EUROPEAN MEDICINES AGENCY

Certificate: 08/21/155899
Request: 82695

Certificate of a Medicinal Product[1]
Certificado de Medicamento[1]
Certificat de Médicament[1]

This Certificate conforms to the format recommended by the World Health Organization. (Explanatory notes attached) / El presente certificado se adapta al formato recomendado por la Organización Mundial de la Salud. (Se adjuntan notas explicativas) / Ce Certificat est conforme à la présentation recommandée par l'Organisation Mondiale de la Santé. (Voir notes explicatives ci-jointes)

No. of Certificate / N° de certificado / N° du certificat: ***08/21/155899***

Exporting (Certifying) region / Región exportadora (que certifica) / Région d'exportation (certificateur) :
European Union / Unión Europea / Union Européenne :

Belgium, Bulgaria, Czechia, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, Sweden and United Kingdom (Northern Ireland).

Bélgica, Bulgaria, Chequia, Dinamarca, Alemania, Estonia, Irlanda, Grecia, España, Francia, Croacia, Italia, Chipre, Letonia, Lituania, Luxemburgo, Hungría, Malta, Paises Bajos, Austria, Polonia, Portugal, Rumanía, Eslovenia, Eslovaquia, Finlandia, Suecia y Reino Unido (Irlanda del Norte).

Belgique, Bulgarie, Tchéquie, Danemark, Allemagne, Estonie, Irlande, Grèce, Espagne, France, Croatie, Italie, Chypre, Lettonie, Lituanie, Luxembourg, Hongrie, Malte, Pays-Bas, Autriche, Pologne, Portugal, Roumanie, Slovénie, Slovaquie, Finlande, Suède et Royaume-Uni (Irlande du Nord).

For the UK, as from 1.1.2021, EU Law applies only to the territory of Northern Ireland (NI) to the extent foreseen in the Protocol on Ireland/NI. / Para el Reino Unido, desde el 1.1.2021, el Derecho de la UE es aplicable al territorio de Irlanda del Norte (IN) según lo estipulado en el Protocolo de Irlanda/IN. / Pour le Royaume-Uni, à partir du 1.1.2021, le droit de l'UE s'applique uniquement au territoire d'Irlande du Nord (IN) dans la mesure prévue par le Protocole sur l'Irlande/IN.

Importing (requesting) country / País importador (solicitante) / Pays importateur (sollicitant):

COLOMBIA

1 Name and pharmaceutical form of the product / Nombre y forma farmaceútica del medicamento / Dénomination et forme pharmaceutique du médicament:

Humira Solution for injection

1.1 Active substance(s)[2] and amount(s) per unit dose or unit volume[3]:
Principio(s) activo(s)[2] y cantidad(es) por unidad de dosis o unidad de volumen[3]:
Substance(s) active(s)[2] et quantité(s) par unité de dose ou unité de volume[3]:

Adalimumab; 40 mg/0.4 ml; 2 pre-filled syringes + 2 alcohol pads

For complete composition including excipients, see attached. [4]/ Para la composición completa incluidos los excipientes, véase información anexa. [4] / La composition complète du médicament, y compris les excipients, voir annexe. [4]

1.2 Is this product subject to a Community Marketing Authorisation? [5]
¿Está sujeto este medicamento a una autorización de comercialización comunitaria? [5]
Ce médicament fait-il l'objet d'une autorisation communautaire de mise sur le marché ? [5]

yes

Confidential

1.3 Is this product actually on the market in the exporting region?
¿Se encuentra este medicamento en el mercado de la región exportadora?
Ce médicament est- il actuellement commercialisé dans la région exportatrice?

yes

2.1 Number in the Community Register of Medicinal Products [7] and date of issue:
Número de autorización de comercialización comunitaria [7] y fecha de emisión:
Numéro au registre communautaire de mise sur le marché [7] et date de délivrance:

EU/1/03/256/013, 25.6.2015

2.2 Community Marketing Authorisation Holder (name and address):
Titular de la autorización de comercialización comunitaria (nombre y dirección):
Titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) :

AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany.

2.3 Status of the Community Marketing Authorisation Holder: [8]
Estatus del titular de la autorización de comercialización comunitaria: [8]
Statut du titulaire de l'autorisation communautaire de mise sur le marché : [8]

c

2.3.1 For categories (b) and (c) the name and address of the manufacturer producing the pharmaceutical form is: [9]
Para las categorías (b) y (c), el nombre y dirección del fabricante que produce la forma farmaceútica es: [9]
Pour les catégories (b) et (c), nom et l'adresse du fabricant de la forme pharmaceutique considérée : [9]

Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse 87 & 99 -101, 88212 Ravensburg, Germany [AND] AbbVie Biotechnology Ltd., KM 59.2, Road No. 2, Barceloneta, Puerto Rico 00617, United States. Site responsible for secondary packaging: Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen 2, 88214 Ravensburg, Germany.

2.4 Is the European Public Assessment Report (EPAR) appended? [10]
¿Se adjunta el informe europeo público de evaluación (EPAR)? [10]
Un rapport européen public d'evaluation (EPAR) est-il annexé ? [10]

no

2.5 Is the attached, officially approved product information included in the Community Marketing Authorisation?[11]
¿Se incluye la información sobre el medicamento adjunto en la autorización de comercialización comunitaria?[11]
L'information sur le médicament, officiellement approuvée, fait elle partie de l'autorisation communautaire de mise sur le marché ? [11]

yes

2.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address): [12]
Solicitante del Certificado, si es diferente del titular de la autorización de comercialización comunitaria (nombre y dirección): [12]
Demandeur du Certificat, s'il est autre que le titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) : [12]

3. Does the Certifying Authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?
¿La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmaceútica?
L'autorité certificatrice organise-t-elle des inspections périodiques de l'usine de production de la forme pharmaceutique?

yes

If no or not applicable, proceed to question 4 / Si no o no aplicable, pase a la pregunta 4 / Si la réponse est non ou sans objet, passer à la question 4.

3.1 Periodicity of routine inspections: ***Frequency of inspections is determined on risk-based approach.***
Periodicidad de las inspecciones de rutina: ***La frecuencia de las inspecciones esta basada en función del riesgo.***
Périodicité des inspections de routine: ***L'évaluation du risque détermine la fréquence des inspections.***

3.2 Has the manufacture of this type of pharmaceutical form been inspected?
¿Se ha inspeccionado la fabricación de este tipo de forma farmaceútica?
La fabrication de ce type de forme pharmaceutique a-t-elle fait l'objet d'une inspection?

yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? [15]
¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud? [15]
Est-ce que l'établissement pharmaceutique est conforme aux BPF recommandées par l'Organisation Mondiale de la Santé ? [15]

yes

4. Does the information submitted by the applicant satisfy the Certifying Authority on all aspects of the manufacture of the product undertaken by another party? [16]
¿La información presentada por el solicitante satisface a la autoridad de certificación en relación a todos los aspectos de la fabricación del medicamento realizada por terceros? [16]
Les informations fournies par le demandeur satisfont-elles aux exigences des autorités certificatrices sur tous les aspects de la fabrication du médicament pris en charge par une tierce partie ? [16]

yes

European Medicines Agency • Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands
Telephone +31 (0)88 781 6000
E-mail certificate@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

EUROPEAN MEDICINES AGENCY

Certificate: 08/21/155899
Request: 82695

Address of the Certifying Authority / Dirección de la autoridad certificadora / Adresse de l'autorité certificatrice :

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Telephone / Teléfono / Téléphone: ***+31 (0)88 781 6000***
Facsimile / Fax / Télécopie:
E-mail / Correo electrónico/ Courrier électronique: ***certificate@ema.europa.eu***

Name of authorised person / Nombre de la persona autorizada / Nom de la personne autorisée:

Signature / Firma / Signature: Alberto Ganan Jimenez
Digitally signed by Alberto Ganan Jimenez
Date: 2021.03.16 16:14:17 +01'00'

Stamp and date / Sello y fecha / Tampon et date: ***16.3.2021***

Declaration

The undersigned, Jan Hein Frederik Siemerink, LL.M, civil-law notary in Amsterdam, officiating in Amsterdam, the Netherlands, herewith declares that the attached document is a true copy of a PDF-document ("certificate of a medicinal product") provided by the European Medicines Agency.

This statement explicitly contains no judgment as (i) to the contents of the attached document and (ii) the authority and/or the competence of the signatory of the attached document (iii) the issuing authority of the document.
The undersigned has not informed the signatory of the document on the contents of the attached document and the consequences which will result from the contents of the attached document. Any and all liability of the undersigned and KB notarissen B.V. is excluded.

Amsterdam, the Netherlands, 22th of March 2021

J.H.F. Siemerink, LL.M., *Civil-law notary*

mr. Jan Hein Frederik Siemerink * Notaris te Amsterdam *

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: THE NETHERLANDS
   This public document
2. has been signed by **mr. J.H.F. Siemerink**
3. acting in the capacity of notary at Amsterdam
4. bears the seal/stamp of aforesaid notary

Certified

5. in Amsterdam 6. on 23-03-2021
7. by the registrar of the district court of Amsterdam
8. no.
9. Seal/stamp: 015797 10. Signature:

F. Wardenaar

RECHTBANK AMSTERDAM

KB notarissen B.V.
Prinses Irenestraat 43
1077 WV Amsterdam
(031(0)20 5407070

EUROPEAN MEDICINES AGENCY

Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the medicinal product and of the applicant for the Certificate in the exporting region at the time of issue. It is for a single product at a given point in time since manufacturing arrangements and approved information for different pharmaceutical forms and different strengths can vary.

[2] Whenever possible, International Non-proprietary Names (INNs) or national non-proprietary names are used.

[3] The formula (complete composition) of the pharmaceutical form is appended.

[4] Provision of the details of quantitative composition is attached on request of the Community Marketing Authorisation Holder.

[5] When applicable, details are appended of any conditions or restrictions applied to the supply and use of the product that is entered into the Community Marketing Authorisation.

[6] Not applicable.

[7] Indicated, when applicable, if the Community Marketing Authorisation has been granted under exceptional circumstances, conditional approval or if the product has not yet been approved.

[8] The person responsible for placing the product on the market:

(a) manufactures the pharmaceutical form;
(b) packages and/or labels a pharmaceutical form manufactured by an independent company; or
(c) is involved in none of the above.

[9] This information can only be provided with the consent of the Community Marketing Authorisation Holder or, in the case of non-registered products, the applicant. Non-completion of this section (2.3.1) indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the Community Marketing Authorisation. If the production site is changed, the Community Marketing Authorisation has to be updated or it is no longer valid.

[10] This refers to the document that summarises the technical basis on which the product has been authorised.

[11] This refers to the product information which forms a part of the Community Marketing Authorisation, such as the Summary of Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the Community Marketing Authorisation Holder. This permission has to be provided to the European Medicines Agency by the applicant.

[13] If applicable the reason why the medicinal product does not have a Community Marketing Authorisation, e.g.:

(a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases - not endemic in the exporting region;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in medicinal products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active substance;
(e) any other reason, as specified.

[14] "Not applicable" means the manufacture is taking place in a region other than that issuing the Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of medicinal products referred to in the Certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No 822, 1992, Annex 1).

[16] This section is to be completed when the Community Marketing Authorisation Holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the Certifying Authority with information to identify the contracting parties responsible for each stage of manufacture of the pharmaceutical form, and the extent and nature of any controls exercised over each of these parties.

EUROPEAN MEDICINES AGENCY

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

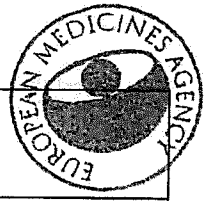
1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

Humira, Solution for injection

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché:

EU/1/03/256/012
EU/1/03/256/013
EU/1/03/256/014
EU/1/03/256/015

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento:
Composition qualitative et quantitative du médicament:



Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units: Cantidades y unidades: Quantités et unités:			
Adalimumab	**40.0 mg**			
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades: Quantités et unités:			
Mannitol **Polysorbate 80** **Water for injections**	**16.8 mg** **0.4 mg** **q.s.**			

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Humira 40 mg solution for injection in pre-filled syringe
Each 0.4 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Humira 40 mg solution for injection in pre-filled syringe with automatic needle guard
Each 0.4 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Humira 40 mg solution for injection in pre-filled pen
Each 0.4 ml single dose pre-filled pen contains 40 mg of adalimumab.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. (injection)

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Humira in combination with methotrexate, is indicated for:

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

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

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

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

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

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

Axial spondyloarthritis without radiographic evidence of AS

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

Psoriatic arthritis

Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Humira has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

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

Paediatric plaque psoriasis

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

Hidradenitis suppurativa (HS)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Humira is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

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

Paediatric ulcerative colitis

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

Uveitis

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

Paediatric Uveitis

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

4.2 Posology and method of administration

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

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

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

Posology

Rheumatoid arthritis

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

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Dose interruption

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

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

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

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

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

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

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

Beyond 16 weeks, patients with inadequate response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage (see section 5.1). If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

EUROPEAN MEDICINES AGENCY

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Hidradenitis suppurativa

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

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Crohn's disease

The recommended Humira induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg at Week 2 (given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Ulcerative colitis

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

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Uveitis

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Special populations

Elderly

No dose adjustment is required.

Renal and/or hepatic impairment

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

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 years of age

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight (Table 1). Humira is administered every other week via subcutaneous injection.

Table 1. Humira Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

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

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

There is no relevant use of Humira in patients aged less than 2 years for this indication.

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis from 6 years of age is based on body weight (Table 2). Humira is administered every other week via subcutaneous injection.

Table 2. Humira Dose for Patients with Enthesitis-Related Arthritis

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis

There is no relevant use of Humira in the paediatric population for the indications of ankylosing spondylitis and psoriatic arthritis.

Paediatric plaque psoriasis

The recommended Humira dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight (Table 3). Humira is administered via subcutaneous injection.

Table 3. Humira Dose for Paediatric Patients with Plaque Psoriasis

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

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

If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.

The safety of Humira in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with Humira in adolescent patients with HS. The posology of Humira in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Humira dose 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 Humira 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

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

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

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric Crohn's disease

The recommended dose of Humira for patients with Crohn's disease from 6 to 17 years of age is based on body weight (Table 4). Humira is administered via subcutaneous injection.

Table 4. Humira Dose for Paediatric Patients with Crohn's disease

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

Patients who experience insufficient response may benefit from an increase in dosage:

- < 40 kg: 20 mg every week
- ≥ 40 kg: 40 mg every week or 80 mg every other week

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

There is no relevant use of Humira in children aged less than 6 years for this indication.

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric ulcerative colitis

The recommended dose of Humira for patients from 6 to 17 years of age with ulcerative colitis is based on body weight (Table 5). Humira is administered via subcutaneous injection.

Table 5. Humira Dose for Paediatric Patients with Ulcerative Colitis

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	• 80 mg at Week 0 (given as two 40 mg injections in one day) and • 40 mg at Week 2 (given as one 40 mg injection)	• 40 mg every other week

≥ 40 kg	• 160 mg at Week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and • 80 mg at Week 2 (given as two 40 mg injections in one day)	• 80 mg every other week

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

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

There is no relevant use of Humira in children aged less than 6 years in this indication.

Humira may be available in different strengths and/or presentations depending on the individual treatment needs.

Paediatric Uveitis

The recommended dose of Humira for paediatric patients with uveitis from 2 years of age is based on body weight (Table 6). Humira is administered via subcutaneous injection.

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

Table 6. Humira Dose for Paediatric Patients with Uveitis

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

When Humira therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Method of administration

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

Humira is available in other strengths and presentations.

4.3 Contraindications

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

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

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

4.4 Special warnings and precautions for use

Traceability

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

Infections

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

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

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

Serious infections

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

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

Tuberculosis

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

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and

X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

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

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

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

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

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

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

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 Humira.

Other opportunistic infections

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

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

Hepatitis B reactivation

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

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV

reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

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

Allergic reactions

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

Immunosuppression

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

Malignancies and lymphoproliferative disorders

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

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

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Humira should be carefully

considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see section 4.8).

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

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

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

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

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. 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 Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

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

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

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

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild

EUROPEAN MEDICINES AGENCY

heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

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

Concurrent administration of biologic DMARDS or TNF-antagonists

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

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

Surgery

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

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 Humira does not worsen or cause strictures.

Elderly

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

Paediatric population

See Vaccinations above.

4.5 Interaction with other medicinal products and other forms of interaction

Humira has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Humira was given together with methotrexate in comparison with use as

monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Humira and anakinra is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

The combination of Humira and abatacept is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

A large number (approximately 2100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

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

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

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

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

Breast-feeding

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and

EUROPEAN MEDICINES AGENCY

have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, Humira can be used during breastfeeding.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defence against infection and cancer.
Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

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

Paediatric population

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

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 7 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping,

undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 7
Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	Neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	Lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**

EUROPEAN MEDICINES AGENCY

System Organ Class	Frequency	Adverse Reaction
	Rare	Leukaemia[1)]
	Not known	Hepatosplenic T-cell lymphoma[1)] Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)], Kaposi's sarcoma
Blood and the lymphatic system disorders*	Very common	Leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	Leucocytosis, thrombocytopenia
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders*	Common	Hypersensitivity, allergies (including seasonal allergy)
	Uncommon	Sarcoidosis[1)], vasculitis
	Rare	Anaphylaxis[1)]
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	Mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	Headache

System Organ Class	Frequency	Adverse Reaction
	Common	Paraesthesias (including hypoesthesia), migraine, nerve root compression
	Uncommon	Cerebrovascular accident[1)], tremor, neuropathy
	Rare	Multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) [1)]
Eye disorders	Common	Visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	Diplopia
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Deafness, tinnitus
Cardiac disorders*	Common	Tachycardia
	Uncommon	Myocardial infarction[1)], arrhythmia, congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	Aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	Asthma, dyspnoea, cough

EUROPEAN MEDICINES AGENCY

System Organ Class	Frequency	Adverse Reaction
	Uncommon	Pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion[1)]
	Rare	Pulmonary fibrosis[1)]
Gastrointestinal disorders	Very common	Abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	Pancreatitis, dysphagia, face oedema
	Rare	Intestinal perforation[1)]
Hepato-biliary disorders*	Very Common	Elevated liver enzymes
	Uncommon	Cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	Hepatitis reactivation of hepatitis B[1)] autoimmune hepatitis[1)]
	Not known	Liver failure[1)]
Skin and subcutaneous tissue disorders	Very Common	Rash (including exfoliative rash)
	Common	Worsening or new onset of psoriasis(including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus
	Uncommon	Night sweats,

System Organ Class	Frequency	Adverse Reaction
		scar
	Rare	Erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)] lichenoid skin reaction[1)]
	Not known	Worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis, systemic lupus erythematosus
	Rare	Lupus-like syndrome[1)]
Renal and urinary disorders	Common	Renal impairment, haematuria
	Uncommon	Nocturia
Reproductive system and breast disorders	Uncommon	Erectile dysfunction
General disorders and administration site conditions*	Very Common	Injection site reaction (including injection site erythema)
	Common	Chest pain, oedema, pyrexia[1)]
	Uncommon	Inflammation
Investigations*	Common	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	Impaired healing

EUROPEAN MEDICINES AGENCY

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies
[1)] including spontaneous reporting data

Hidradenitis suppurativa

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

Uveitis

The safety profile for patients with uveitis treated with Humira every other week was consistent with the known safety profile of Humira.

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

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

The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control – treated patients.

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

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during Humira trials in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 93 paediatric patients with an exposure of 65.3 patient years during a Humira trial in paediatric patients with ulcerative colitis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during a Humira trial in paediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 Humira treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among Humira-treated patients and 3.2 (1.3, 7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

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

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

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

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I – V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control – treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations $\geq$ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations $\geq$ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations $\geq$ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

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

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

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

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

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

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

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

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors.
ATC code: L04AB04

Mechanism of action

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

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

Pharmacodynamic effects

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

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

Clinical efficacy and safety

Rheumatoid arthritis

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

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

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative

EUROPEAN MEDICINES AGENCY

weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

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

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

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

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

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at Week 52. RA studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life. The primary endpoint in RA studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

ACR response

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 8.

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

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

[a] RA study I at 24 weeks, RA study II at 26 weeks, and RA study III at 24 and 52 weeks
[b] 40 mg Humira administered every other week
[c] MTX = methotrexate
**p < 0.01, Humira *versus* placebo

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

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to Humira 40 mg every other week, 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.

In RA study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In RA studies I-IV, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Humira monotherapy at Week 52 and responses were sustained at Week 104 (see Table 9).

Table 9
ACR Responses in RA Study V
(percent of patients)

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

a. p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

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

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

Radiographic response

In RA study III, 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 modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. Humira/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 10).

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

Table 10
Radiographic Mean Changes Over 12 Months in RA Study III

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

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Humira.
[c]Based on rank analysis
[d]Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 11).

Table 11
Radiographic Mean Changes at Week 52 in RA Study V

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

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

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

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

Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of life and physical function

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

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

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

Injection site pain

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

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Humira 40 mg every other week was assessed in 393 patients in two randomised, 24 week double – blind, placebo – controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti – rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open – label period during which patients received Humira 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger AS study I with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with Humira compared to placebo. Significant response was first observed at Week 2 and maintained through 24 weeks (Table 12).

Table 12
Efficacy Responses in Placebo-Controlled AS Study – Study I
Reduction of Signs and Symptoms

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

***,** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between Humira and placebo at Weeks 2, 12 and 24
[a] Assessments in Ankylosing Spondylitis
[b] Bath Ankylosing Spondylitis Disease Activity Index

Humira treated patients had significantly greater improvement at Week 12 which was maintained through Week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

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

Axial spondyloarthritis without radiographic evidence of AS

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

Study nr-axSpA I

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

Thirty-three (18%) patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 146 (79%) patients with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients receive Humira 40 mg every other week subcutaneously for up to an

additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active nr-axSpA in patients treated with Humira compared to placebo (Table 13).

Table 13
Efficacy Response in Placebo-Controlled Study nr-axSpA I

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

[a] Assessment of SpondyloArthritis international Society
[b] Bath Ankylosing Spondylitis Disease Activity Index
[c] Ankylosing Spondylitis Disease Activity Score
[d] mean change from baseline
[e] n=91 placebo and n=87 Humira
[f] high sensitivity C-Reactive Protein (mg/L)
[g] n=73 placebo and n=70 Humira
[h] Spondyloarthritis Research Consortium of Canada
[i] n=84 placebo and Humira
[j] n=82 placebo and n=85 Humira
***, **, * Statistically significant at $p < 0.001$, < 0.01, and < 0.05, respectively, for all comparisons between Humira and placebo.

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

Inhibition of inflammation

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

Quality of life and physical function

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

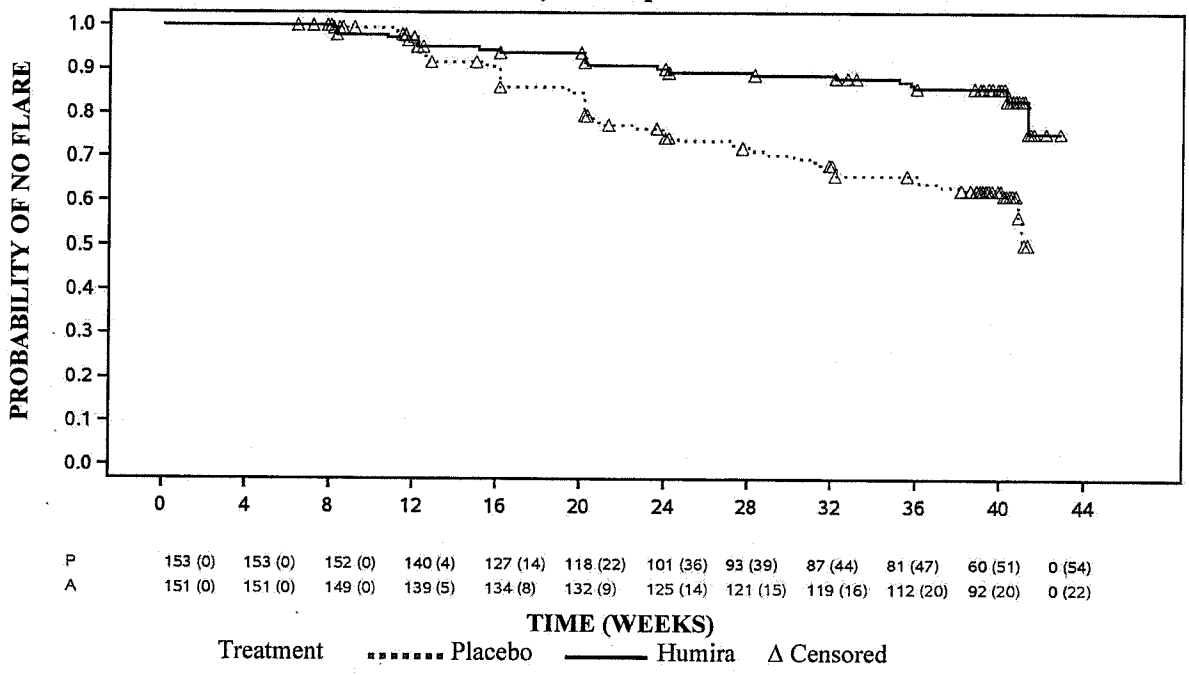
Study nr-axSpA II

673 patients with active nr-axSpA (mean baseline disease activity [BASDAI] was 7.0) who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into

the open-label period of Study nr-axSpA II during which they received Humira 40 mg eow for 28 weeks. These patients also had objective evidence of inflammation in the sacroiliac joints or spine on MRI or elevated hs-CRP. Patients who achieved sustained remission for at least 12 weeks (N=305) (ASDAS < 1.3 at Weeks 16, 20, 24, and 28) during the open-label period were then randomized to receive either continued treatment with Humira 40 mg eow (N=152) or placebo (N=153) for an additional 40 weeks in a double-blind, placebo-controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed Humira 40 mg eow rescue therapy for at least 12 weeks.

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

Figure 1: Kaplan-Meier Curves Summarizing Time to Flare in Study nr-axSpA II



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

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

By Week 68, patients receiving continuous Humira treatment showed statistically significant greater improvement of the signs and symptoms of active nr-axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study (Table 14).

Table 14
Efficacy Response in Placebo-Controlled Period for Study nr-axSpA II

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

[a] Assessment of SpondyloArthritis international Society
[b] Baseline is defined as open label baseline when patients have active disease.
[c] Ankylosing Spondylitis Disease Activity Score
[d] Partial flare is defined as ASDAS $\geq$ 1.3 but < 2.1 at 2 consecutive visits.
***, ** Statistically significant at $p < 0.001$ and < 0.01, respectively, for all comparisons between Humira and placebo.

Psoriatic arthritis

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

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

Table 15
ACR Response in Placebo-Controlled Psoriatic Arthritis Studies (Percent of Patients)

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

*** $p < 0.001$ for all comparisons between Humira and placebo
* $p < 0.05$ for all comparisons between Humira and placebo
N/A not applicable

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

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on 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.

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

In subjects treated with Humira with no radiographic progression from baseline to Week 48 (n=102), 84% continued to show no radiographic progression through 144 weeks of treatment.
Humira treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36) compared to placebo at Week 24. Improved physical function continued during the open label extension up to Week 136.

Psoriasis

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

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

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

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

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at Week 16 (see Tables 16 and 17).

Table 16
Ps Study I (REVEAL) - Efficacy Results at 16 Weeks

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

[a] Percent of patients achieving PASI75 response was calculated as centre-adjusted rate
[b] $p < 0.001$, Humira vs. placebo

Table 17
Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

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

[a] $p < 0.001$ Humira vs. placebo
[b] $p < 0.001$ Humira vs. methotrexate
[c] $p < 0.01$ Humira vs. placebo
[d] $p < 0.05$ Humira vs. methotrexate

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

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

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

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

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

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

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 18). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% (60% of patients) and BSA<10% and ≥5% (40% of patients)).

Table 18: Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

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

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Hidradenitis suppurativa

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

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or 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. Concomitant antibiotic use was not allowed during the study. After

12 weeks of therapy, patients who had received Humira in Period A were re-randomised 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). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

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

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

Clinical Response

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

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 19). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 19: Efficacy Results at 12 Weeks, HS Studies I and II

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

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a] Among all randomised patients.

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

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

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I

and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 20).

Table 20: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

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

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

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

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

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

Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

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

CD study I and CD study II induction of remission and response rates are presented in Table 21.

Table 21
Induction of Clinical Remission and Response
(Percent of Patients)

	CD Study I: Infliximab Naive Patients			**CD Study II: Infliximab Experienced Patients**	
	Placebo N=74	**Humira 80/40 mg N = 75**	**Humira 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

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

* $p < 0.001$

** $p < 0.01$

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

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 22. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

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

Table 22
Maintenance of Clinical Remission and Response
(Percent of Patients)

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

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

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

[a] Of those receiving corticosteroids at baseline

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

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

Quality of life

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

Ulcerative colitis

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

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

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

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

Results from the overall UC-II study population are shown in Table 23.

Table 23
Response, Remission and Mucosal Healing in Study UC-II
(Percent of Patients)

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

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
Clinical response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30% plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1;
*p < 0.05 for Humira *vs.* placebo pairwise comparison of proportions
**p < 0.001 for Humira *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

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

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

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

Hospitalisation rates

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

patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of life

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

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). 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 one non-biologic immunosuppressant were permitted.

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

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

The primary efficacy endpoint in both studies was 'time to treatment failure'. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

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

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 24). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 2).

Table 24
Time to Treatment Failure in Studies UV I and UV II

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

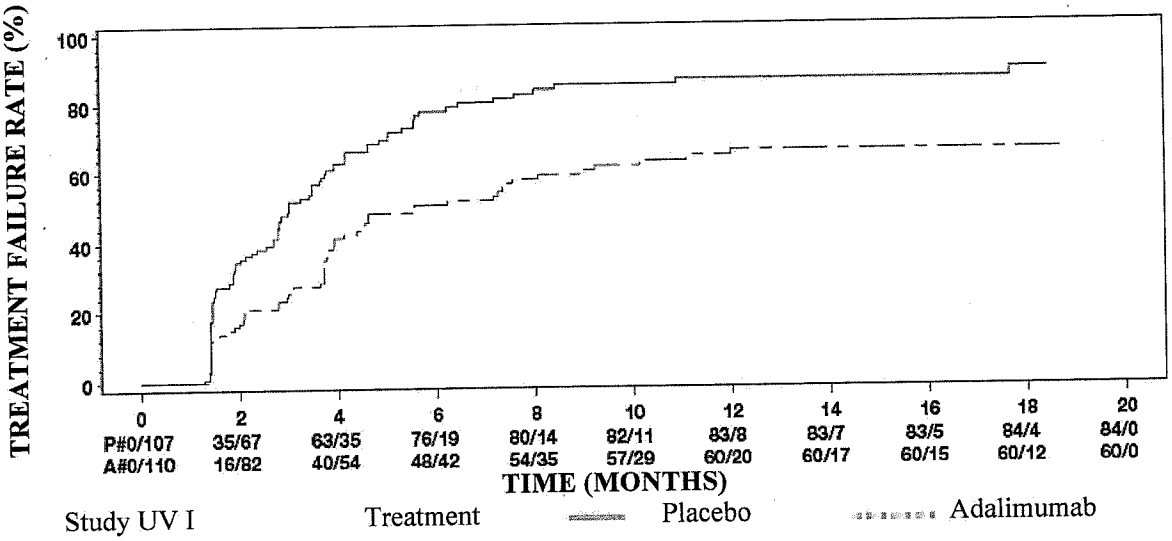
Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

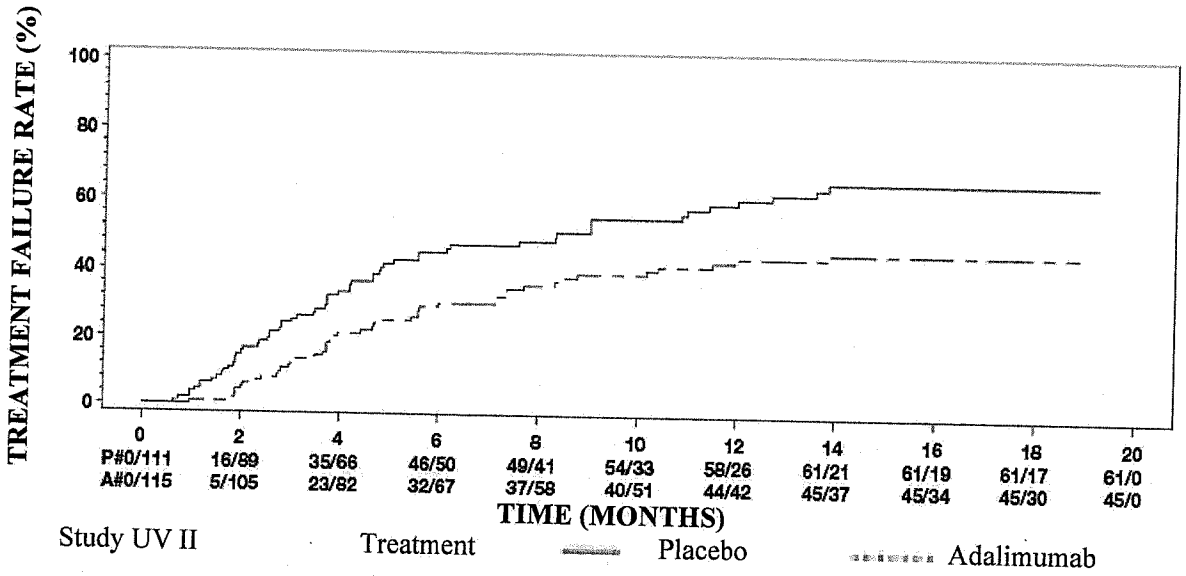
[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

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

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

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)





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

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

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

Quality of Life

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

Immunogenicity

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

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

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86) compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years old or aged 4 and above weighing <15 kg, anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate.

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

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

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

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

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

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

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

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

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

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

In patients with moderately to severely active paediatric ulcerative colitis, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3%.

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

Paediatric population

Juvenile idiopathic arthritis (JIA)

Polyarticular juvenile idiopathic arthritis (pJIA)

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

pJIA I

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind, parallel – group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m^2 up to a maximum of 40 mg 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 25.

Table 25
Distribution of patients by age and adalimumab dose received during the OL LI phase

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

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

Table 26
Ped ACR 30 Responses in the JIA study

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

[a] Ped ACR 30/50/70 responses Week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Amongst those who responded at Week 16 (n=144), the Paediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received Humira throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone. Taking these results into consideration, Humira is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

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

At Week 12 and Week 24, PedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PedACR50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Paediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Paediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received Humira throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-related arthritis

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during

which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 156 for the 26 of 31 (84%) patients in the Humira group who remained in the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Paediatric ACR 50 response, and Paediatric ACR 70 response.

Paediatric plaque psoriasis

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

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

Table 27: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

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

[a] MTX = methotrexate
[b] P=0.027, Humira 0.8 mg/kg versus MTX
[c] P=0.083, Humira 0.8 mg/kg versus MTX

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

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

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Paediatric Crohn's disease

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

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

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 28.

Table 28
Maintenance regimen

Patient Weight	**Low dose**	**Standard dose**
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

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

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 29. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 30.

Table 29
Paediatric CD Study
PCDAI Clinical Remission and Response

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

Table 30 Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission			
	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

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

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

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Paediatric ulcerative colitis

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

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

At Week 8, 62 patients who demonstrated clinical response per Partial Mayo Score (PMS; defined as a decrease in PMS $\geq$ 2 points and $\geq$ 30% from Baseline) were randomized equally to receive double-blind maintenance treatment with Humira at a dose of 0.6 mg/kg (maximum of 40 mg) every week (ew), or a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (eow). Prior to an amendment to

EUROPEAN MEDICINES AGENCY

the study design, 12 additional patients who demonstrated clinical response per PMS were randomized to receive placebo but were not included in the confirmatory analysis of efficacy.

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

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

Efficacy Results

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

Clinical remission rates per PMS at Week 8 for patients in each of the Humira double-blind induction groups are presented in Table 31.

Table 31: Clinical Remission per PMS at 8 Weeks

	Humira[a] Maximum of 160 mg at Week 0 / Placebo at Week 1 N=30	**Humira[b, c] Maximum of 160 mg at Week 0 and Week 1** N=47
Clinical remission	13/30 (43.3%)	28/47 (59.6%)
[a] Humira 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [b] Humira 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [c] Not including open-label Induction dose of Humira 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6 Note 2: Patients with missing values at Week 8 were considered as not having met the endpoint		

At Week 52, clinical remission per FMS in Week 8 responders, clinical response per FMS (defined as a decrease in Mayo Score ≥ 3 points and $\geq 30\%$ from Baseline) in Week 8 responders, mucosal healing (defined as Mayo endoscopy subscore ≤ 1) in Week 8 responders, clinical remission per FMS in Week 8 remitters, and the proportion of subjects in corticosteroid-free remission per FMS in Week 8 responders were assessed in patients who received Humira at the double-blind maximum 40 mg eow (0.6 mg/kg) and maximum 40 mg ew (0.6 mg/kg) maintenance doses (Table 32).

Table 32: Efficacy Results at 52 Weeks

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

[a] Humira 0.6 mg/kg (maximum of 40 mg) every other week
[b] Humira 0.6 mg/kg (maximum of 40 mg) every week
[c] In patients receiving concomitant corticosteroids at baseline
Note: Patients with missing values at Week 52 or who were randomized to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints

Additional exploratory efficacy endpoints included clinical response per the Paediatric Ulcerative Colitis Activity Index (PUCAI) (defined as a decrease in PUCAI $\geq$ 20 points from Baseline) and clinical remission per PUCAI (defined as PUCAI < 10) at Week 8 and Week 52 (Table 33).

Table 33: Exploratory Endpoints Results per PUCAI

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

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

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

Quality of life

Clinically meaningful improvements from Baseline were observed in IMPACT III and the caregiver Work Productivity and Activity Impairment (WPAI) scores for the groups treated with Humira.

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

Paediatric Uveitis

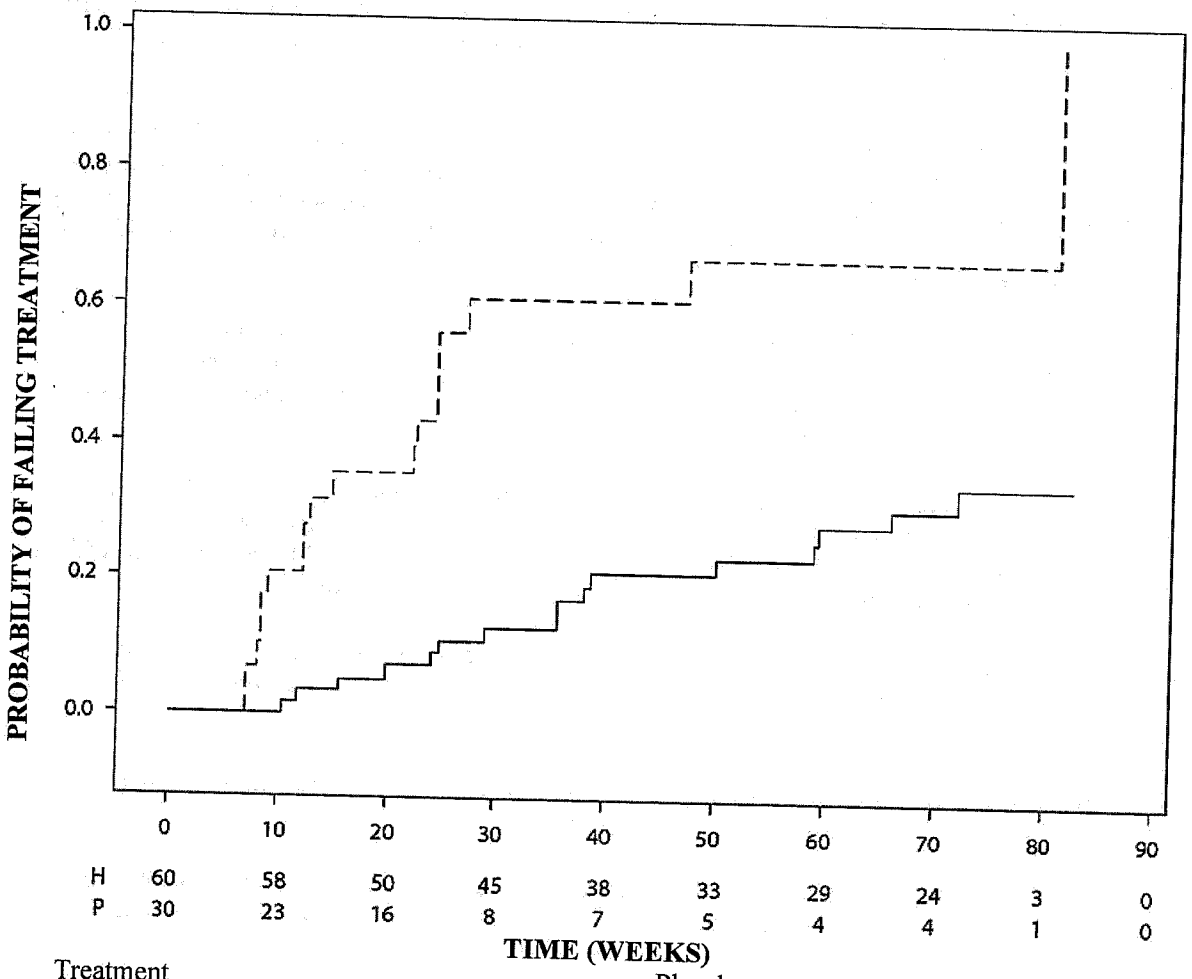
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either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

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

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 3, $P < 0.0001$ from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 3: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

5.2 Pharmacokinetic properties

Absorption and distribution

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

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

Following the administration of 24 mg/m^2 (maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/ml (47.7% CV) with concomitant methotrexate.

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

Following the administration of 24 mg/m^2 (maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/ml with concomitant methotrexate.

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

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

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

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

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related

arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

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

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

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

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

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

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

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

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

Exposure-response relationship in paediatric population

On the basis of clinical trial data in patients with JIA (pJIA and ERA), an exposure-response relationship was established between plasma concentrations and PedACR 50 response. The apparent adalimumab plasma concentration that produces half the maximum probability of PedACR 50 response (EC50) was 3 µg/ml (95% CI: 1-6 µg/ml).

Exposure-response relationships between adalimumab concentration and efficacy in paediatric patients with severe chronic plaque psoriasis were established for PASI 75 and PGA clear or minimal, respectively. PASI 75 and PGA clear or minimal increased with increasing adalimumab concentrations, both with a similar apparent EC50 of approximately 4.5 µg/ml (95% CI 0.4-47.6 and 1.9-10.5, respectively).

Elimination

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

Hepatic or renal impairment

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its outer carton in order to protect from light.

A single Humira pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The syringe or pen must be protected from light, and discarded if not used within the 14-day period.

6.5 Nature and contents of container

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe (0.4 ml sterile solution) with 1 alcohol pad in a blister.
- 2 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.

Humira 40 mg solution for injection in pre-filled syringe with automatic needle guard
Humira 40 mg solution for injection in single-use pre-filled syringe with automatic needle guard. The syringe is made from type I glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe with automatic needle guard (0.4 ml sterile solution) with 1 alcohol pad in a blister.
- 2 pre-filled syringes with automatic needle guard (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled syringes with automatic needle guard (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.

Humira 40 mg solution for injection in pre-filled pen
Humira 40 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled pen (0.4 ml sterile solution), with 2 alcohol pads in a blister.
- 2 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBERS

Humira 40 mg solution for injection in pre-filled syringe
EU/1/03/256/012
EU/1/03/256/013
EU/1/03/256/014
EU/1/03/256/015

Humira 40 mg solution for injection in pre-filled syringe with automatic needle guard
EU/1/03/256/023
EU/1/03/256/024
EU/1/03/256/025

Humira 40 mg solution for injection in pre-filled pen
EU/1/03/256/016
EU/1/03/256/017
EU/1/03/256/018
EU/1/03/256/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 September 2003
Date of latest renewal: 08 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

AbbVie Bioresearch Center
100 Research Drive
Worcester
MA 01605
USA

and

AbbVie Biotechnology Ltd.
Road No. 2, Km. 59.2
Barceloneta
Puerto Rico 00617

and

Lonza Biologics Porriño,S.L
A Relva s/n
36400 O Porriño
Pontevedra, Spain

and

Lonza Biologics Tuas PTE Ltd
35 Tuas South Ave 6
Singapore 637377

and

AbbVie Operations Singapore PTE Ltd
23 Tuas South Avenue 6
Singapore 637022

Name and address of the manufacturer responsible for batch release

AbbVie Biotechnology GmbH
Knollstrasse
67061 Ludwigshafen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Patient Reminder Cards (adult and paediatric) contain the following key elements

- infections, including tuberculosis
- cancer
- nervous system problems
- vaccinations