weeks 52 and 104 n Study DE013 (All Randomized Subjects)**

DAS28		MTX N = 257	HUMIRA N = 274	HUMIRA + MTX N = 268
Week 52	n	184	185	206
	Baseline (mean)	6.3	6.4	6.3
	Change at Week 52 (mean ± SD)	-2.8 ± 1.4 <sup>a</sup>	-2.8 ± 1.5 <sup>b</sup>	-3.6 ± 1.3
	% of subjects in remission (DAS28 < 2.6) at Week 52	20.6% <sup>a</sup>	23.4% <sup>b</sup>	42.9%
Week 104	n	161	158	191
	Baseline (mean)	6.3	6.3	6.3
	Change at Week 104 (mean ± SD)	-3.1 ± 1.4 <sup>a</sup>	-3.2 ± 1.4 <sup>b</sup>	-3.8 ± 1.3
	% of subjects in remission (DAS28 < 2.6) at Week 104	24.9%	25.2%	49.3%

a. P<0.001 fro HUMIRA + MTX versus MTX

b. P< 0.001 for HUMIRA + MTX versus HUMIRA

Definitions: NTX = methotrexate; DAS = disease activity score; SD = standard deviation

### Radiographic Response

In Study DE019, where HUMIRA-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score at Month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The 12-month results are shown in **Table 25**. HUMIRA + methotrexate-treated patients demonstrated less radiographic progression than patients receiving methotrexate alone at Week 52.

**Table 25. Radiographic Mean Changes Over 12 Months in Study DE019 with Background Methotrexate**

LOCF	Placebo + MTX N = 200	HUMIRA <sup>a</sup> + MTX N = 207	HUMIRA <sup>a</sup> + MTX and Placebo + MTX (95% CI <sup>**</sup> )	p-value
Change in Modified Total Sharp Score (Mean)	2.7	0.1	-2.6 (1.4, 3.8)	< 0.001*
Change in Erosions (Mean)	1.6	0	-1.6 (0.9, 2.2)	< 0.001
Change in JSN Score (Mean)	1	0.1	-0.9 (0.3, 1.4)	0.002

a. 40 mg administered every other week

\*Based on analysis of ranked ANCOVA

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

Definition(s): MTX = methotrexate; LOCF = last observation carried forward;  
JSN = joint space narrowing; CI = confidence interval

Data from the open-label extension of Study DE019 indicate that 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 HUMIRA every other week were evaluated radiographically. Among those, 59.3% (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 HUMIRA every other week were evaluated radiographically. Among those, 50.6% (40 patients) showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

In Study DE013, HUMIRA-treated patients had a mean duration of rheumatoid arthritis of less than nine months and had not previously received methotrexate. Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score (TSS). The Week 52 results are shown in Table 26. A statistically significant difference for change in modified total Sharp score, erosion score and JSN were observed at Week 52 and maintained at Week 104.

**Table 26. Radiographic Mean Change (95% Confidence Interval) in Study DE013**

<b>Response</b>		<b>MTX<sup>a</sup></b> <b>N = 257</b>	<b>HUMIRA<sup>a,b</sup></b> <b>N = 274</b>	<b>HUMIRA + MTX</b> <b>N = 268</b>
Week 52	Total Sharp Score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion Score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN Score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
Week 104	Total Sharp Score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion Score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN Score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)

a.  $p < 0.001$  for HUMIRA + MTX versus MTX at Week 52 and Week 104 and for HUMIRA + MTX versus HUMIRA at Week 104

b.  $< 0.01$  for HUMIRA + MTX versus HUMIRA at Week 52

Definitions: MTX = methotrexate; JSN = Joint Space Narrowing

The percentage of patients without progression (change from baseline in modified total Sharp score  $\leq 0.5$ ) was significantly higher with HUMIRA + methotrexate combination therapy compared to methotrexate monotherapy at Week 52 (63.8 and 37.4% respectively,  $p < 0.001$ ) and Week 104 (61.2 and 33.5% respectively,  $p < 0.001$ ).

### Quality of Life and Physical Function Response

In Studies DE009, DE011, DE019 and DE031, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ) from baseline to the end of study, and significantly greater improvement than placebo in the health outcomes as assessed by the Short Form Health Survey (SF-36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study DE019, the mean (CI) improvement in HAQ from baseline at Week 52 was -0.60 (-0.65, -0.55) for the HUMIRA patients and -0.25 (-0.33, -0.17) for placebo + methotrexate ( $p < 0.001$ ) patients. Eighty-two percent (82%) of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ at Week 52 in the double-blind portion of the study maintained that improvement through Week 104 of open-label treatment, and a similar proportion of patients maintained this response through Week 260 (five years) and Week 520 (10 years). After five years, the proportion of subjects who were HAQ responders at the 0.22, 0.50, 0.75 and 1.0 levels were 76.5, 60.0, 47.5 and 30.8% respectively. A total of 149 patients who received HUMIRA for 10 years were assessed for HAQ. After 10 years, the proportions of patients who were HAQ responders at the 0.22, 0.50, 0.75 and 1.0 levels were 73.8 (n = 110), 57.0 (n = 85), 44.3 (n = 66) and 26.2% (n = 39) respectively. Improvement in SF-36 was measured and

maintained up to Week 156 (3 years).

In Study DE013, the active comparator-controlled study in early rheumatoid arthritis, the improvement in the HAQ disability index, and the physical component of the SF -36, showed greater improvement ( $p < 0.001$ ) for the HUMIRA + methotrexate combination therapy versus the methotrexate monotherapy at Week 52, which was maintained through Week 104.

At Week 52 and Week 104 of treatment, 69.4% (186/268) and 63.8% (171/268) of subjects, respectively, treated with HUMIRA + methotrexate combination therapy had a decrease (i.e., improvement) in the disability index of the HAQ of  $\geq 0.3$  units. In comparison, 61.5% (158/257;  $p = 0.562$ ) and 53.3% (137/257;  $p = 0.0146$ ) of subjects treated with methotrexate monotherapy, and 55.1% (151/274;  $p < 0.001$ ) and 48.2% (132/274;  $p < 0.001$ ) of subjects treated with HUMIRA monotherapy had a decrease in the disability index of the HAQ of  $\geq 0.3$  units at Weeks 52 and 104, respectively.

#### 14.6.2 Psoriatic Arthritis

### **Description of Clinical Studies**

The efficacy of HUMIRA was assessed in two randomized, double-blind, placebo-controlled studies in 413 patients. The primary study treated 313 adult patients with moderately to severely active psoriatic arthritis who had an inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy. Of the 313 treated in this study, 158 (50.5%) were described as taking methotrexate at the time of randomization. Doses of HUMIRA 40 mg every other week were administered for 24 weeks. Table 27 summarizes the controlled clinical trials that were done in patients with active psoriatic arthritis.

**Table 27. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriatic Arthritis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
M02-518 (PsA I)	Multicenter, double-blind, randomized, placebo-controlled, stratified by MTX use and extent of psoriasis ( $\geq 3\%$ or $< 3\%$ BSA)	HUMIRA 40 mg eow	151	48.6 $\pm$ 12.5	43.7
		Placebo Subcutaneous 24 weeks	162	49.2 $\pm$ 11.1	45.1
M02-570 (PsA II)	Multicenter, double-blind, randomized, placebo-controlled, stratified by DMARD use (yes, no)	HUMIRA 40 mg eow	51	50.4 $\pm$ 11.0	43.1
		Placebo Subcutaneous 24 weeks	49	47.7 $\pm$ 11.3	49.0
M02-518 and M02-570	Multicenter, double-blind, randomized, placebo-controlled, stratified with MTX (M02-518), and DMARDs (M02-570)	HUMIRA 40 mg eow Placebo Subcutaneous 24 weeks	202 211	49.1 $\pm$ 12.2 48.9 $\pm$ 11.2	43.6 46.0

Definition(s): eow = every other week; MTX = methotrexate; BSA = body surface area; DMARDs = disease-modifying anti-rheumatic drugs

Mean ages across the two studies ranged from 47.7 years (placebo group, Study M02-570) to 50.4 years (HUMIRA group, Study M02-570). Mean weight ranged from 85.5 kg (placebo group, Study M02-518) and 91.5 kg (HUMIRA group, Study M02-570). The percentage of females ranged from 43.1 % (HUMIRA group, Study M02-570) and 45.1% (placebo group, Study M02-518). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 93.8% (placebo group, Study M02-518) to 98.0% (HUMIRA group, Study M02-570). There were no notable differences between the studies in any of the demographic characteristics analyzed. Upon completion of both studies, 383 patients enrolled in an open-label extension study (Table 28) in which HUMIRA 40 mg is administered every other week.

**Table 28. Summary of Open-Label Clinical Trials Evaluating Long-Term Safety and Efficacy in Patients with Psoriatic Arthritis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range) (Years)	Gender (% Female)
M02-537 (PsA III)	Multicenter, open-label, multi-national continuation of studies M02-518 and M02-570.	HUMIRA 40 mg eow Subcutaneous 120 weeks or when commercially available, whichever is later	395	49.0 ± 11.7 (20.0 to 88.0)	44.6

Study M02-518 evaluated the effectiveness and safety of HUMIRA either alone or in combination with concomitant methotrexate in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to NSAID therapy.

Study M02-570 evaluated the effectiveness and safety of HUMIRA either alone or in combination with any concomitant DMARD (except cyclosporine or tacrolimus) in subjects with moderately to severely active psoriatic arthritis who have had an inadequate response to DMARD therapy.

Study M02-537 evaluates the long-term safety and efficacy of HUMIRA 40 mg every other week in the treatment of psoriatic arthritis in subjects who completed the controlled Studies M02-518 and M02-570.

## **Study Results**

### **Clinical Response**

#### **Studies M02-518, M02-570 and M02-537**

HUMIRA was superior to placebo in all measures of disease activity ( $p < 0.001$ ) as shown in Table 29 and Table 30. Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent at the time of the first visit (Week 2), significant at Week 12, and maintained at Week 24 in the double-blind period of the study. Table 31 presents data from the ongoing open-label study regarding improvement in arthritic manifestations of psoriatic arthritis.

Patients with a psoriasis involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. In these patients, the skin lesions of psoriasis were improved with HUMIRA, relative to placebo, as measured by the PASI. Results were similar with and without concomitant methotrexate therapy. The small number of patients with moderate to severe psoriasis requires additional data to adequately assess the PASI response.

**Table 29. ACR and PASI Response in Placebo-Controlled Psoriatic Arthritis Study (Study M02-518) (Percent of Patients)**

Response		Placebo N = 162	HUMIRA <sup>†</sup> 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%
Response		Placebo N = 69	HUMIRA <sup>†</sup> N = 69
PASI 50	Week 12	15%	72%
	Week 24	12%	75%
PASI 75	Week 12	4%	49%
	Week 24	1%	59%

<sup>†</sup>p < 0.001 for all comparisons between HUMIRA and placebo

Definition(s): ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index

**Table 30. Components of Disease Activity in Psoriatic Arthritis (Study M02-518)**

Parameter mean (median)	Placebo <sup>†</sup> N = 162		HUMIRA <sup>†‡</sup> N = 151	
	Baseline	Week 24	Baseline	Week 24
Number of tender joints (Scale 0 to 78)	25.8 (23.0)	22.3 (17.0)	23.3 (19.0)	11.8 (5.0)
Number of swollen joints (Scale 0 to 76)	14.6 (11.0)	12.1 (8.0)	13.4 (10.0)	7.6 (3.0)
Physician global assessment <sup>a</sup>	53.2 (53.0)	46.0 (48.0)	53.5 (54.0)	21.4 (16.0)
Patient global assessment <sup>a</sup>	47.2 (49.0)	47.6 (49.0)	47.5 (48.0)	24.2 (18.5)
Pain <sup>a</sup>	47.6 (47.5)	47.9 (49.0)	50.6 (53.0)	25.4 (19.0)
Disability index (HAQ) <sup>b</sup>	1.0 (1.0)	0.9 (0.8)	1.0 (0.9)	0.6 (0.4)
CRP (mg/dL) <sup>c</sup>	1.4 (0.8)	1.4 (0.7)	1.4 (0.8)	0.5 (0.2)

<sup>†</sup> As observed analysis presented, N at Week 24 may be less than 162 for placebo or 151 for HUMIRA

<sup>‡</sup> p < 0.001 for HUMIRA versus placebo comparisons based on mean change from baseline

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

b. Disability index of the Health Assessment Questionnaire (HAQ); 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

c. C-reactive protein (CRP) normal range: 0 to 0.287 mg/dL

## **Radiographic Response**

Radiographic changes in the hands, wrists, and feet were assessed in the psoriatic arthritis study at baseline and Week 24 during the double-blind period when patients were on HUMIRA or placebo and at Week 48 when all patients were on open-label HUMIRA. A modified total Sharp score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

### **Week 24**

The mean change in modified total Sharp score was evaluated and demonstrated that HUMIRA-treated patients had significantly less progression in their X-rays, compared to placebo-treated patients. As shown in Table 31, the mean change from baseline in both the erosion and the joint space narrowing scores in the HUMIRA treatment group was significantly superior to placebo. As with other TNF agents, the median change in Sharp scores for both patient groups were zero.

**Table 31. Radiographic Mean Changes at Week 24 in Placebo-Controlled Psoriatic Arthritis Study (Study M02-518)<sup>†</sup>**

<b>Response</b>	<b>Placebo N = 152</b>	<b>HUMIRA N = 144</b>	<b>p-value</b>
Total Sharp score	1	-0.2	< 0.001
Erosion score	0.6	0	< 0.001
JSN score	0.4	-0.2	< 0.001

<sup>†</sup> Analysis of patients with X-ray films at both baseline and Week 24.

Definitions: JSN = joint space narrowing

### **Week 48**

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression at Week 48 compared to placebo-treated patients at Week 24 (see Table 32).

**Table 32. Change in Modified Total Sharp Score<sup>‡</sup> in Psoriatic Arthritis (Study M02-537)**

Response		Placebo	HUMIRA	
		N = 141	N = 133	
		Week 24	Week 24	Week 48
Modified Total Sharp Score	Baseline mean	22.1	23.4	23.4
	Mean change ± SD	0.9 ± 3.06	-0.1 ± 1.69**	0.1 ± 2.74**
	Change (range)	-3.5 to 22.0	-6.8 to 12.5	-5.9 to 24.2
Erosion Score	Baseline mean	11.8	12.4	12.4
	Mean change ± SD	0.5 ± 1.91	0.0 ± 0.91**	0.1 ± 1.79*
	Change (range)	-2.2 to 14.5	-2.2 to 7.5	-4.4 to 16.5
JSN score	Baseline mean	10.4	11.0	11.0
	Mean change ± SD	0.4 ± 1.60	-0.1 ± 1.06**	0.0 ± 1.33**
	Change (range)	-3.5 to 10.2	-5.7 to 5.0	-4.0 to 7.7

\* p < 0.05 for the difference between HUMIRA, Week 48 and placebo, Week 24 (primary analysis)

\*\* p < 0.001 for the difference between HUMIRA, Week 48 and placebo, Week 24 (primary analysis)

‡ X-rays with less than 50% assessments were imputed

Definition(s): JSN = joint space narrowing; SD = standard deviation

### **Physical Function Response**

Disability and physical function were assessed in psoriatic arthritis study using Health Assessment Questionnaire Disability Index (HAQ-DI). The HUMIRA-treated patients had significantly greater improvement in the disability index of the HAQ from baseline to Week 24, compared to placebo and were maintained up to Week 84 (see Table 33 and Table 34).

**Table 33. Disability Index of the HAQ (Full Analysis Set) (Study M02-518)**

Disability Index of the HAQ		Placebo		HUMIRA 40 mg eow		p-value <sup>a</sup>
		N = 162		N = 151		
		N	Mean ± SD	N	Mean ± SD	
Week 12	Baseline	154	1.0	142	1.0	< 0.001*
	Change Observed	154	-0.1 ± 0.45	142	-0.4 ± 0.45	
Week 24	Baseline	145	1.0	141	1.0	< 0.001*
	Change Observed	145	-0.1 ± 0.42	141	-0.4 ± 0.49	

\* Statistically significant at the p = 0.001 level

a. p-value for differences between treatment groups from an ANOVA model with treatment group and baseline methotrexate use/extent of psoriasis (≥ 3% BSA, < 3% BSA) as factors

Definition(s): HAQ = Health Assessment Questionnaire; BSA = body surface area; eow = every other week;

SD = standard deviation

**Table 34. Mean Change from baseline in Disability Index of HAQ by Visit (Observed) (Study M02-518 Subjects Randomized to HUMIRA**

Visit	N	Baseline <sup>a</sup> Mean	Visit Mean	Change from Baseline		
				Mean	Standard Deviation	Range (Min to Max)
Week 24	137	1.0	0.6	-0.4	0.48	-1.8 to 1.1
Week 26	137	1.0	0.5	-0.4	0.50	-2.1 to 0.9
Week 30	137	1.0	0.6	-0.4	0.49	-1.9 to 1.0
Week 36	137	1.0	0.6	-0.4	0.50	-1.9 to 1.1
Week 42	135	1.0	0.6	-0.4	0.50	-1.9 to 1.0
Week 48	134	1.0	0.6	-0.4	0.54	-2.3 to 0.9
Week 60	132	1.0	0.5	-0.4	0.49	-1.9 to 0.6
Week 72	129	1.0	0.6	-0.4	0.49	-1.9 to 0.6
Week 84	79	0.9	0.5	-0.4	0.49	-1.9 to 0.8

Note: The disability index of the Health Assessment Questionnaire (HAQ) has a range from 0 to 3 with a higher score indicating a greater extent of functional limitations

a. Last assessment prior to the first HUMIRA injection

A subset of the subjects is still being followed in the ongoing study.

Results from the Short Form Health Survey (SF-36) support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores at Week 24, which were maintained to Week 72.

### 14.6.3 Ankylosing Spondylitis

#### **Study Demographics and Trial Design**

The safety and efficacy of HUMIRA 40 mg every other week were assessed in 393 adult patients in two randomized, 24-week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis who have had an inadequate response to or intolerance to one or more NSAIDs, and who may have additionally failed DMARD therapy. The larger study enrolled 315 adult patients with active ankylosing spondylitis [defined as fulfilling at least two of the following three criteria: (1) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score  $\geq 4$  cm, (2) a visual analogue score (VAS) for total back pain  $\geq 40$  mm, and (3) morning stiffness

≥ 1 hour]. The primary efficacy endpoint was percentage of ASAS 20 responders at Week 12 measured by the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Additional pre-determined endpoints included: response as defined by ASAS 5/6 criteria, ASAS 40/50/70 and partial remission, Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 80 weeks.

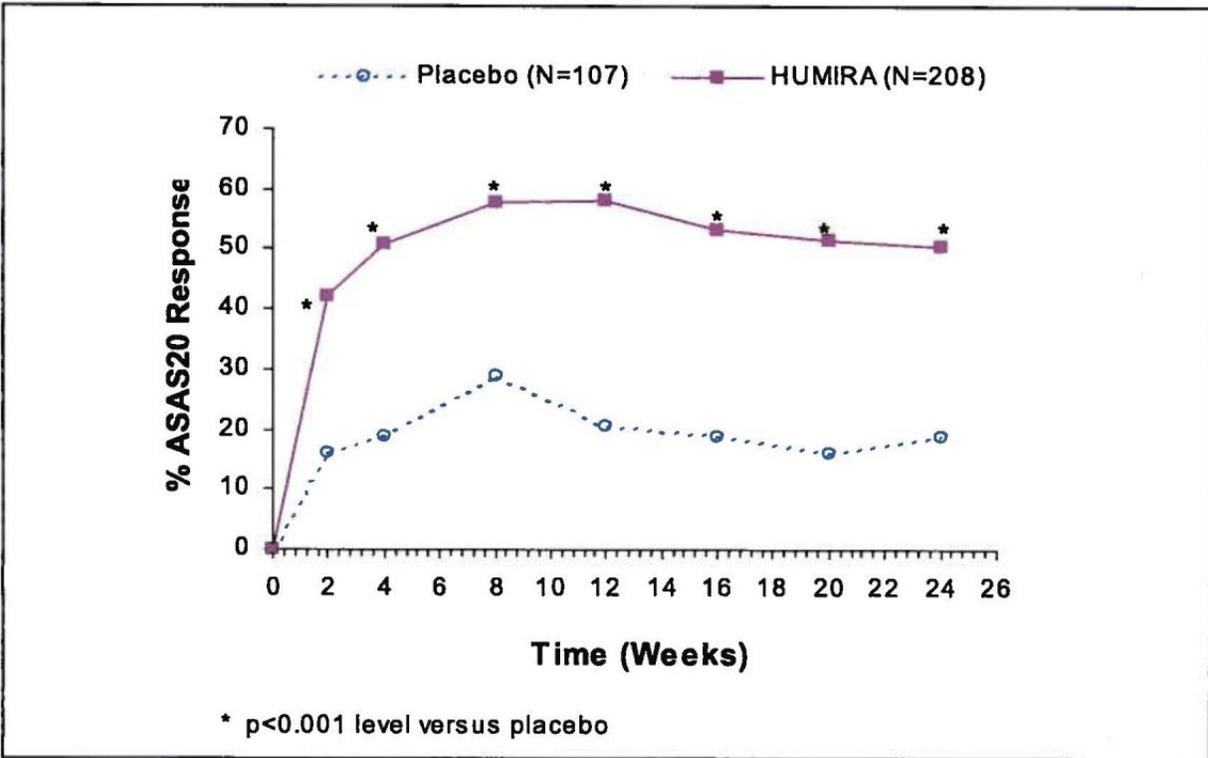
## **Study Results**

### **Clinical Response**

Results showed statistically significant reduction in signs and symptoms of ankylosing spondylitis in patients treated with HUMIRA compared to placebo in Study M03-607. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through Week 24 as shown in Figure 3 and Table 1 Table 35.

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 3. ASAS 20 response by Visit, Study M03-607**



At Week 12, the ASAS 20/50/70 responses were achieved by 58, 38, and 23%, respectively, of patients receiving HUMIRA, compared to 21, 10, and 5% respectively, of patients receiving placebo ( $p < 0.001$ ). At Week 24, the ASAS 20/50/70 responses were achieved by 51, 35 and 24%, respectively, of patients receiving HUMIRA, compared to 19, 11, and 8%, respectively, of patients receiving placebo ( $p < 0.001$ ). These results were sustained in patients receiving open-label HUMIRA through Week 52.

In a sub-group analysis by region an HUMIRA versus placebo treatment group difference was observed between the United States (US) and European (EU) subjects (21.7 and 50.9% respectively). This difference in the treatment effect is driven by the different placebo ASAS 20 response rates (33.3% for US versus 10.2% for EU). However, the HUMIRA ASAS 20 response rates were 55 and 61.1% in the US and EU respectively. A low level of disease activity [defined as a value  $< 20$  (on a scale of 0 to 100 mm) in each of the four ASAS response parameters] was achieved at Week 24 in 22% of HUMIRA-treated patients versus 6% in placebo-treated patients ( $p < 0.001$ ).

Other secondary and additional measures of efficacy such as response as defined by ASAS 5/6 criteria, ASAS 40, metrology (BASMI), enthesitis (MASSES), and disease activity (BASDAI) were statistically significant at Weeks 12 and 24.

**Table 35. Components of Ankylosing Spondylitis Disease Activity in Study M03-607**

Parameters	Placebo N = 107		HUMIRA N = 208	
	Baseline Mean	Week 24 Mean	Baseline Mean	Week 24 Mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity <sup>a</sup>	65	60	63	38
Total Back Pain Inflammation <sup>b</sup>	67	58	65	37
BASFI	6.7	5.6	6.7	3.6
BASDAI* Score	56	51	52	34
CRP*	6.3	5.5	6.3	3.7
	2.2	2	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

\* Statistically significant as  $p < 0.001$  for all comparisons between HUMIRA and placebo at Week 24

Definition(s): BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein (mg/dL)

Similar results (not all statistically significant) were seen in the second randomized trial, a multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis (Study M03-606).

Patients treated with HUMIRA achieved statistically significant greater improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.15 versus -0.95,  $p < 0.001$ ) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (6.93 versus 1.55,  $p < 0.001$ ) compared to placebo-treated patients at Week 12, which were maintained through Week 24.

#### 14.6.4 Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA were assessed in over 1,500 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI]  $\geq 220$  and  $\leq 450$ ) in randomized, double-blind, placebo-controlled studies. Concomitant

stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Table 36 summarizes the controlled clinical trials and Table 37 summarizes the open-label clinical trials that were done in patients with moderately to severely active Crohn's disease.

**Table 36. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in patients with Crohn's Disease**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
M02-403 (CD I)	Randomized, double-blind, placebo-controlled, multicenter, dose ranging study in anti-TNF naïve patients	HUMIRA 160 mg at Week 0 and 80 mg at Week 2; or HUMIRA 80 mg at Week 0 and 40 mg at Week 2; or HUMIRA 40 mg at Week 0 and 20 mg at Week 2	225	39 ± 12 (18 to 74)	55.6
		Placebo  Subcutaneous 4 weeks	74	37 ± 13 (19 to 74)	50.0
M04-691 (CD II)	Randomized, double-blind, placebo-controlled, multicenter study in patients who had lost response to or were intolerant to infliximab	HUMIRA 160 mg at Week 0 and 80 mg at Week 2	159	39.4 ± 11.9 (19 to 75)	68.6
		Placebo  Subcutaneous 4 weeks	166	37.4 ± 11.9 (18 to 75)	60.8

M02-404 (CD III)	Randomized, double-blind, multicenter, placebo-controlled	<u>Initial Open-Label:</u> HUMIRA 80 mg at Week 0 and 40 mg at Week 2  <u>Post-Randomization (Week 4):</u> HUMIRA 40 mg eow	260	36.8 ± 11.5 (17 to 73)	62.7
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		HUMIRA 40 mg ew	257	37.8 ± 12.1 (18 to 75)	61.1
		Placebo	261	36.9 ± 11.4 (18 to 75)	62.1
		Not randomized	76	36.1 ± 13.6 (19 to 75)	60.5
		Subcutaneous 56 weeks			

M05-769 (CD VI)	Randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study.	Patients received OL induction therapy of HUMIRA 160/80 mg at Weeks 0/2, and were stratified by responder status to HUMIRA 40 mg eow or placebo for up to 52 weeks. At Week 52, patients were switched to OL HUMIRA 40 mg eow for up to an additional 36 weeks.)			
		HUMIRA eow	64	37 (18 to 74)	62.5
		Placebo	65	37 (18 to 67)	63.1

Definitions: ew = every week; eow = every other week;; TNF = tumor necrosis factor; OL = open label

**Table 37. Summary of Open-Label Clinical Trials Supporting Safety and Efficacy in Patients with Crohn's Disease**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
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M02-433 (CD IV)	Open-label extension of placebo-controlled Study M02-403	<p>Patients received OL HUMIRA 40 mg at baseline (Week 0) and week 2. At Week 4, patients were assigned to one of three blinded treatment groups (HUMIRA eow, ew, or placebo) or OL HUMIRA eow treatment, based on clinical remission status at baseline. After 1 year (Week 56), patients entered long-term extension phase up to more than 5 years (including preceding M02-403 study); those receiving blinded treatment were switched to OL HUMIRA eow, and those in the OL group continued their OL treatment.</p> <p>All</p>	276	39 (18 – 74)	54.7
M04-690 (CD V)	Open-label extension of placebo-controlled Studies M04-691 or M02-404	<p>Patients entering from a blinded cohort were assigned to OL HUMIRA 40 mg eow; patients entering the study from an OL cohort continued their previous dosing regimen of eow or ew.</p> <p>Study M02-404 cohort</p> <p>Study M04-691 cohort</p>	467  310	All 38 (17 to 75)	All 62.4

Definitions: ew = every week; eow = every other week; OL = open label

### **Description of Clinical Studies**

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, Studies M02-403 and M04-691.

In Study M02-403, 299 TNF-blocker naïve patients were randomized to one of four treatment groups; the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2.

In Study M04-691, 325 patients who had lost response or were intolerant to infliximab were randomized to receive either 160 mg HUMIRA at Week 0 and 80 mg at Week 2 or placebo at

Weeks 0 and 2.

Maintenance of clinical remission was evaluated in Study M02-404.

In Study M02-404, 854 patients received open-label 80 mg HUMIRA at Week 0 and HUMIRA 40 mg at Week 2. At Week 4, patients were stratified by their responder status and previous anti-tumor necrosis factor (TNF) use (no, yes) and randomized to one of three blinded treatment groups: HUMIRA 40 mg every other week, HUMIRA 40 mg every week or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI  $\geq$  70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4. Corticosteroid tapering was permitted after Week 8.

Study M05-769 assessed mucosal healing in 135 patients; patients received open-label induction therapy of HUMIRA 160/80 mg at weeks 0/2, and were stratified by responder status to HUMIRA 40 mg every other week (eow) or placebo for up to 52 weeks. At Week 52, patients were switched to open-label HUMIRA 40 mg eow for up to an additional 36 weeks.

## Study Results

### **Clinical Responses**

#### **Studies M02-403 and M04-691**

A statistically significantly greater percentage of the patients treated with HUMIRA 160/80 mg achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF-blocker naïve (Study M02-403) or had lost response or are intolerant to infliximab (Study M04-691) (Table 38 and Table 39, respectively).

The percentage of subjects who achieved clinical remission with HUMIRA 160/80 mg induction therapy was greater for those receiving corticosteroids versus those who did not.

**Table 38. Induction of Clinical Remission and Response in Infliximab Naïve Patients (Study M02-403) (Percent of Patients)**

<b>Response</b>	<b>Placebo N = 74</b>	<b>HUMIRA 160/80 mg N = 76</b>
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Week 4	Clinical remission	12%	36%*
	Difference <sup>a</sup> (95% CI)		23.4 (10.3, 36.4)
	Clinical response (CR-100)	24%	49%**
	Difference <sup>a</sup> (95% CI)		24.4 (9.5, 39.3)
	Clinical response (CR-70)	34%	58%**
	Difference <sup>a</sup> (95% CI)		24.1 (8.6, 39.6)

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

\* p < 0.001

\*\* p < 0.01

a. Difference refers to the difference between the proportion (%) of HUMIRA-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

**Table 39. Induction of Clinical Remission and Response in Infliximab Experienced Patients (Study M04-691) (Percent of Patients)**

Response		Placebo N = 166	HUMIRA 160/80 mg N = 159
Week 4	Clinical remission	7%	21%*
	Difference <sup>a</sup> (95% CI)		14.2 (6.7, 21.6)
	Clinical response (CR-100)	25%	38%**
	Difference <sup>a</sup> (95% CI)		13.7 (3.7, 23.7)
	Clinical response (CR-70)	34%	52%**
	Difference <sup>a</sup> (95% CI)		17.8 (7.3, 28.4)

p-values are pairwise comparisons of proportions for HUMIRA versus placebo

\* p < 0.001

\*\* p < 0.01

a. Difference refers to the difference between the proportion (%) of HUMIRA-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

Clinical Remission at Week 4 by baseline predictors in infliximab experienced patients is presented in Table 40.

**Table 40. Clinical Remission at Week 4 by Baseline Predictors in Infliximab Experienced Patients (Study M04-69)**

Baseline Predictors		Placebo N = 166	HUMIRA 160/80 mg N = 159
Corticosteroid User		3/73 (4.1)	18/55 (32.7)
Corticosteroid Nonuser		9/93 (9.7)	16/104 (15.4)
Aminosalicylate User		6/60 (10.0)	6/45 (13.3)
Aminosalicylate Nonuser		6/106 (5.7)	28/114 (24.6)
CDAI Score	≤ 300	8/81 (9.9)	24/75 (32.0)
	> 300	4/85 (4.7)	10/84 (11.9)
Definition(s): CDAI = Crohn's disease activity index			

**Study M02-404**

At Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other 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 HUMIRA maintenance groups compared to patients in the placebo maintenance group (Table 41).

**Table 41. Maintenance of Clinical remission and response (percent of Patients) (Study M02-404)**

Response	Placebo N = 170	HUMIRA 40 mg eow N = 172	HUMIRA 40 mg ew N = 157

Week 26	Clinical remission	17%	40%*	47%*
	Difference <sup>a</sup> (95% CI)		22.5 (13.2, 31.7)	29.4 (19.8, 39.1)
	Clinical response (CR-100)	27%	52%*	52%*
Week 56	Difference <sup>a</sup> (95% CI)		25.3 (15.3, 35.3)	25.8 (15.5, 36.0)
	Clinical response (CR-70)	28%	54%*	56%*
	Difference <sup>a</sup> (95% CI)		25.8 (15.8, 35.9)	27.8 (17.5, 38.1)
Week 56	Clinical remission	12%	36%*	41%*
	Difference <sup>a</sup> (95% CI)		24.3 (15.6, 32.9)	29.6 (20.5, 38.7)
	Clinical response (CR-100)	17%	41%*	48%*
Week 56	Difference <sup>a</sup> (95% CI)		24.8 (15.6, 34.0)	31.3 (21.7, 40.9)
	Clinical response (CR-70)	18%	43%*	49%*
	Difference <sup>a</sup> (95% CI)		25.4 (16.9, 34.7)	31.4 (21.7, 41.1)

\* p < 0.001 for HUMIRA versus placebo pairwise comparisons of proportions

a. Difference refers to the difference between the proportion (%) of HUMIRA-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): eow = every other week; ew = every week; CI = confidence interval;

Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150;

Clinical response 100 (CR-100) and clinical response 70 (CR-70)=

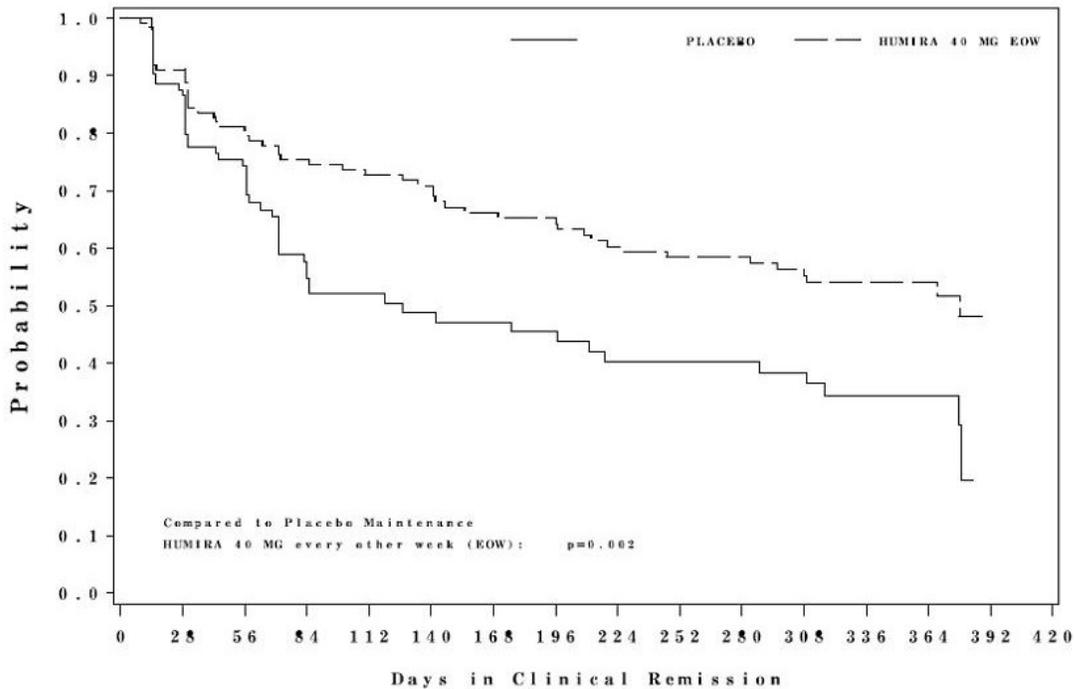
decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

More patients receiving HUMIRA maintenance therapy were able to achieve remission and discontinue corticosteroids for at least 90 days than those receiving placebo at Week 26 (19% HUMIRA every other week and 15% HUMIRA every week versus 3% placebo, p < 0.02) and at Week 56 (29% HUMIRA every other week and 20% HUMIRA every week versus 5% placebo, p < 0.01).

In Study M02-404, 117 patients had at least one draining fistula at Baseline and Screening. Of those, 23 out of 70 in the HUMIRA group (both regimens) and 6 out of 47 in the placebo group had no draining fistula at the last two evaluations.

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group (Figure 4).

**Figure 4. Days in Clinical Remission for Patients Who Had Achieved Clinical Remission (Induction Period) by Week 4 in Study M02-404**



Some patients who experience decrease in their response may benefit from an increase in dose to HUMIRA 40 mg every week. Supportive evidence for a restoration of clinical response as a result of dose escalation was derived from the modified-intent-to treat (mITT) Analysis Set of Study M02-404 in subjects who initially responded but lost response to HUMIRA 40 mg every other week dosing. In those subjects who responded at Week 4, were in remission at Week 12 but lost remission after Week 12, and were dose escalated to HUMIRA 40 mg every week (n = 14), clinical remission was restored in 71% (10/14) of these subjects, with median time to restored clinical remission of 9 weeks.

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Symptoms, overall well-being and functioning were assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ). Treatment with HUMIRA resulted in statistically significant improvements in IBDQ total score which measures bowel symptoms, systemic symptoms, emotional well-being and social functioning, compared with placebo (p < 0.001) at Week 4 in Studies M02-403 and M04-691 and Weeks 26 and 56 in Study M02-404.

### Study M05-769

An endoscopy study (n=135) assessed rates of mucosal healing in patients with moderate to severe Crohn's Disease given either HUMIRA or placebo. After 8 weeks of randomized treatment (Week 12 of study), although the results were not statistically significant (p = 0.056), there was a trend towards higher levels of mucosal healing in subjects given HUMIRA compared with subjects given placebo (mucosal healing in 27.4% (17/62) HUMIRA vs 13.1% (8/61) given placebo. In this study, the placebo group received open-label HUMIRA induction therapy.

#### 14.6.5 Ulcerative Colitis

The safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a scale of 0 to 12 points, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled studies (M06-826 and M06-827) and an open-label extension study. Both studies M06-826 and M06-827 enrolled TNF-blocker naïve patients, but M06-827 also allowed entry of patients who lost response or were intolerant to TNF-blockers. Forty percent (40%) of patients enrolled in Study M06-827 had previously used another TNF-blocker.

Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In Studies M06-826 and M06-827, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients continued to receive at least one of these medications.

Table 42 and Table 43 summarizes the open-label clinical trial that were done in patients with ulcerative colitis (UC).

**Table 42. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Ulcerative Colitis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
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M06-826 (UC I) (ULTRA I)	Randomized, double-blind (Weeks 0 to 8), placebo-controlled, multicenter induction study followed by an open-label extension (Weeks 8 to 52) in anti-TNF naïve subjects	HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4	223*	38 ± 13 (18 to 75)	38.1
		HUMIRA 80 mg at Week 0 and 40 mg eow starting at Week 2	130	42 ± 14 (18 to 75)	40.0
		Placebo	222*	40 ± 13 (18 to 74)	37.4
		Subcutaneous 52 weeks			
M06-827 (UC II) (ULTRA II)	Randomized, double-blind, placebo-controlled, multicenter induction and maintenance study	HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4	248	40 ± 12 (18 to 72)	42.7
		Placebo	246	41 ± 13 (18 to 79)	38.2
		Subcutaneous 52 weeks			

Definitions: ew = every week; eow = every other week \*130 subjects were randomized for the primary efficacy analysis

**Table 43. Summary of Open-Label Clinical Trials Supporting Safety and Efficacy in Patients with Ulcerative Colitis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
M10-223 (UC III)	Open-label extension of controlled Studies M06-826 and M06-827	Patients entering the study from a blinded cohort were assigned to adalimumab 40 mg eow; those entering the study from an open-label cohort continued their previous dosing regimen of adalimumab 40 mg eow or ew.  Subcutaneous up to 292 weeks	498	42 ± 13 (19 to 76)	36.9

Definitions: ew = every week; eow = every other week

### Description of Clinical Studies

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual sub-score > 1) at Week 8 was evaluated in Study M06-826. In Study M06-826, 390 TNF- blocker naïve patients

were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Week 0, 2, 4 and 6. The 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg HUMIRA at Week 0 and 40 mg at Week 2. After Week 2, patients in both HUMIRA treatment groups received 40 mg every other week (eow). Clinical remission was assessed at Week 8.

Induction of clinical remission at Week 8, clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were studied in Study M06-827. In Study M06-827, 518 patients were randomized to receive either HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

## **Study Results**

### *Clinical Responses*

In both Studies M06-826 and M06-827, a greater proportion of subjects induced with 160/80 mg HUMIRA achieved clinical remission versus placebo at Week 8 (Table 44). In Study M06-826, there was no statistically significant difference in clinical remission observed between the HUMIRA 80/40 mg group and the placebo group at Week 8 and no statistically significant difference in clinical response or mucosal healing observed between the HUMIRA 160/80 mg group and the placebo group at Week 8. Response at Week 8 was achieved by 54.6% (71/130) in the HUMIRA 160/80 mg group and 44.6% (58/130) in the placebo group with a treatment difference and 95% confidence interval (CI) of 10.0% (-2.1, 22.1). Mucosal healing at Week 8 was achieved by 46.9% (61/130) in the HUMIRA group and 41.5% (54/130) in the placebo group with a treatment difference and 95% CI of 5.4% (-6.7, 17.4).

In Study M06-827 clinical remission at Week 52 was a co-primary endpoint, achieved by 17.3% (43/248) of the HUMIRA group and 8.5% (21/246) of the placebo group. Sustained clinical remission (at both Weeks 8 and 52) was achieved by 8.5% (21/248) of the HUMIRA group and 4.1% (10/246) of the placebo group. Among those treated with HUMIRA who were in remission at Week 8, 51% (21/41) were in remission at Week 52. In the HUMIRA group 46.8% (116/248) patients moved to open label escape therapy for lack of response and 54.9% (135/246) patients in the placebo group. During the double-blind period, 5.6% (14/248) in the HUMIRA group and 7.7% (19/246) in the placebo group withdrew without final evaluation due to non-colitis related reasons (not lack of efficacy or colitis related adverse event). In the HUMIRA group 79 (31.9%) patients completed the Week 8 and 52 visits and 56 (22.8%) patients in the placebo group.

Response at Week 8 and at Week 52 were achieved in 50.4% (125/248) and 30.2% (75/248) of the HUMIRA group and 34.6% (85/246) and 18.3% (45/246) in the placebo group respectively with a treatment difference and 95% CI of 15.9% (7.0, 24.2) and 11.9% (4.3, 19.2). Sustained

response (at both Weeks 8 and 52) was achieved by 23.8% (59/248) of the HUMIRA group and 12.2% (30/246) of the placebo group with a treatment difference and 95% CI of 11.6% (4.7, 18.1).

Mucosal healing (endoscopic improvement of the mucosa) at Week 8 and at Week 52 were achieved in 41.1% (102/248) and 25.0% (62/248) in the HUMIRA group and 31.7% (78/246) and 15.4% (38/246) of the placebo group with a treatment difference and 95% CI of 9.4% (0.8, 17.6) and 9.6% (2.3, 16.4). Sustained mucosal healing (at both Weeks 8 and 52) was achieved by 18.5% (46/248) of the HUMIRA group and 10.6% (26/246) of the placebo group with a treatment difference and 95% CI of 8.0% (1.6, 14.0).

In the HUMIRA group, 13.3% (20/150) of the patients who were on corticosteroids at baseline were able to discontinue corticosteroids before Week 52 and achieved remission at Week 52 compared to 5.7% (8/140) in the placebo group.

**Table 44. Study M06-826 and M06-827: Summary of Results of Primary and Ranked co-Primary and Ranked Secondary Endpoints**

Analysis <sup>a</sup>		Placebo	Adalimumab 160/80/40	Treatment Difference (95% CI)
<b>Study M06-826</b>		<b>N = 130</b>	<b>N = 130</b>	
<b>Primary Endpoint</b>				
Clinical remission at Week 8		9.2%	18.5%*	9.2 (0.9, 17.6)
<b>Study M06-827</b>		<b>N = 246</b>	<b>N = 248</b>	
<b>Ranked Co-Primary Endpoints</b>				
1.	Remission at Week 8	9.3%	16.5%*	7.2 (1.2, 12.9)
2.	Remission at Week 52	8.5%	17.3%*	8.8 (2.8, 14.5)

Note: According to the NRI method, all missing remission values were considered to be non-remission. Subjects who switched to OL adalimumab were considered to be non-remitters at and after the time of the switch.

Clinical remission per Mayo score: Mayo score  $\geq 2$  with no individual subscore  $> 1$

Mayo score consists of four subscores (stool frequency [SFS], rectal bleeding [RBS], findings of endoscopy, and physician's global assessment). Mayo scores range from 0-12.

\* $p < 0.05$  for HUMIRA vs. placebo pairwise comparison of proportions

In the subgroup of patients in Study M06-827 with prior TNF-blocker use, the treatment difference for induction of clinical remission was 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.

#### 14.6.6 Hidradenitis Suppurativa

The safety and efficacy of HUMIRA were assessed in two randomized, double-blind, placebo-controlled studies in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to systemic antibiotic therapy. In both studies, patients had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules. Table 45 summarizes the clinical trials in patients with moderate to severe hidradenitis suppurativa.

**Table 45. Summary of Clinical Trials Evaluating Safety and Efficacy in Patients with Hidradenitis Suppurativa**

<b>Study #</b>	<b>Trial Design</b>	<b>Dosage, Route of Administration and Duration</b>	<b>Study Subjects (n)</b>	<b>Mean Age (Range)</b>	<b>Gender (% Female)</b>
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M11-313 (PIONEER I)	Randomized, double-blind, placebo- controlled, 2-period	<p><u>Period A - 12 weeks</u></p> <p>HUMIRA 160 mg at Week 0, 80 mg at Week 2, then 40 mg every week from Week 4 to Week 11; Placebo</p> <p><u>Period B - 24 weeks</u></p> <p>HUMIRA 40 mg every week; HUMIRA 40 mg every other week; Placebo</p> <p>Subcutaneous 36 weeks</p>	307	37.0 (18 to 67)	63.8
M11-810 (PIONEER II)	Randomized, double-blind, placebo- controlled, 2-period	<p><u>Period A - 12 weeks</u></p> <p>HUMIRA 160 mg at Week 0, 80 mg at Week 2, then 40 mg every week from Week 4 to Week 11; Placebo</p> <p><u>Period B - 24 weeks</u></p> <p>HUMIRA 40 mg every week; HUMIRA 40 mg every other week; Placebo</p> <p>Subcutaneous 36 weeks</p>	326	35.5 (18 to 69)	67.8

### Description of Clinical Studies

Both studies consisted of an initial 12-week double-blind treatment period (Period A), and a subsequent 24-week double-blind treatment period (Period B). In Period A, patients received placebo or HUMIRA 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. After 12 weeks of therapy, patients who had received HUMIRA in Period A were re-randomized in Period B to 1 of 3 treatment groups (HUMIRA 40 mg every week, HUMIRA 40 mg every other week, or placebo from Week 12 to Week 35). In Period B, patients who had been randomized to placebo in Period A were assigned to receive

HUMIRA 40 mg every week (M11-313) or placebo (M11-810) in a blinded fashion. In both studies, the randomization in Period A was to be stratified by baseline Hurley Stage (II versus III). A subject's Hurley Stage was determined by the worst Hurley Stage across all affected anatomic regions. Baseline concomitant antibiotic use (yes versus no) was an additional randomisation factor in Study M11-810.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12 as the primary endpoint. Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using HiSCR which was defined as achieving at least a 50% reduction from baseline in AN [total abscess and inflammatory nodule] count plus 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 11point scale.

The majority of patients were female, obese ( $\geq 90$  kg, BMI  $\geq 30$ ), current smokers, and had HS disease duration of over 9 years; the patients had a mean modified Sartorius Score of 131.6, AN count of 12.8, and draining fistula count of 3.8.

Patients participating in Studies M11-313 and M11-810 were eligible to enroll into an open-label extension study (Study M12-555) in which HUMIRA 40 mg was administered every week. Study M12-555 aimed to determine the long-term safety, tolerability and efficacy of adalimumab in subjects with moderate to severe HS for at least 60 weeks.

Throughout all 3 studies, patients used topical antiseptic wash daily.

## **Study Results**

### *Clinical Responses*

#### Studies M11-313 and M11-810

In Period A of Studies M11-313 and M11-810, 40 mg of adalimumab treatment every week resulted in statistically significant greater proportion of patients achieving HiSCR at Week 12 in subjects with moderate to severe HS compared with placebo. Results are shown in Table 46.

**Table 46. Clinical Response at 12 Weeks, M11-313 and M11-810**

Endpoint	M11-313 (PIONEER I)		M11-810 (PIONEER II)	
	Placebo	HUMIRA 40 mg weekly	Placebo	HUMIRA 40 mg weekly

Hidradenitis Suppurativa Clinical Response (HiSCR)	N = 154 40 (26.0%)	N = 153 64 (41.8%)	N = 163 45 (27.6%)	N = 163 96 (58.9%)
Difference (95% CI) <sup>a</sup>	15.9 % (5.3%, 26.5%)		31.5% (20.7, 42.2%)	
<i>P</i> -value <sup>b</sup>	0.003		< 0.001	

- a. 95% CI for stratum-adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of two treatment groups, adjusting for baseline Hurley Stage (II/III) in M11-313 and adjusting for baseline Hurley Stage (II/III) and baseline antibiotic use (Yes/No) in M11-810.
- b. *P*-value was calculated from the Cochran-Mantel-Haenszel test adjusting for baseline Hurley Stage (II/III) in M11-313, and adjusting for baseline Hurley Stage (II/III) and baseline antibiotic use (Yes/No) in M11-810

At Week 12, a significantly higher proportion of patients treated with HUMIRA in Study M11-810 experienced at least a 30% decrease in HS-related skin pain versus placebo (45.7% vs 20.7%,  $P < 0.001$ ), whereas the difference was not significant in Study M11-313 (27.9% vs 24.8%,  $P = 0.628$ ). During the initial 12 weeks of treatment, 13.7% of patients treated with HUMIRA experienced flare compared to 35.7% in the placebo group in Study M11-313. The corresponding observed percentage was 11.0% and 35.0% for the HUMIRA and placebo group, respectively, in Study M11-810.

Among patients who were randomized to HUMIRA in Period A, achieved HiSCR at Week 12, and re-randomized to HUMIRA every week (N = 52), HUMIRA every other week (N = 52) and placebo (N = 53), 24 (46.2%), 22 (42.3%), and 32 (60.4%) discontinued prior to Week 36, respectively; 17 (32.7%), 20 (38.5%), and 27 (50.9%) discontinued primarily due to experiencing protocol specified loss of response.

In patients with at least a partial response ( $\geq 25\%$  improvement in AN count) to HUMIRA 40 mg weekly at Week 12, the proportion of patients achieving HiSCR at Week 24 was 57.1% in HUMIRA 40 mg weekly, 51.4% in HUMIRA 40 mg every other week and 32.9% in the placebo group. The corresponding proportion at Week 36 was 55.7% in HUMIRA 40 mg weekly, 40.0% in HUMIRA 40 mg every other week and 30.1% in the placebo group.

#### 14.6.7 Plaque Psoriasis

##### Study Demographics and Trial Design

The safety and efficacy of HUMIRA 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 randomized, double-blind, well-controlled studies.

Table 47 summarizes the controlled clinical trials that were done in patients with moderate to severe plaque psoriasis.

**Table 47. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriasis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
M03-656 (Ps I)	<p><u>Period A:</u> Double-blind, placebo-controlled treatment period in patients with moderate to severe chronic plaque psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10%); patients were randomly assigned (2:1) to receive HUMIRA or placebo</p> <p><u>Period B:</u> Open-label treatment period; all patients who achieved a <math>\geq</math> PASI 75 response at Week 16 received HUMIRA</p> <p><u>Period C:</u> Double-blind, placebo-controlled treatment period; patients who maintained a <math>\geq</math> PASI 75 response at Week 33 and were originally randomized to active therapy in Period A were rerandomized (1:1) to receive HUMIRA or placebo</p>	<u>Initial Dose</u> HUMIRA 80 mg			
		<u>Period A - 16 weeks</u> HUMIRA 40 mg eow	814	44.1 $\pm$ 13.2	32.9
		Placebo	398	45.4 $\pm$ 13.4	35.4
		<u>Period B - 17 weeks</u> HUMIRA 40 mg eow	606	43.9 $\pm$ 13.2	30.7
		<u>Period C - 19 weeks</u> HUMIRA 40 mg eow	250	44.3 $\pm$ 13.0	29.6
		Placebo	240	43.4 $\pm$ 13.2	25.4
M04-716 (Ps II)	Randomized, double-blind, double-dummy, multicenter, placebo- and active-controlled study in patients with moderate to severe plaque psoriasis (PASI $\geq$ 10, BSA $\geq$ 10%) who were candidates for systemic therapy or phototherapy and had inadequate response to topical therapy	HUMIRA 80 mg followed by 40 mg eow	108	42.9 $\pm$ 12.6	35.2
		Placebo	53	40.7 $\pm$ 11.4	34.0
		MTX capsules (7.5 to 25.0 mg)	110	41.6 $\pm$ 12.0	33.6
		Subcutaneous and oral 16 weeks			

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
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M02-528 (Ps III)	Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study in patients with moderate to severe plaque psoriasis (BSA $\geq$ 5%) and inadequate response to topical therapy	HUMIRA 80 mg followed by 40 mg eow	45	45.8 $\pm$ 11.6	28.9
		HUMIRA 80 mg followed by 40 mg ew	50	43.8 $\pm$ 13.3	34.0
		Placebo Subcutaneous 12 weeks	52	43.3 $\pm$ 13.1	34.6
M13-674 (Ps IV)	<p><u>Period A:</u> Double-blind, placebo-controlled treatment period during which patients with moderate to severe nail psoriasis (PGA and PGA-F of at least moderate disease severity; a target-fingernail mNAPSI <math>\geq</math> 8 together with either BSA <math>\geq</math> 10% or a total mNAPSI score of <math>\geq</math> 20 with <math>\geq</math> 5% BSA involvement) were randomized in a 1:1 ratio to receive HUMIRA or placebo</p> <p><u>Period B:</u> Open-label treatment period; all patients received HUMIRA</p>	<p><u>Period A - 26 weeks</u></p> <p>HUMIRA 80 mg followed by 40 mg eow</p> <p>Placebo</p> <p><u>Period B - 26 weeks</u></p> <p>HUMIRA 40 mg eow</p> <p>Subcutaneous 52 weeks</p>	217	46.7 $\pm$ 12.0	15.7

Definition(s): ew = every week; eow = every other week; MT X = methotrexate; PASI = Psoriasis Area and Severity Index; BSA = body surface area; PGA = Physician's Global Assessment; PGA-F: Physician's Global Assessment of Fingernail Psoriasis; mNAPSI = Modified Nail Psoriasis Severity Index

Across all treatment groups of Study M03-656, the mean baseline Psoriasis Area and Severity Index (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%).

Across all treatment groups of Study M04-716, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (0.4%) to "moderate" (47.8%) to "severe" (45.6%) to "very severe" (6.3%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where HUMIRA was given for at least an additional 108 weeks. 1,468 patients received at least one dose of HUMIRA during the open-label trial. 1,018/1,468 (69%) patients received adalimumab for a minimum of 108 weeks. Patients from Study M03-656 who enrolled into the open-label trial may have received up to 160 weeks of continuous HUMIRA

exposure in the first portion of the extension. 183/233 (79%) eligible patients from Study M03-656 completed 160 weeks from the first dose of adalimumab in M03-656 to the end of the first portion of the extension trial.

## **Study Results**

### *Clinical Response*

In Studies M03-656, M04-716 and M02-528, 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 M03-656 and M04-716 and Week 12 for Study M02-528. Other evaluated outcomes in Studies M03-656, M04-716 and M02-528 included the PGA and other PASI measures.

Study M03-656 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 Study M03-656, response to HUMIRA was rapid, with significantly greater improvements compared to placebo in mean percentage PASI, PASI 75/90 response rates, and PGA clear or minimal scores by Week 4, the first study visit (all  $p < 0.001$  vs. placebo).

In Studies M03-656 and M04-716, more patients randomized to HUMIRA than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16 (see Table 48 and Table 49). Other relevant clinical parameters, including PASI 90, PASI 100 (corresponding to a complete clearance of psoriasis skin signs) and PGA of “clear or minimal,” were also improved over placebo.

In Study M04-716, superior results were achieved for PASI 75, PASI 90, PASI 100 and PGA of “clear or minimal” in patients randomized to the HUMIRA treatment group versus those randomized to receive methotrexate.

**Table 48. Psoriasis Study M03-6656 Efficacy Results at Week 16 (Percent of Patients)**

<b>Response</b>	<b>Placebo N = 398</b>	<b>HUMIRA 40 mg eow N = 814</b>
≥ PASI 75	6.5%	70.9% <sup>a</sup>
≥ PASI 90	1.8%	45.0% <sup>a</sup>
PASI 100	0.8%	20.0% <sup>a</sup>
PGA: Clear/minimal	4.3%	62.2% <sup>a</sup>

a.  $p < 0.001$  for HUMIRA versus placebo

Definition(s): eow = every other week; PASI = Psoriasis Area Severity index; PGA = physician's global assessment

**Table 49. Psoriasis Study M04-716 Efficacy results at Week 16 (Percent of Patients)**

<b>Response</b>	<b>Placebo N = 53</b>	<b>MTX N = 110</b>	<b>HUMIRA 40 mg eow N = 108</b>
≥ PASI 75	18.9%	35.5%	79.6% <sup>a,b</sup>
≥ PASI 90	11.3%	13.6%	51.9% <sup>a,b</sup>
PASI 100	1.9%	7.3%	16.7% <sup>c,d</sup>
PGA: Clear/minimal	11.3%	30.0%	73.1% <sup>a,b</sup>

a.  $p < 0.001$  for HUMIRA versus placebo

b.  $p < 0.001$  for HUMIRA versus methotrexate

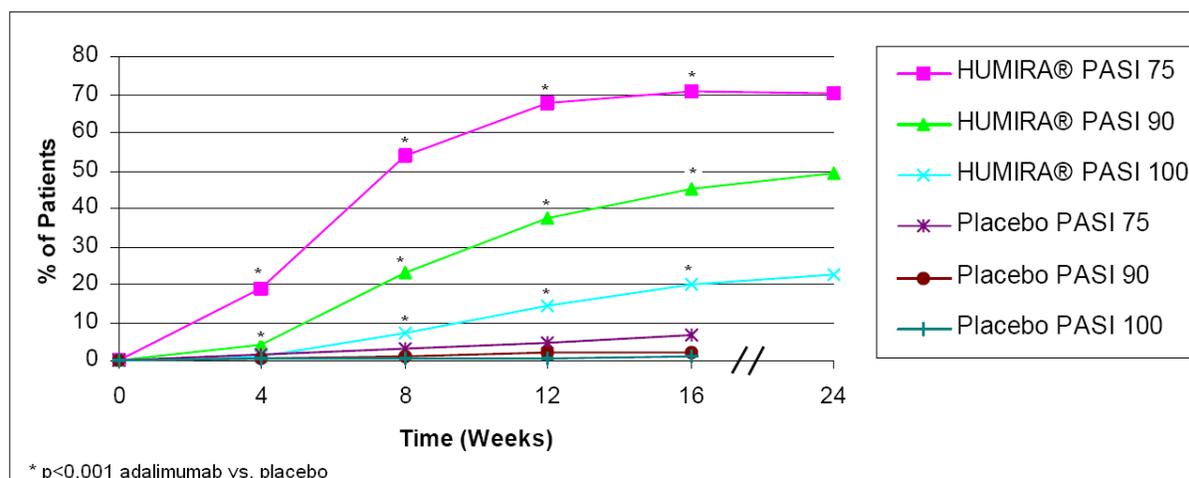
c.  $p < 0.01$  for HUMIRA versus placebo

d.  $p < 0.05$  for HUMIRA versus methotrexate

Definition(s): MTX = methotrexate; eow = every other week; PASI = Psoriasis Area Severity Index; PGA = physician's global assessment

PASI 75, PASI 90 and PASI 100 Responses from Week 0 to Week 24 for Study M03-656 are presented in Figure 5.

**Figure 5.** Psoriasis Study M03-656 Response Rate from Seek 0 to Week 24



Results from Study M02-528 supported the efficacy demonstrated in Studies M03-656 and M04-716.

In Study M03-656, patients who were PASI 75 responders and were re-randomized to continue HUMIRA 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-randomized to placebo at Week 33 (4.9% versus 28.4%,  $p < 0.001$ ).

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous HUMIRA therapy for 52 weeks in Psoriasis Study M03-656, and continued HUMIRA in the open-label extension trial. The proportion of patients with full skin clearance (PASI 100) was generally maintained through Week 108 [31.8% at OLE entry ( $n=74/233$ ); 30.1% at Week 108 ( $n=69/229$  (total of 160 weeks))].

A total of 94 patients were randomized to HUMIRA therapy in Psoriasis Study M04-716, and continued HUMIRA in the open label extension trial. The proportion of patients with PASI 75 after an additional 108 weeks of open-label therapy was 58.1% ( $n=54/93$ ) (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA “moderate” or worse) was approximately 5 months [95% C.I. (127, 146 days)]. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, 69.1% (123/178) for patients who relapsed and 88.8% (95/107) for patients who did not relapse during the withdrawal period.

In the open-label extension study, 349/1,256 (27.8%) patients dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50% and were evaluated 12 weeks after dose escalation, and 93/349 (26.6%) patients achieved PASI 75 response.

There were no clinical trials conducted to evaluate the efficacy and safety of HUMIRA in psoriatic arthritis patients with both active arthritis and moderate to severe psoriasis.

Study M13-674 evaluated the proportion of patients who achieved “clear” or “minimal” nail psoriasis with at least a 2-grade improvement on the 5-point Physician’s Global Assessment of Fingernail Psoriasis (PGA-F) scale and at least a 75% improvement in Modified Nail Psoriasis Severity Index (mNAPSI 75) at Week 26. At Week 26, a statistically significantly higher proportion of patients in the HUMIRA group achieved a PGA-F and mNAPSI 75 response compared with placebo (see Table 50. Nail Psoriasis Study M13-674 Efficacy Results at 26 Weeks).

**Table 50. Nail Psoriasis Study M13-674 Efficacy Results at 26 Weeks**

<b>Response</b>	<b>Placebo N = 108</b>	<b>HUMIRA 40 mg eow N = 109</b>
PGA-F clear/minimal and $\geq 2$ -grade improvement	6.9%	48.9% <sup>a,b</sup>
$\geq$ mNAPSI 75	3.4%	46.6% <sup>a,b</sup>

a.  $p < 0.001$  for HUMIRA versus placebo

b. Across all the strata,  $P$  value was calculated according to the Cochran-Mantel-Haenszel test adjusted for strata. If zero frequency occurred, strata were dropped and  $P$  value was calculated based on Chi-square test (or adjusted Chi-square test based on Campbell (2007) if expected count  $< 5$  in any cell).

### **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 Study M03-656 and Study M04-716.

In Study M03-656, patients receiving HUMIRA demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 and 16. The DLQI result was maintained at Week 52.

In Study M04-716, patients receiving HUMIRA 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 Study M03-656. The HUMIRA-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

#### 14.6.8 Uveitis

The safety and efficacy of HUMIRA 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 randomized, double-masked, placebo-controlled studies (M10-877 and M10-880) and an ongoing open-label extension study (M11-327). Patients received placebo or HUMIRA 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.

Table 51. Summary of Clinical Trials Supporting Safety and Efficacy in Patients with Uveitis summarizes the controlled and open-label extension clinical trials in patients with uveitis.

**Table 51. Summary of Clinical Trials Supporting Safety and Efficacy in Patients with Uveitis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
M10-877 (VISUAL I)	Randomized, double-masked, placebo-controlled, multicenter study	HUMIRA 80 mg loading dose, followed by 40 mg given eow starting at Week 1	110	42.7 ± 15.6 (18 to 81)	53.6
		Placebo	107	42.6 ± 14.2 (18 to 79)	60.7
		Subcutaneous Up to 80 weeks			
M10-880 (VISUAL II)	Randomized, double-masked, placebo-controlled, multicenter study	HUMIRA 80 mg loading dose, followed by 40 mg given eow SC starting at Week 1	115	42.9 ± 12.9 (18 to 75)	57.4
		Placebo	111	42.2 ± 13.98 (20 to 29)	64.9
		Subcutaneous Up to 80 weeks			
M11-327 (VISUAL III)	Open-label extension of controlled Studies M10-877 and M10-880 for patients who had either discontinued from the lead-in studies for having met “treatment failure” criteria (active uveitis subgroup) or had completed the lead-in studies without treatment failure (inactive uveitis subgroup)	HUMIRA 40 mg eow  Subcutaneous Up to 362 weeks	424	43.4 ± 14.1 (19.0 to 81.0)	58.7

Definition(s): eow = every other week; SC = subcutaneous

### Description of Clinical Studies

The primary efficacy endpoint in both controlled studies was “time to treatment failure”. Treatment failure was defined by a multi-component measurement assessing the loss of disease control based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Study M10-877 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 standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study M10-880 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.

Study M11-327 evaluated the long-term safety and efficacy of HUMIRA 40 mg every other week in the treatment of uveitis, during which corticosteroid/immunosuppressant treatments could be initiated, maintained, escalated, tapered, or discontinued as needed.

### Study Results

#### *Clinical Responses*

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure over the course of the study in patients treated with HUMIRA versus patients receiving placebo (Table 52, Figure 6 and Figure 7).

**Table 52. Time to treatment Failure in Uveitis Studies**

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Weeks/Months)	HR <sup>a</sup>	CI 95% for HR <sup>a</sup>	P value <sup>b</sup>
<b>Time to Treatment Failure At or After Week 6 in Study M10-877</b>						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	13.0/3.0	-	-	-
HUMIRA	110	60 (54.5)	24.4/5.6	0.50 <sup>b</sup>	0.36, 0.70 <sup>b</sup>	< 0.001
<b>Time to Treatment Failure At or After Week 2 in Study M10-880</b>						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	36.1/8.3	-	-	-
HUMIRA	115	45 (39.1)	NE <sup>c</sup>	0.57 <sup>b</sup>	0.39, 0.84 <sup>b</sup>	0.004

Note: Treatment failure at or after Week 6 (Study M10-877), or at or after Week 2 (Study M10-880), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

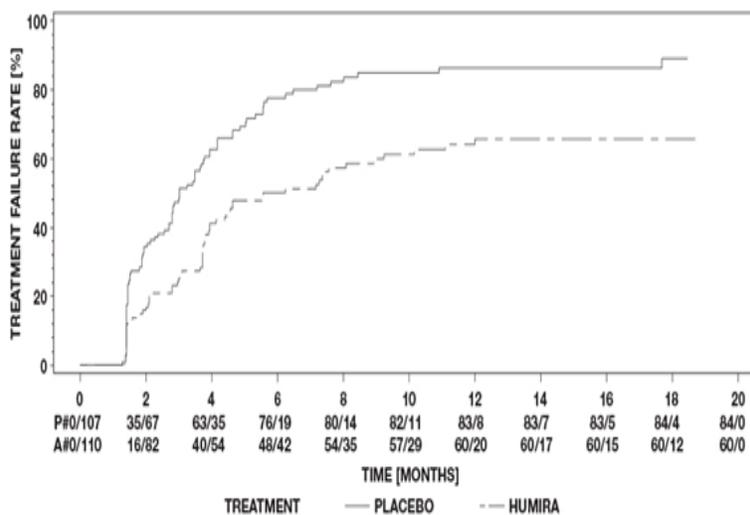
a. HR of HUMIRA vs placebo from proportional hazards regression with treatment as factor.

b. 2-sided *P* Value from log rank test.

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

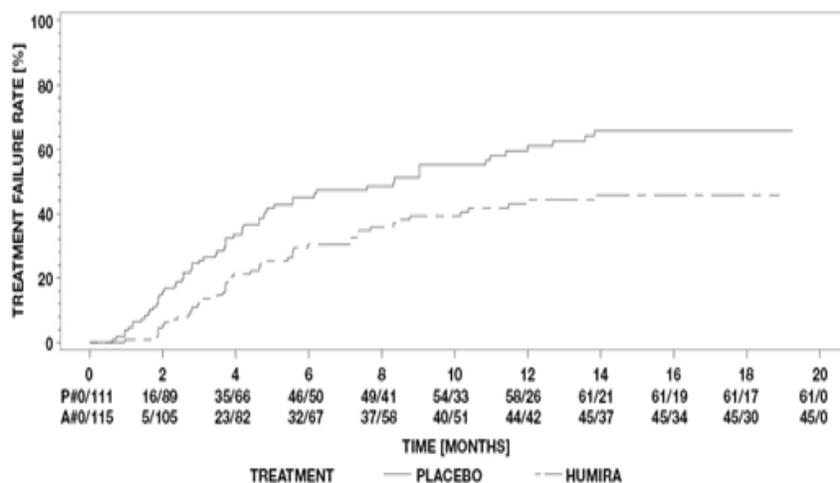
Note: Pt. # = placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk)

**Figure 6. Kaplan-Meier Curves Summarizing Time to treatment Failure on-or-after Week 6 (Study M10-877)**



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

**Figure 7. Kaplan-Meier Curves Summarizing Time to Treatment failure on-or-after Week 2 (Study M10-880)**



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

In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between HUMIRA and placebo groups.

## Pediatric

### Polyarticular Juvenile Idiopathic Arthritis

#### **Study Demographics and Trial Design**

The safety and efficacy of HUMIRA was assessed in two studies (Studies DE038 and M10-444) 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).

Table 53 summarizes the clinical trials that were done in patients with polyarticular JIA.

**Table 53. Summary of Clinical Trial Evaluating Safety and Efficacy in Patients with Polyarticular Juvenile Idiopathic Arthritis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range) (Years)	Gender (% Female)
DE038 (JIA I)	Multicenter, double-blind, randomized, placebo-controlled, open-label extension	<u>OL LI Phase</u> 24 mg adalimumab/m <sup>2</sup> BSA (up to a maximum of 40 mg total body dose) subcutaneous eow	171	11.3 ± 3.53 (4 to 17)	78.9%
		<u>DB Phase</u> 24 mg adalimumab/m <sup>2</sup> BSA (up to a maximum of 40 mg total body dose) subcutaneous eow  or Placebo subcutaneous eow	133	11.6 ± 3.61 (4 to 17)	77.4%
		<u>OLE BSA Phase</u> 24 mg adalimumab/m <sup>2</sup> BSA (up to a maximum of 40 mg total body dose) subcutaneous eow	128	12.0 ± 3.59 (4 to 18)	76.6%
		<u>OLE FD Phase</u> 20 mg adalimumab subcutaneous eow, < 30 kg body weight  or 40 mg adalimumab subcutaneous eow, ≥ 30 kg body weight	106	13.7 ± 3.82 (6 to 20)	73.6%
M10-444 (JIA II)	Multicenter, open-label	24 mg adalimumab/m <sup>2</sup> BSA (up to a maximum of 20 mg total body dose) subcutaneous eow	32	3.04 ± 0.723 (2.0 to 4.6)	87.5%

Definitions: BSA = body surface area; DB = double-blind; eow = every other week; OL BSA = open label body surface area  
OL FD = open-label fixed dose; OL LI = open label lean in; SC = subcutaneous

### **Study DE038**

The safety and efficacy of HUMIRA were assessed in a multicentre, randomized, double-blind, parallel-group study in 171 pediatric patients (4 to 17 years old at the time of enrollment) with moderate or severe polyarticular juvenile idiopathic arthritis (JIA). In the open-label lead in phase (OL LI) patients were stratified into two groups, methotrexate (MTX)-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 ( $\leq 0.2$  mg/kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m<sup>2</sup> up to a maximum of 40 mg HUMIRA 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 54.

**Table 54. Distribution of Patients by Age and HUMIRA 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

Patients demonstrating a Pediatric ACR 30 response at Week 16 were eligible to be randomized into the double blind (DB) phase and received either HUMIRA 24 mg/m<sup>2</sup> up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of  $\geq 30\%$  from baseline in  $\geq 3$  of 6 Pediatric ACR core criteria,  $\geq 2$  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 enroll into the open label extension phase.

The primary efficacy variable was the proportion of patients in the non-MTX stratum who experienced disease flare in the double-blind phase. Key secondary endpoints were analysis and comparison of disease flare at Week 48 including the proportion of patients with disease flare in those treated with MTX, time to onset (from double blind Baseline) of flare for patients in the non-MTX stratum, and time to onset (from double blind Baseline) of flare for patients treated with MTX. Subjects were clinically assessed at baseline, and for clinical response to adalimumab at Weeks 2, 4 and then every 4 weeks up to Week 48 or at early termination and throughout the OLE phases.

### **Study M10-444**

The safety and efficacy of HUMIRA was assessed in an open-label, multicenter 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 primary objective of the study was the evaluation of safety. The patients received 24 mg/m<sup>2</sup> body surface area (BSA) of HUMIRA up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks up to a maximum of 120 weeks duration. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

## **Study Results**

**Table 55. Major Efficacy Results in the JIA Study (DE038)**

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

<sup>a</sup> p = 0.031

\* N and PedACR30 response rates are from the Open-Label Lead-In phase prior to the randomization to the Double-Blind phase.

Twelve patients were treated for 6 years or longer.

The percentage of patients achieving PedACR30 responses were higher (94% vs. 74%) and, fewer patients developed antibodies (5.9% vs. 25.6%) when treated with the combination of HUMIRA and MTX compared to HUMIRA monotherapy. Therefore, HUMIRA is recommended for use in combination with MTX, and for use as monotherapy only in patients for whom MTX use is not appropriate.

### **Adolescent Hidradenitis Suppurativa (HS)**

No clinical trials were conducted in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS (12 to 17 years of age weighing  $\geq$  30 kg) is predicted using pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations based on demonstrated efficacy and exposure-response relationship in adult HS patients (see **14.5**

## CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Adult, 14.5.6 Hidradenitis Suppurativa).

The disease course, pathophysiology and drug effects in adolescents are assumed to be similar to adults at the same exposure levels. Safety of the recommended adalimumab dose in adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and pediatric patients at similar or higher exposures.

### Pediatric Uveitis

#### **Study Demographics and Trial Design**

The safety and efficacy of HUMIRA were assessed in a randomized, double-masked, controlled study of 90 pediatric 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. Participants were randomized applying a ratio of 2:1 (HUMIRA: placebo) stratified by centre. Patients received either placebo or 20 mg HUMIRA (if < 30 kg) or 40 mg HUMIRA (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate for up to 18 months. Concomitant stable dosages of systemic ( $\leq 0.2$  mg/kg/day of prednisolone equivalent) and topical corticosteroids (maximum 6 drops/day) were permitted at study entry followed by a mandatory reduction in topical corticosteroids (maximum 2 drops/day) within 3 months. Table 56 summarizes the controlled clinical trial done in pediatric patients with uveitis.

**Table 56. Summary of Controlled Clinical trial Supporting Safety and Efficacy in Pediatric Patients with Uveitis**

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
SYCAMORE	Randomized, double-masked, placebo-controlled,	HUMIRA fixed-dose of 20 mg (if BW < 30 kg at Baseline) or 40 mg (if BW ≥ 30 kg at Baseline)	60	9.07 ± 3.94 (3.04 to 17.97)	78.3 %
		Placebo	30	8.56 ± 3.79	76.7%

		Subcutaneous every 2 weeks for up to 18 months		(2.57 to 16.9)	
Definition(s): BW = body weight					

### Description of Clinical Studies

The primary efficacy endpoint was “time to treatment failure”. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, 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.

### Study Results

#### Clinical Results

HUMIRA delayed the time to treatment failure, as compared to placebo (See Figure 8 and Table 57). These results are based on the 2<sup>nd</sup> interim analysis, which was performed when 90 patients out of a total planned sample size of 114 patients had been randomized in the study.

**Table 57. Results of Time to Treatment Failure Analysis in the Pediatric Uveitis Study**

<b>Treatment/ Reason for Failure</b>	<b>N</b>	<b>Failure n (%)</b>	<b>Median Time to Failure (Weeks)<sup>a</sup></b>	<b>HR<sup>b</sup></b>	<b>99.9% CI for HR<sup>b,c</sup></b>	<b>P value<sup>c,d</sup></b>
Placebo	30	18 (60.0)	24.1	-	-	-
Anterior segment inflammation or ocular co- morbidity		7 (23.3)				

Use of prohibited concomitant medication		10 (33.3)				
Suspension of study treatment		1 (3.3)				
HUMIRA <sup>e</sup>	60	16 (26.7)	NE <sup>f</sup>	0.25	0.08, 0.79	< 0.0001
Anterior segment inflammation or ocular co-morbidity		2 (3.3)				
Use of prohibited concomitant medication		11 (18.3)				
Suspension of study treatment		4 (6.7)				

Definition(s): CI = Confidence Interval; HR = Hazard Ratio

a Estimated based on Kaplan-Meier curve.

b HR of HUMIRA versus placebo from proportional hazards regression with treatment as factor.

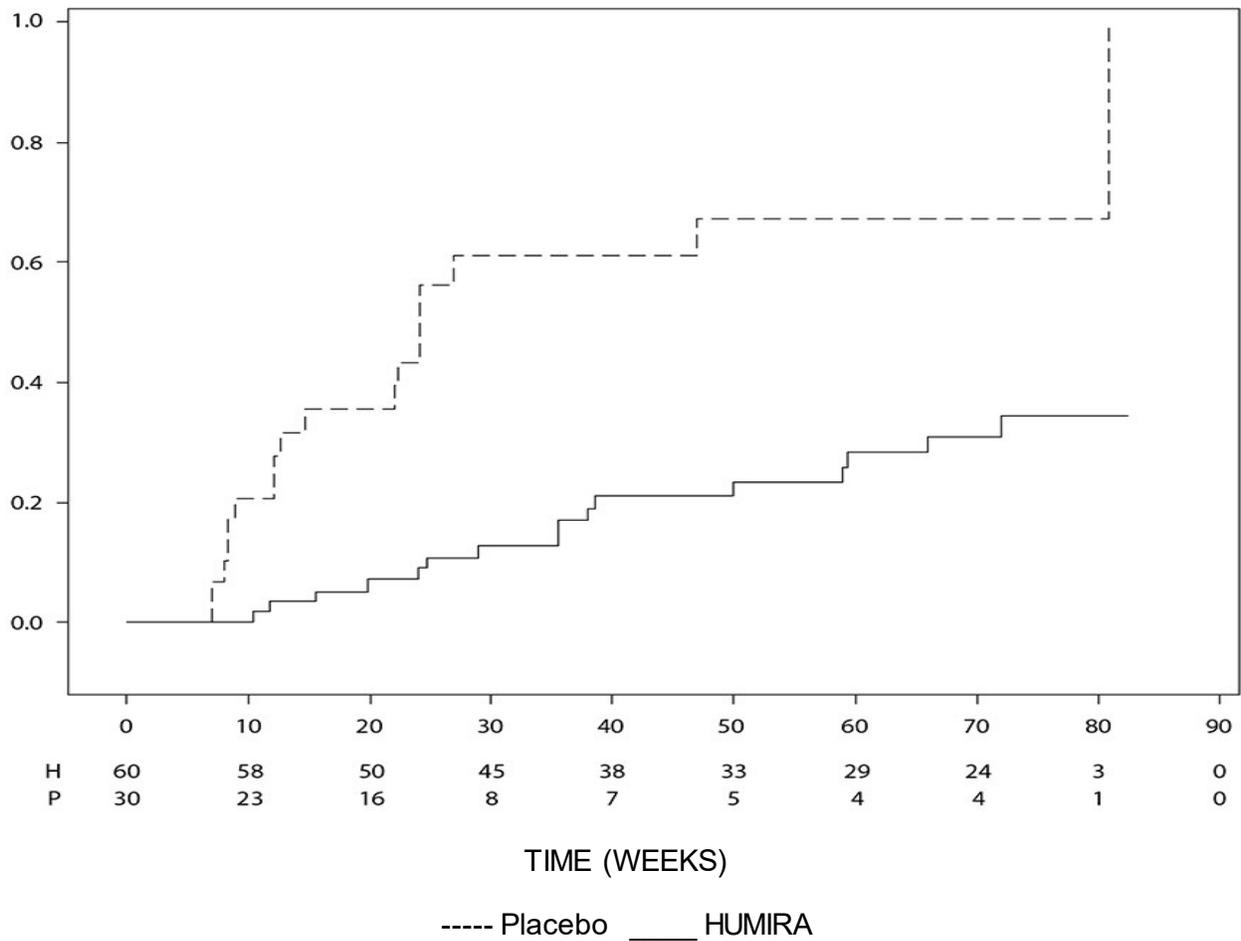
c Significance level of 0.001 was used at the interim analysis based on the Peto-Haybittle stopping rule.

d Derived from log rank test.

e One HUMIRA patient had two reasons for treatment failure (use of prohibited concomitant medication and suspension of study treatment).

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

**Figure 8. Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Pediatric Uveitis Study (Vertical Scale = Probability of Failing Treatment)**



## 15 NON-CLINICAL TOXICOLOGY

### 15.1 Comparative Non-Clinical Pharmacology and Toxicology

#### 15.1.1 Comparative Non-clinical Pharmacodynamics

#### **In Vitro Studies**

Comparative *in vitro* studies were performed to demonstrate similarity between AVT02 and Humira (adalimumab, EU and US) with respect to the Fab-related mode of action, as well as the Fc-mediated effector functional activities.

Binding to soluble TNF $\alpha$  as well as subsequent inhibition of TNF $\alpha$ -mediated activities (apoptosis, cytokine release and T-cell activation) were assessed for AVT02 and Humira and found to be similar. In addition, binding to membrane bound TNF $\alpha$  and the associated reverse signaling (resulting in apoptosis) were also demonstrated to be similar between AVT02 and Humira.

Similarity for Fc-mediated effector function activities was assessed by Fc $\gamma$ R binding assays (Fc $\gamma$ RIIIa, 158F and 158V, resp., Fc $\gamma$ RIa, Fc $\gamma$ RIIa, Fc $\gamma$ RIIb and Fc $\gamma$ RIIIb), by analysis of binding to C1q and FcRn, and in cell based assays for antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). In all cases, AVT02 was demonstrated to be similar to Humira.

#### 15.1.2 Comparative Toxicology

Comparative *in vivo* toxicology studies evaluating the similarity of the toxicity profile of AVT02 with that of Humira were not conducted.

#### 15.2 Non-Clinical Toxicology – Reference Biologic Drug.

### **General Toxicology**

#### **Acute Toxicity – Single-Dose Studies**

Three single-dose toxicity studies (two in mouse and one in rat) were conducted to obtain the qualitative and quantitative information about the acute toxicity profile of adalimumab after single intravenous administration.

In a mouse study, a single dosage of adalimumab (898 mg/kg) or vehicle control (phosphate buffered saline, PBS) was administered via a tail vein (5/sex/group). The animals were examined for clinical signs for 14 days after treatment. Necropsy was performed 14 days after treatment.

At the highest technically feasible dosage of 898 mg/kg adalimumab based on a 10 mL/kg injection volume and the highest available drug concentration, no deaths occurred. No clinical

sign was observed that could be attributed to adalimumab. Body weight gains of the drug-treated mice were comparable to those of the control mice. Pathomorphology did not reveal any toxicologically relevant change. The minimal lethal dosage of adalimumab in mice is greater than 898 mg/kg.

A second single-dose study was done in mice and included an investigation of the formation of MAHAs. Four groups of mice (5/sex/group) were included in this study. The animals were treated intravenously with either a single dosage of vehicle (PBS), or 1.6 mg/kg, 16 mg/kg, or 786 mg/kg of adalimumab (drug substance batch AFP603). Clinical signs, especially the hair coat, were assessed. Blood samples were collected before treatment and at Weeks 3, 5, 7, 9, 11, and 13 after drug administration to determine the adalimumab concentration in serum with an ELISA and to detect MAHA formation with two different ELISA techniques. All animals were sacrificed and subjected to gross examination upon termination of the study. Spleen and skin were evaluated histopathologically.

The general department of the mice and the body weight gains were not affected by treatment with adalimumab. One male at 1.6 mg/kg died on Day 13 during blood sampling under halothane anesthesia. The death of this animal was considered to be associated with the halothane anesthesia and not associated with the adalimumab treatment. Local hair loss in the nasolabial area associated with loss of tactile hairs was observed in all females at 1.6 mg/kg and four out of five females in the control group from Week 5 onwards. The results indicate that the hair loss is not associated with adalimumab treatment since the same effect also was observed in the control mice.

The serum concentration curve of adalimumab was plotted for one mouse from each group. In the control and 1.6 mg/kg groups, the adalimumab serum concentration was always less than 0.6 mcg/mL, whereas at 16 mg/kg group, 70 mcg/mL was found at Week 3. No adalimumab was detected from Week 5 onwards at this dose. At 786 mg/kg group, a concentration as high as 484 mcg/mL was found at Week 3 and a measurable concentration of adalimumab was found up to nine weeks post injection.

The time course of MAHA development also was measured in one mouse from each group. MAHAs were not detected in the control mouse or any pre-treatment sample. Using a double sandwich (double antigen) MAHA assay (called MAHA-1 assay in the report) sensitive to inhibition by adalimumab in the blood, MAHAs were detected as early as Week 5 for the mouse treated at 1.6 mg/kg and not detected until Week 11 for the mouse treated at 16 mg/kg, whereas MAHAs were not detected at any time point for the mouse treated at 786 mg/kg, which was attributed to the assay interference by the high concentrations of circulating adalimumab. Using a direct capture (sandwich) MAHA assay (called MAHA-2 assay in the report) that is less sensitive to adalimumab interference, MAHAs were detected from Week 5 onwards in mice at

1.6 mg/kg and 16 mg/kg and at Weeks 9 and 13 in the 786 mg/kg mouse. Once the kinetics and titers were determined from the sample mouse of each group, MAHAs in all mice treated with adalimumab were analyzed at a dilution of 1:1000 at Week 5 for the 1.6 mg/kg and 16 mg/kg mice, and at Week 13 for the 786 mg/kg mice by the direct capture MAHA assay. MAHAs were detected in all samples, indicating that all the adalimumab-treated mice were MAHA positive after a single intravenous injection.

In the rat single-dose study, a single dosage of adalimumab (898 mg/kg, drug substance batch AF601-Ex pool) or vehicle control (PBS) was administered via a tail vein (5/sex/group). The animals were examined for clinical signs for 14 days after drug administration. Necropsy was performed 14 days after treatment.

At the highest technically feasible dosage of 898 mg/kg adalimumab based on a 10 mL/kg injection volume and the highest available drug concentration, no deaths occurred. Drug-related clinical signs were not observed. Body weight gains of the drug-treated rats were comparable to those of the control rats. Necropsy showed slightly to moderately enlarged spleens in three males at 898 mg/kg, and slightly enlarged spleens in three males in the control group. Histopathology of the enlarged spleens revealed moderate to marked extramedullary hematopoiesis. These changes were not attributed to the drug treatment because they were observed in the control group as well as in the treatment group.

In summary, adalimumab is well tolerated at the highest technically feasible dose and the minimal lethal dose after a single intravenous injection is greater than 898 mg/kg in mice and rats. Adalimumab is immunogenic in mice after a single intravenous dose.

## **Long-Term Toxicity – Multiple-Dose Studies**

### **Mouse (Four-Week Study)**

In a four-week mouse study, the mice were randomly distributed into three study groups. The highest dose in this study provided 16 times the maximum dosage of 10 mg/kg used in early clinical studies.

The mice were intravenously administered either vehicle control (PBS) or adalimumab (drug substance batch AFP603) once per week on days 1, 8, 15, 22, and 29. The main study group was terminated on Day 30 and the recovery study group was allowed to recover for four weeks without further treatment after the last dose. The mice were observed for drug-related clinical signs at least once daily. Body weight and food consumption was recorded once weekly. Blood samples (0.3 mL) in the main and recovery study groups were collected from the retro-orbital venous plexus under light ether anesthesia on Days 30 and 57 (recovery group only) from mice chosen for hematology, clinical biochemistry and immunogenicity analyses

There was no clinical sign of toxicity or behavioral changes related to drug treatment. Body weight and body weight gain of drug-treated animals remained in the same range as controls over the treatment and recovery periods.

The results of the toxicokinetic evaluation, using adalimumab level values from pooled serum, revealed that weekly iv administrations of 32, 70.9 and 157.2 mg/kg of adalimumab to mice for four weeks resulted in an increase of serum C<sub>max</sub> and AUC values (C<sub>max</sub>: 1193, 1528, 4231 mcg/mL in males, 794, 2069, 5028 mcg/mL in females; AUC: 66782, 104612, 190342 mcg•h/mL in males, 81598, 120693, 240366 mcg•h/mL in females). A slightly lower terminal half-life was observed for male mice than for female mice (97 to 112 hours versus 134 to 259 hours). The AUC values increased in a slightly less than proportional manner and were somewhat higher in female mice. There was, however a high degree of variability in the data.

Significant formation of MAHAs was detected in male and female mice in all drug-treated groups starting on the 8th day after the first administration. The level of MAHAs increased with subsequent doses. Significant differences were observed between 32.0 mg/kg and 70.9 mg/kg dosages ( $p < 0.01$ ) and the 32.0 mg/kg and 157.2 mg/kg dosages ( $p < 0.01$ ), but not between the 70.9 mg/kg and 157.2 mg/kg dosages ( $p > 0.05$ ). This indicates that the MAHAs are detected at all dose levels. Whether the differences between dose levels are due to assay interference or true differences in immunogenicity can not be determined.

### **Monkey (Four-Week Study)**

A four-week study was performed to investigate the potential toxicity of adalimumab in *cynomolgus* monkeys. A total of 32 monkeys (16 males and 16 females) were distributed randomly into four dosage groups, and were administered either the vehicle control (PBS), or adalimumab at 32, 70.9, or 157.2 mg/kg (drug substance batch AFP603) via intravenous injection (*vena saphena magna* of the right or left hind leg). The injections were given once per week on days 1, 8, 15, 22, and 29 for a total of five doses.

The toxicokinetic results showed a dose-proportional increase of serum maximum concentration (C<sub>max</sub>) of adalimumab and serum AUC. The central volume of distribution ( $V_c = \text{dose} / C(0)$ ) was  $39.7 \pm 7.9$  mL/kg (mean  $\pm$  standard deviation). The AUCs corresponding to single-dose amounts of 32, 70.9, and 157.2 mg/kg, were  $201317 \pm 88835$ ,  $359667 \pm 127283$  and  $808900 \pm 200581$  mcg•h/mL, respectively. The terminal half-life was  $13.5 \pm 4.6$  days and the clearance was  $0.20 \pm 0.07$  mL/h/kg. No sex dependency of pharmacokinetic parameters and no influence of dose on total clearance were noted.

Immunohistochemistry data showed a minimal decrease of CD21<sup>+</sup> B-cells in the spleen follicles of the male monkeys treated with 70.9 and 157.2 mg/kg.) A reduced cytoplasmic immunostaining of IgG and IgM was also observed in the germinal centers of the follicles in

most treated monkeys at all doses. No such change was observed in the follicles in the lymph nodes. All these changes were very subtle and generally reversible. Therefore, these changes were considered to be the result of pharmacologically functional effects of adalimumab rather than toxicological effects. No deposits of immune-complexes were found in kidney, lung, liver, skin, spleen, thymus, lymph nodes, skeletal muscle, and heart.

### **Monkey (39-Week Study)**

A 39-week study in *cynomolgus* monkeys was done to evaluate the potential toxicity and reversibility of any toxic effect of adalimumab. A total of 32 animals (16 males and 16 females) were randomly distributed into four groups, and were administered either vehicle control (PBS buffer) or adalimumab at 32, 82.9, or 214.8 mg/kg. The test article or control agent was administered by intravenous injection into a vena saphena magna, once per week for 39 weeks (total of 40 injections).

There were no significant differences in clinical signs of toxicity or behavior and food consumption over the treatment and recovery periods in the drug-treated groups as compared to the control animals. Body weights of the animals treated with 32 and 82.9 mg/kg were not affected as compared with the control animals. In the 214.8 mg/kg group, a slight, transient decrease in the body weight was observed in test Week 4, and completely recovered from test Week 6 onwards. The body weights of the female animals in this group were decreased slightly from test Week 2 onwards. The decreases were not statistically significant at  $p \leq 0.01$  as compared with the control animals and were within the normal fluctuation of body weight.

The examination of immune complexes showed a reduced antigen expression of IgG and IgM in the follicular dendritic cells of the spleen in all drug-treated monkeys. Concomitantly, the follicular dendritic cells were reduced in number and the normally dense network was altered. In parallel, the IgG or IgM positive plasma cell count increased slightly in the spleen independently of the different compartments. These changes were considered to be the pharmacologically functional effects of adalimumab rather than toxicological effects.

Toxicokinetic results reported in Report No. MPF/EBB 9741 showed an increase of steady-state serum concentrations and AUC values. At dosages of 32, 82.9, and 214.8 mg/kg of adalimumab, the corresponding  $C_{max}$  (mean  $\pm$  standard deviation) at five minutes after the last administration were  $2731 \pm 467$ ,  $6527 \pm 2450$ ,  $13563 \pm 1740$  mcg/mL and the corresponding serum AUCs were  $304774 \pm 74634$ ,  $617368 \pm 233959$ , and  $1299965 \pm 228114$  mcg•h/mL, respectively. The corresponding clearances were  $0.11 \pm 0.04$ ,  $0.16 \pm 0.07$ , and  $0.17 \pm 0.03$  mL/h/kg, respectively. The terminal half-life, evaluated from data obtained during the recovery phase of two male and two female monkeys, was  $16.2 \pm 3.4$  days. No sex dependency of pharmacokinetic parameters and no influence of dose on the clearance were noted.

The distribution of adalimumab in the vascular compartment was broad in the lungs, liver, and skin at 214.8 mg/kg. Cartilage staining in the bronchi with anti-adalimumab antibodies was observed in several treated monkeys at 32 mg/kg onwards. In the synovial membrane, adalimumab was detected in the vascular compartment mainly at 214.8 mg/kg, and additionally in one male monkey at 82.9 mg/kg.

Most of the immunohistochemical changes observed in kidneys, spleen, and lungs were found to be reversible. However, the cellular diminution in the thymus in males was partially reversed and did not reach the cellularity of the control animals after a 20-week recovery period. No adalimumab could be detected after the 20-week recovery period in the vessels of the organs and tissues examined.

### **Carcinogenicity**

No carcinogenicity study was performed for adalimumab.

### **Genotoxicity**

#### **In Vitro Genotoxicity**

The mutagenic potential of adalimumab was tested in the Ames test and in the *Escherichia coli* reverse mutation assay. These tests are based on the ability of the test article to induce reverse mutations in selected loci of bacteria. *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537, as well as *Escherichia coli* strain WP2 uvrA were used. Adalimumab (drug substance batch AF601-Ex pool) was tested at concentrations of 0, 20, 100, 500, 2500 and 5000 mcg/plate. Three plates were used per dose. Positive controls and a vehicle control (PBS buffer) were included in each experiment. Both the standard plate test (Ames test) and preincubation test with and without the addition of an exogenous metabolic activation system (S-9 fraction prepared from the livers of Aroclor 1254 treated rats) were performed. The results were considered positive if the revertant rate of a treatment group was at least twice that of the spontaneous revertant rate (vehicle control), a dose-response relationship occurred, and the experiments were reproducible.

No bacteriotoxic effect, such as reduced His<sup>-</sup> or Trp<sup>-</sup> background growth and decreased number of His<sup>+</sup> or Trp<sup>+</sup> revertants, were observed in adalimumab-treated plates when compared to the vehicle control. There was no increase in the number of mutant colonies under any experimental conditions in any strain of bacteria for the test article, whereas the positive controls showed the expected response when compared to the vehicle control. Therefore, the test substance is not mutagenic either in the Ames test or in the *E. coli* reverse mutation assays.

## **In Vivo Genotoxicity**

The potential clastogenic and spindle poison effects of adalimumab were tested in an in vivo micronucleus assay in NMRI mice after a single intravenous dose. The mice were randomly allocated into eight groups: two vehicle control groups (five mice/sex/group), four treatment groups (five mice/sex/group), and two positive control groups (five mice/group). The mice were intravenously treated once either with the vehicle control (PBS buffer); 224.5, 449.0, or 898 mg/kg (two groups) of adalimumab (drug substance batch AF601-Ex pool); or positive controls of 20 mg cyclophosphamide (two male and three female) or 0.15 mg/kg vincristine (three male and two female). All animals were sacrificed 24 hours after treatment except for one vehicle control group and one 898 mg/kg group, which were sacrificed 48 hours after dosing.

Bone marrow slides were prepared and stained with eosin and methylene solution, followed by Giemsa stain. The slides were examined microscopically for the following parameters: number of polychromatic erythrocytes (PCE), number of PCE containing micronuclei (MN), number of normochromatic erythrocytes (NCE), number of NCE containing MN, number of small MN, and number of large MN. The ratio of PCE to NCE was calculated. The results were considered positive if the following criteria were met: a dose-related and significant increase in the number of micronucleated PCE at the 24-hour and/or 48-hour intervals, and the proportion of cells containing MN exceeded both the values of the concurrent negative control range and the negative historical control range.

The number of PCE and NCE containing MN in the adalimumab-treated groups was not significantly different from the concurrent, negative controls at any of the sacrificed intervals. However, the percentage of small MN in PCE in the cyclophosphamide-treated group and the percentage of large MN in PCE in the vincristine-treated group increased significantly as compared with the vehicle control. The ratio of PCE to NCE in all dose groups was always in the same range as that of the control values, suggesting normal erythropoiesis.

The results indicate that adalimumab does not have clastogenic activity or spindle poison effects. Also, no inhibition of erythropoiesis induced by the treatment with adalimumab was observed in NMRI mice.

## **Reproductive and Developmental Toxicology**

In pregnant monkeys, adalimumab was distributed into the serum of the fetus and into the amnion fluid showing a distribution pattern that would be expected of a human IgG in a pregnant woman. No drug-related toxicity was observed. Distribution of adalimumab into the milk was not determined.

## 16 SUPPORTIVE PRODUCT MONOGRAPHS

HUMIRA® (adalimumab), Submission Control No.: 225872,  
Date of Approval: June 25, 2019  
AbbVie Corporation

40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection  
mg in 0.1 mL sterile solution (100 mg/mL) subcutaneous injection  
20 mg in 0.2 mL sterile solution (100 mg/mL) subcutaneous injection  
40 mg in 0.4 mL sterile solution (100 mg/mL) subcutaneous injection  
80 mg in 0.8 mL sterile solution (100 mg/mL) subcutaneous injection

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSimlandi™

#### Adalimumab injection

Read this carefully before you start taking Simlandi and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Simlandi.

Simlandi is a biosimilar biologic drug (biosimilar) to the reference biologic drug HUMIRA. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

**Simlandi treatment should be started and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), Ankylosing spondylitis (AS), adult Crohn's disease (CD), adult ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), psoriasis (Ps), or adult and pediatric uveitis, and familiar with the Simlandi efficacy and safety profile.**

#### Serious Warnings and Precautions

- **Allergic reactions:** If you/your child develop a severe rash, swollen face or difficulty breathing while taking adalimumab, call your/your child's doctor right away.
- **Hepatoplenic T-cell lymphoma:** Very rare reports of hepatosplenic T-cell lymphoma (HSTCL), a rare serious lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most patients had also been treated with other medications for Crohn's disease and the majority were in adolescent and young adult males. The link between HSTCL and adalimumab is not clear.
- **Other cancers:** There have been very rare cases of certain kinds of cancer in patients taking adalimumab or other TNF- blockers. Some patients receiving adalimumab have developed types of cancer called non-melanoma skin cancer. Tell your/your child's doctor if you/your child have a bump or open sore that does not heal. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you/your child take adalimumab or other TNF-blockers, your/your child's risk may increase. There have been cases of lymphoma and other cancers, including unusual types, in children, adolescents and young adults taking TNF-blocking agents, including adalimumab, which sometimes resulted in death. For children

and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.

- **Lupus-like symptoms:** Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you/your child have chest pains that do not go away, shortness of breath, joint pain or a rash on your/your child's cheeks or arms that gets worse in the sun, call your/your child's doctor right away. Your/your child's doctor may decide to stop your/your child's treatment.
- **Nervous system diseases:** There have been rare cases of disorders that affect the nervous system of people taking adalimumab or other TNF-blockers. Signs that you/your child could be experiencing a problem affecting your/your child's nervous system include: numbness or tingling, problems with your/your child's vision, weakness in your/your child's legs, and dizziness.
- **Serious infections:** There have been rare cases where patients taking adalimumab or other TNF-blocking agents have developed serious infections. Some of these cases have been life-threatening. Such infections include tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis). Infection causes include tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria), and very rare cases of hepatitis B infection relapse.
- **Blood problems:** In some instances, patients treated with TNF-blocking agents may develop low blood counts, such as anemia (low red blood cells) or low platelets. If you/your child develop symptoms such as persistent fever, bleeding, or bruising, you should contact your/your child's doctor right away.

### What is Simlandi used for?

Simlandi is a medicine that is used in:

- adults with rheumatoid arthritis, which is an inflammatory disease of the joints.
- adults with psoriatic arthritis, which is an inflammatory disease of the joints and skin.
- adults with ankylosing spondylitis, which is a form of arthritis.
- adults with Crohn's disease, which is an inflammatory disease of the digestive tract.
- pediatrics with polyarticular juvenile idiopathic arthritis who are 2 years of age and older and require a full 40 mg dose based on body weight.
- adults with ulcerative colitis, which is an inflammatory disease of the bowel (colon).
- adults or adolescents (12 to 17 years of age, weighing  $\geq 30$  kg) with moderate to severe hidradenitis suppurativa (HS) who have not responded to antibiotics. HS is a painful, progressive, chronic inflammatory skin disease that causes nodules, abscesses, sinus tracts and fistulas under the breasts, underarms, buttocks and groin.
- adults with psoriasis, which is an inflammatory disease of the skin. The doctor prescribed Simlandi to

- reduce the signs and symptoms of your plaque psoriasis.
- adults with uveitis, which is an inflammatory disease of the eye.
- children (weighing  $\geq 30$  kg) with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye.

Patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, psoriasis, or uveitis may be given other medicines for their disease before they are given Simlandi. If you have adult ulcerative colitis or you have Crohn's disease, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simlandi to reduce the signs and symptoms of your disease.

### **How does Simlandi work?**

Simlandi is a recombinant fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) that specifically binds to tumor necrosis factor- $\alpha$  (TNF) and blocks its interaction with the p55 (TNFR1) and p75 (TNFR2) cell surface TNF receptors, thereby neutralizing the effect of TNF in inflammatory conditions. Simlandi is approved as a biosimilar to Humira (adalimumab).

People with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, adult ulcerative colitis, hidradenitis suppurativa or psoriasis have too much of TNF-alpha in their bodies. The extra TNF-alpha in your/your child's body can attack normal healthy body tissues and cause inflammation, especially in the tissues of your bones, cartilage, joints, digestive tract and skin. By binding to TNF-alpha, adalimumab decreases the inflammation process of these diseases.

Simlandi helps reduce the signs and symptoms of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis (such as pain and swollen joints), may help improve your/your child's ability to perform daily activities (such as getting dressed, walking and climbing stairs), and may help prevent further damage to your/your child's bones and joints. In addition, Simlandi helps reduce the signs and symptoms of ankylosing spondylitis (back pain and morning stiffness), and adult Crohn's disease or adult ulcerative colitis (abdominal pain and diarrhea).

Simlandi is also used to treat inflammatory lesions (nodules and abscesses) in adults and adolescents (12 to 17 years of age, weighing  $\geq 30$  kg) with hidradenitis suppurativa.

Simlandi also helps reduce the signs and symptoms of psoriasis (such as pain, itching and scaly patches on skin).

Simlandi helps control uveitis by reducing the risk of inflammation and loss of vision in adult and pediatric patients.

Simlandi, however, can also lower your/your child's body's ability to fight infections. Taking Simlandi can make you/your child more prone to getting infections or make any infection you/your child have worse.

### **What are the ingredients in Simlandi**

Medicinal ingredient:

Adalimumab

Non-medicinal ingredients:

Polysorbate 80, sodium chloride, sucrose, and water for injection.

**Simlandi comes in the following dosage forms:**

40 mg in 0.4 mL sterile solution (100 mg/mL) for injection  
(Pre-filled Syringe with needle guard and Autoinjector)

80 mg in 0.8 mL sterile solution (100 mg/mL) for subcutaneous injection  
(Pre-filled Syringe with needle guard)

**Do not use Simlandi if:**

- you/your child has a known hypersensitivity (allergy) to adalimumab or any of its components. For a complete listing, (see **6 DOSAGE FORMS, COMPOSITION AND PACKAGING**).
- you/your child has a severe infection such as sepsis (an infection of the blood), tuberculosis (a serious infection usually affecting the lungs) and opportunistic infections (infections that can occur when your defence system against infections is weak (See **Serious Warnings and Precautions Box**).
- you/your child has moderate to severe heart failure (when the heart does not pump normally (see **Serious Warnings and Precautions Box**).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Simlandi. Talk about any health conditions or problems you may have, including if:**

- you are taking anakinra or abatacept (other biologic drugs);
- a surgery is planned for you in the near future;
- you suffer from congestive heart failure (see **Do not use Simlandi if**);
- you suffer from any form of cytopenia (a condition where you do not have enough blood cells);
- you have lasting fever, bruising, bleeding or paleness;
- you develop lupus-like symptoms (such as rash, fever, fatigue, headache, painful joints)
- you have a history of tuberculosis;
- you have a history of fungal infections;
- you have a history of hepatitis B (an infection of the liver)

- you have a history of cancer such as leukemia (a cancer of the blood);
- you have a history of lymphoma (a cancer affecting the white blood cells)

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Other warnings you should know about:**

If you/your child received Simlandi while pregnant, your/her baby may be at higher risk for getting an infection for up to approximately five months after the last dose of Simlandi received during pregnancy. It is important that you tell your/her baby's doctors and other healthcare professionals about your/her Simlandi use during pregnancy so they can decide when your/her baby should receive any vaccine.

**BEFORE you/your child use Simlandi, talk to the doctor or pharmacist if:**

- you/your child have or have had any kind of infection including an infection that is in only one place in your/your child's body (such as an open cut or sore), or an infection that is in your/your child's whole body (such as the flu). Having an infection could put you/your child at risk for serious side effects from Simlandi. If you are unsure, ask your/your child's doctor.
- You/your child have a history of infections that keep coming back or other conditions that might increase your/your child's risk of infections, including fungal infections.
- you/your child have ever had tuberculosis, or if you/your child have been in close contact with someone who has had tuberculosis. If you/your child develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your/your child's doctor right away. Your/your child's doctor will need to examine you/your child for tuberculosis and perform a skin test.
- you/your child resided or travelled to areas where there is a greater risk for certain kinds of infections such as tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, or parasitic infections. These infections are caused by a bacteria or a fungus that can affect the lungs or other parts of your/your child's body. If you/your child take Simlandi, these may become active or more severe. If you don't know if you/your child have lived in or travelled to an area where these infections are common, ask your/your child's doctor.
- you/your child have ever had liver injury or hepatitis B virus infection or are at risk of developing this infection. Signs and symptoms include the following: yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain, fever, dark brown-coloured urine, vomiting, and abdominal pain. If you/your child experience any of these signs and symptoms, contact your/your child's doctor immediately. These symptoms may occur several months after starting therapy with Simlandi.
- you/your child experience any numbness or tingling or have ever had a disease that affects your/your child's nervous system like multiple sclerosis or Guillain-Barré syndrome.

- you/your child have or have had heart failure.
- you/your child are scheduled to have major surgery or dental procedures.
- you/your child are scheduled to be vaccinated for anything. It is recommended that pediatric patients, if possible, be brought up to date with all immunizations according to current guidelines before starting Simlandi.
- you/your child are taking other medicines for your/your child's rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, or other conditions. You/your child can take other medicines provided your/your child's doctor has prescribed them or has told you it is acceptable that you/your child take them while you/your child are taking Simlandi. It is important that you tell your/your child's doctor about any other medicines you/your child are taking for other conditions (for example, high blood pressure medicine) before you/your child start taking Simlandi.
- you are taking other medicines for your Crohn's disease or other conditions. You can take other medicines provided your doctor has prescribed them or has told you it is acceptable that you take them while you are taking Simlandi. It is important that you tell the doctor about any other medicines you are taking for other conditions before you start taking Simlandi.
- you/your child are taking any over-the-counter drugs, herbal medicines and vitamin and mineral supplements.
- you/your child are pregnant or could become pregnant.
- you/your child are breast-feeding or plan to breast-feed.

***If you are not sure or have any questions about any of this information, ask your/your child's doctor.***

**The following may interact with Simlandi:**

Other TNF-blockers such as:

- etanercept (Enbrel®),
- abatacept (Orencia®)
- anakinra (Kineret®)
- infliximab (Remicade®)
- certolizumab pegol ((Cimzia®)
- golimumab (Simponi®)

**How to take Simlandi**

Simlandi is administered by injection under the skin (by subcutaneous injection).

For instructions on the use of Simlandi, each carton contains the following:

- this Patient Medication Information Leaflet,
- a detailed, illustrated Information for the User,
- a Quick Reference Guide.

For step-wise instructions explaining how to inject Simlandi, please also refer to the detailed, illustrated Information for the User for both the pre-filled syringe and the Autoinjector.

For quick reference, you may also use the Quick Reference Guide for the pre-filled syringe and the Autoinjector.

Please carefully read the following instructions and the illustrated instructions in the **Information for the User** and follow them step-by-step. You will be assisted by your/your child's doctor or assistant on the technique of injection. Do not attempt to inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example, a healthcare professional, a family member or friend.

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

### **Setting Up**

- Remove one dosing tray containing a Simlandi Autoinjector or Pre-filled Syringe with needle guard from the carton in the refrigerator.
  - Do not shake or drop the Autoinjector or pre-filled syringe.
  - Do not use the Autoinjector or pre-filled syringe if it is frozen or if it has been left in direct sunlight.
  - If you are using the Autoinjector, only remove the caps **immediately** before injection.
- Set up the following on a clean, flat working surface:
  - One Simlandi Autoinjector
  - The alcohol swab provided

-OR-

- One pre-filled syringe of Simlandi for injection
  - The alcohol swab provided
- If you do not have all of the pieces you need to give yourself/your child an injection, call your pharmacist. Use only the items provided in the carton your Simlandi prescription comes in.

- Make sure that the name Simlandi appears on the dosing tray and on the Autoinjector or pre-filled syringe label.
- Check the expiry date on the Autoinjector or pre-filled syringe. Do not use the product if the date has passed the month and year shown.
- Make sure the liquid in the Autoinjector or pre-filled syringe is clear and colourless. Do not use the Autoinjector or pre-filled syringe if the liquid is cloudy or if flakes or particles can be seen.
- Have a puncture-proof container nearby for disposing the used Autoinjector, pre-filled syringe and needles.

**FOR YOUR/YOUR CHILD'S PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS**

**Choosing and Preparing the Injection Site**

- Wash your hands thoroughly.
- Choose a site on the front of your/your child's thighs or abdomen. If you choose your/your child's abdomen, you should avoid the area two inches around your/your child's navel.
- Choose a different site each time you give yourself/your child an injection. Each new injection should be given at least one inch from the site you used before. Do **NOT** inject into areas where the skin is tender, bruised, red or hard or where you/your child have scars or stretch marks.
- You may find it helpful to keep notes on the location of previous injections.
- Wipe the injection site where Simlandi is to be injected with the alcohol swab provided, using a circular motion. Do **NOT** touch this area again before giving the injection.

**Preparing the Dose for Injection**

**Simlandi Autoinjector**

- Hold the Autoinjector with the clear cap pointing up. Check the appearance of the solution through the window on the side of the Autoinjector to make sure the liquid is clear and colourless. Do not use the Autoinjector if the liquid is cloudy or discoloured or has flakes or particles in it. Do not use if frozen or if it has been left in direct sunlight.

**Simlandi Pre-filled syringe**

- Remove the needle cover from the syringe, taking care not to touch the needle with your fingers or allowing it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle, this is acceptable.

## **Injecting Simlandi**

### **Simlandi Autoinjector**

- Only remove the clear cap **immediately** before injection. Throw the clear cap away; do not put the clear cap back on the Autoinjector, as this could damage the needle.
- Turn the Autoinjector so that the orange needle sleeve points to the injection site.
- Squeeze the skin at the injection site to make a raised area and hold it firmly.
- Place the orange needle sleeve straight up (90° angle) from the injection site and hold the Autoinjector so that you can see the window.
- Push and keep pushing the Autoinjector down onto the injection site.
  - The first “click” will signal the start of the injection.
  - The injection may take 10 seconds to complete after this first “click”
- Keep pushing the Autoinjector down onto the injection site.
- The injection is complete when the orange indicator has stopped moving and you may hear a second “click”.

**DO NOT** lift up or let go of the pressure from the injection site until you have confirmed that the injection is complete.

- When the injection is completed, slowly pull the Autoinjector from the skin. The orange needle sleeve will cover the needle tip

If there are more than a few drops of liquid on the injection site, call your healthcare provider for help.

- After completing the injection, place a cotton ball or gauze pad on the skin of the injection site

#### **DO NOT RUB**

Slight bleeding at the injection site is normal.

- Put your used needles, Autoinjector and sharps in an approved disposal container.

### **Simlandi Pre-Filled Syringe**

- Holding the prefilled syringe in one hand, gently pull the needle cover off with the other hand.
  - Throw the needle cover away and never recap
  - Do not touch the needle with your finger or let the needle touch anything.
  - You may see a drop of liquid at the end of the needle. This is normal
- Hold the body of the prefilled syringe in one hand between the thumb and index finger, like a pencil.
  - Do not pull back on the plunger at any time.
- Gently squeeze the area of cleaned skin at the injection site with your other hand and hold firmly.
- Insert the needle into the squeezed area of skin at about a 45o angle using a quick dart-like movement.
- After the needle is in, let go of the skin.
- Slowly push the plunger all the way in until all of the liquid is injected and the prefilled syringe is empty.

- Slowly lift your finger from the plunger. The plunger will move up with your finger and retract (remove) the needle from the injection site into the needle guard.
  - The needle will not retract unless all the liquid is injected.
  - Speak to your doctor or pharmacist if you think you have not given the full dose.
- After completing the injection, place a cotton ball or gauze pad on the skin of the injection site,
  - DO NOT RUB**
  - Slight bleeding at the injection site is normal.
- Put your used needles, syringe and sharps in an approved disposal container.
- Other items may be put in the household trash.

### **Disposing of Supplies**

- You should always check with your/your child's healthcare provider (e.g., doctor, nurse, or pharmacist) for instructions on how to properly dispose of used needles and syringes (including the Autoinjector). Do **NOT** use the same needle and syringe more than once. You should follow any special provincial or local laws regarding the proper disposal of needles and syringes. **Do NOT throw used needles or syringes (including the Autoinjector) in the household trash or recycling bin.**
- Dispose of used needles and syringes (including the Autoinjector) in a container made especially for this purpose (sharps container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labelled "Used Syringes". Do not use glass or clear plastic containers.
- Always keep the container out of the reach of children.
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your/your child's doctor, nurse or pharmacist. **DO NOT THROW THE CONTAINER IN THE HOUSEHOLD TRASH OR RECYCLING BIN.**
- The used alcohol pads may be placed in the trash, unless otherwise instructed by your/your child's doctor, nurse or pharmacist.

### **Usual Dose:**

#### **Adults with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis:**

- The recommended dose is 40 mg administered every other week as a subcutaneous injection.

#### **Adults with Crohn's Disease or Ulcerative Colitis:**

- The recommended induction dose is 160 mg at Week 0, followed by 80 mg at Week 2 administered by subcutaneous injection. The first dose of 160 mg can be given in one day (four 40 mg injections or two 80 mg injections) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day). The second dose of 80 mg at Week 2 is given as two 40 mg injections or one 80 mg injection in one day.
- The recommended maintenance dose regimen is 40 mg every other week beginning at Week

4.

**Adults with Hidradenitis Suppurative:**

- The recommended initial dose is 160 mg, followed by 80 mg two weeks later administered by subcutaneous injection. The first dose of 160 mg at Week 0 can be given in one day (four 40 mg injections or two 80 mg injections) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day) or split over two consecutive days (two 40 mg injections or one 80 mg injection each day). The second dose of 80 mg at Week 2 is given as two 40 mg injections or one 80 mg injection in one day.
- The recommended maintenance dose regimen is 40 mg every week beginning four weeks after the initial dose.

**Adults with Psoriasis or Uveitis:**

- The recommended dose is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose administered by subcutaneous injection. The first dose of 80 mg can be given as two 40 mg injections or one 80 mg injection.

**Adolescents, 12 to 17 years of age weighing  $\geq$  30 kg, with Hidradenitis Suppurativa:**

- The recommended initial dose is 80 mg administered by subcutaneous injection (two 40 mg injections or one 80 mg injection), followed by 40 mg every other week starting one week later. Depending on your/your child's response, the doctor may increase the dose to 40 mg every week.

**Polyarticular juvenile idiopathic arthritis, weighing  $\geq$  30 kg:**

- The recommended dose of SIMLANDI is 40 mg subcutaneously every other week. SIMLANDI is only available for children who require the full 40 mg dosage. The autoinjector and pre-filled syringe are not designed to deliver a portion of the 40 mg dose.

**Pediatric uveitis, weighing  $\geq$  30 kg:**

- The recommended dose of SIMLANDI is 40 mg subcutaneously every other week. SIMLANDI is only available for children who require the full 40 mg dosage. The autoinjector and pre-filled syringe are not designed to deliver a portion of the 40 mg dose.

**Overdose:**

If you think you, or a person you are caring for, have taken too much Simlandi, contact a health care professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you/your child forget to give yourself/your child an injection, you/your child should inject the missed dose of Simlandi as soon as you/your child remember. Then administer the next dose as you would have on the originally scheduled date.

### **What are the possible side effects from using Simlandi?**

These are not all the possible side effects you may have when taking Simlandi.

Like all medicines, Simlandi can cause side effects. Most side effects are mild to moderate. However, some may be serious and require treatment.

Tell your/your child's doctor immediately if you/your child experience any of the following:

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- sudden weight gain; this is possibly indicative of new or worsening heart failure
- bruising or bleeding very easily, looking very pale; this could mean a blood problem such as low red blood cells (anemia) or low platelets (other cells found in the blood)

Tell the doctor as soon as possible if you/your child notice any of the following:

- signs of infection such as fever, fatigue, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- arm or leg pain, swelling or redness
- bump or open sore that does not heal
- red scaly patches or raised bumps that are filled with pus; this could be new or worsening hidradenitis suppurativa, new or worsening psoriasis or a skin infection
- alopecia (loss of hair)
- changes in the colour of the skin
- changes in the colour of your/your child's urine (dark or red)
- worsening of the appearance of a scar
- night sweats
- weight loss
- pain in the abdomen or chest

If you experience any side effects not listed here, contact your healthcare professional.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN</b>
--

<b>AND WHAT TO DO ABOUT THEM</b>			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b> Injection site reaction		√	
<b>COMMON</b> Cough and cold symptoms, including sore throat Headache Rash Nausea Pneumonia Fever Abdominal pain	√     √	√  √ √ √ √	√
<b>RARE</b> Tuberculosis Other serious infections Nerve disorder Appendicitis Blood clots: abdominal pain, chest pain, leg or arm pain with redness and swelling Bladder infection Hepatitis (jaundice, [yellow skin, dark urine], abdominal pain, tiredness)		√ √ √ √ √ √ √	√ √ √ √ √ √

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional

### Reporting Side Effects

You can report any side suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store between 2 and 8°C (in a refrigerator) in the original carton until ready to use. **DO NOT FREEZE Simlandi.** Protect from light. Refrigerated Simlandi remains stable until the expiration date printed on the Autoinjector or pre-filled syringe. Do not use beyond the expiration date.

When needed, for example when you/your child are travelling, a Simlandi Autoinjector or pre-filled syringe can be stored at room temperature (up to 25°C/77°F) for a single maximum period of 14 days.

Once taken out of the refrigerator for room temperature storage, a Simlandi Autoinjector or pre-filled syringe must be used within 14 days, even if it is put back in the refrigerator. If not used within 14 days, the Simlandi Autoinjector or pre-filled syringe must be discarded. You should record the date when the Simlandi autoinjector or pre-filled syringe is first removed from the refrigerator.

Care should be taken to avoid dropping or crushing the product as it contains a glass syringe.

Keep Simlandi and all other medicines out of the reach and sight of children.

**If you want more information about Simlandi:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html>), the manufacturer's website [<https://www.jamppharma.com>], or by calling 1-866-399-9091 #2.

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