CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125057Orig1s397

Trade Name:	HUMIRA
Generic or Proper Name:	adalimumab
Sponsor:	AbbVie Inc.
Approval Date:	June 30, 2016

Indication:

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:

- **Rheumatoid Arthritis (RA):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- **Psoriatic Arthritis (PsA):** Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS):** Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD):** Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely

active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

- **Pediatric Crohn's Disease:** Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
- **Hidradenitis Suppurativa (HS):** The treatment of moderate to severe hidradenitis suppurativa.
- **Uveitis (UV):** The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/S-397

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Dawn Territo
Associate Director, Regulatory Affairs
1 North Waukegan Road, Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Ms. Territo:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received September 3, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Humira (adalimumab).

This Prior Approval supplemental biologics application provides for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling text submitted on June 27, 2016.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide, and Instructions for Use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125057/S-397**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, this requirement is not applicable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Eithu Z. Lwin, Regulatory Project Manager, at (301) 796-0728.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
06/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) injection, for subcutaneous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):
- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

RECENT MAJOR CHANGES

Indications and Usage, Hidradenitis Suppurativa (1.9)	9/2015
Indications and Usage, Uveitis (1.10)	6/2016
Dosage and Administration, Plaque Psoriasis and Uveitis (2.6)	6/2016
Dosage and Administration, Hidradenitis Suppurativa (2.7)	9/2015
Dosage and Administration, General Considerations for Administration (2.9)	11/2015
Warnings and Precautions, Malignancies (5.2)	6/2016
Warnings and Precautions, Neurologic Reactions (5.5)	6/2016
Warnings and Precautions, Immunizations (5.10)	6/2016

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
- **Rheumatoid Arthritis (RA) (1.1):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA) (1.2):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- **Psoriatic Arthritis (PsA) (1.3):** Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS) (1.4):** Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD) (1.5):** Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- **Pediatric Crohn's Disease (1.6):** Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC) (1.7):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps) (1.8):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
- **Hidradenitis Suppurativa (HS) (1.9):** The treatment of moderate to severe hidradenitis suppurativa.
- **Uveitis (UV) (1.10)**: The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

DOSAGE AND ADMINISTRATION

- Administered by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):
- 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Juvenile Idiopathic Arthritis (2.2):
- *10 kg (22 lbs) to <15 kg (33 lbs):* 10 mg every other week
- *15 kg (33 lbs) to < 30 kg (66 lbs):* 20 mg every other week
- *≥ 30 kg (66 lbs):* 40 mg every other week

Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.5):
- Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
- Second dose two weeks later (Day 15): 80 mg
  - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
- For patients with Ulcerative Colitis only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Pediatric Crohn's Disease (2.4):
- ***17 kg (37 lbs) to < 40 kg (88 lbs):***
  - Initial dose (Day 1): 80 mg (two 40 mg injections in one day)
  - Second dose two weeks later (Day 15): 40 mg
    - Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week.
- ***≥ 40 kg (88 lbs):***
  - Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
  - Second dose two weeks later (Day 15): 80 mg (two 40 mg injections in one day)
    - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.

Plaque Psoriasis or Uveitis (2.6):
- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Hidradenitis Suppurativa (2.7):
- Initial dose (Day 1): 160 mg (given as four 40 mg injections on Day 1 or as two 40 mg injections per day on Days 1 and 2)
- Second dose two weeks later (Day 15): 80 mg (two 40 mg injections in one day)
- Third (Day 29) and subsequent doses: 40 mg every week.

DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.4 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe (3)
- Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe (3)
- Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- *Serious infections:* Do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- *Invasive fungal infections:* For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1)
- *Malignancies:* Incidence of malignancies was greater in HUMIRA-treated patients than in controls (5.2)
- *Anaphylaxis or serious allergic reactions* may occur (5.3)
- *Hepatitis B virus reactivation:* Monitor HBV carriers during and several

months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- *Demyelinating disease:* Exacerbation or new onset, may occur (5.5)
- *Cytopenias, pancytopenia:* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- *Heart failure:* Worsening or new onset, may occur (5.8)
- *Lupus-like syndrome:* Stop HUMIRA if syndrome develops (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Abatacept:* Increased risk of serious infection (5.1, 5.11, 7.2)
- *Anakinra:* Increased risk of serious infection (5.1, 5.7, 7.2)
- *Live vaccines:* Avoid use with HUMIRA (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions (5.2)]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

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

1.2 Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

1.4 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

1.5 Adult Crohn's Disease

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

1.6 Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

1.7 Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.7)]*.

1.8 Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions (5)]*.

1.9 Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

1.10 Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

2 DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg administered every other week. Methotrexate (MTX), other non-biologic DMARDS, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with HUMIRA. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Juvenile Idiopathic Arthritis

The recommended dose of HUMIRA for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HUMIRA.

Patients (2 years of age and older)	**Dose**
10 kg (22 lbs) to <15 kg (33 lbs)	10 mg every other week (10 mg Prefilled Syringe)
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week (20 mg Prefilled Syringe)
≥30 kg (66 lbs)	40 mg every other week (HUMIRA Pen or 40 mg Prefilled Syringe)

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

2.3 Adult Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease (CD) is 160 mg initially on 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 (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* or MTX may be continued during treatment with HUMIRA if necessary. The use of HUMIRA in CD beyond one year has not been evaluated in controlled clinical studies.

2.4 Pediatric Crohn's Disease

The recommended HUMIRA dose regimen for pediatric patients 6 years of age and older with Crohn's disease (CD) is based on body weight as shown below:

Pediatric Patients	Induction Dose	Maintenance Dose Starting at Week 4 (Day 29)
17 kg (37 lbs) to < 40 kg (88 lbs)	• 80 mg on Day 1 (administered as two 40 mg injections in one day); and • 40 mg two weeks later (on Day 15)	• 20 mg every other week
≥ 40 kg (88 lbs)	• 160 mg on Day 1 (administered as four injections in one day or as two 40 mg injections per day for two consecutive days); and • 80 mg two weeks later (on Day 15) (administered as two 40 mg injections in one day)	• 40 mg every other week

2.5 Ulcerative Colitis

The recommended HUMIRA dose regimen for adult patients with ulcerative colitis (UC) is 160 mg initially on 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 (Day 15). Two weeks later (Day 29) continue with a dose of 40 mg every other week.

Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine and 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* may be continued during treatment with HUMIRA if necessary.

2.6 Plaque Psoriasis or Uveitis

The recommended dose of HUMIRA for adult patients with plaque psoriasis (Ps) or Uveitis (UV) is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of HUMIRA in moderate to severe chronic Ps beyond one year has not been evaluated in controlled clinical studies.

2.7 Hidradenitis Suppurativa

The recommended dose of HUMIRA for adult patients with hidradenitis suppurativa (HS) is 160 mg (given as four 40 mg injections on Day 1 or as two 40 mg injections per day on Days 1 and 2), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly dosing two weeks later (Day 29).

2.8 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection *[see Warnings and Precautions (5.1)]*.

2.9 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA or a caregiver may inject HUMIRA using either the HUMIRA Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

You may leave HUMIRA at room temperature for about 15 to 30 minutes before injecting. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the HUMIRA Pen, prefilled syringe, or single-use institutional use vial for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HUMIRA does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe. NOTE: Instruct patients sensitive to latex not to handle the gray needle cover of the 27 gauge HUMIRA Pen and prefilled syringe because it contains natural rubber latex *[see How Supplied/Storage and Handling (16) for specific information]*.

Instruct patients using the HUMIRA Pen or prefilled syringe to inject the full amount in the syringe, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

The HUMIRA single-use institutional use vial is for administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

- **Pen**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.

Injection: 40 mg/0.4 mL of HUMIRA is provided by a single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle and a black needle cover.

- **Prefilled Syringe**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
  Injection: 40 mg/0.4 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle and a black needle cover.
  Injection: 20 mg/0.4 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
  Injection: 10 mg/0.2 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
- **Single-Use Institutional Use Vial**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use, glass vial for institutional use only.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;

- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being

performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated

patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

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

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting 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.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.2)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations (8.1, 8.4)]*.

5.11 Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions (5.1)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based 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; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with 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. 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 subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. 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 patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs 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.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the

recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

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

(approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%

Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%
* Laboratory test abnormalities were reported as adverse reactions in European trials ** Does not include injection site erythema, itching, hemorrhage, pain or swelling		

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions (5), Adverse Reactions (6)]*. Important findings and differences from adults are discussed in the following paragraphs.

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

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

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

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

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

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

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

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do

not suggest the need for dose adjustment of either HUMIRA or MTX *[see Clinical Pharmacology (12.3)]*.

7.2 Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions (5.7 and 5.11)]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

7.3 Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations (8.4)]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies (14.2)]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions (6.1)]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies (14.6)]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

8.5 Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen), as a single-use, 1 mL prefilled glass syringe, or as a single-use institutional use vial. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2.

Each 40 mg/0.4 mL prefilled syringe or prefilled pen delivers 0.4 mL (40 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab 40 mg, mannitol 16.8 mg, polysorbate 80 0.4 mg, and Water for Injection, USP.

Each 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-use institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 20 mg/0.4 mL prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab 20 mg, citric acid monohydrate 0.52 mg, dibasic sodium phosphate dihydrate 0.61 mg, mannitol 4.8 mg, monobasic sodium phosphate dihydrate 0.34 mg, polysorbate 80 0.4 mg, sodium chloride 2.47 mg, sodium citrate 0.12 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 10 mg/0.2 mL prefilled syringe delivers 0.2 mL (10 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab 10 mg, citric acid monohydrate 0.26 mg, dibasic sodium phosphate dihydrate 0.31 mg, mannitol 2.4 mg, monobasic sodium phosphate dihydrate 0.17 mg, polysorbate 80 0.2 mg, sodium chloride 1.23 mg, sodium citrate 0.06 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

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

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

12.3 Pharmacokinetics

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

The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies.

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

In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 µg/mL and 8.5 to 12 µg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

In patients with CD, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 µg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg HUMIRA every other week.

In patients with UC, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 µg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg HUMIRA every other week, and approximately 15 µg/mL at Week 52 in UC patients who increased to a dose of 40 mg HUMIRA every week.

In patients with Ps, the mean steady-state trough concentration was approximately 5 to 6 µg/mL during HUMIRA 40 mg every other week monotherapy treatment.

In subjects with HS, 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 concentrations at Week 12 through Week 36 were approximately 7 to 11 µg/mL during HUMIRA 40 mg every week treatment.

In patients with UV, the mean steady concentration was approximately 8 to 10 µg/mL during HUMIRA 40 mg every other week treatment.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

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

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

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

In Study JIA-I for patients with polyarticular JIA who were 4 to 17 years of age, the mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.6 µg/mL and 8.1 µg/mL, respectively. In Study JIA-II for patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, the mean steady-state trough serum adalimumab concentrations for patients receiving HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.0 µg/mL and 7.9 µg/mL, respectively.

In pediatric subjects with CD weighing ≥ 40 kg, the mean ±SD serum adalimumab concentrations were 15.7±6.5 mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 10.5±6.0 mcg/mL at Week 52 following subcutaneous doses of 40 mg every other week. In pediatric subjects with CD weighing < 40 kg, the mean ±SD serum adalimumab concentrations were 10.6±6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 6.9±3.6 mcg/mL at Week 52 following subcutaneous doses of 20 mg every other week.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥18 years of age with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 5 years.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active RA of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 2.

Table 2. ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	HUMIRA	HUMIRA	Placebo/MTX	HUMIRA/MTX
		40 mg every other week	40 mg weekly		40 mg every other week
	N=110	N=113	N=103	N=200	N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*
* $p<0.01$, HUMIRA *vs.* placebo					

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (EOW) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

Table 3. Components of ACR Response in Studies RA-II and RA-III

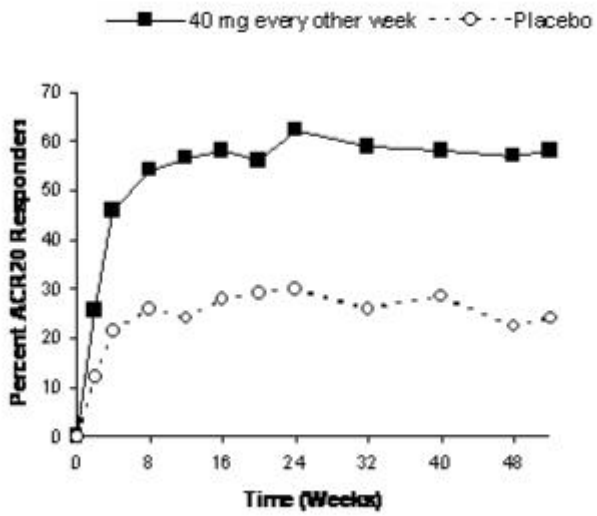
	Study RA-II				Study RA-III			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week
[b] Visual analogue scale; 0 = best, 10 = worst
[c] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* $p<0.001$, HUMIRA *vs.* placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

Figure 1. Study RA-III ACR 20 Responses over 52 Weeks



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

In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 4).

Table 4. ACR Response in Study RA-V (Percent of Patients)

Response	**MTX[b] N=257**	**HUMIRA[c] N=274**	**HUMIRA/MTX N=268**
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period
[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20
$p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response
[c] $p<0.001$, HUMIRA/MTX *vs.* HUMIRA

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 5. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 5. Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002
*95% confidence intervals for the differences in change scores between MTX and HUMIRA. **Based on rank analysis				

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6. Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	**HUMIRA[a,b] N=274**	**HUMIRA/MTX N=268**
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)
* mean (95% confidence interval)				

[a] p<0.001, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks
[b] p<0.01, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

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

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX (p<0.001) patients. Sixty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open-label treatment. Mean improvement in the SF-36 was maintained through the end of measurement at week 156 (3 years).

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement (p<0.001) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA was assessed in two studies (Studies JIA-I and JIA-II) in patients with active polyarticular juvenile idiopathic arthritis (JIA).

Study JIA-I

The safety and efficacy of HUMIRA were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 patients who were 4 to 17 years of age with polyarticular JIA. In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All patients had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDS. Patients who received prior treatment with any biologic DMARDS were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, HUMIRA was administered based on body surface area at a dose of 24 mg/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of HUMIRA SC every other week if their weight was less than 30 kg and with 40 mg of HUMIRA SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either HUMIRA or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

Study JIA-I Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who received HUMIRA experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study.

Study JIA-II

HUMIRA was assessed in an open-label, multicenter study in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active polyarticular JIA. Most patients (97%) received at least 24 weeks of HUMIRA treatment dosed 24 mg/m^2 up to a maximum of 20 mg every other week as a single SC injection up to a maximum of 120 weeks duration. During the study, most patients used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs. The primary objective of the study was evaluation of safety *[see Adverse Reactions (6.1)]*.

14.3 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis (PsA). Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active PsA (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of plaque psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric PsA (N=77); or (5) AS-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with PsA who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with

the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

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

Table 7. ACR Response in Study PsA-I (Percent of Patients)

	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%

* p<0.001 for all comparisons between HUMIRA and placebo

Table 8. Components of Disease Activity in Study PsA-I

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

* p<0.001 for HUMIRA *vs.* placebo comparisons based on median changes
[a] Scale 0-78
[b] Scale 0-76
[c] Visual analog scale; 0=best, 100=worst
[d] Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e]	Normal range: 0-0.287 mg/dL

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

Radiographic Response

Radiographic changes were assessed in the PsA 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 by readers blinded to treatment group to assess the radiographs.

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 9).

Table 9. Change in Modified Total Sharp Score in Psoriatic Arthritis

	Placebo N=141	**HUMIRA N=133**	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change ± SD	0.9 ± 3.1	-0.1 ± 1.7	-0.2 ± 4.9*
* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)			

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of HUMIRA every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with HUMIRA showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function based on the HAQ-DI was maintained for up to 84 weeks through the open-label portion of the study.

14.4 Ankylosing Spondylitis

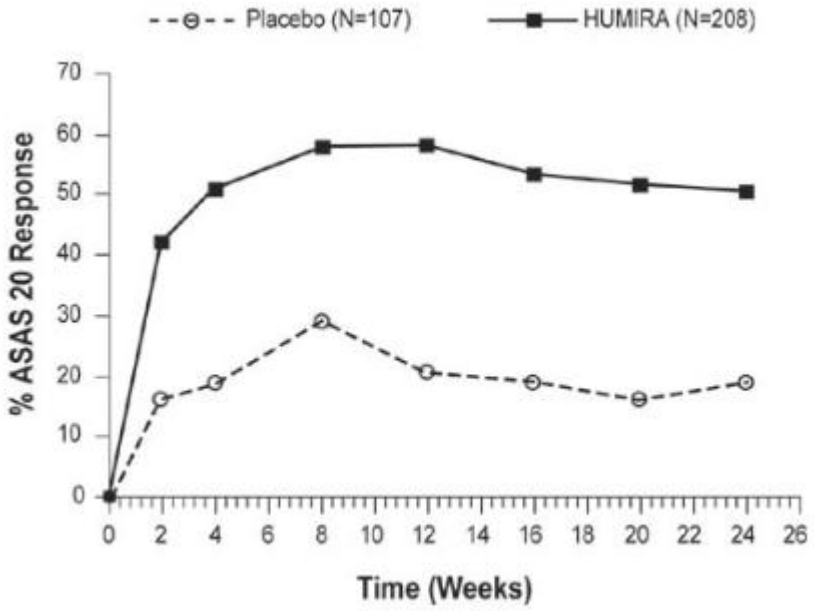
The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness

≥ 1 hour. 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.

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 10.

Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

Figure 2. ASAS 20 Response By Visit, Study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p < 0.001$). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table 10. Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		HUMIRA N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a*]	65	60	63	38

Total back pain*	67	58	65	37
Inflammation[b*]	6.7	5.6	6.7	3.6
BASFI[c*]	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8
CRP[f*]	2.2	2.0	1.8	0.6

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

A second randomized, multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 *vs.* -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 *vs.* 1.9) compared to placebo-treated patients at Week 24.

14.5 Adult Crohn's Disease

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

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

In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at

Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI ≥70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg HUMIRA achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II) (see Table 11).

Table 11. Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		CD-II	
	Placebo N=74	**HUMIRA 160/80 mg N=76**	**Placebo N=166**	**HUMIRA 160/80 mg N=159**
Week 4				
Clinical remission	12%	36%*	7%	21%*
Clinical response	34%	58%**	34%	52%**
Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points. * p<0.001 for HUMIRA *vs.* placebo pairwise comparison of proportions ** p<0.01 for HUMIRA *vs.* placebo pairwise comparison of proportions				

Maintenance of Clinical Remission

In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 12). The group that received HUMIRA therapy every week did not demonstrate significantly higher remission rates compared to the group that received HUMIRA every other week.

Table 12. Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo	**40 mg HUMIRA every other week**
	N=170	**N=172**
Week 26		
Clinical remission	17%	40%*
Clinical response	28%	54%*
Week 56		

Clinical remission	12%	36%*
Clinical response	18%	43%*
Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points. *p<0.001 for HUMIRA vs. placebo pairwise comparisons of proportions		

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA every other week group maintained remission for a longer time than patients in the placebo maintenance group. Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

14.6 Pediatric Crohn's Disease

A randomized, double-blind, 52-week clinical study of 2 dose levels of HUMIRA (Study PCD-I) was conducted in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease (defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30).[2] Enrolled patients had over the previous two year period an inadequate response to corticosteroids or an immunomodulator (i.e., azathioprine, 6-mercaptopurine, or methotrexate). Patients who had previously received a TNF blocker were allowed to enroll if they had previously had loss of response or intolerance to that TNF blocker.

Patients received open-label induction therapy at a dose based on their body weight (≥40 kg and <40 kg). Patients weighing ≥40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing <40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥40 kg and <40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥40 kg and 20 mg every other week for patients weighing <40 kg. The low dose was 20 mg every other week for patients weighing ≥40 kg and 10 mg every other week for patients weighing <40 kg.

Concomitant stable dosages of corticosteroids (prednisone dosage ≤40 mg/day or equivalent) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted throughout the study.

At Week 12, patients who experienced a disease flare (increase in PCDAI of ≥ 15 from Week 4 and absolute PCDAI > 30) or who were non-responders (did not achieve a decrease in the PCDAI of ≥ 15 from baseline for 2 consecutive visits at least 2 weeks apart) were allowed to dose-escalate (i.e., switch from blinded every other week dosing to blinded every week dosing); patients who dose-escalated were considered treatment failures.

At baseline, 38% of patients were receiving corticosteroids, and 62% of patients were receiving an immunomodulator. Forty-four percent (44%) of patients had previously lost response or were intolerant to a TNF blocker. The median baseline PCDAI score was 40.

Of the 192 patients total, 188 patients completed the 4 week induction period, 152 patients completed 26 weeks of treatment, and 124 patients completed 52 weeks of treatment. Fifty-one percent (51%) (48/95) of patients in the low maintenance dose group dose-escalated, and 38% (35/93) of patients in the high maintenance dose group dose-escalated.

At Week 4, 28% (52/188) of patients were in clinical remission (defined as PCDAI ≤ 10).

The proportions of patients in clinical remission (defined as PCDAI ≤ 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52.

At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group (Table 13). The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing ≥ 40 kg. Every week dosing is not the recommended maintenance dosing regimen *[see Dosage and Administration (2.4)]*.

Table 13. Clinical Remission and Clinical Response in Study PCD-I

	Low Maintenance Dose[†] (20 or 10 mg every other week) N = 95	**High Maintenance Dose[#] (40 or 20 mg every other week) N = 93**
Week 26		
Clinical Remission[‡]	28%	39%
Clinical Response[§]	48%	59%
Week 52		
Clinical Remission[‡]	23%	33%
Clinical Response[§]	28%	42%

[†]The low maintenance dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing < 40 kg.
[#]The high maintenance dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg.
[‡]Clinical remission defined as PCDAI ≤ 10.
[§]Clinical response defined as reduction in PCDAI of at least 15 points from baseline.

14.7 Ulcerative Colitis

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

Concomitant stable doses of aminosalicylates and immunosuppressants were permitted. In Studies UC-I and II, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients received at least one of these medications.

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscores > 1) at Week 8 was evaluated in both studies. Clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were evaluated in Study UC-II.

In Study UC-I, 390 TNF-blocker naïve patients were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Weeks 0, 2, 4 and 6. The 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg HUMIRA at Week 0 and 40 mg at Week 2. After Week 2, patients in both HUMIRA treatment groups received 40 mg every other week (eow).

In Study UC-II, 518 patients were randomized to receive either HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52) (Table 14).

Table 14. Induction of Clinical Remission in Studies UC-I and UC-II and Sustained Clinical Remission in Study UC-II (Percent of Patients)

	Study UC-I			Study UC-II		
	Placebo N=130	**HUMIRA 160/80 mg N=130**	**Treatment Difference (95% CI)**	**Placebo N=246**	**HUMIRA 160/80 mg N=248**	**Treatment Difference (95% CI)**
Induction of Clinical Remission (Clinical Remission at Week 8)	9.2%	18.5%	9.3%* (0.9%, 17.6%)	9.3%	16.5%	7.2%* (1.2%, 12.9%)
Sustained Clinical Remission (Clinical Remission at both Weeks 8 and 52)	N/A	N/A	N/A	4.1%	8.5%	4.4%* (0.1%, 8.6%)

Clinical remission is defined as Mayo score ≤ 2 with no individual subscores > 1.
CI=Confidence interval
* p<0.05 for HUMIRA *vs.* placebo pairwise comparison of proportions

In Study UC-I, there was no statistically significant difference in clinical remission observed between the HUMIRA 80/40 mg group and the placebo group at Week 8.

In Study UC-II, 17.3% (43/248) in the HUMIRA group were in clinical remission at Week 52 compared to 8.5% (21/246) in the placebo group (treatment difference: 8.8%; 95% confidence interval (CI): [2.8%, 14.5%]; p<0.05).

In the subgroup of patients in Study UC-II with prior TNF-blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study

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

14.8 Plaque Psoriasis

The safety and efficacy of HUMIRA were assessed in randomized, double-blind, placebo-controlled studies in 1696 adult subjects with moderate to severe chronic plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy.

Study Ps-I evaluated 1212 subjects with chronic Ps with ≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, subjects received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, subjects who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg HUMIRA every other week. After 17 weeks of open label therapy, subjects who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%).

Study Ps-II evaluated 99 subjects randomized to HUMIRA and 48 subjects randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Subjects received placebo, or an initial dose of 80 mg HUMIRA at Week 0 followed by 40 mg every other week starting at Week 1 for 16 weeks. Across all treatment groups the mean baseline PASI score was 21 and the baseline PGA score ranged from "moderate" (41%) to "severe" (51%) to "very severe" (8%).

Studies Ps-I and II evaluated the proportion of subjects who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 15 and 16).

Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52.

Table 15. Efficacy Results at 16 Weeks in Study Ps-I Number of Subjects (%)

	HUMIRA 40 mg every other week	Placebo
	N = 814	N = 398
PGA: Clear or minimal*	506 (62%)	17 (4%)
PASI 75	578 (71%)	26 (7%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red		

coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration

Table 16. Efficacy Results at 16 Weeks in Study Ps-II Number of Subjects (%)

	HUMIRA 40 mg every other week	Placebo
	N = 99	N = 48
PGA: Clear or minimal*	70 (71%)	5 (10%)
PASI 75	77 (78%)	9 (19%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Additionally, in Study Ps-I, subjects on HUMIRA who maintained a PASI 75 were re-randomized to HUMIRA (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with HUMIRA, more subjects on HUMIRA maintained efficacy when compared to subjects who were re-randomized to placebo based on maintenance of PGA of "clear" or "minimal" disease (68% *vs.* 28%) or a PASI 75 (79% *vs.* 43%).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. During the withdrawal period, no subject experienced transformation to either pustular or erythrodermic psoriasis. A total of 178 subjects who relapsed re-initiated treatment with 80 mg of HUMIRA, then 40 mg eow beginning at week 1. At week 16, 69% (123/178) of subjects had a response of PGA "clear" or "minimal".

14.9 Hidradenitis Suppurativa

Two randomized, double-blind, placebo-controlled studies (Studies HS-I and II) evaluated the safety and efficacy of HUMIRA in a total of 633 adult subjects with moderate to severe hidradenitis suppurativa (HS) with Hurley Stage II or III disease and with at least 3 abscesses or inflammatory nodules. In both studies, subjects 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 and continued through Week 11. Subjects used topical antiseptic wash daily. Concomitant oral antibiotic use was allowed in Study HS-II.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as 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 (see Table 17). 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.

In both studies, a higher proportion of HUMIRA- than placebo-treated subjects achieved HiSCR (see Table 17).

Table 17. Efficacy Results at 12 Weeks in Subjects with Moderate to Severe Hidradenitis Suppurativa

	HS Study I		HS Study II*	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)	N = 154 40 (26%)	N = 153 64 (42%)	N=163 45 (28%)	N=163 96 (59%)
*19.3% of subjects in Study HS-II continued baseline oral antibiotic therapy during the study.				

In both studies, from Week 12 to Week 35 (Period B), subjects who had received HUMIRA were re-randomized to 1 of 3 treatment groups (HUMIRA 40 mg every week, HUMIRA 40 mg every other week, or placebo). Subjects who had been randomized to placebo were assigned to receive HUMIRA 40 mg every week (Study HS-I) or placebo (Study HS-II).

During Period B, flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

14.10 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 randomized, 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. The primary efficacy endpoint in both studies was ´time to treatment failure´.

Treatment failure was a multi-component outcome defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA).

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

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

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with HUMIRA versus patients receiving placebo. In both studies, all

components of the primary endpoint contributed cumulatively to the overall difference between HUMIRA and placebo groups (Table 18).

Table 18. Time to Treatment Failure in Studies UV I and UV II

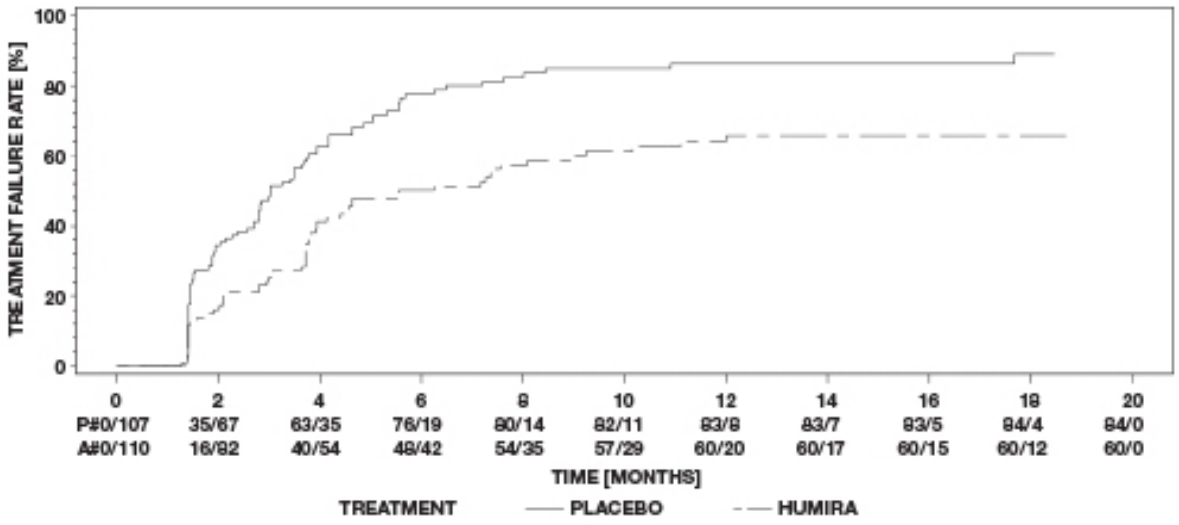
	UV I			UV II		
	Placebo (N = 107)	HUMIRA (N = 110)	HR [95% CI][a]	Placebo (N = 111)	HUMIRA (N = 115)	HR [95% CI][a]
Failure[b] n (%)	84 (78.5)	60 (54.5)	0.50 [0.36, 0.70]	61 (55.0)	45 (39.1)	0.57 [0.39, 0.84]
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]	N/A	8.3 [4.8, 12.0]	NE[c]	N/A

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

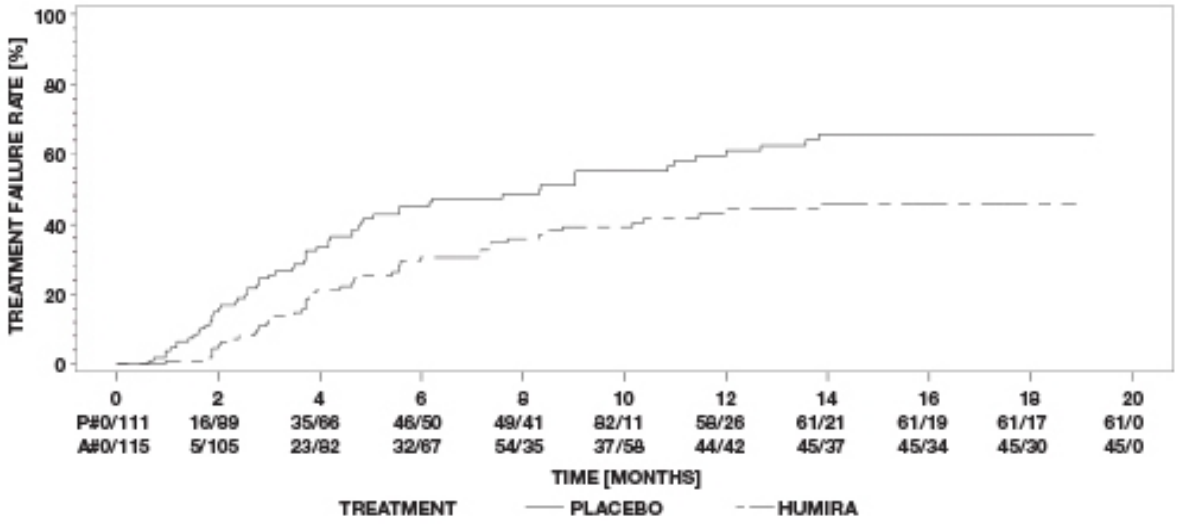
[b] Treatment failure at or after Week 6 in Study UV I, or at or after Week 2 in Study UV II, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.

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

Figure 3: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)



Study UV I



Study UV II

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

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 17 Registries, 2000-2007.
2. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12:439-447.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

- **HUMIRA Pen Carton - 40 mg/0.8 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-02.
- **HUMIRA Pen Carton - 40 mg/0.4 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-02.
- **HUMIRA Pen 40 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-06.
- **HUMIRA Pen 40 mg/0.4 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-06.
- **HUMIRA Pen 40 mg/0.8 mL - Psoriasis/Uveitis Starter Package**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis/Uveitis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-07.
- **HUMIRA Pen 40 mg/0.4 mL - Psoriasis/Uveitis Starter Package**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis/Uveitis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-04.
- **Prefilled Syringe Carton - 40 mg/0.8 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch

needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-02.

- **Prefilled Syringe Carton - 40 mg/0.4 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0243-02.
- **Prefilled Syringe Carton - 20 mg/0.4 mL**
  HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge, ½ inch needle, providing 20 mg/0.4 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-9374-02.
- **Prefilled Syringe Carton - 10 mg/0.2 mL**
  HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge, ½ inch needle, providing 10 mg/0.2 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-6347-02.
- **HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (6 count)**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Pediatric Starter Package). Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-06.
- **HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count)**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 3 dose trays (Pediatric Starter Package). Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-03.
- **Single-Use Institutional Use Vial Carton - 40 mg/0.8 mL**
  HUMIRA is supplied for institutional use only in a carton containing a single-use, glass vial, providing 40 mg/0.8 mL of HUMIRA. The vial stopper is not made with natural rubber latex. The NDC number is 0074-3797-01.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed.

Store in original carton until time of administration to protect from light.

If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray.

Do not store HUMIRA in extreme heat or cold.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the gray needle cap of the 27 gauge HUMIRA Pen and prefilled syringe contains natural rubber latex *[see How Supplied/Storage and Handling (16) for specific information]*.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

Instructions on Injection Technique

Inform patients that the first injection is to be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, instruct them in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of HUMIRA *[see Instructions for Use]*.

For patients who will use the HUMIRA Pen, tell them that they:

- Will hear a **loud 'click'** when the plum-colored activator button is pressed. The loud click means the **start** of the injection.
- Must keep holding the HUMIRA Pen against their squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds.
- Will know that the injection has finished when the yellow marker fully appears in the window view and stops moving.

Instruct patients to dispose of their used needles and syringes or used Pen in a FDA-cleared sharps disposal container immediately after use. **Instruct patients not to dispose of loose needles and syringes or Pen in their household trash.** Instruct patients that if they do not have

a FDA-cleared sharps disposal container, they may use a household container that is made of a heavy-duty plastic, can be closed with a tight-fitting and puncture-resistant lid without sharps being able to come out, upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

Instruct patients that when their sharps disposal container is almost full, they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients that there may be state or local laws regarding disposal of used needles and syringes. Refer patients to the FDA's website at http://www.fda.gov/safesharpsdisposal for more information about safe sharps disposal, and for specific information about sharps disposal in the state that they live in.

Instruct patients not to dispose of their used sharps disposal container in their household trash unless their community guidelines permit this. Instruct patients not to recycle their used sharps disposal container.

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

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MEDICATION GUIDE
HUMIRA® (Hu-MARE-ah)
(adalimumab)
injection

Read the Medication Guide that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about HUMIRA?
HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. **Serious infections have happened in people taking HUMIRA. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.**

- Your doctor should test you for TB before starting HUMIRA.
- Your doctor should check you closely for signs and symptoms of TB during treatment with HUMIRA.

You should not start taking HUMIRA if you have any kind of infection unless your doctor says it is okay.

Before starting HUMIRA, tell your doctor if you:

- think you have an infection or have symptoms of infection such as:
  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
  - weight loss
- are being treated for an infection

- get a lot of infections or have infections that keep coming back
- have diabetes
- have TB, or have been in close contact with someone with TB
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use HUMIRA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B
- use the medicine ORENCIA® (abatacept), KINERET® (anakinra), RITUXAN® (rituximab), IMURAN® (azathioprine), or PURINETHOL® (6–mercaptopurine, 6-MP).
- are scheduled to have major surgery

After starting HUMIRA, call your doctor right away if you have an infection, or any sign of an infection.

HUMIRA can make you more likely to get infections or make any infection that you may have worse.

Cancer

- For children and adults taking TNF-blockers, including HUMIRA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children, teenagers, and young adults using TNF-blockers.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers including HUMIRA your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn't heal.
- Some people receiving TNF blockers including HUMIRA developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6–MP).

What is HUMIRA?

HUMIRA is a medicine called a Tumor Necrosis Factor (TNF) blocker. HUMIRA is used:

- To reduce the signs and symptoms of:
  - **moderate to severe rheumatoid arthritis (RA) in adults.** HUMIRA can be used alone, with methotrexate, or with certain other medicines.
  - **moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children** 2 years and older. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
  - **psoriatic arthritis (PsA) in adults.** HUMIRA can be used alone or with certain other medicines.
  - **ankylosing spondylitis (AS) in adults.**
  - **moderate to severe Crohn's disease (CD) in adults** when other treatments have not worked well enough.
  - **moderate to severe Crohn's disease (CD) in children** 6 years and older when other treatments have not worked well enough.
  - **moderate to severe hidradenitis suppurativa (HS) in adults.**

- In adults, to help get **moderate to severe ulcerative colitis (UC)** under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if HUMIRA is effective in people who stopped responding to or could not tolerate TNF-blocker medicines.
- **To treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps) in adults** who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- **To treat non-infectious intermediate, posterior and panuveitis (UV) in adults.**

What should I tell my doctor before taking HUMIRA?
HUMIRA may not be right for you. Before starting HUMIRA, tell your doctor about all of your health conditions, including if you:

- have an infection. See **"What is the most important information I should know about HUMIRA?"**
- have or have had cancer.
- have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using HUMIRA. Children should be brought up to date with all vaccines before starting HUMIRA.
- are allergic to rubber or latex. Tell your doctor if you have any allergies to rubber or latex.
  - The gray needle cover for the HUMIRA Pen 40 mg/0.8 mL, HUMIRA 40 mg/0.8 mL prefilled syringe, HUMIRA 20 mg/0.4 mL prefilled syringe, and HUMIRA 10 mg/0.2 mL prefilled syringe contains natural rubber or latex.
  - The black needle cover for the HUMIRA Pen 40 mg/0.4 mL, HUMIRA 40 mg/0.4 mL prefilled syringe and the vial stopper on the HUMIRA institutional use vial are not made with natural rubber or latex.
- are allergic to HUMIRA or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HUMIRA.
- are pregnant or plan to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed.
- have a baby and you were using HUMIRA during your pregnancy. Tell your baby's doctor before your baby receives any vaccines.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your doctor if you use:

- ORENCIA® (abatacept), KINERET® (anakinra), REMICADE® (infliximab), ENBREL® (etanercept), CIMZIA® (certolizumab pegol) or SIMPONI® (golimumab), because you should not use HUMIRA while you are also using one of these medicines.
- RITUXAN® (rituximab). Your doctor may not want to give you HUMIRA if you have received RITUXAN® (rituximab) recently.
- IMURAN® (azathioprine) or PURINETHOL® (6–mercaptopurine, 6-MP).

Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take HUMIRA?

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take

an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than you were prescribed.**

- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject HUMIRA.
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (1-800-448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after they have been shown how to prepare and inject HUMIRA.
- **Do not** try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA.
- Do not miss any doses of HUMIRA unless your doctor says it is okay. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. In case you are not sure when to inject HUMIRA, call your doctor or pharmacist.
- If you take more HUMIRA than you were told to take, call your doctor.

What are the possible side effects of HUMIRA?

HUMIRA can cause serious side effects, including:

See "What is the most important information I should know about HUMIRA?"

- **Serious Infections.**
  Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with HUMIRA and during treatment with HUMIRA. Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking HUMIRA. People who had a negative TB skin test before receiving HUMIRA have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking HUMIRA:
  - cough that does not go away
  - low grade fever
  - weight loss
  - loss of body fat and muscle (wasting)

- **Hepatitis B infection in people who carry the virus in their blood.**
  If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use HUMIRA. Your doctor should do blood tests before you start treatment, while you are using HUMIRA, and for several months after you stop treatment with HUMIRA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:
  - muscle aches
  - feel very tired
  - dark urine
  - skin or eyes look yellow
  - little or no appetite
  - vomiting
  - clay-colored bowel movements
  - fever
  - chills
  - stomach discomfort
  - skin rash

- **Allergic reactions.** Allergic reactions can happen in people who use HUMIRA. Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:
  - hives
  - trouble breathing
  - swelling of your face, eyes, lips or mouth

- **Nervous system problems.** Signs and symptoms of a nervous system problem include:

numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.

- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have. Call your doctor right away** if you get new worsening symptoms of heart failure while taking HUMIRA, including:
  - shortness of breath
  - sudden weight gain
  - swelling of your ankles or feet
- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may improve when you stop HUMIRA.
- **Liver Problems.** Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
  - feel very tired
  - poor appetite or vomiting
  - skin or eyes look yellow
  - pain on the right side of your stomach (abdomen)
- **Psoriasis.** Some people using HUMIRA had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with HUMIRA.

Call your doctor or get medical care right away if you develop any of the above symptoms. Your treatment with HUMIRA may be stopped.

Common side effects with HUMIRA include:

- injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
- upper respiratory infections (including sinus infections)
- headaches
- rash

These are not all the possible side effects with HUMIRA. Tell your doctor if you have any side effect that bothers you or that does not go away. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HUMIRA?

- Store HUMIRA in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, Pen or prefilled syringe. Do not use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to 14 days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within 14 days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.

- Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.

Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

General information about the safe and effective use of HUMIRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that is written for health professionals. For more information go to www.HUMIRA.com or you can enroll in a patient support program by calling 1-800-4HUMIRA (1-800-448-6472).

What are the ingredients in HUMIRA?

Active ingredient: adalimumab

HUMIRA Pen 40 mg/0.8 mL, HUMIRA 40 mg/0.8 mL prefilled syringe, HUMIRA 20 mg/0.4 mL prefilled syringe, HUMIRA 10 mg/0.2 mL prefilled syringe, and HUMIRA 40 mg/0.8 mL institutional use vial:

Inactive ingredients: citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium chloride, sodium citrate and Water for Injection. Sodium hydroxide is added as necessary to adjust pH.

HUMIRA Pen 40 mg/0.4 mL and HUMIRA 40 mg/0.4 mL prefilled syringe:

Inactive ingredients: mannitol, polysorbate 80, and Water for Injection.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 06/2016

03-B352

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.8 ML

SINGLE-USE PEN

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

IMPORTANT:

- Do not use HUMIRA if frozen, even if it has been thawed.
- The HUMIRA Pen contains glass. Do not drop or crush the Pen because the glass inside may break.
- Do not remove the gray cap or the plum-colored cap until right before your injection.
- When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud “click” sound.
  - You must practice injecting HUMIRA with your doctor or nurse so that you are not startled by this click when you start giving yourself the injections at home.
  - The loud click sound means the start of the injection.
  - You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.

See the section below called **“Prepare the HUMIRA Pen”**.

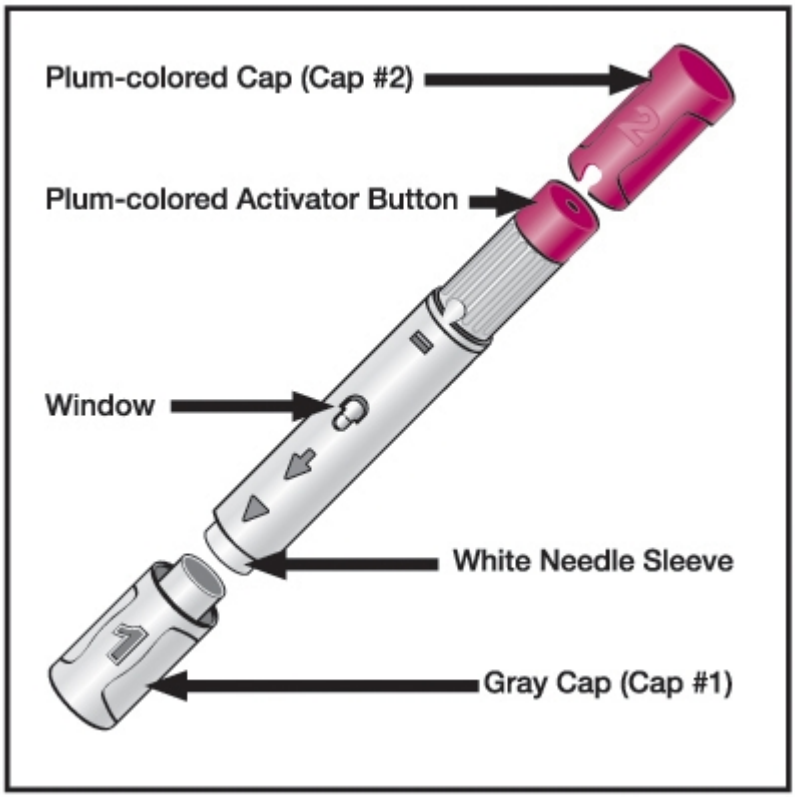
Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
  - 1 alcohol swab
  - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
  - 1 HUMIRA Pen (See Figure A)
  - FDA-cleared sharps disposal container for HUMIRA Pen disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA Pen out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the gray or plum-colored caps while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist. The diagram below shows what the HUMIRA Pen looks like. See Figure A.

Figure A



Check the carton, dose tray, and HUMIRA Pen.

1. Make sure the name HUMIRA appears on the carton, dose tray, and HUMIRA Pen label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - you drop or crush your HUMIRA Pen.
   - the seals on the top or bottom of the carton are broken or missing.
   - the expiration date on the carton, dose tray, and Pen has passed.
   - the HUMIRA Pen has been frozen or left in direct sunlight.
   - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).

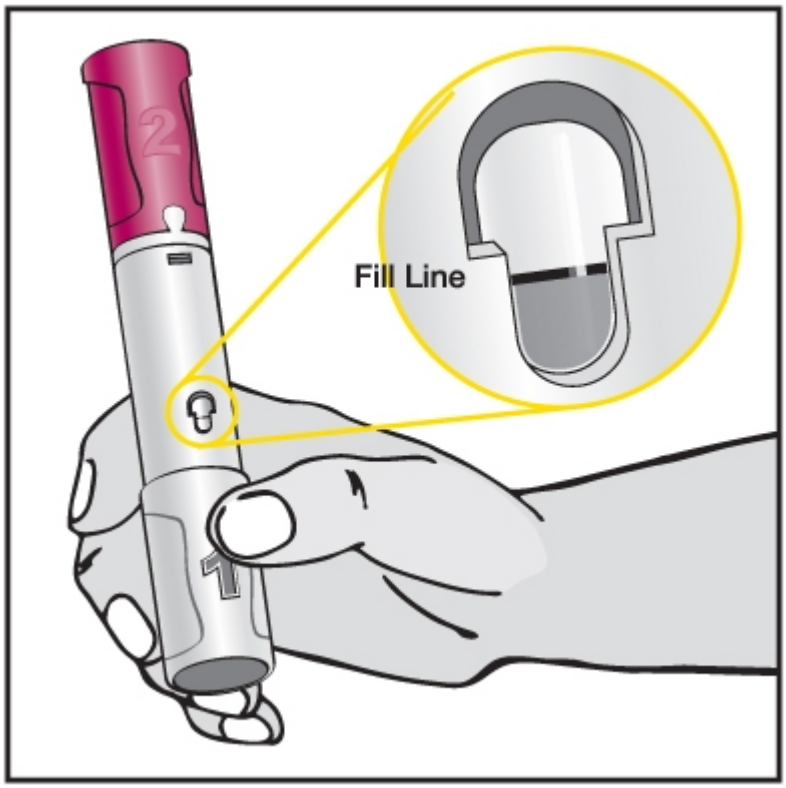
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

3. Hold the Pen with the gray cap (Cap # 1) pointed down.

4. Make sure the amount of liquid in the Pen is at the fill line or close to the fill line seen through the window. This is the full dose of HUMIRA that you will inject. See Figure B.

5. If the Pen does not have the full amount of liquid, **do not use that Pen**. Call your pharmacist.

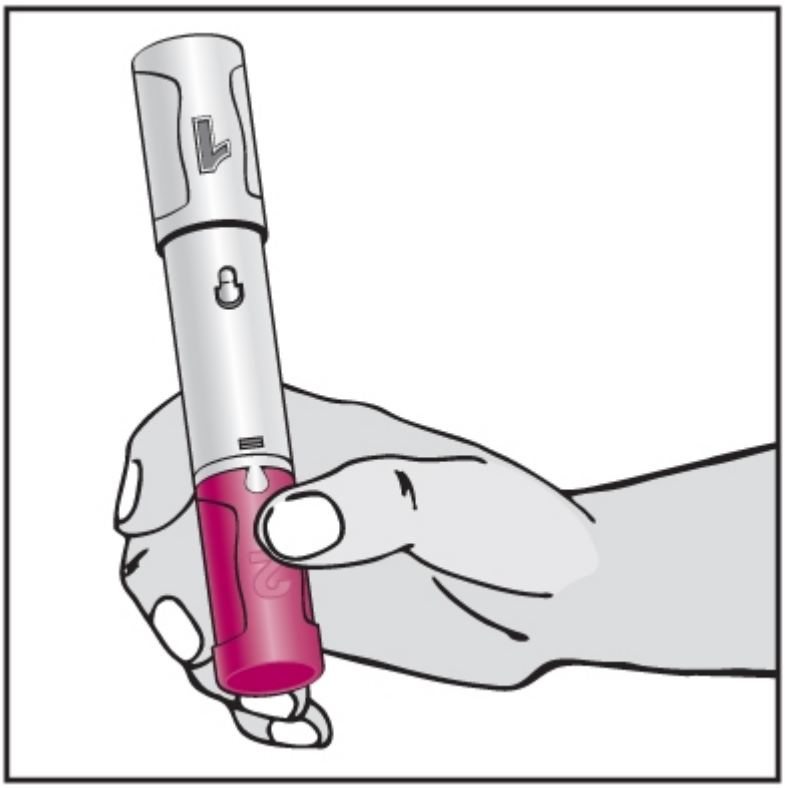
Figure B



6. Turn the Pen over and hold the Pen with the gray cap (Cap # 1) pointed up. See Figure C.

7. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. **Do not use** your HUMIRA Pen if the liquid is cloudy, discolored, or if it has flakes or particles in it. Call your pharmacist. It is normal to see one or more bubbles in the window.

Figure C

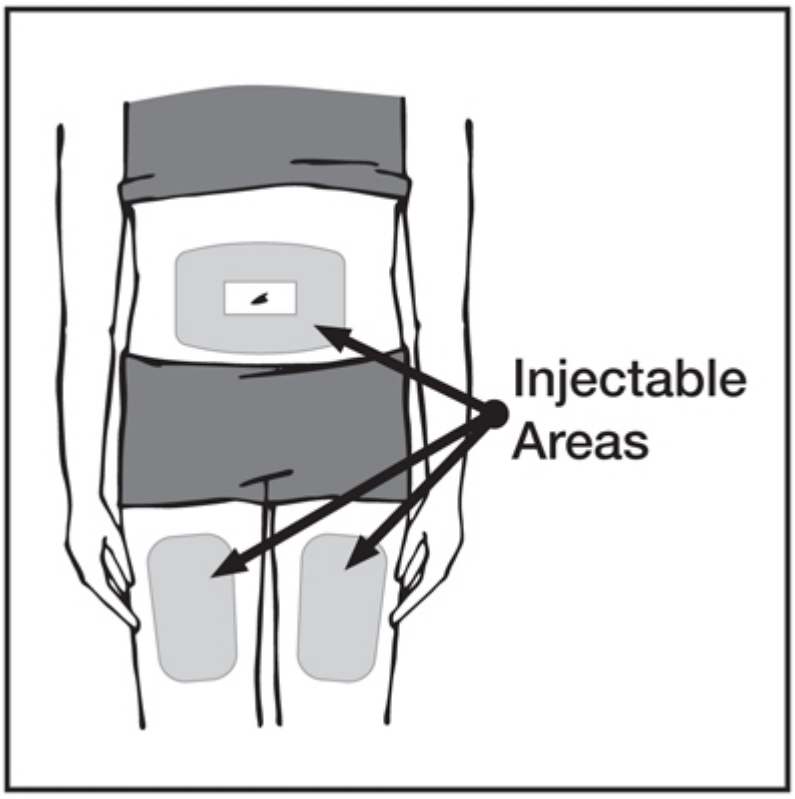


Choose the Injection Site

8. Wash and dry your hands well.

9. Choose an injection site on:
   - the front of your thighs or
   - your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure D.

Figure D



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject HUMIRA into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks
- If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

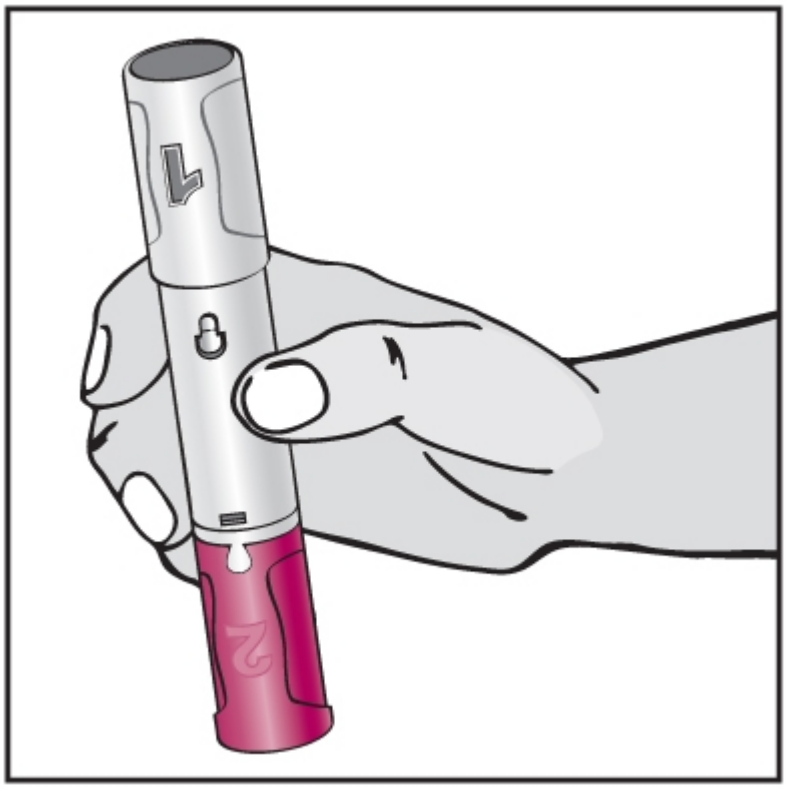
10. Wipe the injection site with an alcohol prep (swab) using a circular motion.
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

Preparing the HUMIRA Pen

11. **Do not remove the gray cap (Cap # 1) or the plum-colored cap (Cap # 2) until right before your injection.**

12. Hold the middle of the Pen (gray body) with one hand so that you are not touching the gray cap (Cap # 1) or the plum-colored cap (Cap # 2). Turn the Pen so that the gray cap (Cap # 1) is pointing up. See Figure E.

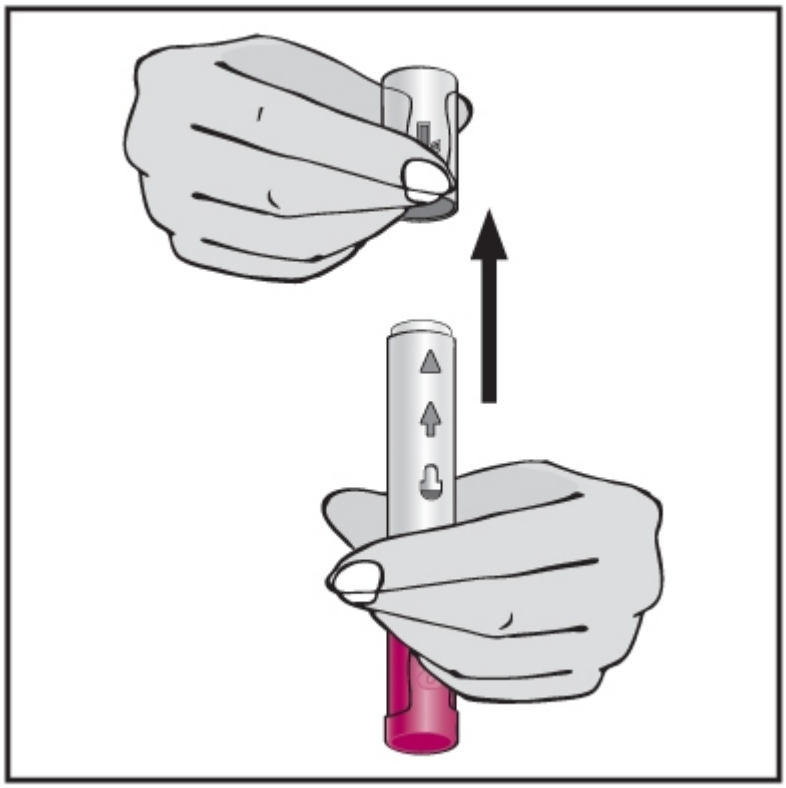
Figure E



13. With your other hand, pull the gray cap (Cap # 1) straight off (do not twist the cap). Make sure the small gray needle cover of the syringe has come off with the gray cap (Cap # 1). See Figure F.

14. Throw away the gray cap (Cap # 1).

Figure F



- **Do not** put the gray cap (Cap # 1) back on the Pen. Putting the gray cap (Cap # 1) back on may damage the needle.
- The white needle sleeve, which covers the needle, can now be seen.
- **Do not** touch the needle with your fingers or let the needle touch anything.
- You may see a few drops of liquid come out of the needle. This is normal.

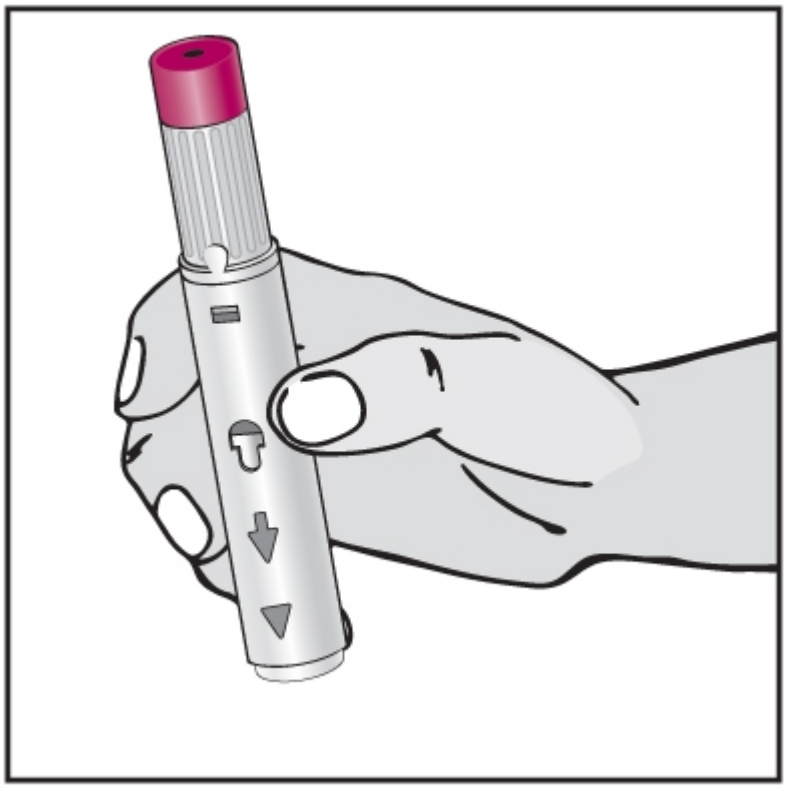
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- Do not put the plum-colored cap (Cap # 2) back on the Pen because it could cause medicine to come out of the syringe.

The plum-colored activator button:

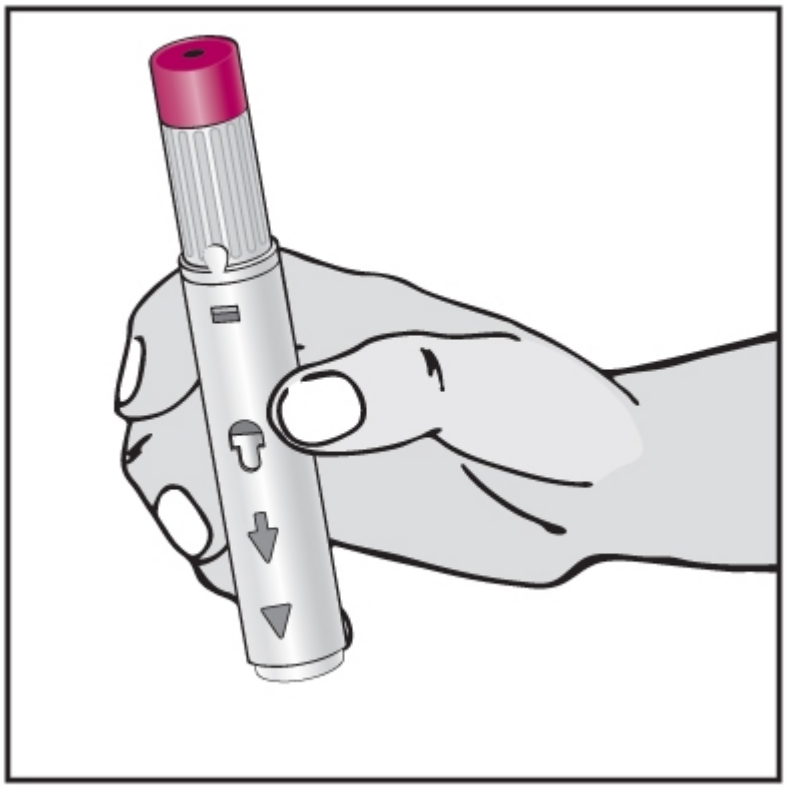
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

Figure G



- **Do not** press the plum-colored activator button until you are ready to inject HUMIRA. Pressing the plum-colored activator button will release the medicine from the Pen.
- Hold the Pen so that you can see the window. See Figure H. It is normal to see one or more bubbles in the window.

Figure H



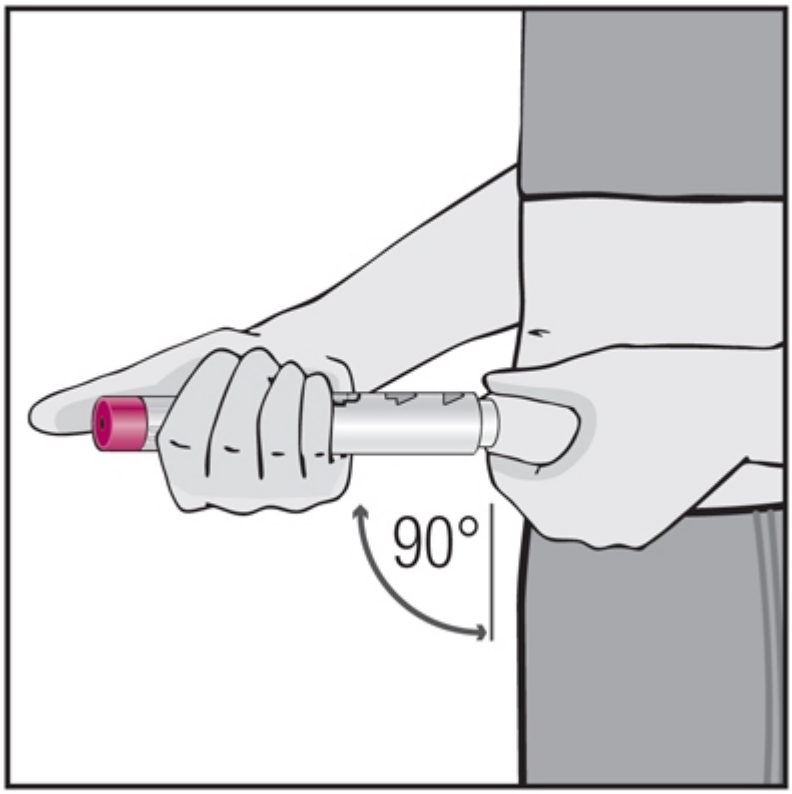
Position the Pen and Inject HUMIRA

16. Position the Pen:
    - Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

Figure I

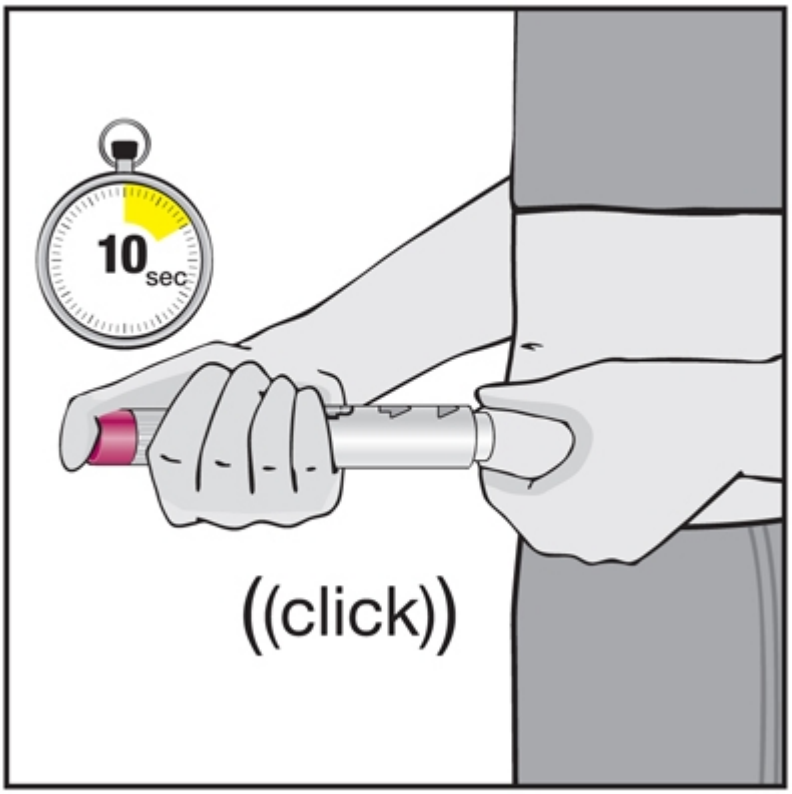
17. Place the white end of the Pen straight (at a 90º angle) and flat against the raised area of your skin that you are squeezing. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin. See Figure J.

Figure J



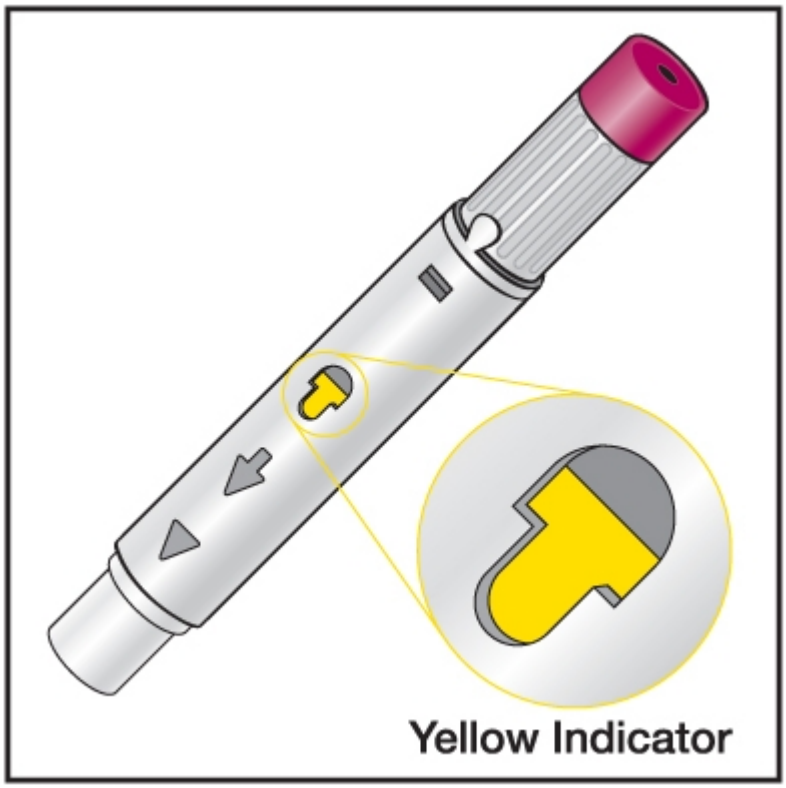
18. Inject HUMIRA
    - With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

Figure K



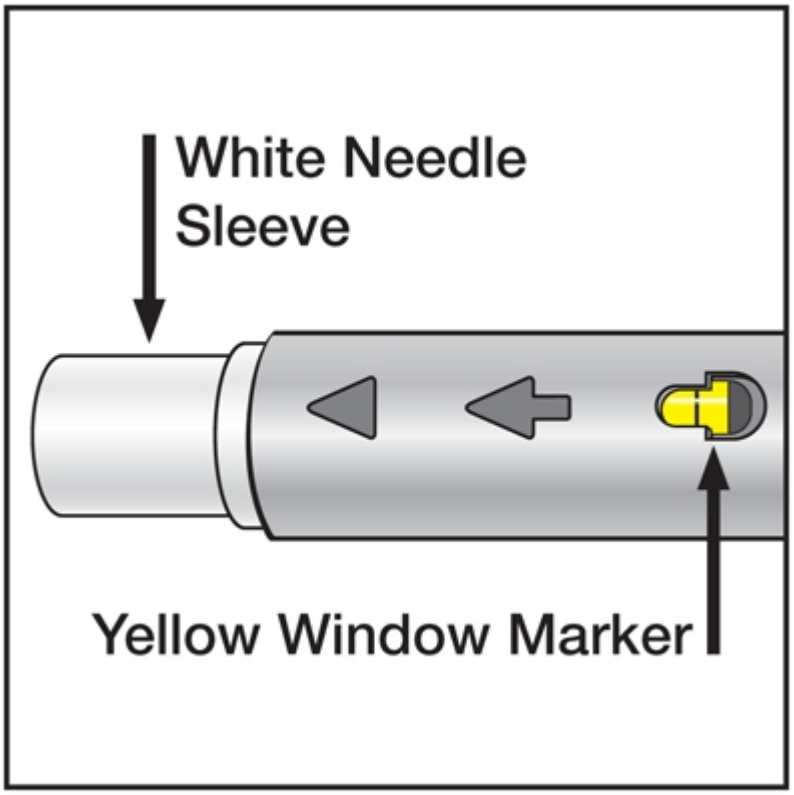
- You will hear a loud ‘click’ when you press the plum-colored activator button. The loud click means the start of the injection.
- Keep pressing the plum-colored activator button and continue to hold the Pen against your squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds, so count slowly to ten. Keep holding the Pen against the squeezed, raised skin of your injection site for the whole time so you get the full dose of medicine.
- You will know that the injection has finished when the yellow marker fully appears in the window view and stops moving. See Figure L.

Figure L



19. When the injection is finished, slowly pull the Pen from your skin. The white needle sleeve will move to cover the needle tip. See Figure M.
    - Do not touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure M



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

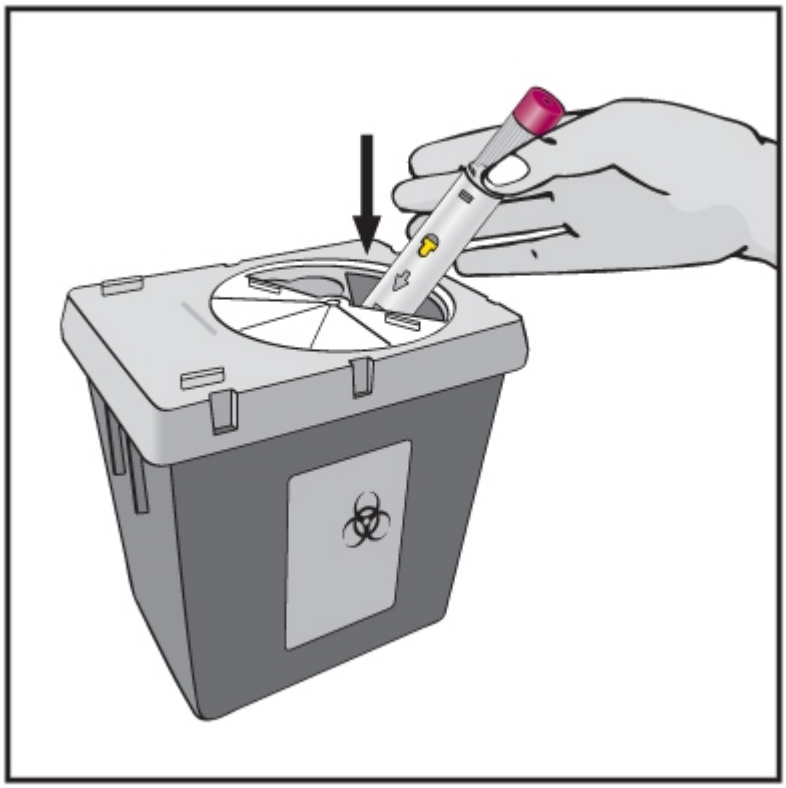
20. Dispose of your used HUMIRA Pen. See the section **"How should I dispose of the used HUMIRA Pen?"**

21. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of the used HUMIRA Pen?

- Put your Pen in a FDA-cleared sharps disposal container right away after use. See Figure N. **Do not throw away (dispose of) the Pen in your household trash.**
- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure N



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, never re-use your HUMIRA Pens.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.

- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or Pen. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a Pen if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03- B355

Revised: 06/2016

Instructions For Use

HUMIRA® (Hu-MARE-ah)

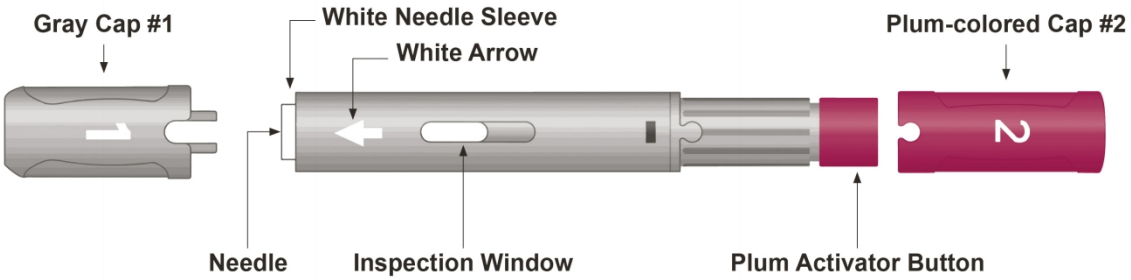
(adalimumab)

40 mg/0.4 mL

Single-Use Pen

Before Injecting: Your healthcare provider should show you how to use HUMIRA before you use it for the first time. Call your healthcare provider or **1-800-4HUMIRA** (1-800-448-6472) if you need help.

Figure A
HUMIRA Single-Use Pen



Do not use the Pen and call your healthcare provider or pharmacist if:

- Liquid is cloudy, discolored, or has flakes or particles in it
- Expiration date has passed
- Liquid has been frozen (even if thawed) or left in direct sunlight
- The Pen has been dropped or crushed

Keep the caps on until right before injection. Keep HUMIRA out of reach of children.

Read Instructions on All Pages Before Using the HUMIRA Pen

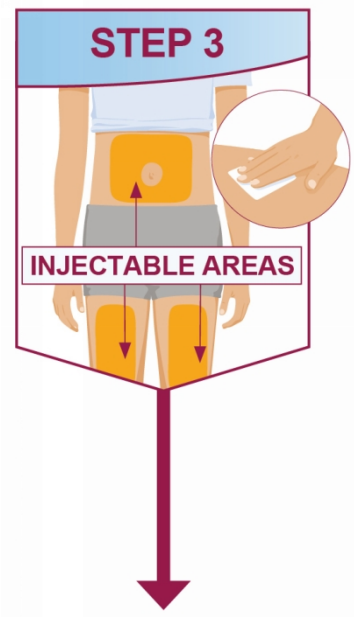
Take HUMIRA out of the refrigerator.
Leave HUMIRA at room temperature for **15 to 30 minutes** before injecting.

- **Do not** remove the Gray or Plum-colored Caps while allowing HUMIRA to reach room temperature
- **Do not** warm HUMIRA in any other way. For example, **do not** warm it in a microwave or in hot water.
- **Do not** use the Pen if liquid has been frozen (even if thawed)

Check expiration date on the Pen label. **Do not** use the Pen if expiration date has passed.
Place the following on a clean, flat surface:

- 1 single-use Pen and alcohol swab
- 1 cotton ball or gauze pad (not included)
- Puncture-resistant sharps disposal container (not included). See Step 9

Wash and dry your hands.

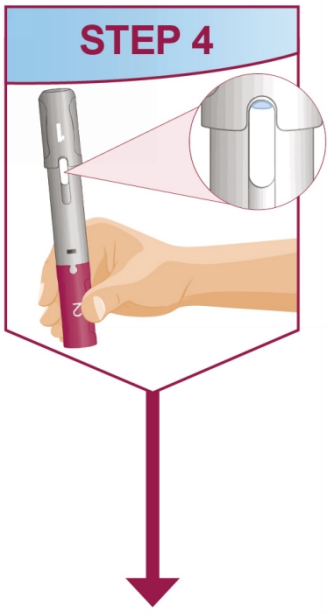


Choose an injection site:

- On the front of your thighs or
- Your abdomen (belly) at least 2 inches from your navel (belly button)
- Different from your last injection site

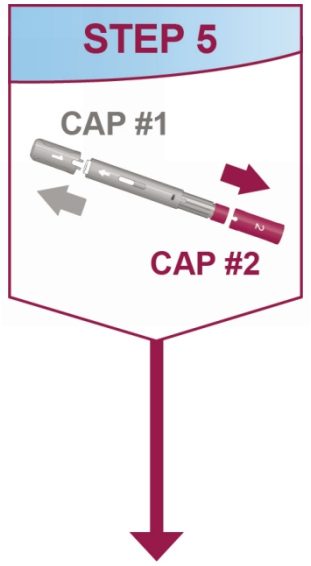
Wipe the injection site in a circular motion with the alcohol swab.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques



Hold the Pen with the Gray Cap #1 facing up.
Check the window.

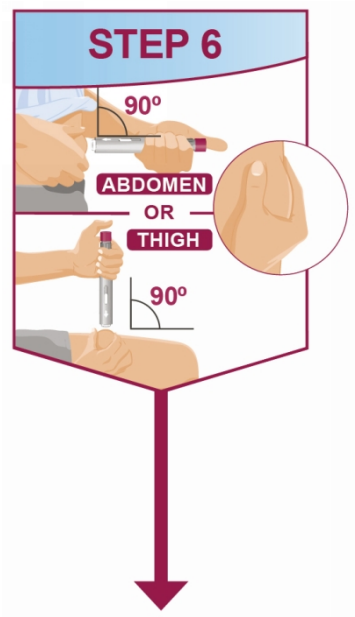
- It is normal to see 1 or more bubbles in the window
- Make sure the liquid is clear and colorless
- **Do not** use the Pen if the liquid is cloudy or has particles
- **Do not** use the Pen if it has been dropped or crushed



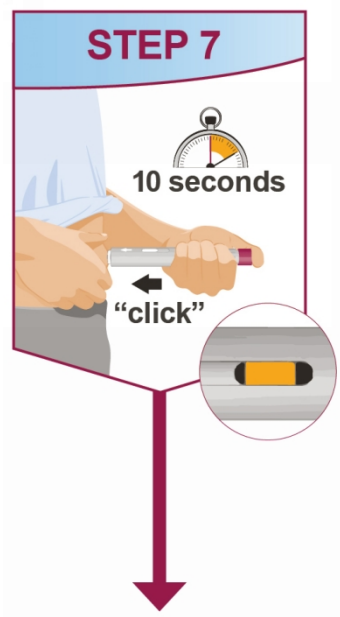
Pull the Gray Cap #1 straight off.
Throw the cap away.

- It is normal to see a few drops of liquid come out of the needle

Pull the Plum-colored Cap #2 straight off.
Throw the cap away.
Turn the Pen so that the white arrow points toward the injection site.

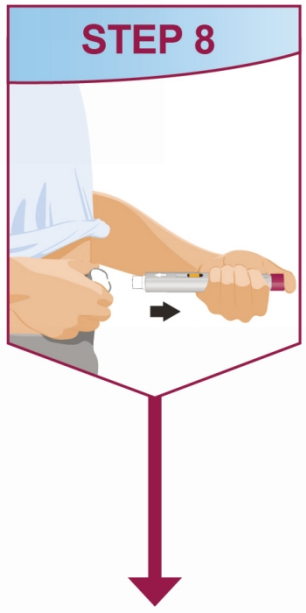


Squeeze the skin at your injection site to make a raised area and hold it firmly.
Point the white arrow toward the injection site.
Place the white needle sleeve straight **(90° angle)** against the injection site.
Hold the Pen so that you can see the inspection window.



Push and keep pushing the Pen **down** against the injection site.
Press the plum activator button and count slowly for **10** seconds.

- A loud "click" will signal the **start** of the injection
- **Keep pushing** the Pen **down** against the injection site
- Injection is complete when the yellow indicator has stopped moving



When the injection is completed, slowly pull the Pen from the skin. The white needle sleeve will cover the needle tip.
If there are more than a few drops of liquid on the injection site, call **1-800-4HUMIRA** (1-800-448-6472) for help.
After completing the injection, place a cotton ball or gauze pad on the skin of the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal

How should I dispose the used HUMIRA Pen?

- Put your used needles, Pens, and sharps in a FDA cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes, and the Pen in the household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal

container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

The Pen caps, alcohol swab, cotton ball or gauze pad, dose tray, and packaging may be placed in your household trash.

Questions About Using the HUMIRA Pen

What if I have not received in-person training from a healthcare provider?

- Call your healthcare provider or **1-800-4HUMIRA (1-800-448-6472)** or visit www.HUMIRA.com if you need help

How do I know when the injection is complete?

- The yellow indicator has stopped moving. This takes up to **10** seconds

What should I do if there are more than a few drops of liquid on the injection site?

- Call **1-800-4HUMIRA (1-800-448-6472)** for help

What if I do not have an FDA-cleared sharps disposal container or proper household container?

- Call **1-800-4HUMIRA (1-800-448-6472)** for a free FDA-cleared sharps disposal container

Always keep the Pen and the sharps disposal container out of reach of children.

Keep a record of the dates and locations of your injections. To help remember when to take HUMIRA, mark your calendar ahead of time.

abbvie

This Instructions For Use has been approved by the U.S. Food and Drug Administration.

Manufactured by AbbVie Inc. North Chicago, IL 60064 U.S.A.

US License Number 1889 03-B356 Revised 06/2016

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.8 ML, 20 MG/0.4 ML AND 10 MG/0.2 ML

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that

you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

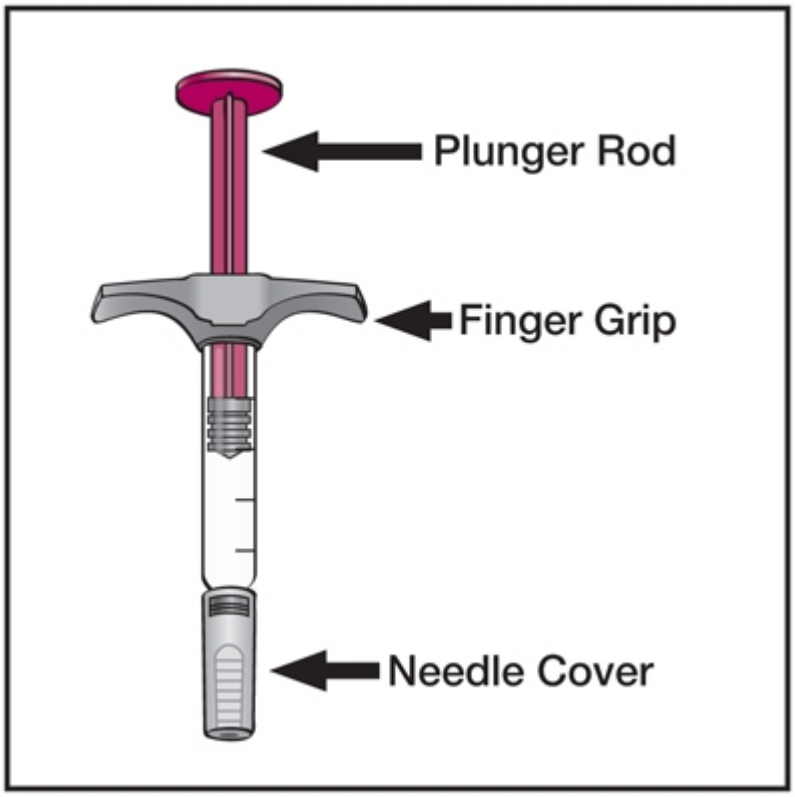
- You will need the following supplies for each injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
  - 1 alcohol swab
  - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
  - 1 HUMIRA prefilled syringe (See Figure A)
  - FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA prefilled syringe out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the needle cover while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist.

The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - the seals on top or bottom of the carton are broken or missing.
   - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and **do not** use if the date has passed.
   - the prefilled syringe that has been frozen or left in direct sunlight.
   - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).
   - the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

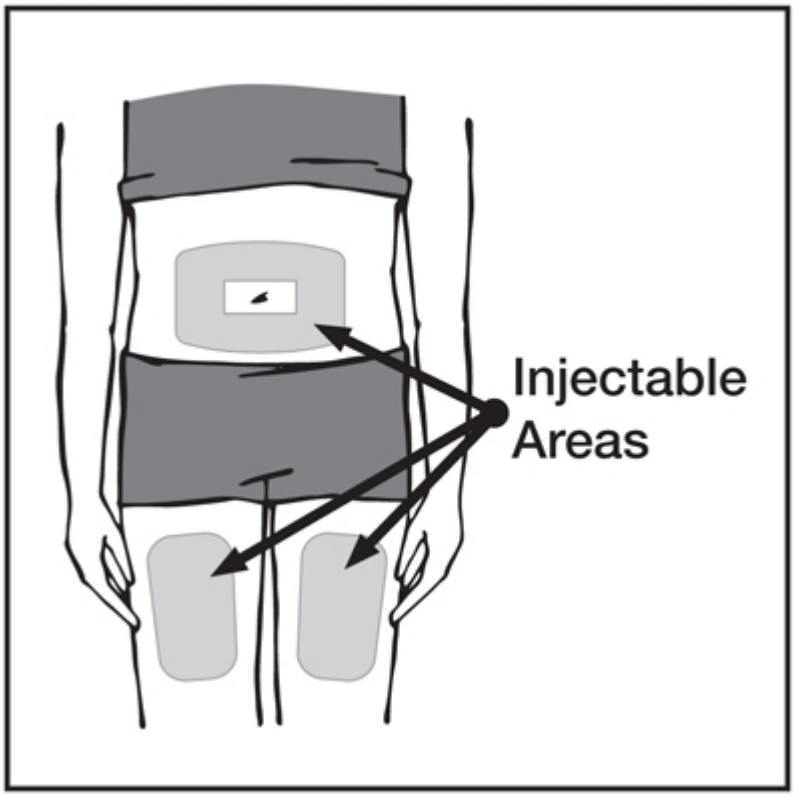
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

Choose the Injection Site

3. Wash and dry your hands well.

4. Choose an injection site on:
   - the front of your thighs or
   - your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



   - Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
   - **Do not** inject into skin that is:

- sore (tender)
- bruised
- red
- hard
- scarred or where you have stretch marks

- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

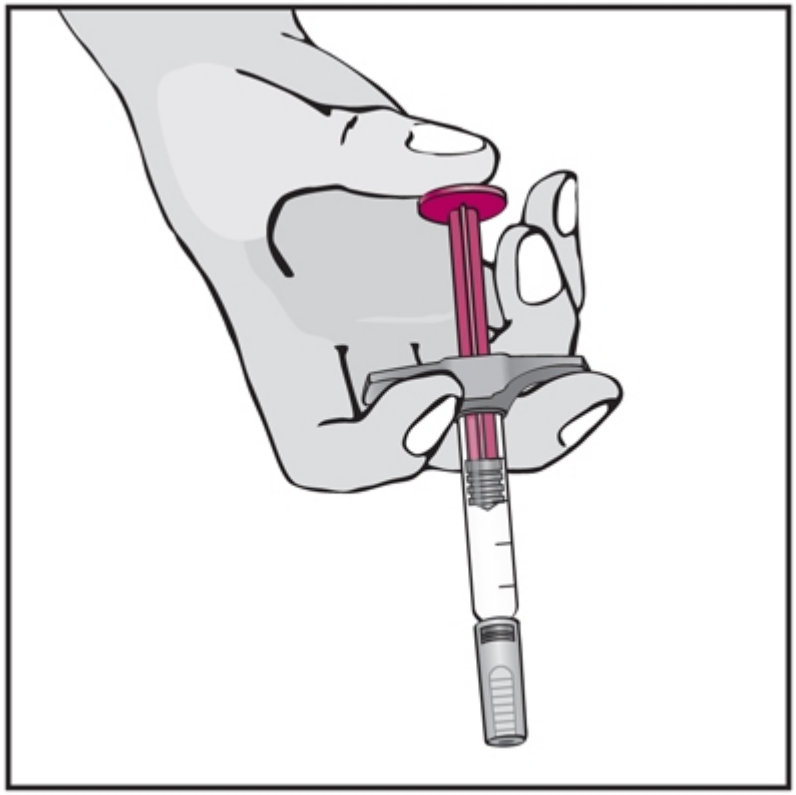
5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Check the fluid level in the syringe:
- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

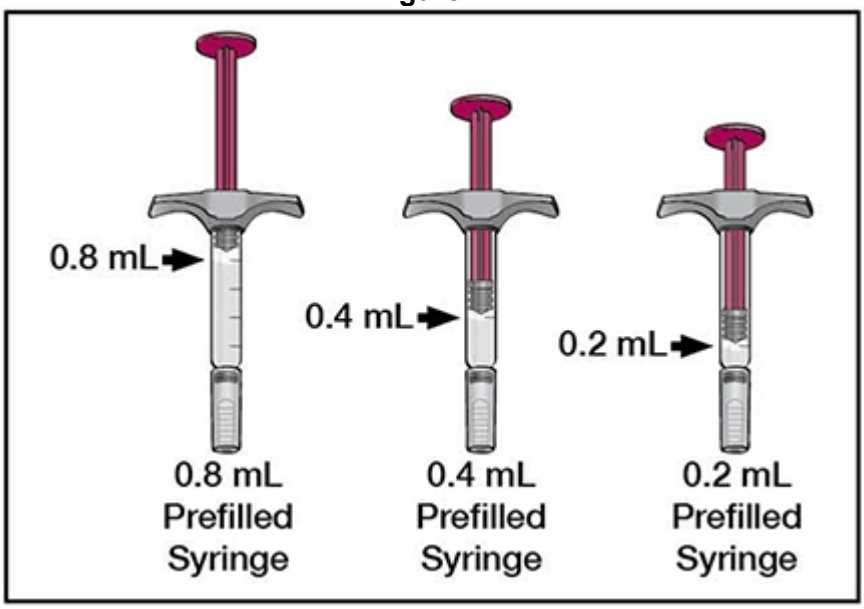
Figure C



- Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the:
  - 0.8 mL line for the 40 mg prefilled syringe. See Figure D.
  - 0.4 mL line for the 20 mg prefilled syringe. See Figure D.

- 0.2 mL line for the 10 mg prefilled syringe. See Figure D.

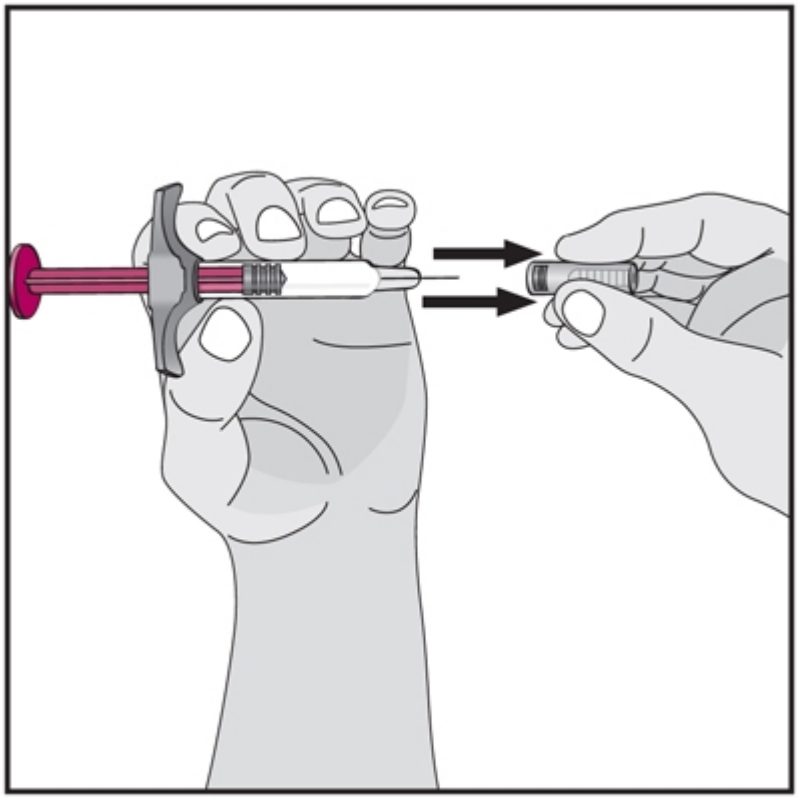
Figure D



8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

9. Remove the needle cover:
- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.
- Throw away the needle cover.

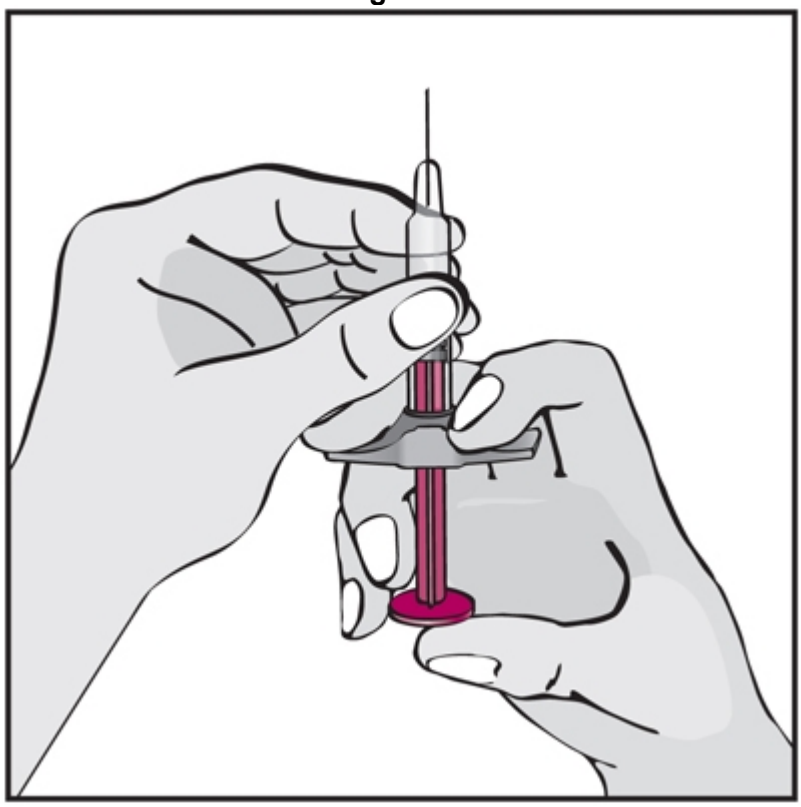
Figure E



- Do not touch the needle with your fingers or let the needle touch anything.

10. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure F.

Figure F



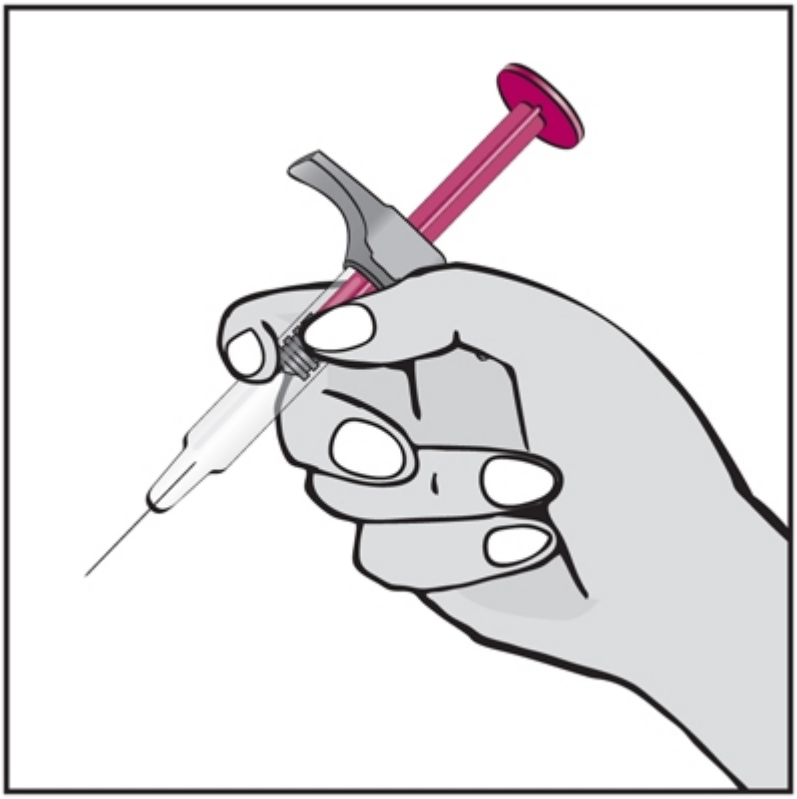
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

11. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure G.

Figure G



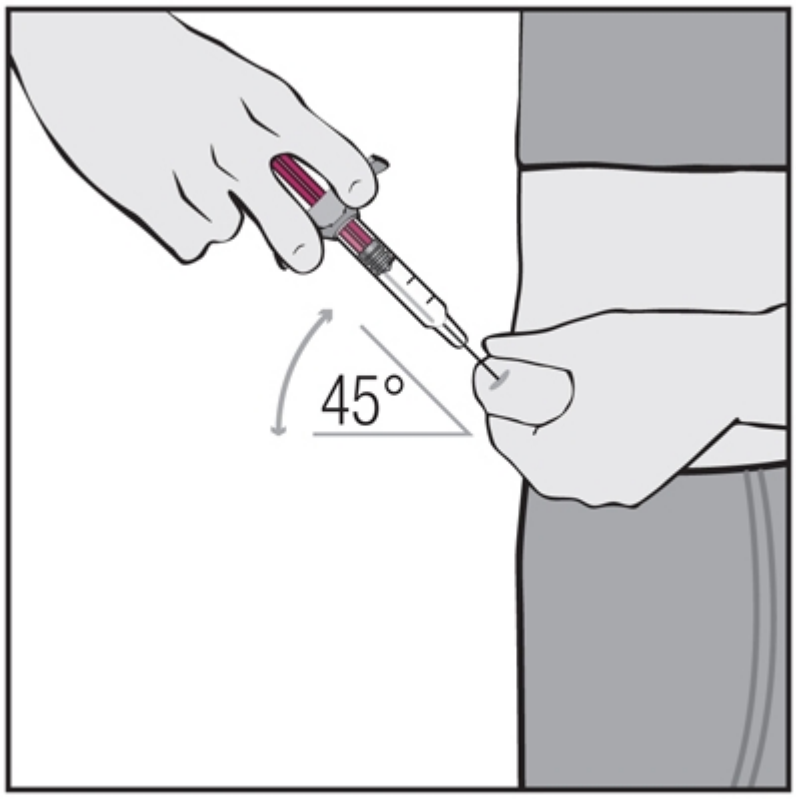
- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure H.

Figure H

Inject HUMIRA

12. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure I.

Figure I

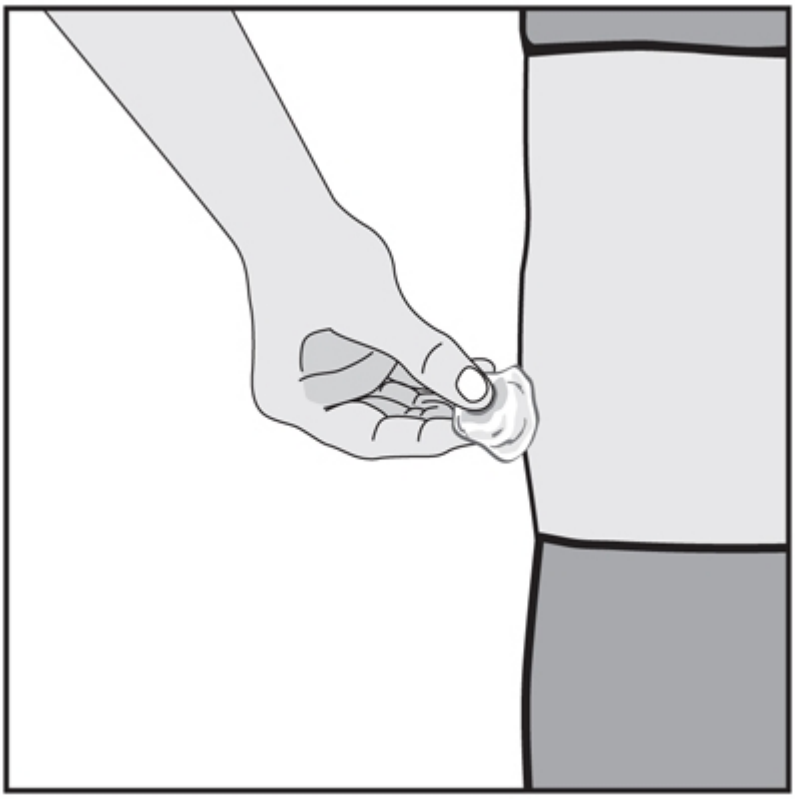


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure J.

Figure J



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 12 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

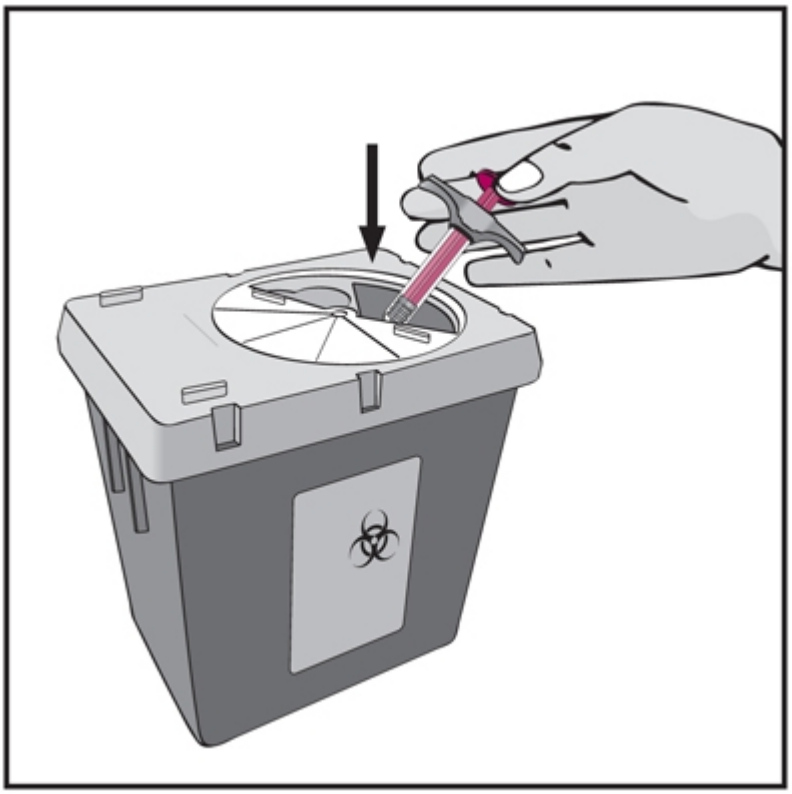
13. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

14. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure K. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- Do not try to touch the needle.

Figure K



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or prefilled syringe. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03-B353

Revised: 06/2016

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.4 ML

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.

  Find a clean, flat surface to place the supplies on.
  - 1 alcohol swab

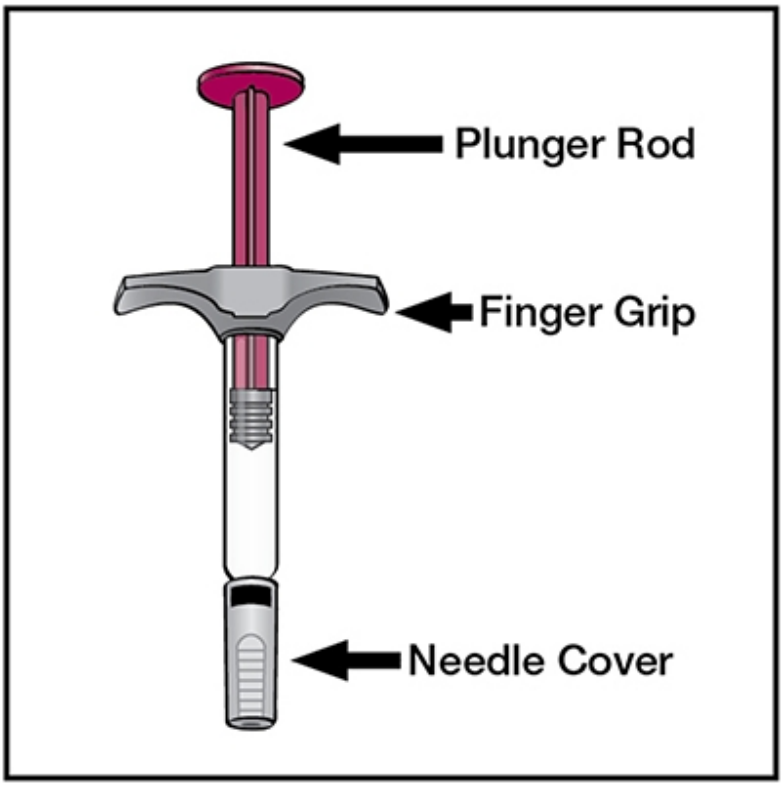
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA prefilled syringe (See Figure A)
- FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA prefilled syringe out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the needle cover while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist.

The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - the seals on top or bottom of the carton are broken or missing.
   - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and **do not use** if the date has passed.
   - the prefilled syringe that has been frozen or left in direct sunlight.
   - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).

- the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

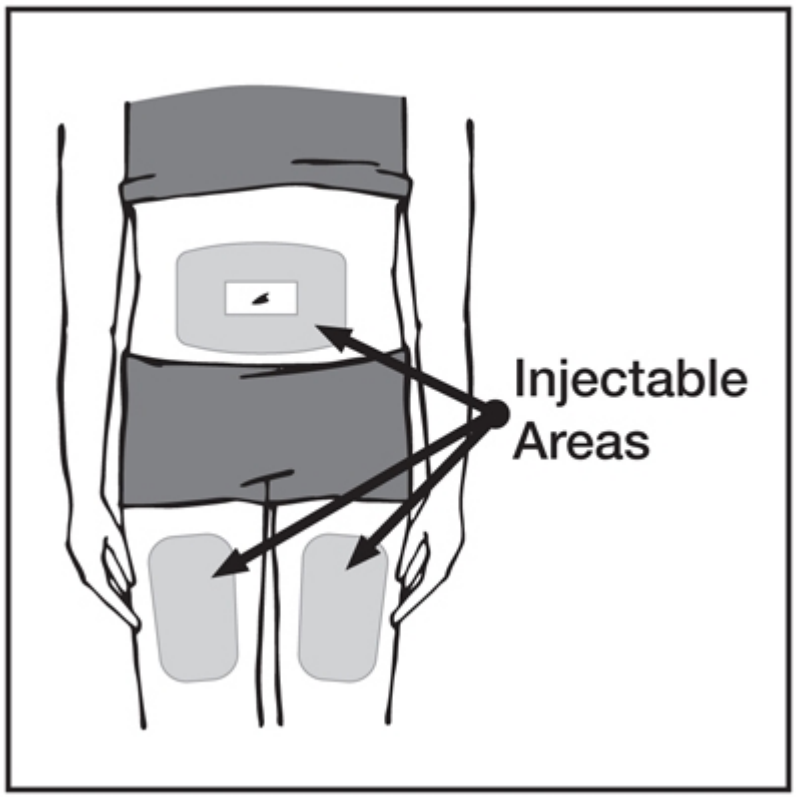
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

Choose the Injection Site

3. Wash and dry your hands well.

4. Choose an injection site on:
- the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks
- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

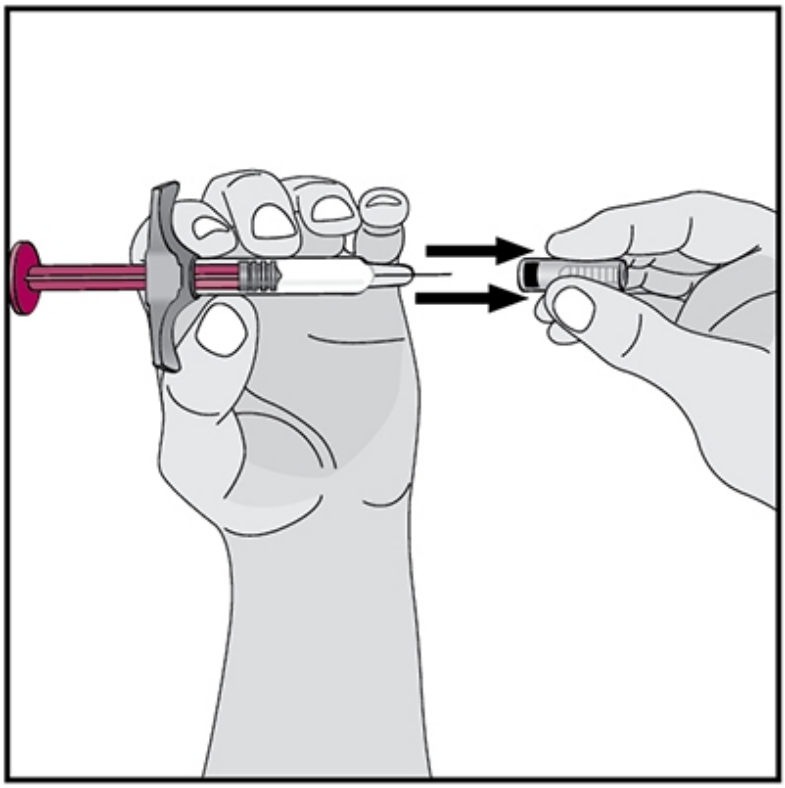
5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Remove the needle cover:
- Always hold the prefilled syringe by the body of the syringe.
- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure C.
- Throw away the needle cover.

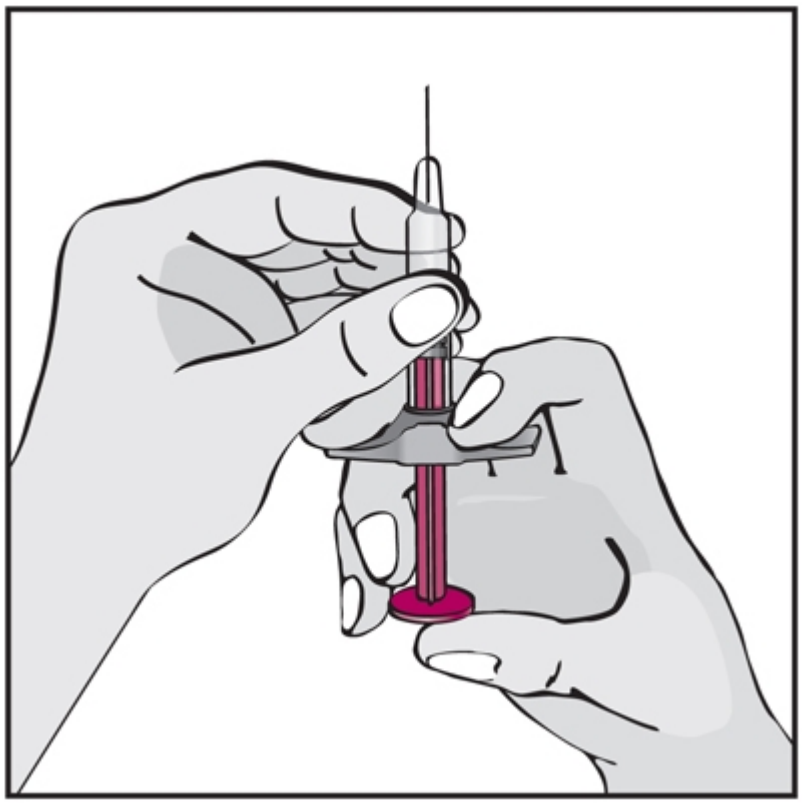
Figure C



- Do not touch the needle with your fingers or let the needle touch anything.

8. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure D.

Figure D



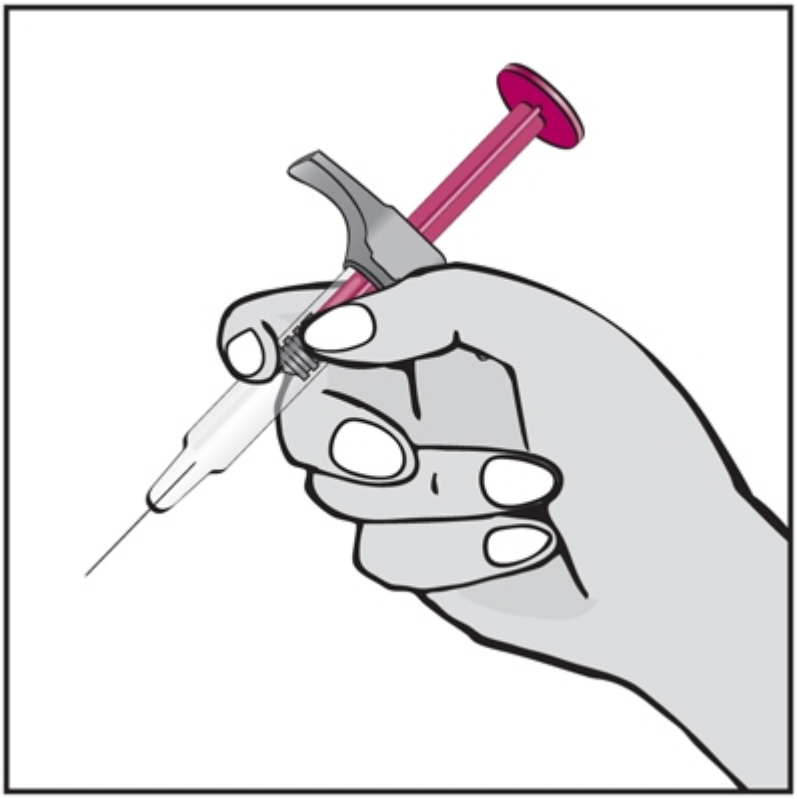
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

9. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure E.

Figure E



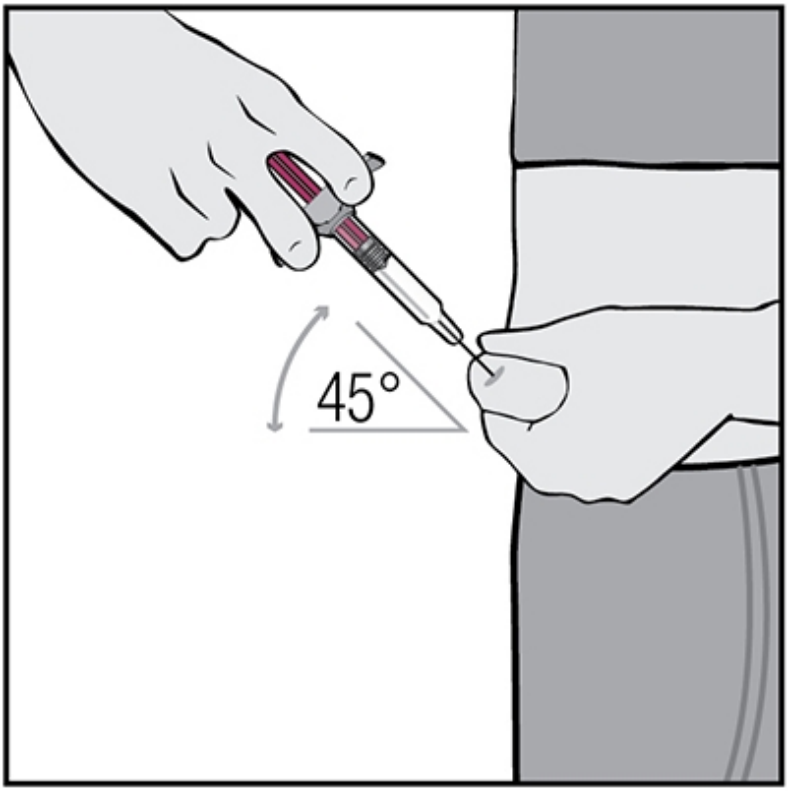
- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure F.

Figure F

Inject HUMIRA

10. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure G.

Figure G

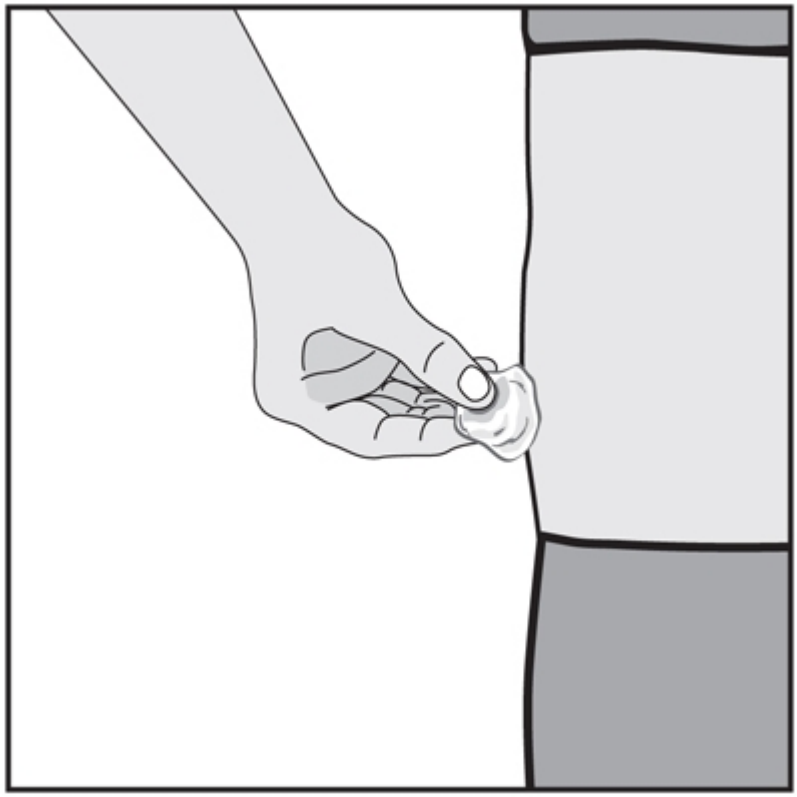


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure H.

Figure H



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 10 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

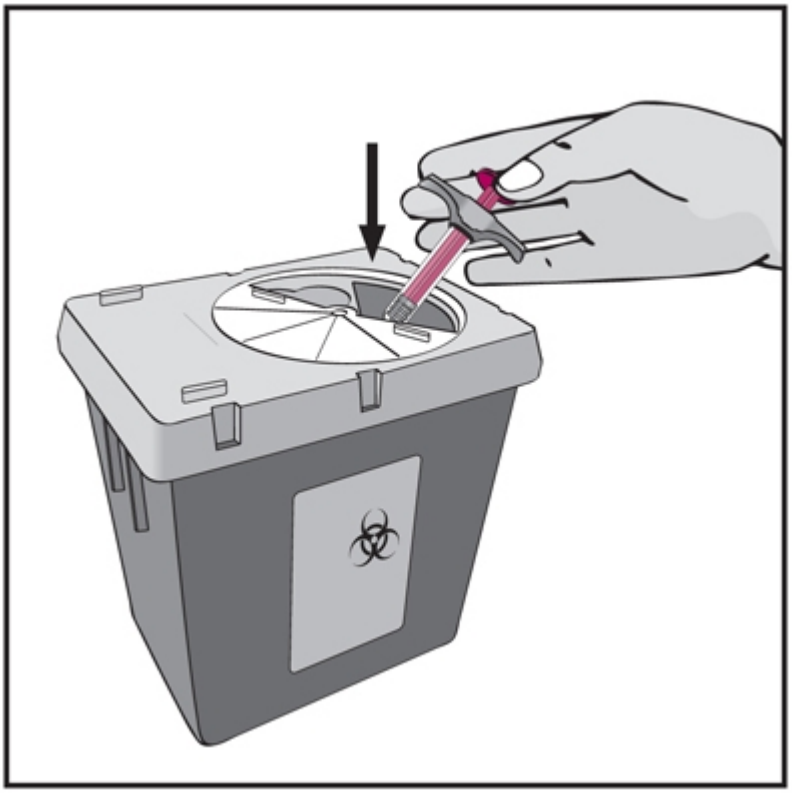
11. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

12. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure I. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- Do not try to touch the needle.

Figure I



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or prefilled syringe. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03-B354

Revised: 06/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

SUMMARY REVIEW

Deputy Division Director Summary Review of BLA 125057
Supplement 397

Date	June 30, 2016
From	Wiley A. Chambers, M.D.
NDA/BLA # **Supplement#**	BLA 125057 S-397
Applicant	AbbVie, Inc
Date of Submission	September 3, 2015
Name	Humira (adalimumab)
Dosage forms / Strength	Injection: 40 mg/0.8 mL in a single-use prefilled pen Injection: 40 mg/0.4 mL in a single-use prefilled pen Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use
Proposed Indication(s)	The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
Action:	Approval

1. Introduction

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody for human tumor necrosis factor (TNF)-α. Tumor necrosis factor (TNF) is a cytokine that is involved in normal inflammatory and immune responses. Adalimumab was first approved for the treatment of rheumatoid arthritis in the United States in December 2002 and subsequently has been approved for the following indications: Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis and Plaque Psoriasis.

The applicant seeks to add a new indication to the product labeling for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

2. Background

Currently Approved Drugs for the Treatment of Uveitis include

Drug	Intended Population
fluocinolone acetonide implant (Retisert)	Patients, age 7 and older, with chronic recurrent non-infectious posterior uveitis
dexamethasone intravitreal implant (Ozurdex)	Patients ≥ 18 y.o. with non-infectious intermediate or posterior uveitis
Triamcinolone suspension	Inflammatory conditions of the eye
Prednisone tablets	Inflammatory conditions of the eye
Dexamethasone injection	Inflammatory conditions of the eye

3. CMC/Device

No new product quality data are included with this submission.

4. Nonclinical Pharmacology/Toxicology

No new toxicity studies were submitted to this supplemental BLA. One pharmacology study was submitted and reviewed. Findings from this study did not impact the product insert label. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) addressed the adequacy of the PLLR conversion included in the labeling for this supplement. There were no other revisions to the nonclinical sections of the previously approved label. Accordingly, there are no new concerns/recommendations from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

The applicant has provided a pharmacokinetic report (R&D/15/1161), which assesses the impact of immunogenicity on pharmacokinetic (PK), efficacy, and safety in two phase 3 studies, i.e. Study M10-877 and Study M10-880. The re-analysis of immunogenicity samples was performed using the new improved Anti-Adalimumab Antibodies (AAA). The mean adalimumab concentrations appeared lower in uveitis patients with detected serum levels of AAA (AAA+) compared to patients without any serum levels of AAA (AAA-). The serum adalimumab concentrations remained lower in AAA+ patients throughout the study. These results were in agreement with the previously observed relationship between formation of AAA and reduced serum adalimumab concentrations in AAA+ patients with other indications. There was no clear impact of immunogenicity on adalimumab efficacy in noninfectious uveitis patients. Additionally, in non-infectious uveitis patients, no new safety risks were identified that are associated with the adalimumab immunogenicity.

6. Clinical Microbiology

Not applicable. This is not an anti-infective product.

7. Clinical/Statistical- Efficacy

The clinical development program was designed to demonstrate the efficacy of adalimumab in both active and inactive non-infectious uveitis in patients with a range of etiologies and anatomical subtypes of intermediate uveitis, posterior uveitis, or panuveitis. The program included two randomized, double-masked, placebo-controlled studies (Studies M10-877 and M10-880), each with a sub-study of Japanese subjects, and 1 open-label extension (OLE) study (Study M11-327), which included subjects who elected to roll over from the other studies. Each study was designed to measure the time to treatment failure following a mandated taper of corticosteroid treatments. The adalimumab dose regimen in the placebo-controlled studies was an 80 mg subcutaneous (SC) loading dose at baseline, followed by 40 mg every other week starting at Week 1.

The efficacy results for Study M10-877 and Study M10-880 cannot be directly compared and no integrated efficacy data set was generated because the study populations differed at baseline and have different initial time points from which the measurement for the primary and other key efficacy endpoints were established. The primary efficacy endpoint for both pivotal studies (Studies M10-877 and M10-880) assessed the inability to achieve or maintain disease control (time to treatment failure) on or after Week 6 or Week 2 for studies M10-877 and M10-880, respectively.

Time to Treatment Failure at or After Week 6 in Study M10-877 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR[a]	*P* value
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[b]	0.36, 0.70	< 0.001[c]
Adjusted for baseline IMM usage (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[a]	0.36, 0.70	< 0.001[d]

a. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

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

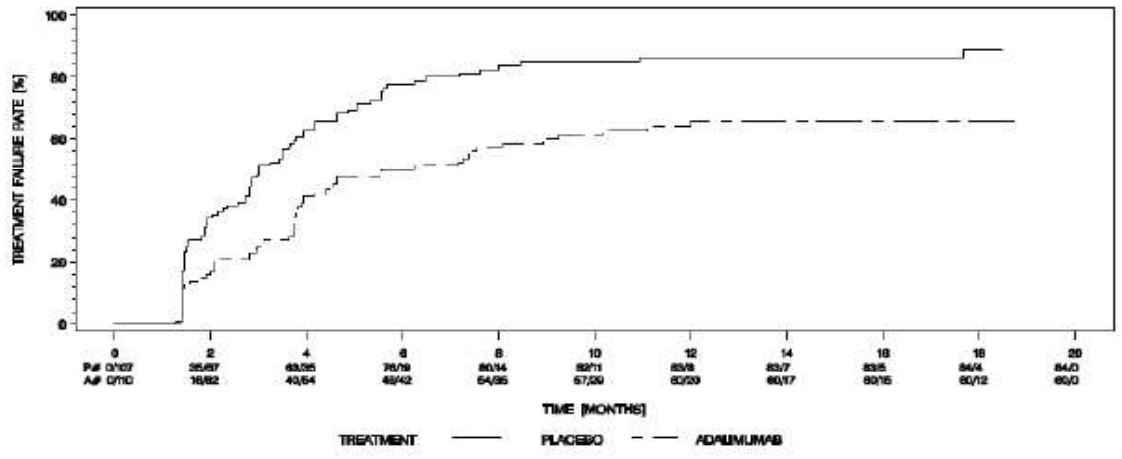
c. 2-sided *P* value from log rank test.

d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 6 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-877 CSR Table 14.2_1.1.1.M Table 14.2_1.2.M

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 6 in Study M10-877 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Cross reference: Study M10-877 CSR Figure 14.2_1.1.4.M

Study M10-877 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure. Adalimumab prolonged the time to treatment failure compared to placebo by approximately 2.5 months (5.6 months versus 3 months).

Time to Treatment Failure at or After Week 2 in Study M10-880 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR	*P* value
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.57[a]	0.39, 0.84	0.004[b]
Adjusted for baseline IMM usage (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.58[c]	0.39, 0.85	0.005[d]

NE = not estimable (fewer than half of at-risk subjects had an event)

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

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

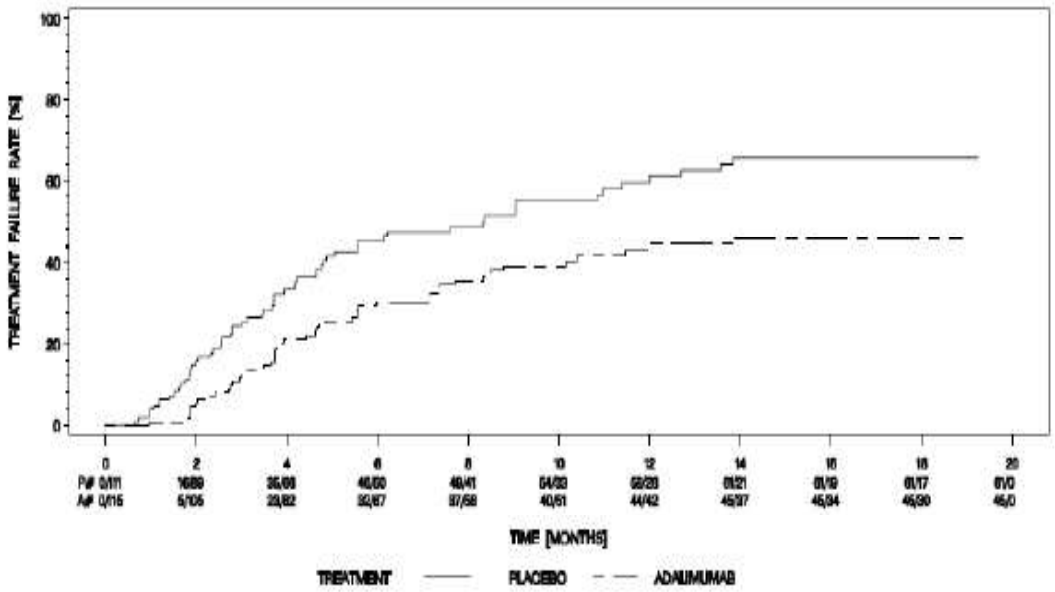
c. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 2 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-880 CSR Table 14.2__1.1.1.M, Table 14.2__1.2.M

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 2 in Study M10-880 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Study M10-880 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure by at least 10 months. The median time to treatment failure in the placebo group was 8.3 months. The median time in the adalimumab group was > 18 months (total study duration).

The statistical and clinical teams agreed with the analyses and the following summary:

Table 1: Time to Treatment Failure (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo (N=107)	Adalimumab (N=110)	HR (95% CI)[a]	Placebo (N=111)	Adalimumab (N=115)	HR (95% CI)[a]
Failure[1] (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.57 (0.39, 0.84)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
Component of Treatment Failure						
New Active Inflammatory Lesions						
Events, n (%)	29 (27.1)	17 (15.5)	0.38 (0.21, 0.69)	17 (15.3)	12 (10.4)	0.55 (0.26, 1.15)
Anterior Chamber Cell Grade						
Events[2], n (%)	34 (31.8)	24 (21.8)	0.51 (0.30, 0.86)	30 (27.0)	27 (23.5)	0.70 (0.42, 1.18)
Vitreous Haze Grade						
Events[2], n (%)	39 (36.4)	16 (14.5)	0.32 (0.18, 0.58)	11 (9.9)	11 (9.6)	0.79 (0.34, 1.81)
Worsening of BCVA by ≥ 15 Letters Relative to Best State Achieved						
Events, n (%)	27 (25.2)	23 (20.9)	0.56 (0.32, 0.98)	23 (20.7)	10 (8.7)	0.33 (0.16, 0.70)

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
[1] Treatment failure at or after Week 6 in Study 877, or at or after Week 2 in Study 880, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
[2] Study 877: Inability to achieve ≤ 0.5[*] at Week 6 and/or 2-step increase relative to best state achieved after Week 6; Study 880: 2-step increase relative to best state achieved at or after Week 2.
Source: Tables 22 and 25 of Study 877 Report and Tables 22 and 24 of Study 880 Report.

Analyses of the components, while described above were not predefined, potentially overlap and are not weighted by severity or clinical consequences. No inference can be made of their statistical or clinical significance.

8. Safety

The primary safety assessment relies on the clinical studies which supported the indications previously approved. The results of the studies in uveitis demonstrated a consistent safety profile. In the Uveitis studies, the total number of subjects that discontinued was similar between treatment groups for all categories except adverse reactions.

There were three subjects died in the uveitis clinical development program. They are described in the clinical and CDTL reviews. Two of the three subjects had significant medical history that was likely the cause of death. One subject (M11-327) had lymphoma which could have potentially been related to the treatment drug since it is known to increase the risk of malignancy.

The following nonfatal serious adverse events were reported in more than one patient while being treated with Adalimumab in the uveitis studies:

	Placebo-Controlled Analysis Set		All ADA Set
	Placebo (N = 250)	Adalimumab (N = 250)	Adalimumab (N = 464)
MedDRA PT	**n (%)**	**n (%)**	**n (%)**
Subjects with any SAE	16 (6.4)	25 (10.0)	85 (18.3)
Pneumonia	0	2 (0.8)	5 (1.1)
Cataract	0	1 (0.4)	4 (0.9)
Demyelination	0	1 (0.4)	2 (0.4)
Tuberculosis	0	1 (0.4)	2 (0.4)
Urinary tract infection	0	1 (0.4)	3 (0.6)
Retinal detachment	1 (0.4)	0	2 (0.4)

The most commonly reported adverse events, occurring more frequently in the adalimumab group than the placebo group were nasopharyngitis, arthralgia, fatigue, urinary tract infections, back pain, insomnia, cough, eye pain, sinusitis, upper respiratory tract infections, ocular blurring and pain in the extremities. These events occurred in approximately 5-18 percent of patients.

In summary, there is evidence from adequate and well-controlled clinical trials that adalimumab demonstrates an acceptable safety profile in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control**.**

Specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns with the use of adalimumab. The types of adverse events that occurred during this development program are adequately addressed in the current label.

There is currently a Medication Guide approved for adalimumab. There are no changes recommend with the approval of the new uveitis indication.

There are no new PMR/PMC's recommended based on the approval of this supplement.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

The safety of adalimumab in pediatric patients has been adequately evaluated in studies for Juvenile Idiopathic Arthritis and Pediatric Crohn's disease. The applicant received orphan status designation for the current indication and therefore is exempt from a requirement to conduct additional studies under PREA.

11. Other Relevant Regulatory Issues

This submission was of sufficient quality to allow for a substantive review. The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice (GCP).

OSI
The Office of Scientific Investigations completed a Clinical Inspection Summary dated 5/11/2016. Three clinical investigator sites were inspected. DSI investigations determined that the Dayani site (2030) had two significant protocol deviations. The two deviations were for subjects (b) (6) and (b) (6) (both randomized to adalimumab) enrolled in M10-877 who "met treatment failure criteria and were not withdrawn within 14 days." A statistical analysis for the primary efficacy endpoint excluding all 11 subjects from that site (5 in placebo, and 6 in adalimumab) was conducted and did not change the overall results.

Financial Disclosures
AbbVie has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were five (5) subinvestigators who disclosed financial ties to the applicant. A review of these arrangements does not raise questions about the integrity of the results.

12. Labeling

The Office of Prescription Drug Promotion (OPDP) completed a review of the draft Package Insert (PI), Medication Guide (MG) and Instructions for Use (IFU) for Humira (adalimumab) on 6/8/2016. OPDP has no comments on the PI, MG or IFU.

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton labeling on 5/24/2016. DMEPA found the proposed labeling acceptable and did not have any recommendations.

The Division of Medical Policy Programs (DMPP) completed a review of the Medication Guide (MG) and Instructions for Use (IFU) on 6/7/2016.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) completed a review of the relevant Pregnancy and Lactation Labeling (PLLR) package insert sections on 5/25/2016. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Pharmacology/Toxicology completed a review of the package insert section 8 and 13 on 5/23/2016.

The Division of Pediatric and Maternal Health (DPMH) completed a memorandum dated 3/24/2016 and revised subsections 8.1, 8.2, and 17 in the Humira labeling for compliance with the PLLR.

The Office of Surveillance and Epidemiology (OSE)/ Office of Pharmacovigilance and Epidemiology (OPE) completed a review of the PLLR on 4/20/2016.

The Center for Drug Evaluation and Research/Office of Biotechnology Products completed a review on 5/4/2016. The carton labeling for Humira Pen (adalimumab) Psoriasis/Uveitis Starter Packages for both formulations (40 mg/0.8 mL and 40 mg/0.4 mL) were reviewed and found to comply with the applicable regulations. The carton labeling submitted on September 3, 2015, and March 23, 2016, was found acceptable.

13. Regulatory Action/Risk Benefit Assessment

- Regulatory Action

BLA 125057/S-397 Humira (adalimumab) will be approved for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients with the labeling attached in this review submitted 6/27/2016.

- Risk Benefit Assessment

Humira (adalimumab) has been shown to be effective in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control. Overall, the submission specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns with the use of adalimumab. The types of adverse events that occurred during this development program are adequately addressed in the current label.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There is currently a Medication Guide approved for adalimumab. There are no changes recommended with the approval of the new uveitis indication.

- Recommendation for other Postmarketing Requirements and Commitments

There are no new PMR/PMC's recommended based on the approval of this supplement.

- Recommended Comments to Applicant

There were no comments for the applicant.

100 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
06/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 27, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	BLA 125057 S-397
Applicant	AbbVie, Inc
Date of Submission	September 3, 2015
PDUFA Goal Date	July 3, 2016
Proprietary Name / Established (USAN) names	Humira (adalimumab)
Dosage forms / Strength	Injection: 40 mg/0.8 mL in a single-use prefilled pen Injection: 40 mg/0.4 mL in a single-use prefilled pen Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use
Proposed Indication(s)	The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
Recommended:	Approval

1. Introduction

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody for human tumor necrosis factor (TNF)-α. Tumor necrosis factor (TNF) is a cytokine that is involved in normal inflammatory and immune responses including non-infectious uveitis. Elevated levels of TNF are thought to play a role in autoimmune disorders and immune-mediated disorders. Adalimumab is believed to decrease the inflammatory process by binding to TNF-alpha and blocking its interaction with cell surface TNF receptors.

Adalimumab was first approved for the treatment of rheumatoid arthritis in the United States in December 2002 and subsequently has been approved for the following indications: Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis and Plaque Psoriasis.

The applicant seeks to add the following new indication to the product labeling for Humira:
Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

2. Background

Approved Drugs for the Treatment of Uveitis

Drug	Endpoint	Treatment Effect	Intended Population
fluocinolone acetonide implant (Retisert)	recurrence of uveitis (i.e., ≥ 2 step increase in cells or flare) in the study eye within 34 weeks following implantation	54% vs. 7% (trial 1) 40% vs. 14% (trial 2)	Patients, age 7 and older, with chronic recurrent non-infectious posterior uveitis
dexamethasone intravitreal implant (Ozurdex)	proportion of patients with vitreous haze score of 0 (no inflammation) at week 8	47% vs. 12%	Patients ≥ 18 y.o. with non-infectious intermediate or posterior uveitis
Triamcinolone suspension	DESI		Inflammatory conditions of the eye
Prednisone tablets	DESI		Inflammatory conditions of the eye
Dexamethasone injection	DESI		Inflammatory conditions of the eye

August 2009 – PIND meeting was held with the applicant. The general development plan was to conduct two phase 3 safety and efficacy trials with an extension safety trial continuing treatment of patients from the phase 3 trials. The proposed endpoint definition for treatment failure for the phase 3 trials was not agreed to by the Agency.

June 2013 – The applicant sought guidance on using patient reported outcomes. Guidance was provided in the event that the applicant chose to use the VFQ-25 as an endpoint for their clinical trial.

February 2015 – The request to the Agency for Breakthrough Therapy was denied since there was insufficient evidence indicating that adalimumab provided substantial improvement over available therapy.

July 2015 – pre-sBLA meeting. It was conveyed to the Applicant that the supplement would likely not qualify for priority review and that (b) (4) (b) (4).

3. CMC/Device

Per the CMC memorandum dated 2/4/2016 in DARRTS for this supplemental application:

No new product quality data are included with this submission. Pursuant to 21 CFR 25.31(e) and FDA's Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (R1), dated July 1998, AbbVie requested a categorical exclusion from the requirement to included an environmental assessment for this sBLA. The request was considered appropriate.

This BLA efficacy supplement is approvable from a CMC perspective. There are no CMC related PMRs recommended for this BLA efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

Per the Pharmacology/Toxicology review (DTOP) dated 12/17/2015 in DARRTS for this supplemental application and the Pharmacology/Toxicology review (DPARP) dated 5/23/2016:

The applicant seeks approval of a dosing regimen within range of those previously approved by the FDA. No new toxicity studies were submitted to this supplemental BLA given that the toxicity profile of adalimumab has been well established. One pharmacology study was submitted and reviewed in the nonclinical review dated December 17, 2015). Findings from this study did not impact the product insert label.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) addressed the adequacy of the PLLR conversion included in the labeling for this supplement. There were no other revisions to the nonclinical sections of the previously approved label. Accordingly, there are no new concerns/recommendations from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

Per the Clinical Pharmacology review dated 5/26/2016 in DARRTS for this supplemental application:

The applicant has provided a pharmacokinetic report (R&D/15/1161), which assesses the impact of immunogenicity on pharmacokinetic (PK), efficacy, and safety in two phase 3 studies, i.e. Study M10-877 and Study M10-880. The re-analysis of immunogenicity samples was performed using the new improved Anti-Adalimumab Antibodies (AAA).

The mean adalimumab concentrations appeared lower in uveitis patients with detected serum levels of AAA (AAA+) compared to patients without any serum levels of AAA (AAA-). In addition, the serum adalimumab concentrations remained lower in AAA+ patients throughout the study. These results are in agreement with the previously observed relationship between formation of AAA and reduced serum adalimumab concentrations in AAA+ patients with other indications. However, there was no clear impact of immunogenicity on adalimumab efficacy in noninfectious uveitis patients. Additionally, in non-infectious uveitis patients, no new safety risks were identified that are associated with the adalimumab immunogenicity.

6. Clinical Microbiology

Not applicable. This is not an anti-infective product.

7. Clinical/Statistical- Efficacy

Per the Clinical review dated 6/6/2016 and the Statistical review dated 5/26/2016:

The clinical development program was designed to demonstrate the efficacy of adalimumab in both active and inactive non-infectious uveitis in patients with a range of etiologies [including Birdshot choroidopathy, Sarcoidosis, Vogt-Koyanagi-Harada (VKH), Behçet's disease, Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA)] and anatomical subtypes of intermediate uveitis, posterior uveitis, or panuveitis. The program included 2 global, randomized, double-masked, placebo-controlled studies (Studies M10-877 and M10-880), each with a separate sub-study of Japanese subjects, and 1 open-label extension (OLE) study (Study M11-327), which included subjects who elected to roll over from the 2 pivotal studies.

Each Phase 3 study was designed to measure the time to treatment failure following a mandated taper of corticosteroid treatments. The adalimumab dose regimen in the placebo-controlled studies was an 80 mg subcutaneous (SC) loading dose at baseline, followed by 40 mg every other week starting at Week 1.

The efficacy results for Study M10-877 and Study M10-880 cannot be directly compared and no integrated efficacy data set was generated because the study populations differed at baseline and have different initial timepoints from which the measurement for the primary and other key efficacy endpoints were established. The primary efficacy endpoint for both pivotal studies (Studies M10-877 and M10-880) assessed the inability to achieve or maintain disease control (time to treatment failure) on or after Week 6 or Week 2 for studies M10-877 and M10-880, respectively.

Time to Treatment Failure at or After Week 6 in Study M10-877 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR[a]	*P* value
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[b]	0.36, 0.70	< 0.001[c]
Adjusted for baseline IMM usage (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[a]	0.36, 0.70	< 0.001[d]

a. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

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

c. 2-sided *P* value from log rank test.

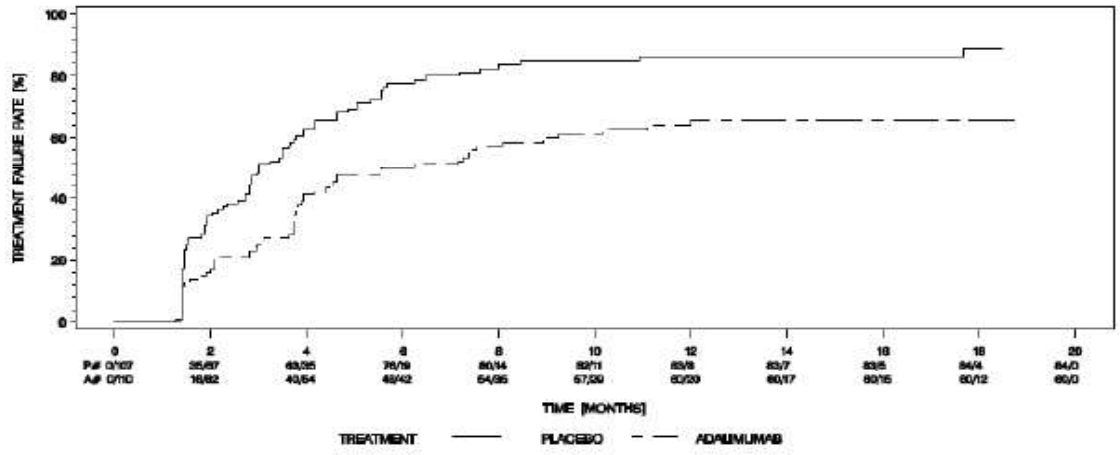
d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 6 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-877 CSR Table 14.2_1.1.1.M Table 14.2_1.2.M

Study M10-877 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure. Adalimumab prolongs the time to treatment failure compared to placebo (5.6 months versus 3 months).

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 6 in Study M10-877 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Cross reference: Study M10-877 CSR Figure 14.2 1.1.4.M

Reasons for Treatment Failure Study M10-877 on or After Week 6 in Study M10-877 (ITT; Main Study Data)

Variable	Placebo N = 107 n (%)	Adalimumab N = 110 n (%)	Total N = 217 n (%)
Chorioretinal/retinal vascular lesions			
Yes	29 (27.1)	17 (15.5)	46 (21.2)
No	78 (72.9)	93 (84.5)	171 (78.8)
AC cell grade			
Yes	34 (31.8)	24 (21.8)	58 (26.7)
No	73 (68.2)	86 (78.2)	159 (73.3)
VH grade			
Yes	39 (36.4)	16 (14.5)	55 (25.3)
No	68 (63.6)	94 (85.5)	162 (74.7)
Visual acuity			
Yes	27 (25.2)	23 (20.9)	50 (23.0)
No	80 (74.8)	87 (79.1)	167 (77.0)

Ref: M10-877 CSR Table 24

Time to Treatment Failure at or After Week 2 in Study M10-880 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR	*P* value
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.57[a]	0.39, 0.84	0.004[b]
Adjusted for baseline IMM usage (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.58[c]	0.39, 0.85	0.005[d]

NE = not estimable (fewer than half of at-risk subjects had an event)

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

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

c. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

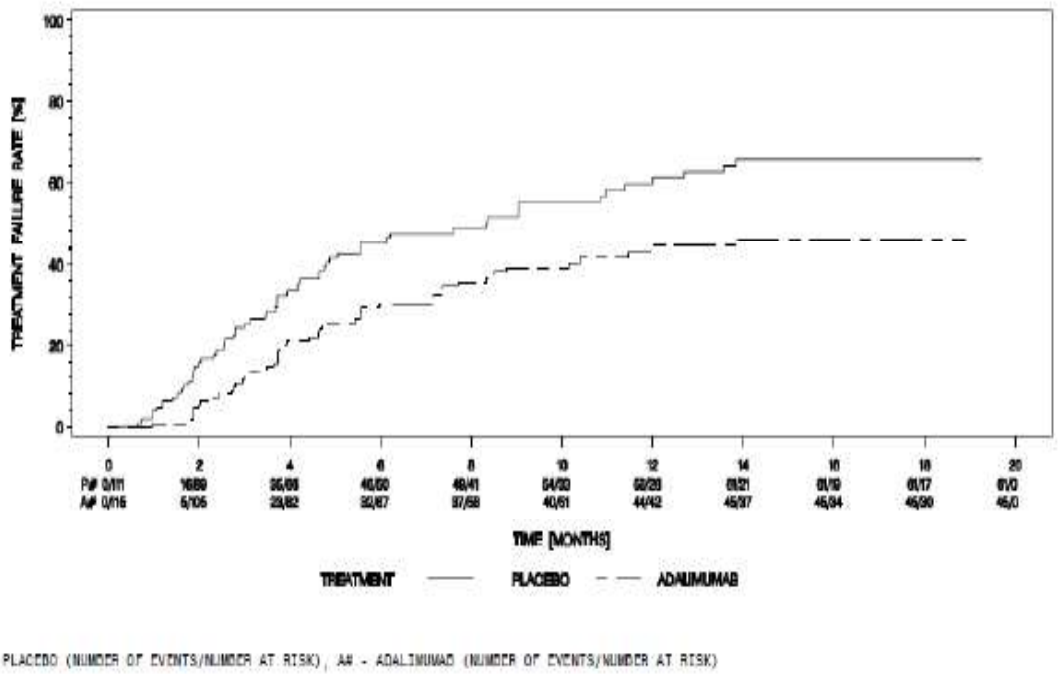
d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 2 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-880 CSR Table 14.2_1.1.1.M Table 14.2_1.2.M

Study M10-880 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure. The median time to treatment failure in the placebo group was 8.3 months. The median time in the adalimumab group was > 18 months (total study duration)

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 2 in Study M10-880 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Reasons for Treatment Failure Study M10-880 at or After Week 2 (ITT; Main Study Data)

Variable	Placebo N = 111 n (%)	Adalimumab N = 115 n (%)	Total N = 226 n (%)
Chorioretinal/retinal vascular lesions			
Yes	17 (15.3)	12 (10.4)	29 (12.8)
No	94 (84.7)	103 (89.6)	197 (87.2)
AC cell grade			
Yes	30 (27.0)	27 (23.5)	57 (25.2)
No	81 (73.0)	88 (76.5)	169 (74.8)
VH grade			
Yes	11 (9.9)	11 (9.6)	22 (9.7)
No	100 (90.1)	104 (90.4)	204 (90.3)
Visual acuity			
Yes	23 (20.7)	10 (8.7)	33 (14.6)
No	88 (79.3)	105 (91.3)	193 (85.4)

Ref: M10-880 CSR Table 23

The Statistical Reviewer concluded "results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients treated with placebo."

Table 1: Time to Treatment Failure (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo (N=107)	Adalimumab (N=110)	HR (95% CI)[a]	Placebo (N=111)	Adalimumab (N=115)	HR (95% CI)[a]
Failure[1] (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.57 (0.39, 0.84)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
Component of Treatment Failure						
New Active Inflammatory Lesions						
Events, n (%)	29 (27.1)	17 (15.5)	0.38 (0.21, 0.69)	17 (15.3)	12 (10.4)	0.55 (0.26, 1.15)
Anterior Chamber Cell Grade						
Events[2], n (%)	34 (31.8)	24 (21.8)	0.51 (0.30, 0.86)	30 (27.0)	27 (23.5)	0.70 (0.42, 1.18)
Vitreous Haze Grade						
Events[2], n (%)	39 (36.4)	16 (14.5)	0.32 (0.18, 0.58)	11 (9.9)	11 (9.6)	0.79 (0.34, 1.81)
Worsening of BCVA by ≥ 15 Letters Relative to Best State Achieved						
Events, n (%)	27 (25.2)	23 (20.9)	0.56 (0.32, 0.98)	23 (20.7)	10 (8.7)	0.33 (0.16, 0.70)

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
[1] Treatment failure at or after Week 6 in Study 877, or at or after Week 2 in Study 880, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
[2] Study 877: Inability to achieve ≤ 0.5[+] at Week 6 and/or 2-step increase relative to best state achieved after Week 6; Study 880: 2-step increase relative to best state achieved at or after Week 2.
Source: Tables 22 and 25 of Study 877 Report and Tables 22 and 24 of Study 880 Report.

Analysis of the Components of the Primary Endpoint
The analyses of the components of the primary endpoint are presented below. They were not predefined, and no inference can be made of their statistical significance.

Efficacy Summary Statement

There is evidence from adequate and well-controlled clinical trials that adalimumb is effective in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control**.**

8. Safety

Per the Clinical review dated 6/6/2016 in DARRTS for this supplemental application:

Placebo-Controlled Analysis Set: Any event with onset or worsening at or after the first dosing date, and

- before first application of open-label study drug in the extension study or up to 70 days after the last double-masked study drug injection (whatever is the earliest) for subjects who rolled over into the open-label extension study, or
- up to 70 days after the last double-masked study drug injection for subjects who did not roll over in the open label extension study.

All Adalimumab Analysis Set: Any event with onset or worsening at or after the first dose of adalimumab treatment and up to 70 days (equivalent to 5 half-lives of adalimumab) after the last study drug injection or until the data cut-off date in Study M11-327, whatever is the earliest.

Subject Disposition

Subject Disposition (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set			All ADA Set
Subjects Who:	Placebo N = 250	Adalimumab N = 250	Total N = 500	Adalimumab (N = 464)
Premature discontinuation of study				
Yes	26 (10.4)	33 (13.2)	59 (11.8)	156 (33.6)
No	224 (89.6)	217 (86.8)	441 (88.2)	9 (1.9)
Ongoing				299 (64.4)
Premature discontinuation due to (any reason)[a]				
TEAE	10 (4.0)	21 (8.4)	31 (6.2)	71 (15.3)
Lack of efficacy	6 (2.4)	1 (0.4)	7 (1.4)	31 (6.7)
Withdrew consent	3 (1.2)	4 (1.6)	7 (1.4)	19 (4.1)
Lost to follow-up	3 (1.2)	4 (1.6)	7 (1.4)	9 (1.9)
Other	8 (3.2)	7 (2.8)	15 (3.0)	47 (10.1)

a. Subjects (b) (6) and (b) (6) who discontinued due to treatment failure also had an AE leading to discontinuation. These 4 subjects (2 adalimumab and 2 placebo) were considered completers and were not counted under premature discontinuation due to the TEAE category presented in this table.

Notes: Subjects who discontinued are counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Subjects who did not prematurely discontinue include: 1) subjects who discontinued due to treatment failure, 2) subjects who completed Week 80 without treatment failure, and 3) subjects who had to terminate the study because the planned number of treatment failures was reached.

Cross reference: Table 2.1__2.1 Table 2.1__2.2

Ref. Section 2.7.4, Summary of Clinical Safety, Table 2

The total number of subjects that discontinued was similar between treatment groups for all categories except adverse reactions.

Exposure

Extent of Exposure (Placebo-Controlled Analysis Set)

Exposure	**Placebo** N=250	**Adalimumab** N=250
Total number of doses received		
Mean±SD	14.1 ± 11.2	18.7 ± 13.54
Median (min – max)	10 (2 – 42)	11 (2 – 43)
Duration of treatment (days)		
Mean±SD	175 ± 165.57	241.6 ± 191.07
Median (min – max)	105 (6 – 585)	166.5 (14 – 576)

Ref. Section 2.7.4 Summary of Clinical Safety, Table 3

Extent of Exposure (All Adalimumab Analysis Set)

Exposure	**Adalimumab** N=464
Total number of doses received	
Mean±SD	41.1 ± 28.63
Median (min – max)	34.5 (1 – 122)
Duration of treatment (weeks)	
Mean±SD	81.1 ± 57.58
Median (min – max)	68.1 (1.6 – 243.4)

Ref. Section 2.7.4 Summary of Clinical Safety, Table 4

Deaths

Three subjects died in the uveitis clinical development program.

In Study M10-877, Subject (b) (6), an 80-year-old female with a history of chronic kidney disease and multiple cardiac risk factors randomized to the adalimumab group, died on Day 37 (3 days posttreatment) as a result of renal failure.

In Study M10-880, Subject (b) (6), a 62-year-old male with a history of multiple cardiac risk factors and previous aortic aneurysm randomized to the adalimumab group, died on Day 54 (18 days after last dose) as a result of aortic dissection and cardiac tamponade.

In Study M11-327, Subject (b) (6), a 71-year-old female, died on Day 195 (94 days after the first dose of adalimumab and 23 days posttreatment) as a result of B-cell lymphoma.

All deaths that occurred during the development program were in the adalimumab treated group. Two of the three subjects had significant medical history that was likely the cause of death. One subject (M11-327) had lymphoma which could have potentially been related to the treatment drug since it is known to increase the risk of malignancy.

Nonfatal Serious Adverse Events

	Placebo-Controlled Analysis Set		**All ADA Set**
	Placebo (N = 250)	**Adalimumab (N = 250)**	**Adalimumab (N = 464)**
MedDRA PT	**n (%)**	**n (%)**	**n (%)**
Subjects with any SAE	16 (6.4)	25 (10.0)	85 (18.3)
Pneumonia	0	2 (0.8)	5 (1.1)
Accidental overdose	0	1 (0.4)	1 (0.2)
Anaphylactic reaction	0	1 (0.4)	1 (0.2)
Angle closure glaucoma	0	1 (0.4)	1 (0.2)
Aortic dissection	0	1 (0.4)	1 (0.2)
Blindness transient	0	1 (0.4)	1 (0.2)
Bronchitis	0	1 (0.4)	1 (0.2)
Calculus ureteric	0	1 (0.4)	1 (0.2)
Carcinoid tumour of the gastrointestinal tract	0	1 (0.4)	1 (0.2)
Cardiac tamponade	0	1 (0.4)	1 (0.2)
Cataract	0	1 (0.4)	4 (0.9)
Demyelination	0	1 (0.4)	2 (0.4)

Dysarthria	0	1 (0.4)	1 (0.2)
Dysphagia	0	1 (0.4)	1 (0.2)
Epistaxis	0	1 (0.4)	1 (0.2)
Fibula fracture	0	1 (0.4)	1 (0.2)
Fluid overload	0	1 (0.4)	1 (0.2)
Glioblastoma multiforme	0	1 (0.4)	1 (0.2)
Ligament rupture	0	1 (0.4)	1 (0.2)
Lung adenocarcinoma stage IV	0	1 (0.4)	1 (0.2)
Lupus-like syndrome	0	1 (0.4)	1 (0.2)
Neovascularisation	0	1 (0.4)	1 (0.2)
Neutropenia	0	1 (0.4)	1 (0.2)
Pilonidal cyst	0	1 (0.4)	1 (0.2)
Pleurisy	0	1 (0.4)	1 (0.2)
Pneumonia Legionella	0	1 (0.4)	1 (0.2)
Renal failure chronic	0	1 (0.4)	1 (0.2)
Status migrainosus	0	1 (0.4)	1 (0.2)
Tendon rupture	0	1 (0.4)	1 (0.2)
Tuberculosis	0	1 (0.4)	2 (0.4)
Upper respiratory tract infection	0	1 (0.4)	1 (0.2)
Urinary tract infection	0	1 (0.4)	3 (0.6)
Urticaria	0	1 (0.4)	1 (0.2)
Deep vein thrombosis	2 (0.8)	0	0
Abortion induced	1 (0.4)	0	0
Arthritis	1 (0.4)	0	0
Choroidal neovascularisation	1 (0.4)	0	0
Gastroenteritis viral	1 (0.4)	0	0
Hepatitis acute	1 (0.4)	0	0
Humerus fracture	1 (0.4)	0	0
Hyperparathyroidism primary	1 (0.4)	0	0
Hypertensive crisis	1 (0.4)	0	0
Meningitis aseptic	1 (0.4)	0	0
Osteonecrosis	1 (0.4)	0	0
Pyelonephritis acute	1 (0.4)	0	0
Retinal detachment	1 (0.4)	0	2 (0.4)
Sepsis	1 (0.4)	0	0
Subretinal fluid	1 (0.4)	0	0
Tonsillitis	1 (0.4)	0	0
Wrist fracture	1 (0.4)	0	0

There are no significant differences in the rate of serious non-fatal adverse events.

Common Adverse Events

Adverse Events Reported in ≥ 2% of Subjects in Either Treatment Group

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
	N	%	N	%	N (%)	%
Nasopharyngitis	31	12.4	44	17.6	114	26.6
Arthralgia	25	10	38	15.2	81	17.5
Headache	33	13.2	30	12	73	15.7
Fatigue	17	6.8	26	10.4	53	11.4
Urinary tract infection	11	4.4	21	8.4	50	10.8
Back pain	10	4	19	7.6	31	6.7
Injection site pain	13	5.2	10	4	19	4.1
Insomnia	11	4.4	18	7.2	24	5.2

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
Uveitis	17	6.8	20	8	93	20
Cough	10	4	18	7.2	42	9.1
Eye pain	8	3.2	18	7.2	36	7.8
Sinusitis	6	2.4	12	4.8	29	6.3
Upper respiratory tract infection	7	2.8	15	6	45	9.7
ALT increased	3	1.2	10	4	22	4.7
Visual acuity reduced	12	4.8	10	4	30	6.5
Anxiety	2	0.8	11	4.4	18	3.9
Pain in extremity	5	2	12	4.8	26	5.6
Vision blurred	8	3.2	12	4.8	29	6
Nausea	16	6.4	10	4	33	7.1
AST increased	2	0.8	9	3.6	23	5
Cystoid macular edema	13	5.2	10	4	37	8
Injection site erythema	1	0.4	5	2	11	2.4
Muscle spasms	5	2	9	3.6	22	4.7
Myalgia	4	1.6	11	4.4	25	5.4
Bronchitis	10	4	10	4	33	7.1
Hypertension	6	2.4	11	4.4	26	5.6
Paraesthesia	1	0.4	10	4	18	3.9
Pruritus	6	2.4	10	4	21	4.5
Pyrexia	8	3.2	10	4	27	5.8
Hyperhidrosis	3	1.2	9	3.6	11	2.4
Oropharyngeal pain	8	3.2	10	4	27	5.8
Pharyngitis	3	1.2	8	3.2	19	4.1
Rash	9	3.6	9	3.6	23	5
Vitreous floaters	10	4	10	4	27	5.8
Dry eye	12	4.8	9	3.6	20	4.3
Dyspnea	7	2.8	8	3.2	11	2.4
Intraocular pressure increased	4	1.6	9	3.6	22	4.7
Peripheral edema	3	1.2	9	3.6	15	3.2
Palpitations	2	0.8	8	3.2	11	2.4
Abdominal pain	5	2	6	2.4	11	2.4
Epistaxis	1	0.4	7	2.8	11	2.4
Joint swelling	3	1.2	6	2.4	11	2.4
Arthritis	4	1.6	5	2	9	1.9
Erythema	6	2.4	7	2.8	18	3.9
Injection site rash	1	0.4	7	2.8	15	3.2
Peripheral swelling	3	1.2	5	2	11	2.4
Posterior capsule opacification	2	0.8	5	2	13	2.8
Abdominal pain upper	6	2.4	6	2.4	15	3.2
Alopecia	9	3.6	6	2.4	21	4.5
Blood creatinine increased	5	2	6	2.4	8	1.7
Blood pressure increased	1	0.4	5	2	6	1.3
Conjunctivitis	4	1.6	6	2.4	16	3.4
Allergic conjunctivitis	4	1.6	6	2.4	20	4.3
Dizziness	7	2.8	5	2	12	2.6

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
Dry mouth	3	1.2	6	2.4	7	1.5
Gastroenteritis	2	0.8	6	2.4	15	3.2
Malaise	4	1.6	6	2.4	9	1.9
Musculoskeletal stiffness	5	2	6	2.4	10	2.2
Neck pain	4	1.6	5	2	8	1.7
Oral herpes	1	0.4	5	2	12	2.6
Rash pustular	0	0	6	2.4	10	2.2
Tinnitus	5	2	5	2	6	1.3
Tremor	1	0.4	6	2.4	6	1.3
Vomiting	8	3.2	6	2.4	11	2.4
Acne	9	3.6	5	2	9	1.9
Cataract	6	2.4	4	1.6	25	5.4
Contusion	8	3.2	5	2	7	1.5
Diabetes mellitus	0	0	5	2	9	1.9
Diarrhea	12	4.8	5	2	23	5
Ligament sprain	0	0	5	2	9	1.9
Muscular weakness	0	0	5	2	7	1.5
Nasal congestion	3	1.2	5	2	10	2.2
Weight increased	2	0.8	5	2	8	1.7
Conjunctival hemorrhage	5	2	3	1.2	14	3
Dyspepsia	7	2.8	4	1.6	12	2.6
Influenza	13	5.2	4	1.6	23	5
Injection site bruising	5	2	4	1.6	8	1.7
Migraine	5	2	4	1.6	10	2.2
Eye pruritus	5	2	2	0.8	4	0.9
Photophobia	6	2.4	1	0.4	6	1.3

Adverse events highlighted in the above table are those that are higher in the adalimumab group versus placebo and occur at a rate ≥ 5% in the adalimumab group. This cut-off is used to be able to compare the currently labeled adverse event rate with those seen in the uveitis program. The types of adverse events that occurred during this development program are adequately addressed in the current label.

Safety Summary Statement

There is evidence from adequate and well-controlled clinical trials that adalimumb demonstrates an acceptable safety profile in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control**.**

Overall, the submission specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns with the use of adalimumab. The types of adverse events that occurred during this development program are adequately addressed in the current label.

There is currently a Medication Guide approved for adalimumab. There are no changes recommend with the approval of the new uveitis indication.

There are no new PMR/PMC's recommended based on the approval of this supplement.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

The safety of adalimumab in pediatric patients has been adequately evaluated in studies for Juvenile Idiopathic Arthritis and Pediatric Crohn's disease. The applicant received orphan status designation for the current indication and therefore is exempt from a requirement to conduct additional studies under PREA.

11. Other Relevant Regulatory Issues

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the applicant. The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice (GCP).

OSI
The Office of Scientific Investigations completed a Clinical Inspection Summary dated 5/11/2016.

For BLA 125057/S-397, three clinical investigator sites were inspected. DSI investigations determined that the Dayani site (2030) had two significant protocol deviations. The two deviations were for subjects (b) (6) and (b) (6) (both randomized to adalimumab) enrolled in M10-877 who "met treatment failure criteria and were not withdrawn within 14 days." A statistical analysis for the primary efficacy endpoint excluding all 11 subjects from that site (5 in placebo, and 6 in adalimumab) was conducted and did not change the overall results.

Financial Disclosures
Abbvie has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were five (5) subinvestigators who disclosed financial ties to the applicant. A review of these arrangements does not raise questions about the integrity of the results.

12. Labeling

The Office of Prescription Drug Promotion (OPDP) completed a review of the draft Package Insert (PI), Medication Guide (MG) and Instructions for Use (IFU) for Humira (adalimumab), for subcutaneous use for the supplemental BLA application S-397 (supplement 397) on 6/8/2016. OPDP has no comments on the PI, MG or IFU.

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton labeling for BLA 125057/S-397 on 5/24/2016. DMEPA found the proposed labeling acceptable and did not have any recommendations.

The Division of Medical Policy Programs (DMPP) completed a review of the Medication Guide (MG) and Instructions for Use (IFU) on 6/7/2016.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) completed a review of the relevant Pregnancy and Lactation Labeling (PLLR) package insert sections on 5/25/2016. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Pharmacology/Toxicology completed a review of the package insert section 8 and 13 on 5/23/2016.

The Division of Pediatric and Maternal Health (DPMH) completed a memorandum dated 3/24/2016 and revised subsections 8.1, 8.2, and 17 in the Humira labeling for compliance with the PLLR.

The Office of Surveillance and Epidemiology (OSE)/ Office of Pharmacovigilance and Epidemiology (OPE) completed a review of the PLLR on 4/20/2016.

The Center for Drug Evaluation and Research/Office of Biotechnology Products completed a review on 5/4/2016. The carton labeling for Humira Pen (adalimumab) Psoriasis/Uveitis Starter Packages for both formulations (40 mg/0.8 mL and 40 mg/0.4 mL) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [December 1, 2015 to April 30, 2016]. Labeling deficiencies were not identified. The carton labeling submitted on September 3, 2015, and March 23, 2016, was found acceptable.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

BLA 125057/S-397 Humira (adalimumab) is recommended for approval for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients with the labeling attached in this review submitted 6/27/2016.

- Risk Benefit Assessment

The BLA 125057/S-397 review team recommends approval with the labeling attached to this review.

Humira (adalimumab) has been shown to be effective in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control. Overall, the submission specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns with the use of adalimumab. The types of adverse events that occurred during this development program are adequately addressed in the current label.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There is currently a Medication Guide approved for adalimumab. There are no changes recommended with the approval of the new uveitis indication.

- Recommendation for other Postmarketing Requirements and Commitments

There are no new PMR/PMC's recommended based on the approval of this supplement.

- Recommended Comments to Applicant

There were no comments for the applicant.

97 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
06/30/2016

WILEY A CHAMBERS
06/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	SE-1
Application Number(s)	BLA 125057/S-397 IND 105,723
Priority or Standard	Standard
Submit Date(s)	September 3, 2015
Received Date(s)	September 3, 2015
PDUFA Goal Date	July 3, 2016
Division / Office	DTOP/OAP
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	April 26, 2016
Established Name	adalimumab
(Proposed) Trade Name	Humira
Therapeutic Class	monoclonal antibody
Applicant	AbbVie, Inc
Formulation(s)	solution
Dosing Regimen	80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.
Indication(s)	The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

Intended Population(s)	Adults ≥ 18 y.o. with non-infectious intermediate, posterior and panuveitis

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Adalimumab is recommended for approval for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

1.2 Risk Benefit Assessment

Adalimumb has been shown to be effective in prolonging the time to recurrence of symptoms in patients who used steroids to maintain disease control. Overall, the submission specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns with the use of adalimumab. The types of adverse events that occurred during this development program are adequately addressed in the current label.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is currently a Medication Guide approved for adalimumab. There are no changes recommend with the approval of the new uveitis indication.

1.4 Recommendations for Postmarket Requirements and Commitments

N/A – There are no new PMR/PMC's recommended based on the approval of this supplement.

2 Introduction and Regulatory Background

2.1 Product Information

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody for human tumor necrosis factor (TNF)-α. Tumor necrosis factor (TNF) is a cytokine that is involved in normal inflammatory and immune responses including non-infectious uveitis. Elevated levels of TNF are thought to play a role in autoimmune disorders and immune-mediated disorders. Adalimumab is believed to decrease the inflammatory process by binding to TNF-alpha and blocking its interaction with cell surface TNF receptors.

Adalimumab was first approved for the treatment of rheumatoid arthritis in the United States in December 2002 and subsequently has been approved for the following indications: Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis and Plaque Psoriasis.

The applicant seeks to add the following new indication to the product labeling for Humira:

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved Drugs for the Treatment of Uveitis

Drug	Endpoint	Treatment Effect	Intended Population
fluocinolone acetonide implant (Retisert)	recurrence of uveitis (i.e. ≥ 2 step increase in cells or flare) in the study eye within 34 weeks following implantation	54% vs. 7% (trial 1) 40% vs. 14% (trial 2)	Patients, age 7 and older, with chronic recurrent non-infectious posterior uveitis
dexamethasone intravitreal implant (Ozurdex)	proportion of patients with vitreous haze score of 0 (no inflammation) at week 8	47% vs. 12%	Patients ≥ 18 y.o. with non-infectious intermediate or posterior uveitis
Triamcinolone	DESI		Inflammatory conditions of the eye
Prednisone	DESI		Inflammatory conditions of the eye
Dexamethasone	DESI		Inflammatory conditions of the eye

2.3 Availability of Proposed Active Ingredient in the United States

Adalimumab is an approved product and has been marketed as Humira since 2002.

2.4 Important Safety Issues with Consideration to Related Drugs

Adalimumab has a black box warning in the label for serious infections and malignancy. It is known to cause an increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.

Additionally, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including adalimumab. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including adalimumab.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

August 2009 – PIND meeting was held with the applicant. The general development plan was to conduct two phase 3 safety and efficacy trials with an extension safety trial enrolling those patients from the phase 3 trials that responded to treatment was agreed to. The proposed endpoint definition for treatment failure for the phase 3 trials was not agreed to by the Agency.

June 2013 – The applicant sought guidance on using patient reported outcomes. Guidance on what would be required to use the VFQ-25 as an endpoint for their clinical trial was provided to the applicant.

February 2015 – The request to the Agency for Breakthrough Therapy was denied since there was insufficient evidence indicating that adalimumab provided substantial improvement over available therapy.

July 2015 – pre-sBLA meeting. It was conveyed to the Applicant that the supplement would likely not qualify for priority review and that (b) (4) .

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the sponsor.

3.2 Compliance with Good Clinical Practices

The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice (GCP).

DSI investigations resulted in determining that the Dayani site (2030) had two significant protocol deviations. The two deviations were for subjects (b) (6) and (b) (6) (both randomized to adalimumab) enrolled in M10-877 who "met treatment failure criteria and were not withdrawn within 14 days". A statistical analysis for the primary efficacy endpoint excluding all 11 subjects from that site (5 in placebo, and 6 in adalimumab) was conducted and did not change the overall results.

3.3 Financial Disclosures

The development program to evaluate the safety and efficacy of adalimumab for the treatment of uveitis consisted of two phase 3 safety and efficacy trials (M10-877 and M10-880) and an open-label extension trial (M10-327). There were a total of 67 study sites for study M10-877 and 62 study sites for M10-880.

Details of the disclosable financial arrangements for the clinical investigators who participated in the development program are summarized in the following table.

Investigator	Site	Disclosure	Number of Subjects		
			Study M10-877	Study M10-880	Study M11-327
(b) (6)		Payments > $25,000			(b) (6)
		Payments > $25,000			
		Payments > $25,000			
		Payments > $25,000			
		Equity interest > $50,000			

Abbvie has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were five (5) subinvestigators who disclosed financial ties to the sponsor. A review of these arrangements do not raise questions about the integrity of the results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Humira is registered and marketed as solution for injection in a single-use prefilled syringe and a prefilled pen for subcutaneous (sc) use, each containing 40 mg adalimumab in 0.8 mL buffer solution (50 mg/mL). The pre-filled syringes formulation used in uveitis clinical studies (Studies M10-877 and M10-880) was the same as the current marketed formulation. No additional chemistry studies were conducted for this filing.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

See pharm/tox review.

4.4 Clinical Pharmacology

The clinical pharmacology and immunogenicity of adalimumab have been characterized in healthy subjects as well as in patients in the approved indications (rheumatoid arthritis, Crohn's Disease, ulcerative colitis, plaque psoriasis, PsA, and AS); these data were provided in previous submissions.

The pharmacokinetics (PK) and immunogenicity of adalimumab were evaluated in uveitis subjects in the 2 pivotal Phase 3 studies. See Biopharmacuetics review for detailed discussion.

4.4.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta).

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 IC50 of 1-2 X 10^{-10}M).

4.4.2 Pharmacodynamics

N/A – not conducted as part of this application.

4.4.3 Pharmacokinetics

In the Phase 3 Studies M10-877 and M10-880, following adalimumab 80 mg at baseline and 40 mg eow starting at Week 1, the mean serum adalimumab concentrations reached steady state levels after the initial dose (8 – 10 µg/mL) and were maintained constant through Week 52 during adalimumab 40 mg eow treatment. Adalimumab exposure was comparable between Studies M10-877 and M10-880.

See Biopharmacuetics review for detailed discussion.

Summary of Serum Adalimumab Concentrations (µg/mL) for Subjects with Uveitis (Studies M10-877 and M10-880)

	Mean ± Standard Deviation (Range), N						
	Week						
Study	0	1 or 2[a]	8	12	27	36	52
M10-877 (N = 118)	0 ± 0 (0 – 0), 117	7.80 ± 2.87 (1.47 – 18.4), 114	8.34 ± 4.86 (0 – 21.2), 84	9.09 ± 5.12 (0 – 23.0), 72	9.46 ± 6.25 (0 – 31.4), 38	9.45 ± 5.90 (0 – 21.3), 32	10.0 ± 6.25 (0 – 22.0), 20
M10-880 (N = 131)	0 ± 0 (0 – 0), 131	10.1 ± 3.79 (0.311 – 21.0), 130	8.50 ± 5.17 (0 – 25.0), 113	9.53 ± 5.36 (0 – 23.9), 97	9.36 ± 7.00 (0 – 46.8), 70	9.01 ± 5.63 (0 – 28.8), 59	8.72 ± 5.28 (0 – 27.1), 43

a Week 1 for Study M10-877 and Week 2 for Study M10-880.

Note: All subjects (non-Japanese and Japanese) included in the analysis.

Cross reference: Study M10-877 PK Report R&D/14/1026, Study M10-880 PK report R&D/15/0207

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study ID/ Locations	Enrollment Goal/ Enrolled/Study Status	Study Design/ Duration of Treatment	Study & Control Drugs Dose, Route & Regimen	Diagnosis Inclusion Criteria	Primary Endpoints
M10-877 (VISUAL I)/ Main Study: Australia, Israel, Latin America, North America, and Europe Japan Sub-Study: Japan	266/239 (223 ex-Japanese subjects and 16 Japanese subjects in a Japan sub-study) Completed	Phase 3, randomized, double-masked, placebo-controlled, multicenter study, including a Japan Sub-Study Up to 80 weeks	Adalimumab 80 mg loading dose, followed by 40 mg given eow SC starting at Week 1 or matching placebo All subjects received a standardized prednisone burst of 60 mg/day at study entry followed by a protocol-defined mandatory taper schedule, in which all subjects continuing in the study were to discontinue prednisone no later than Week 15.	Males and females ≥ 18 years of age with a diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis. Active disease at the baseline as defined by at least 1 of the following in at least 1 eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent): - Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion - ≥ 2+ anterior chamber (AC) cells (SUN criteria) - ≥ 2+ vitreous haze (NEI/SUN criteria) - Subject was on oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for at least 2 weeks prior to screening and remained on the same dose from Screening to Baseline visit	Time to treatment failure (inability to achieve and maintain disease control) analyzed using a composite of 4 components of the primary endpoint: inflammatory, chorioretinal and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity (see criteria specific to subjects with active uveitis at baseline CSE [R&D/15/0264] Section 2.7.3.1.2; and Table 1)

Study ID/ Locations	Enrollment Goal/ Enrolled/Study Status	Study Design/ Duration of Treatment	Study & Control Drugs Dose, Route & Regimen	Diagnosis Inclusion Criteria	Primary Endpoints
M10-880 (VISUAL II) Main Study: Australia, Israel, Latin America, North America, and Europe Japan Sub-Study: Japan	250/261[a] (229 ex-Japanese subjects and 32 Japanese subjects in a Japan sub-study) Completed	Phase 3, randomized, double-masked, placebo-controlled, multicenter study, including a Japan sub-study Up to 80 weeks	Adalimumab 80 mg loading dose, followed by 40 mg given eow SC starting at Week 1 or matching placebo.	Males and females ≥ 18 years of age with a diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis. Inactive disease at the baseline as defined by ≥ 28 days prior to the Baseline visit has inactive disease and was taking ≥ 10 mg of oral prednisone to maintain this inactive state and fulfillment of all 3 of the following criteria at the Screening and Baseline visits for both eyes: - Without active, inflammatory chorioretinal and/or inflammatory retinal vascular lesions. - AC cell grade ≤ 0.5+ according to SUN criteria - VH grade ≤ 0.5+ according to NEI/SUN criteria On oral prednisone 10 to 35 mg/day (or oral corticosteroid equivalent) at Baseline and the dose had not been increased in the past 28 days or decreased in the past 14 days. Must have had a documented history of experiencing at least 1 disease flare within 18 months of the Screening visit. This flare had to have occurred during or up to a maximum of 28 days after tapering off the oral corticosteroid therapy.	Time to treatment failure (inability to maintain disease control) analyzed using a composite of 4 components of the primary endpoint: inflammatory, chorioretinal and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity (see criteria specific to subjects with inactive uveitis at baseline CSE [R&D/15/0264] Section 2.7.3.1.2; and Table 1)

Study ID/ Locations	Enrollment Goal/ Enrolled/Study Status	Study Design/ Duration of Treatment	Study & Control Drugs Dose, Route & Regimen	Diagnosis Inclusion Criteria	Primary Endpoints
M11-327 (VISUAL III)/ Australia, Israel, Latin America, North America, Europe, and Japan	400/423 Ongoing	Open-label multicenter study/ Study to be completed in 2018	Open-label adalimumab 40 mg dose eow SC regardless of treatment assignment in the randomized, double-masked studies.	Subject must have successfully enrolled in either Study M10-877 or Study M10-880 and either met the endpoint of treatment failure, completed the study, or remained in the study until the study was stopped.	Long-term safety and efficacy of adalimumab 40 mg given eow subcutaneously (SC) in subjects with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who participated in Studies M10-877 or M10-880.

a Although target enrollment was approximately 250 subjects for Study M10-880, enrollment of 261 subjects was required to meet the treatment failure events targeted.

5.2 Review Strategy

The safety and efficacy of adalimumab for the proposed indication was based on the review of 2 randomized, double-masked, placebo-controlled studies (Studies M10-877 and M10-880), and 1 open-label extension (OLE) study (Study M11-327), which includes subjects who elected to roll over from the 2 pivotal studies. Description of the trial design for each study is included in section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical development program was designed to demonstrate the efficacy of adalimumab in both active and inactive non-infectious uveitis in patients with a range of etiologies [including Birdshot choroidopathy, Sarcoidosis, Vogt-Koyanagi-Harada (VKH), Behçet's disease, Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA)] and anatomical subtypes of intermediate uveitis, posterior uveitis, or panuveitis.

The program included 2 global, randomized, double-masked, placebo-controlled studies (Studies M10-877 and M10-880), each with a separate sub-study of Japanese subjects, and 1 open-label extension (OLE) study (Study M11-327), which included subjects who elected to roll over from the 2 pivotal studies.

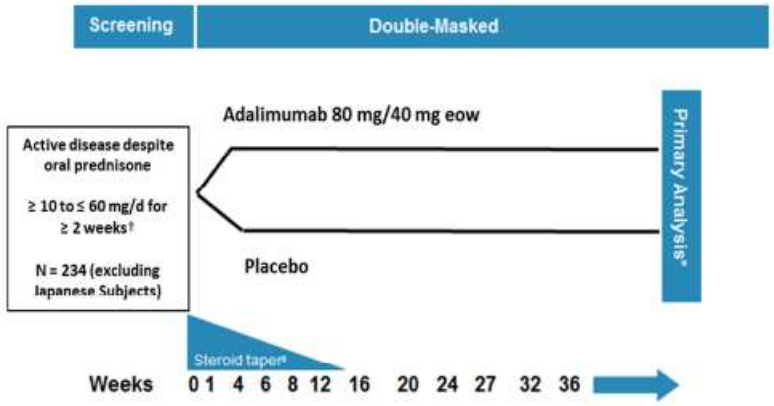
Each Phase 3 study was designed to measure the time to treatment failure following a complete elimination of steroid through a protocol mandated taper.

The adalimumab dose regimen in the placebo-controlled studies was an 80 mg subcutaneous (SC) loading dose at baseline, followed by 40 mg eow starting at Week 1.

Study M10-877 assessed the ability of adalimumab to control active uveitis in a population entering the study with active disease. This study enrolled subjects who had active uveitis at baseline and all subjects were treated with a standardized prednisone burst of 60 mg/day

followed by a protocol-defined mandatory steroid taper schedule. The prednisone burst given to induce a quiescent state and the mandatory taper was designed to observe if adalimumab would prolong the time to treatment failure.

Study Design Schematic for Study M10-877



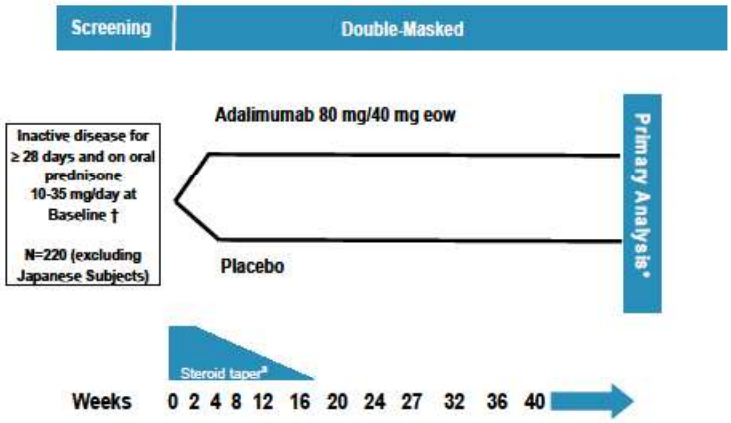
* The study ended when the 138th event of treatment failure (in ex-Japan subjects only) had occurred.

† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.

a Prednisone 60 mg per day was given at Baseline followed by a taper from Weeks 2 – 15. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Weeks 1 – 9.

Study M10-880 was similarly designed but enrolled patients with inactive uveitis to assess the ability of adalimumab to maintain quiescence upon steroid tapering. Subjects should have had inactive disease for ≥ 28 days prior to baseline and were required to be on a dose of oral prednisone 10 to 35 mg/day at baseline (or oral corticosteroid equivalent).

Study Design Schematic for Study M10-880



* The study was to end when approximately 96 (84 to 107) treatment failures (in ex-Japan subjects only) had occurred.

† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.

a Prednisone taper was to occur from Week 2 up to Week 19. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Week 1 to Week 9.

Study M11-327 is ongoing to evaluate the long-term safety and efficacy of adalimumab 40 mg given every other week (eow) SC in subjects with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who participated in Study M10-877 or Study M10-880.

The primary efficacy endpoint for both pivotal studies (Studies M10-877 and M10-880) assessed the inability to achieve or maintain disease control (time to treatment failure) on or after Week 6 or Week 2 for studies M10-877 and M10-880, respectively. By definition, subjects who completed Week 80 without treatment failure, or who had to discontinue the study because the planned number of treatment failures was reached, were considered completers.

The 4 components of treatment failure were inflammatory chorioretinal and/or inflammatory retinal vascular lesions, AC cell grade, VH grade, and visual acuity.

Treatment Failure Criteria for Studies M10-877 and M10-880

	Treatment Failure[a]		
	Study M10-877		Study M10-880
Parameter	Week 6 Visit	All Other Visits After Week 6	Week 2 Visit and All Subsequent Visits
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to baseline
AC Cell grade (SUN Criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to baseline[b]
VH grade (NEI/SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to baseline[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to baseline

ETDRS = Early treatment diabetic retinopathy study; BCVA = best corrected visual acuity

a To be considered a treatment failure, ≥ 1 of these 4 criteria needed to be present in at least 1 eye.

b A 2-step increase was represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

Nine ranked secondary variables were tested in hierarchical order for statistical significance between the adalimumab and placebo groups within each pivotal study. While these 9 variables were the same for both pivotal studies, the initial timepoint from which the variables were measured differ.

Ranked Secondary Endpoints for Studies M10-877 and M10-880

Ranked Secondary Endpoints	
Study M10-877	**StudyM10-880**
1. Change in AC cell grade in each eye from best state achieved prior to Week 6 to the Final/Early Termination visit.	1. Change in AC cell grade in each eye from baseline to the Final/Early Termination visit.
2. Change in vitreous haze grade (NEI/SUN criteria) in each eye from best state achieved prior to Week 6 to the Final/Early Termination visit.	2. Change in vitreous haze grade (NEI/SUN criteria) in each eye from baseline to the Final/Early Termination visit.
3. Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from best state achieved prior to Week 6 to the Final/Early Termination visit.	3. Change in logMAR BCVA in each eye from baseline to the Final/Early Termination visit.
4. Time to OCT evidence of macular edema (cystic formation) in at least one eye on or after Week 6.	4. Time to OCT evidence of macular edema based on central retinal thickness (CRT) in at least 1 eye at or after Week 2.
5. Percent change in CRT in each eye from best state achieved prior to Week 6 to the Final/Early Termination visit.	5. Percent change in CRT in each eye from baseline to the Final/Early Termination visit.
6. Change in NEI VFQ-25 total score from best state achieved prior to Week 6 to the Final/Early Termination visit.	6. Change in NEI/VFQ-25 total score from baseline to the Final/Early Termination visit.
7. Change in VFQ-25 subscore distance vision from best state achieved prior to Week 6 to the Final/Early termination visit.	7. Change in VFQ-25 subscore distance vision from baseline to the Final/Early termination visit.
8. Change in VFQ-25 subscore near vision from best state achieved prior to Week 6 to the Final/Early termination visit.	8. Change in VFQ-25 subscore near vision or from baseline to the Final/Early termination visit.
9. Change in VFQ-25 subscore ocular pain from best state achieved prior to Week 6 to the Final/Early termination visit.	9. Change in VFQ-25 subscore ocular pain from baseline to the Final/Early termination visit.

Ref. Table 2 2.7.3 Summary of Clinical Efficacy

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

6.1.1 Methods

The description of the individual clinical trial designs is contained in section 5.3.

The 2 pivotal studies were similar in study design but represented two distinct patient populations based on different key eligibility and baseline disease activity criteria. The efficacy results for Study M10-877 and Study M10-880 cannot be directly compared and no integrated efficacy data set was generated because the study populations differed at baseline and have different initial timepoints from which the measurement for the primary and other key efficacy endpoints were established.

6.1.2 Demographics

Subject Demographics (Placebo-Controlled and All Adalimumab Analysis Sets)

Demographic Characteristic	Placebo-Controlled Analysis Set				All ADA Set
	Placebo (N = 250)	Adalimumab (N = 250)	Total (N = 500)	*P* value[a]	Adalimumab (N = 464)
Sex, n (%)				0.172	
Female	156 (62.4)	141 (56.4)	297 (59.4)		270 (58.2)
Male	94 (37.6)	109 (43.6)	203 (40.6)		194 (41.8)
Race, n (%)				0.838	
White	187 (74.8)	185 (74.0)	372 (74.4)		343 (73.9)
Black	20 (8.0)	17 (6.8)	37 (7.4)		33 (7.1)
Asian	29 (11.6)	31 (12.4)	60 (12.0)		58 (12.5)
Amer. Indian/Alaska Native	2 (0.8)	0	2 (0.4)		2 (0.4)
Other	10 (4.0)	15 (6.0)	25 (5.0)		24 (5.2)
Multi-race	2 (0.8)	2 (0.8)	4 (0.8)		4 (0.9)
Asian race, n (%)[b]					
Chinese	3 (10.3)	1 (3.2)	4 (6.7)		4 (6.9)
Japanese	24 (82.8)	24 (77.4)	48 (80.0)		46 (79.3)
Korean	0	0	0		0
Taiwanese	0	1 (3.2)	1 (1.7)		1 (1.7)
Singaporean	0	0	0		0
Malaysian	0	1 (3.2)	1 (1.7)		1 (1.7)
Other	2 (6.9)	3 (9.7)	5 (8.3)		5 (8.6)
Japanese/Korean	0	1 (3.2)	1 (1.7)		1 (1.7)

Demographic Characteristic	Placebo-Controlled Analysis Set				All ADA Set
	Placebo (N = 250)	Adalimumab (N = 250)	Total (N = 500)	*P* value[a]	Adalimumab (N = 464)
Ethnicity, n (%)					
Hispanic or Latino	49 (19.6)	36 (14.4)	85 (17.0)		81 (17.5)
No ethnicity	201 (80.4)	214 (85.6)	415 (83.0)		383 (82.5)
Age, years				0.932	
Mean ± SD	43.2 ± 14.14	43.3 ± 14.06	43.3 ± 14.09		42.9 ± 14.14
Median (min – max)	43.0 (18 – 79)	43.5 (18 – 81)	43.0 (18 – 81)		42.5 (18 – 81)
Age distribution, n (%)					
< 40 years	111 (44.4)	99 (39.6)	210 (42.0)		199 (42.9)
40 – < 65 years	120 (48.0)	129 (51.6)	249 (49.8)		228 (49.1)
≥ 65 years	19 (7.6)	22 (8.8)	41 (8.2)		37 (8.0)
Weight, kg[c,d]				0.635	
Mean ± SD	79.6 ± 22.95	78.6 ± 19.91	79.1 ± 21.47		79.1 ± 21.63
Median (min – max)	77.0 (42 – 222)	75.0(38 – 174)	76.5 (38 – 222)		76.5 (38 – 222)
Height, cm[c,d]				0.174	
Mean ± SD	167.0 ± 9.96	168.2 ± 10.36	167.6 ± 10.17		167.7 ± 10.27
Median (min – max)	165.0 (138 – 200)	168.0 (142 – 207)	167.0 (138 – 207)		168.0 (138 – 207)

a. *P* value for differences between treatment groups from one-way ANOVA for continuous endpoints and chi-square test for categorical endpoints.
b. Only for subjects with race: Asian.
c. Placebo N = 249, adalimumab N = 249, total N = 498 for Placebo Controlled Analysis Set.
d. N = 462 for All Adalimumab Set.
Note: A subject may be a user of 1 type of tobacco, an ex-user of another type of tobacco, and a non-user of another type of tobacco. A subject was counted in the category closest to user.
Cross reference: Table 2.2 1.1.1, Table 2.2 1.1.2, Table 2.2 1.2.1, Table 2.2 1.2.2, Table 2.2 1.3.1, Table 2.2 1.3.2

Ref. Section 2.7.4 Summary of Clinical Safety, Table 5.

Reviewers Comments:
There were no statistical significant differences in demographics between the treatment groups.

6.1.3 Subject Disposition

Patient Disposition (M10-877 and M10-880)

	ITT (n)					
	Active Uveitis Subjects (Study M10-877)			Inactive Uveitis Subjects (Study M10-880)		
Subjects who:	Placebo N = 107	Adalimumab N = 110	Total N = 217	Placebo N = 111	Adalimumab N = 115	Total N = 226
Completed Week 80	4	12	16	17	30	47
Completed < Week 80[a]	12	20	32	17	26	43
Treatment failure	84	60	144	61	45	106
	ITT (n, %)			ITT (n, %)		
Prematurely discontinued study drug (placebo/adalimumab)	7 (6.5)	18 (16.4)	25 (11.5)	16 (14.4)	14 (12.2)	30 (13.3)
Discontinuation due to[b]						
AE	3 (2.8)	10 (9.1)	13 (6.0)	7 (6.3)	10 (8.7)	17 (7.5)
Lack of efficacy	2 (1.9)	1 (0.9)	3 (1.4)	3 (2.7)	0	3 (1.3)
Withdrew consent	0	2 (1.8)	2 (0.9)	3 (2.7)	2 (1.7)	5 (2.2)
Lost to follow-up	0	4 (3.6)	4 (1.8)	3 (2.7)	0	3 (1.3)
Other[c]	3 (2.8)	5 (4.5)	8 (3.7)	3 (2.7)	2 (1.7)	5 (2.2)

a. Subjects who had to terminate the study because the planned number of treatment failures was reached.
b. Subjects who prematurely discontinued study drug (placebo/adalimumab) were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
c. Reasons for discontinuation from the study recorded as "other" included any reason for discontinuation excluding AE, lack of efficacy, withdrew consent, and lost to follow-up.
Cross reference: Study M10-877 CSR Table 14.1__1.1.M, Table 14.1__2.1.1.M; Study M10-880 CSR Table 14.1__1.1.M, Table 14.1__2.1.1.M

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for both pivotal studies (Studies M10-877 and M10-880) assessed the inability to achieve or maintain disease control (time to treatment failure) on or after Week 6 or Week 2 for studies M10-877 and M10-880, respectively. The main-study-data analysis set was used for the primary efficacy analysis.

Analysis Sets for M10-877 and M10-880

1. Main Study Data (excluding Japan Sub-Study Data):

- ITT set: All randomized subjects recruited outside Japan excluding subjects for which efficacy source data was incomplete and/or there were general GCP compliance issues
- mITT set: All randomized subjects recruited outside Japan plus subjects excluded from ITT set
- Safety set: All subjects recruited outside Japan who received at least 1 dose of study drug.

2. Integrated Data (Main Study Data + Japan Sub-Study Data)

3. Japan Sub-Study Data

Subjects by Study and Treatment Group									
Analysis Set	**Main Study Data**			**Integrated Data**			**Japan Sub-Study Data**		
Active Uveitis Subjects (Study M10-877) by Treatment Group, n									
	Pbo	**Ada**	**Total**	**Pbo**	**Ada**	**Total**	**Pbo**	**Ada**	**Total**
ITT	107	110	217	115	118	233	8	8	16
mITT	112	111	223	120	119	239	NA	NA	NA
Safety set[a]	112	111	223	120	119	239	8	8	16
Inactive Uveitis Subjects (Study M10-880) by Treatment Group, n									
	Pbo	**Ada**	**Total**	**Pbo**	**Ada**	**Total**	**Pbo**	**Ada**	**Total**
ITT	111	115	226	127	131	258	16	16	32
mITT	114	115	229	130	131	261	NA	NA	NA
Safety set[a]	114	115	229	130	131	261	16	16	32

Ada = adalimumab; NA = not applicable; Pbo = placebo

a. The actual treatment received by these subjects was the same as their randomization assignment.

Ref. Section 2.7.3 Summary of Clinical Efficacy, Table 3.

Primary Efficacy Endpoint

Time to Treatment Failure at or After Week 6 in Study M10-877 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR[a]	*P* value
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[b]	0.36, 0.70	< 0.001[c]
Adjusted for baseline IMM usage (ITT)						
Placebo	107	84 (78.5)	3.0			
Adalimumab	110	60 (54.5)	5.6	0.50[a]	0.36, 0.70	< 0.001[d]

a. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

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

c. 2-sided *P* value from log rank test.

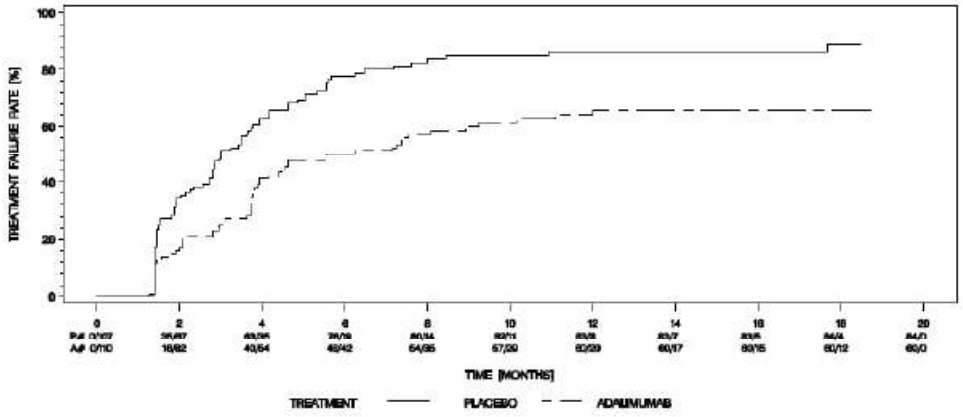
d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 6 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-877 CSR Table 14.2__1.1.1.M, Table 14.2__1.2.M

Reviewers Comments: *Study M10-877 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure. Adalimumab prolongs the time to treatment failure compared to placebo (5.6 months versus 3 months).*

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 6 in Study M10-877 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Cross reference: Study M10-877 CSR Figure 14.2 1.1.4.M

Reasons for Treatment Failure Study M10-877 on or After Week 6 in Study M10-877 (ITT; Main Study Data)

Variable	Placebo N = 107 n (%)	Adalimumab N = 110 n (%)	Total N = 217 n (%)
Chorioretinal/retinal vascular lesions			
Yes	29 (27.1)	17 (15.5)	46 (21.2)
No	78 (72.9)	93 (84.5)	171 (78.8)
AC cell grade			
Yes	34 (31.8)	24 (21.8)	58 (26.7)
No	73 (68.2)	86 (78.2)	159 (73.3)
VH grade			
Yes	39 (36.4)	16 (14.5)	55 (25.3)
No	68 (63.6)	94 (85.5)	162 (74.7)
Visual acuity			
Yes	27 (25.2)	23 (20.9)	50 (23.0)
No	80 (74.8)	87 (79.1)	167 (77.0)

Ref: M10-877 CSR Table 24

Time to Treatment Failure at or After Week 2 in Study M10-880 (ITT Population)

Analysis Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR	95%CI for HR	*P* value
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.57[a]	0.39, 0.84	0.004[b]
Adjusted for baseline IMM usage (ITT)						
Placebo	111	61 (55.0)	8.3			
Adalimumab	115	45 (39.1)	NE	0.58[c]	0.39, 0.85	0.005[d]

NE = not estimable (fewer than half of at-risk subjects had an event)

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

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

c. HR of adalimumab versus placebo from proportional hazards regression with treatment and baseline IMM usage as factors.

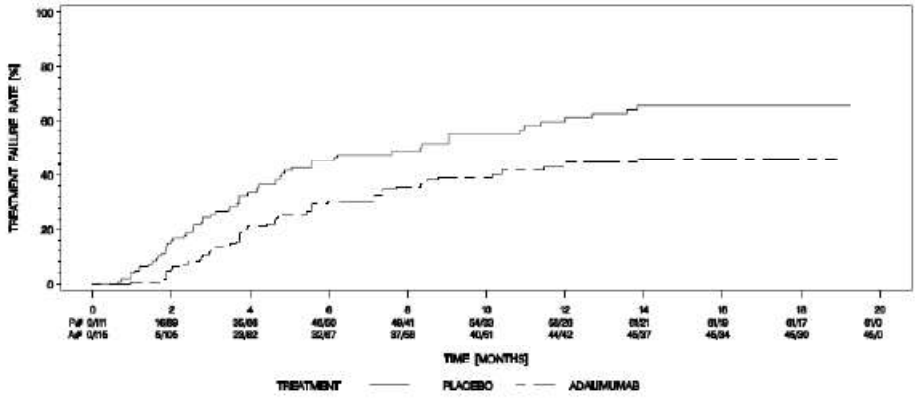
d. 2-sided *P* value from proportional hazards regression with treatment and baseline IMM usage as factors.

Note: Treatment failure at or after Week 2 was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

Cross reference: Study M10-880 CSR Table 14.2__1.1.1.M, Table 14.2__1.2.M

Reviewers Comments: *Study M10-880 met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab and placebo in the time to treatment failure. The median time to treatment failure in the placebo group was 8.3 months. The median time in the adalimumab group was > 18 months (total study duration)*

Kaplan-Meier Curve Summarizing Time to Treatment Failure on or After Week 2 in Study M10-880 (ITT; Main Study Data)



NOTE: P# - PLACEBO (NUMBER OF EVENTS/NUMBER AT RISK), A# - ADALIMUMAB (NUMBER OF EVENTS/NUMBER AT RISK)

Reasons for Treatment Failure Study M10-880 at or After Week 2 (ITT; Main Study Data)

Variable	Placebo N = 111 n (%)	Adalimumab N = 115 n (%)	Total N = 226 n (%)
Chorioretinal/retinal vascular lesions			
Yes	17 (15.3)	12 (10.4)	29 (12.8)
No	94 (84.7)	103 (89.6)	197 (87.2)
AC cell grade			
Yes	30 (27.0)	27 (23.5)	57 (25.2)
No	81 (73.0)	88 (76.5)	169 (74.8)
VH grade			
Yes	11 (9.9)	11 (9.6)	22 (9.7)
No	100 (90.1)	104 (90.4)	204 (90.3)
Visual acuity			
Yes	23 (20.7)	10 (8.7)	33 (14.6)
No	88 (79.3)	105 (91.3)	193 (85.4)

Ref: M10-880 CSR Table 23

Reviewer's Comment:
The analysis of the components of the primary endpoint are presented below for completeness. They were not predefined and no inference can be made of their statistical significance.

Components of the Primary Endpoint, Time to Treatment Failure in Study M10-877 (ITT; Main Study Data)

Endpoint Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR[a]	95% CI for HR[b]	*P* value[c]
Active Inflammatory Lesions						
All ITT subjects (N = 217)						
Placebo	107	29 (27.1)	8			
Adalimumab	110	17 (15.5)	NE[d]	0.38	0.21, 0.69	0.001
Subjects with active inflammatory lesions at baseline (N = 143)						
Placebo	63	25 (39.7)	5.3			
Adalimumab	80	17 (21.3)	NE[d]	0.36	0.19, 0.68	< 0.001
Anterior Chamber Cell Grade						
All ITT subjects (N = 217)						
Placebo	107	34 (31.8)	NE[d]			
Adalimumab	110	24 (21.8)	NE[d]	0.51	0.30, 0.86	0.010
Subjects with AC cell grade ≥ 1 at baseline (N = 86)						
Placebo	42	20 (47.6)	4.2			
Adalimumab	44	19 (43.2)	7.4	0.50	0.26, 0.96	0.032
Vitreous Haze Grade						
All ITT subjects (N = 217)						
Placebo	107	39 (36.4)	6.2			
Adalimumab	110	16 (14.5)	NE[d]	0.32	0.18, 0.58	< 0.001
Subjects with vitreous haze grade ≥ 1 at baseline (N = 149)						
Placebo	72	33 (45.8)	5.7			
Adalimumab	77	15 (19.5)	NE[d]	0.36	0.19, 0.66	< 0.001
Subjects with vitreous haze grade ≥ 2 at baseline (N = 107)						
Placebo	52	26 (50.0)	5.6			
Adalimumab	55	11 (20.0)	NE[d]	0.32	0.15, 0.64	< 0.001
logMAR Best Corrected Visual Acuity						
All ITT subjects (N = 217)						
Placebo	107	27 (25.2)	10.9			
Adalimumab	110	23 (20.9)	NE[d]	0.56	0.32, 0.98	0.040

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

b. 95% CI for HR.

c. 2-sided *P* value from log rank test.

d. Not estimable = Less than half of at-risk subjects had an event.

Note: Treatment failure due to a specific component at or after Week 6 was counted as event. Drop outs due to reasons other than treatment failure due to a specific component were censored at the time of dropping out.

Cross reference: Study M10-877 CSR Table 14.2__6.1.1.M, Table 14.2__6.2.1.M, Table 14.2__6.3.1.M, Table 14.2__6.4.1.M, Table 14.2__6.5.1.M, Table 14.2__6.6.1.M, Table 14.2__6.7.1.M, Table 14.2__6.8.1.M.PH

Components of the Primary Endpoint, Time to Treatment Failure, in Study M10-880 (ITT Population)

Endpoint Treatment	N	Failure N (%)	Median Time to Failure (Months)	HR[a]	95% CI[b]	*P* value[c]
Active Inflammatory Lesions						
All ITT subjects (N = 226)						
Placebo	111	17 (15.3)	NE[d]			
Adalimumab	115	12 (10.4)	NE[d]	0.55	0.26, 1.15	0.105
Anterior Chamber Cell Grade						
All ITT subjects (N = 226)						
Placebo	111	30 (27.0)	NE[d]			
Adalimumab	115	27 (23.5)	NE[d]	0.70	0.42, 1.18	0.180
Vitreous Haze Grade						
All ITT subjects (N = 226)						
Placebo	111	11 (9.9)	NE[d]			
Adalimumab	115	11 (9.6)	NE[d]	0.79	0.34, 1.81	0.569
logMAR Best Corrected Visual Acuity						
All ITT subjects (N = 226)						
Placebo	111	23 (20.7)	NE[d]			
Adalimumab	115	10 (8.7)	NE[d]	0.33	0.16, 0.70	0.002

a. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
b. 95% CI for HR.
c. 2-sided *P* value from log rank test.
d. Not estimable = Less than half of at-risk subjects had an event.
Note: Treatment failure due to a specific component at or after Week 2 was counted as event. Drop outs due to reasons other than treatment failure due to a specific component were censored at the time of dropping out.
Cross reference: Study M10-880 CSR Table 14.2 6.1.1.M, Table 14.2 6.2.1.M, Table 14.2 6.3.1.M, Table 14.2 6.4.1.M

6.1.5 Analysis of Secondary Endpoints(s)

Nine ranked secondary variables were tested in hierarchical order for statistical significance between the adalimumab and placebo groups in Studies M10-877 and M10-880.

Summary of Ranked Secondary Efficacy Variables in Study M10-877 (ITT; Main Study Data)

	Placebo N = 107		Adalimumab N = 110		
Ranked Secondary Variable	**n[a]**	**Mean**	**n[a]**	**Mean**	***P* value**
1. Change in AC cell grade in each eye from best state achieved prior to Week 6 to the Final/Early termination visit					
Left eye	102	0.59	101	0.35	
Right eye	102	0.69	101	0.36	
Mean difference of adalimumab minus placebo (95% CI)		–0.29 (–0.51, –0.07)			0.011[b]
2. Change in VH grade in each eye from best state achieved prior to Week 6 to the final/early termination visit					
Left eye	103	0.33	101	0.11	
Right eye	103	0.45	101	0.13	
Mean difference of adalimumab minus placebo (95% CI)		–0.27 (–0.43, –0.11)			< 0.001[b]
3. Change in logMAR BCVA in each eye from best state achieved prior to Week 6 to the Final/Early termination visit					
Left eye	103	0.12	101	0.07	
Right eye	103	0.13	101	0.04	
Mean difference of adalimumab minus placebo (95% CI)		–0.07 (–0.11, –0.02)			0.003[b]
4. Time to OCT evidence of macular edema (months) in at least 1 eye on or after Week 6 (only in subjects without macular edema at baseline)	45	6.2[c]	55	11.1[c]	
HR (95% CI)		0.70 (0.39, 1.26)			0.231[d]
5. Percent change in CRT in each eye from best state achieved prior to Week 6 to the Final/Early termination visit					
Left eye	100	20.2	100	9.6	
Right eye	102	22.0	101	8.2	
Mean difference of adalimumab minus placebo (95% CI)		–11.4 (–20.9, –1.8)			0.020[e]

Ranked Secondary Variable	Placebo N = 107 n[a]	Placebo N = 107 Mean	Adalimumab N = 110 n[a]	Adalimumab N = 110 Mean	*P* value
6. Change in VFQ-25 total score from best state achieved prior to Week 6 to the Final/Early termination visit	102	−5.50	101	−1.30	
Mean difference of adalimumab minus placebo (95% CI)		4.20 (1.02, 7.38)			0.010[f]
7. Change in VFQ-25 subscore distance vision from best state achieved prior to Week 6 to the Final/Early termination visit	102	−5.64	101	−3.77	
Mean difference of adalimumab minus placebo (95% CI)		1.86 (−2.03, 5.75)			0.346[f]
8. Change in VFQ-25 subscore near vision from best state achieved prior to Week 6 to the Final/Early termination visit	102	−8.09	101	−2.97	
Mean difference of adalimumab minus placebo (95% CI)		5.12 (0.34, 9.90)			0.036[f]
9. Change in VFQ-25 subscore ocular pain from best state achieved prior to Week 6 to the Final/Early termination visit	102	−12.62	101	−2.60	
Mean difference of adalimumab minus placebo (95% CI)		10.02 (4.86, 15.19)			< 0.001[f]

a. For each endpoint, n = number of subjects with non-missing value.
b. From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment as factor adjusted for clustered observations.
c. Median time to OCT evidence of macular edema.
d. 2-sided *P* value from log rank test.
e. From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment and OCT machine as factors adjusted for clustered observations.
f. From ANOVA of change from best state achieved prior to Week 6 to Final/Early termination visit with treatment as factor.

Cross reference: Study M10-877 CSR Table 14.2__2.1.1.M, Table 14.2__3.1.1.M, Table 14.2__4.1.1.M

Reviewer's Comments:
Statistical significance in favor of adalimumab was met for the first three secondary endpoints (change in AC cell grade, change in VH grade and change in BCVA).

Summary of Ranked Secondary Efficacy Variables in Study M10-880 (Main Study Data)

	Placebo N = 111		Adalimumab N = 115		
Ranked Secondary Variable	**n[a]**	**Mean**	**n[a]**	**Mean**	***P* value**
1. Change in AC cell grade in each eye from baseline to Final/Early Termination visit (LOCF)					
Left eye	110	0.57	115	0.41	
Right eye	110	0.53	115	0.40	
Mean difference of adalimumab minus placebo (95% CI)		−0.14 (−0.37, −0.08)			0.218[b]
2. Change in VH grade in each eye from baseline to Final/Early Termination visit (LOCF)					
Left eye	110	0.33	115	0.16	
Right eye	110	0.27	115	0.18	
Mean difference of adalimumab minus placebo (95% CI)		−0.13 (−0.28, −0.01)			0.070[b]
3. Change in logMAR BCVA in each eye from baseline to Final/Early Termination visit (LOCF)					
Left eye	110	0.06	115	0.01	
Right eye	110	0.02	115	−0.01	
Mean difference of adalimumab minus placebo (95% CI)		−0.04 (−0.08, 0.01)			0.096[b]
4. Time to OCT evidence of macular edema based on CRT (months; median) in at least 1 eye at or after Week 2 (only in subjects without macular edema at baseline)	95	NE	90	NE	
HR (95% CI)		0.75[c] (0.34, 1.69)			0.491[d]
5. Percent change in CRT in each eye from baseline to Final/Early Termination visit (LOCF)					
Left eye	107	6.4	114	4.5	
Right eye	108	7.7	113	5.4	
Mean difference of adalimumab minus placebo (95% CI)		−2.3 (−8.5, 3.8)			0.451[e]

Ranked Secondary Variable	Placebo N = 111 n[a]	Placebo N = 111 Mean	Adalimumab N = 115 n[a]	Adalimumab N = 115 Mean	*P* value
6. Change in VFQ-25 total score from baseline to Final/Early Termination visit (LOCF)	109	1.24	115	3.36	
Mean difference of adalimumab minus placebo (95% CI)		2.12 (–0.84, 5.08)			0.160[f]
7. Change in VFQ-25 subscore distance vision from baseline to Final/Early Termination visit (LOCF)	109	0.76	115	2.64	
Mean difference of adalimumab minus placebo (95% CI)		1.88 (–2.53, 6.29)			0.401[f]
8. Change in VFQ-25 subscore near vision from baseline to Final/Early Termination visit (LOCF)	109	3.98	115	3.88	
Mean difference of adalimumab minus placebo (95% CI)		–0.10 (–4.81, 4.61)			0.967[f]
9. Change in VFQ-25 subscore ocular pain from baseline to Final/Early Termination visit (LOCF)	109	2.87	115	3.42	
Mean difference of adalimumab minus placebo (95% CI)		0.56 (–4.56, 5.68)			0.830[f]

a. For each endpoint, n = number of subjects with non-missing value.
b. From ANOVA of change from baseline to Final/Early termination visit with treatment as factor adjusted for clustered observations.
c. HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
d. 2-sided *P* value from log rank test.
e. From ANOVA of change from baseline to Final/Early termination visit with treatment and OCT machine as factors adjusted for clustered observations.
f. From ANOVA of change from baseline to Final/Early termination visit with treatment as factor.

Cross reference: Study M10-880 CSR Table 14.2__2.1.1.M, Table 14.2__3.1.1.M, Table 14.2__4.1.1.M

Reviewer's Comments:
Statistical significance was not achieved for any of the secondary endpoints tested.

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

Primary and ranked secondary efficacy variables were analyzed in the ITT set in the following subgroups:

- Sex (male/female)
- Age (< 30, ≥ 30 to < 50, ≥ 50 years) at Baseline
- Race (white, non-white [further broken down into black, Asian, American Indian/Alaska Native, Native Hawaiian or Pacific Islander, multi race, other])

- Duration of uveitis (< 1, ≥ 1 year)
- Type of uveitis (intermediate uveitis versus posterior uveitis versus panuveitis)
- Diagnosis (idiopathic/other versus birdshot choroidopathy versus multifocal choroiditis and panuveitis versus Vogt Koyanagi Harada versus sarcoid versus Behcet's)
- Number of uveitis flares in the past 12 months (1, 2, ≥ 3)
- Time since last flare (< 6, ≥ 6 months) at Baseline
- Prednisone dose at last flare (< 15, ≥ 15 to < 30, ≥ 30 mg/day)
- Duration of current flare (< 60, ≥ 60 days) at Baseline
- Duration of current flare (< 1, ≥ 1 to < 2, ≥ 2 to < 3, ≥ 3 months) at Baseline
- OCT evidence of macular edema at Baseline (yes, no) (based on central reader assessment at Baseline)
- IMM usage at Baseline (yes, no)
- Topical corticosteroids (i.e., corticosteroid eye drops) at Baseline (yes, no)
- Protocol deviation "wrong treatment/incorrect dose regarding prednisone" (yes, no)
- Geographic region (North America [Canada, US], Western and Eastern Europe [Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Portugal, Spain, Switzerland, and the United Kingdom])

The results showed that the groups for the analyses for the primary and secondary endpoints were either too small to deliver valid results, or the results showed an overlap in the confidence intervals.
Ref. Study M10-887 CSR and Study M10-880 CSR Section 11.4.1.4

Japan Sub-Study Data

A total of 16 subjects in study M10-877 and 32 subjects in study M10-880 were randomized and enrolled. The sample sizes of these sub-studies were too small to draw any conclusions about the comparisons between the treatment groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The adalimumab dose regimen in the placebo-controlled studies was an 80 mg subcutaneous (SC) loading dose at baseline, followed by 40 mg eow starting at Week 1. This is the approved dosing regimen for plaque psoriasis indication. The maintenance dose of 40mg eow is approved for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. There were no other dosing regimens evaluated.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was no loss of therapeutic effect with the use of adalimumab noted during the phase 3 trials. Long-term efficacy data continue to be collected in ongoing study M11-327.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

7.1 Methods

The following analysis sets were utilized for the safety analysis:

- Placebo-Controlled Analysis Set (N = 500) – Includes all subjects who received at least 1 dose of randomized double-masked adalimumab (N = 250) or placebo (N = 250) in Study M10-877 or Study M10-880.

- All Adalimumab Analysis Set (N = 464) – Includes all subjects in studies M10-877, M10-880 or M11-327who received at least 1 dose of adalimumab (double-masked or open-label).

All summaries/analyses involving adverse events (AEs) include treatment-emergent AEs only (TEAEs). A TEAE is defined as:

Placebo-Controlled Analysis Set: Any event with onset or worsening at or after the first dosing date, and

- before first application of open-label study drug in the extension study or up to 70 days after the last double-masked study drug injection (whatever is the earliest) for subjects who rolled over into the open-label extension study, or

- up to 70 days after the last double-masked study drug injection for subjects who did not roll over in the open label extension study.

All Adalimumab Analysis Set: Any event with onset or worsening at or after the first dose of adalimumab treatment and up to 70 days (equivalent to 5 half-lives of adalimumab) after the last study drug injection or until the data cut-off date in Study M11-327, whatever is the earliest.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.1.

7.1.2 Categorization of Adverse Events

MedDRA nomenclature was used to code adverse events. The number and percent of patients reporting adverse events was tabulated based on the system organ class and preferred term. Summary table were generated for all adverse events regardless of causality as well as for treatment-related adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were integrated from the 2 pivotal studies and the ongoing Study M11-327 using a data cut of 30 April 2015.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Extent of Exposure (Placebo-Controlled Analysis Set)

Exposure	**Placebo** N=250	**Adalimumab** N=250
Total number of doses received		
Mean±SD	14.1 ± 11.2	18.7 ± 13.54
Median (min – max)	10 (2 – 42)	11 (2 – 43)
Duration of treatment (days)		
Mean±SD	175 ± 165.57	241.6 ± 191.07
Median (min – max)	105 (6 – 585)	166.5 (14 – 576)

Ref. Section 2.7.4 Summary of Clinical Safety, Table 3

Extent of Exposure (All Adalimumab Analysis Set)

Exposure	**Adalimumab** N=464
Total number of doses received	
Mean±SD	41.1 ± 28.63
Median (min – max)	34.5 (1 – 122)
Duration of treatment (weeks)	
Mean±SD	81.1 ± 57.58
Median (min – max)	68.1 (1.6 – 243.4)

Ref. Section 2.7.4 Summary of Clinical Safety, Table 4

7.2.2 Explorations for Dose Response

N/A - See section 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

Adequate animal testing has been conducted prior to and subsequent to the first approval of adalimumab in 2002. Any additional testing done for this clinical program did not raise any new issues related to the use of this drug.

7.2.4 Routine Clinical Testing

Adequate routine clinical tests have been conducted prior to and subsequent to the first approval of adalimumab in 2002. Any additional testing done for this clinical program did not raise any new issues related to the use of this drug.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate in vivo and in vitro testing has been conducted prior to and subsequent to the first approval of adalimumab in 2002. Any additional testing done for this clinical program did not raise any new issues related to the use of this drug.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse events for similar TNF blocking drugs include serious infections and malignancy. Both are currently included in class labeling and were evaluated during the uveitis program.

7.3 Major Safety Results

7.3.1 Deaths

Three subjects died in the uveitis clinical development program.

In Study M10-877, Subject (b) (6), an 80-year-old female with a history of chronic kidney disease and multiple cardiac risk factors randomized to the adalimumab group, died on Day 37 (3 days posttreatment) as a result of renal failure.

In Study M10-880, Subject (b) (6), a 62-year-old male with a history of multiple cardiac risk factors and previous aortic aneurysm randomized to the adalimumab group, died on Day 54 (18 days after last dose) as a result of aortic dissection and cardiac tamponade.

In Study M11-327, Subject (b) (6), a 71-year-old female, died on Day 195 (94 days after the first dose of adalimumab and 23 days posttreatment) as a result of B-cell lymphoma.

Reviewer's Comments:
All deaths that occurred during the development program were in the adalimumab treated group. Two of the three subjects had significant medical history that was likely the cause of death. One subject (M11-327) had lymphoma which could have potentially been related to the treatment drug since it is known to increase the risk of malignancy.

7.3.2 Nonfatal Serious Adverse Events

	Placebo-Controlled Analysis Set		**All ADA Set**
	Placebo (N = 250)	**Adalimumab (N = 250)**	**Adalimumab (N = 464)**
MedDRA PT	**n (%)**	**n (%)**	**n (%)**
Subjects with any SAE	16 (6.4)	25 (10.0)	85 (18.3)
Pneumonia	0	2 (0.8)	5 (1.1)
Accidental overdose	0	1 (0.4)	1 (0.2)
Anaphylactic reaction	0	1 (0.4)	1 (0.2)
Angle closure glaucoma	0	1 (0.4)	1 (0.2)
Aortic dissection	0	1 (0.4)	1 (0.2)
Blindness transient	0	1 (0.4)	1 (0.2)
Bronchitis	0	1 (0.4)	1 (0.2)
Calculus ureteric	0	1 (0.4)	1 (0.2)

Carcinoid tumour of the gastrointestinal tract	0	1 (0.4)	1 (0.2)
Cardiac tamponade	0	1 (0.4)	1 (0.2)
Cataract	0	1 (0.4)	4 (0.9)
Demyelination	0	1 (0.4)	2 (0.4)
Dysarthria	0	1 (0.4)	1 (0.2)
Dysphagia	0	1 (0.4)	1 (0.2)
Epistaxis	0	1 (0.4)	1 (0.2)
Fibula fracture	0	1 (0.4)	1 (0.2)
Fluid overload	0	1 (0.4)	1 (0.2)
Glioblastoma multiforme	0	1 (0.4)	1 (0.2)
Ligament rupture	0	1 (0.4)	1 (0.2)
Lung adenocarcinoma stage IV	0	1 (0.4)	1 (0.2)
Lupus-like syndrome	0	1 (0.4)	1 (0.2)
Neovascularisation	0	1 (0.4)	1 (0.2)
Neutropenia	0	1 (0.4)	1 (0.2)
Pilonidal cyst	0	1 (0.4)	1 (0.2)
Pleurisy	0	1 (0.4)	1 (0.2)
Pneumonia Legionella	0	1 (0.4)	1 (0.2)
Renal failure chronic	0	1 (0.4)	1 (0.2)
Status migrainosus	0	1 (0.4)	1 (0.2)
Tendon rupture	0	1 (0.4)	1 (0.2)
Tuberculosis	0	1 (0.4)	2 (0.4)
Upper respiratory tract infection	0	1 (0.4)	1 (0.2)
Urinary tract infection	0	1 (0.4)	3 (0.6)
Urticaria	0	1 (0.4)	1 (0.2)
Deep vein thrombosis	2 (0.8)	0	0
Abortion induced	1 (0.4)	0	0
Arthritis	1 (0.4)	0	0
Choroidal neovascularisation	1 (0.4)	0	0
Gastroenteritis viral	1 (0.4)	0	0
Hepatitis acute	1 (0.4)	0	0
Humerus fracture	1 (0.4)	0	0
Hyperparathyroidism primary	1 (0.4)	0	0
Hypertensive crisis	1 (0.4)	0	0
Meningitis aseptic	1 (0.4)	0	0
Osteonecrosis	1 (0.4)	0	0
Pyelonephritis acute	1 (0.4)	0	0

Retinal detachment	1 (0.4)	0	2 (0.4)
Sepsis	1 (0.4)	0	0
Subretinal fluid	1 (0.4)	0	0
Tonsillitis	1 (0.4)	0	0
Wrist fracture	1 (0.4)	0	0

Reviewer's Comments: *There are no significant differences in the rate of serious non-fatal adverse events.*

7.3.3 Dropouts and/or Discontinuations

Subject Disposition (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set			All ADA Set
Subjects Who:	Placebo N = 250	Adalimumab N = 250	Total N = 500	Adalimumab (N = 464)
Premature discontinuation of study				
Yes	26 (10.4)	33 (13.2)	59 (11.8)	156 (33.6)
No	224 (89.6)	217 (86.8)	441 (88.2)	9 (1.9)
Ongoing				299 (64.4)
Premature discontinuation due to (any reason)[a]				
TEAE	10 (4.0)	21 (8.4)	31 (6.2)	71 (15.3)
Lack of efficacy	6 (2.4)	1 (0.4)	7 (1.4)	31 (6.7)
Withdrew consent	3 (1.2)	4 (1.6)	7 (1.4)	19 (4.1)
Lost to follow-up	3 (1.2)	4 (1.6)	7 (1.4)	9 (1.9)
Other	8 (3.2)	7 (2.8)	15 (3.0)	47 (10.1)

a. Subjects (b) (6) and (b) (6) who discontinued due to treatment failure also had an AE leading to discontinuation. These 4 subjects (2 adalimumab and 2 placebo) were considered completers and were not counted under premature discontinuation due to the TEAE category presented in this table.

Notes: Subjects who discontinued are counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Subjects who did not prematurely discontinue include: 1) subjects who discontinued due to treatment failure, 2) subjects who completed Week 80 without treatment failure, and 3) subjects who had to terminate the study because the planned number of treatment failures was reached.

Cross reference: Table 2.1__2.1, Table 2.1__2.2

Ref. Section 2.7.4, Summary of Clinical Safety, Table 2

Reviewers Comment: *The total number of subjects that discontinued was similar between treatment groups for all categories except adverse reactions.*

Patients with Adverse Events Leading to Study Discontinuation (Safety Set; Main Study Data)

Treatment	Study / Patient Number (b) (6)	Age (y)	Gender	Race	AE Leading to Withdrawal
Adalimumab		56	F	W	Lupus-like syndrome
Adalimumab		30	F	W	Demyelination
Adalimumab		39	F	A	Tuberculosis
Adalimumab		25	M	W	Fatigue, Malaise
Adalimumab		43	F	W	Mycobacterium TB test positive
Adalimumab		46	F	O	Mycobacterium TB test positive
Adalimumab		24	M	W	Mycobacterium TB test positive
Adalimumab		25	M	A	Mycobacterium TB test positive
Adalimumab		54	F	W	Suicidal ideation
Adalimumab		28	M	W	Decreased Visual Acuity
Adalimumab		77	M	W	Increased light chain analysis
Adalimumab		80	F	W	Chronic renal failure
Adalimumab		58	M	W	Glioblastoma multiforme
Adalimumab		66	M	W	Choroidal neovascularization
Adalimumab		74	M	W	Bronchitis
Adalimumab		42	F	W	Status migrainosus
Adalimumab		56	F	W	Neutropenia
Adalimumab		45	F	W	Hepatic steatosis
Adalimumab		35	F	W	Dermatitis
Adalimumab		62	M	W	Aortic dissection, cardiac tamponade
Adalimumab		49	F	W	Pulmonary sarcoidosis
Placebo		55	F	W	Acute hepatitis
Placebo		60	M	W	Cystoid macular edema
Placebo		35	M	W	Macular edema
Placebo		31	F	W	Drug intolerance

	(b) (6)				
Placebo		49	M	W	Eye deposit, vitreous detachment
Placebo		54	M	W	Pulmonary sarcoidosis
Placebo		30	F	W	Mycobacterium TB test positive
Placebo		51	F	W	Colon adenoma
Placebo		55	F	W	Macular rash
Placebo		67	F	W	Acquired color blindness
Placebo		29	F	W	Allergic dermatitis

Ref: M10-877 clinical study report Table 46 andM10-880 clinical study report Table 43

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

The following adverse events reported during the uveitis clinical development program are of special interest with the use of adalimumab and other TNF blockers. Those that are specific interest and known to have a class effect include infections, malignancy, demyelinating disorders and immune reactions.

	Placebo-Controlled Analysis Set					All Adalimumab Analysis Set	
	Placebo (N = 250) (PYs = 119.76)		Adalimumab (N = 250) (PYs = 165.39)			Adalimumab (N = 464) (PYs = 721.43)	
Category	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	*P* value[a]	n (%)	E (E/100 PYs)
Any TEAE	201 (80.4)	1148 (958.6)	218 (87.2)	1581 (955.9)	0.052	423 (91.2)	4290 (594.6)
Any uveitis-related AE by investigator	65 (26.0)	128 (106.9)	77 (30.8)	127 (76.8)		219 (47.2)	580 (80.4)
Any uveitis-related AE by adjudication	52 (20.8)	78 (65.1)	60 (24.0)	82 (49.6)		193 (41.6)	407 (56.4)
Infections	89 (35.6)	172 (143.6)	122 (48.8)	243 (146.9)	0.004	275 (59.3)	763 (105.8)
Serious infection	4 (1.6)	5 (4.2)	7 (2.8)	8 (4.8)		27 (5.8)	33 (4.6)
Legionella infection	0	0	1 (0.4)	1 (0.6)		1 (0.2)	1 (0.1)
Diverticulitis	0	0	0	0		2 (0.4)	3 (0.4)
Opportunistic infection (excl. oral candidiasis and TB)	0	0	0	0		2 (0.4)	2 (0.3)
Oral candidiasis	0	0	2 (0.8)	2 (1.2)		2 (0.4)	2 (0.3)
TB	1 (0.4)	1 (0.8)	5 (2.0)	5 (3.0)		19 (4.1)	19 (2.6)
Active TB	0	0	1 (0.4)	1 (0.6)		2 (0.4)	2 (0.3)
Latent TB	1 (0.4)	1 (0.8)	4 (1.6)	4 (2.4)		17 (3.7)	17 (2.4)
Parasitic infections	0	0	0	0		2 (0.4)	2 (0.3)
Malignancies	0	0	4 (1.6)	4 (2.4)		12 (2.6)	12 (1.7)
Lymphoma	0	0	0	0		1 (0.2)	1 (0.1)
NMSC	0	0	1 (0.4)	1 (0.6)		5 (1.1)	5 (0.7)
Other malignancies	0	0	3 (1.2)	3 (1.8)		6 (1.3)	6 (0.8)
Allergic reactions (including angioedema, anaphylaxis)	13 (5.2)	17 (14.2)	15 (6.0)	21 (12.7)		32 (6.9)	38 (5.3)
Lupus-like reactions and systemic lupus erythematosus	0	0	1 (0.4)	1 (0.6)		1 (0.2)	1 (0.1)
Vasculitis	2 (0.8)	2 (1.7)	1 (0.4)	3 (1.8)		5 (1.1)	8 (1.1)
Cutaneous vasculitis	0	0	0	0		0	0
Non-cutaneous vasculitis	2 (0.8)	2 (1.7)	1 (0.4)	3 (1.8)		5 (1.1)	8 (1.1)
Sarcoidosis	2 (0.8)	4 (3.3)	6 (2.4)	8 (4.8)		8 (1.7)	11 (1.5)
MI	0	0	0	0		1 (0.2)	1 (0.1)
Pulmonary embolism	0	0	0	0		1 (0.2)	1 (0.1)
Interstitial lung disease	0	0	0	0		1 (0.2)	1 (0.1)
Intestinal perforation	0	0	0	0		1 (0.2)	1 (0.1)
Pancreatitis	0	0	0	0		1 (0.2)	1 (0.1)
Erythema multiforme	0	0	0	0		1 (0.2)	1 (0.1)
Worsening and new onset of psoriasis	1 (0.4)	1 (0.8)	0	0		2 (0.4)	2 (0.3)
Demyelinating disorders	0	0	1 (0.4)	1 (0.6)		6 (1.3)[b]	6 (0.8)
Hematologic disorders, including pancytopenia	1 (0.4)	1 (0.8)	4 (1.6)	5 (3.0)		12 (2.6)	17 (2.4)
Hepatologic events	1 (0.4)	1 (0.8)	2 (0.8)	2 (1.2)		5 (1.1)	6 (0.8)
Adalimumab administration related medication errors	0	0	0	0		0	0
Injection site reactions	22 (8.8)	23 (19.2)	31 (12.4)	65 (39.3)		64 (13.8)	135 (18.7)

Ref. 2.7.4 Summary of Clinical Safety Table 9

Reviewer's Comments: *Overall, these submission specific adverse events are consistent with the known profile for adalimumab. They do not raise any new safety concerns.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse Events Reported in ≥ 2% of Subjects in Either Treatment Group

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
	N	%	N	%	N (%)	%
Nasopharyngitis	31	12.4	44	17.6	114	26.6
Arthralgia	25	10	38	15.2	81	17.5
Headache	33	13.2	30	12	73	15.7
Fatigue	17	6.8	26	10.4	53	11.4
Urinary tract infection	11	4.4	21	8.4	50	10.8
Back pain	10	4	19	7.6	31	6.7
Injection site pain	13	5.2	10	4	19	4.1
Insomnia	11	4.4	18	7.2	24	5.2
Uveitis	17	6.8	20	8	93	20
Cough	10	4	18	7.2	42	9.1
Eye pain	8	3.2	18	7.2	36	7.8
Sinusitis	6	2.4	12	4.8	29	6.3
Upper respiratory tract infection	7	2.8	15	6	45	9.7
ALT increased	3	1.2	10	4	22	4.7
Visual acuity reduced	12	4.8	10	4	30	6.5
Anxiety	2	0.8	11	4.4	18	3.9
Pain in extremity	5	2	12	4.8	26	5.6
Vision blurred	8	3.2	12	4.8	29	6
Nausea	16	6.4	10	4	33	7.1
AST increased	2	0.8	9	3.6	23	5
Cystoid macular edema	13	5.2	10	4	37	8
Injection site erythema	1	0.4	5	2	11	2.4
Muscle spasms	5	2	9	3.6	22	4.7

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
Myalgia	4	1.6	11	4.4	25	5.4
Bronchitis	10	4	10	4	33	7.1
Hypertension	6	2.4	11	4.4	26	5.6
Paraesthesia	1	0.4	10	4	18	3.9
Pruritus	6	2.4	10	4	21	4.5
Pyrexia	8	3.2	10	4	27	5.8
Hyperhidrosis	3	1.2	9	3.6	11	2.4
Oropharyngeal pain	8	3.2	10	4	27	5.8
Pharyngitis	3	1.2	8	3.2	19	4.1
Rash	9	3.6	9	3.6	23	5
Vitreous floaters	10	4	10	4	27	5.8
Dry eye	12	4.8	9	3.6	20	4.3
Dyspnea	7	2.8	8	3.2	11	2.4
Intraocular pressure increased	4	1.6	9	3.6	22	4.7
Peripheral edema	3	1.2	9	3.6	15	3.2
Palpitations	2	0.8	8	3.2	11	2.4
Abdominal pain	5	2	6	2.4	11	2.4
Epistaxis	1	0.4	7	2.8	11	2.4
Joint swelling	3	1.2	6	2.4	11	2.4
Arthritis	4	1.6	5	2	9	1.9
Erythema	6	2.4	7	2.8	18	3.9
Injection site rash	1	0.4	7	2.8	15	3.2
Peripheral swelling	3	1.2	5	2	11	2.4
Posterior capsule opacification	2	0.8	5	2	13	2.8
Abdominal pain upper	6	2.4	6	2.4	15	3.2
Alopecia	9	3.6	6	2.4	21	4.5
Blood creatinine increased	5	2	6	2.4	8	1.7
Blood pressure	1	0.4	5	2	6	1.3

	Placebo-Controlled Analysis Set				All Adalimumab Analysis Set	
Adverse Event	Placebo (N=250)		Adalimumab (N=464)		Adalimumab (N=464)	
increased						
Conjunctivitis	4	1.6	6	2.4	16	3.4
Allergic conjunctivitis	4	1.6	6	2.4	20	4.3
Dizziness	7	2.8	5	2	12	2.6
Dry mouth	3	1.2	6	2.4	7	1.5
Gastroenteritis	2	0.8	6	2.4	15	3.2
Malaise	4	1.6	6	2.4	9	1.9
Musculoskeletal stiffness	5	2	6	2.4	10	2.2
Neck pain	4	1.6	5	2	8	1.7
Oral herpes	1	0.4	5	2	12	2.6
Rash pustular	0	0	6	2.4	10	2.2
Tinnitus	5	2	5	2	6	1.3
Tremor	1	0.4	6	2.4	6	1.3
Vomiting	8	3.2	6	2.4	11	2.4
Acne	9	3.6	5	2	9	1.9
Cataract	6	2.4	4	1.6	25	5.4
Contusion	8	3.2	5	2	7	1.5
Diabetes mellitus	0	0	5	2	9	1.9
Diarrhea	12	4.8	5	2	23	5
Ligament sprain	0	0	5	2	9	1.9
Muscular weakness	0	0	5	2	7	1.5
Nasal congestion	3	1.2	5	2	10	2.2
Weight increased	2	0.8	5	2	8	1.7
Conjunctival hemorrhage	5	2	3	1.2	14	3
Dyspepsia	7	2.8	4	1.6	12	2.6
Influenza	13	5.2	4	1.6	23	5
Injection site bruising	5	2	4	1.6	8	1.7
Migraine	5	2	4	1.6	10	2.2
Eye pruritus	5	2	2	0.8	4	0.9
Photophobia	6	2.4	1	0.4	6	1.3

Reviewer's Comments: *Adverse events highlighted in the above table are those that are higher in the adalimumab group versus placebo and occur at a rate ≥ 5% in the adalimumab group. This cut-off is used to be able to compare the currently labeled adverse event rate with those seen in the uveitis program. The types of adverse events that occurred during this development program are adequately addressed in the current label.*

7.4.2 Laboratory Findings

There was a higher rate of elevated liver enzymes reported in the adverse event section for subjects on adalimumab. Approximately, 2.4% of patients Humira patients and 2.4% of controls had ALT elevations ≥ 3 x ULN. Per the current label, TNF blockers are associated with hepatic reactions including acute liver failure. In the phase 3 trials in patients with RA, PsA and AS, ALT elevations ≥ 3 x ULN occurred in 3.5% of Humira patients and 1.5% of control-treated controls.

Subjects with ALT Elevations (Placebo-Controlled and All Adalimumab Analysis Sets)

	Placebo-Controlled Analysis Set		All ADA Set
	Placebo (N = 250)	Adalimumab (N = 250)	Adalimumab (N = 464)
Subjects with:	n (%)	n (%)	n (%)
ALT ≥ 3 × ULN	2 (0.8)	2 (0.8)	11 (2.4)
ALT ≥ 5 × ULN	3 (1.2)	3 (1.2)	4 (0.9)
ALT ≥ 10 × ULN	0	1 (0.4)	2 (0.4)
ALT ≥ 20 × ULN	1 (0.4)	0	0

7.4.3 Vital Signs

There were no clinically significant changes in vital sign values for adalimumab observed in the clinical trials.

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

N/A – *no additional safety studies were conducted to address a specific safety concern*

7.4.6 Immunogenicity

Per the approved label: "Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment".

In the Phase 3 Studies M10-877 and M10-880, the percentage of subjects testing positive for autoimmune antibodies (AAA) who received adalimumab 40 mg eow was 4.8% (12/249). This is consistent with the RA trials where AAA formation was approximately 5% (58/1062).

7.5 Other Safety Explorations

Specific drug interactions or dose dependency were not evaluated in the uveitis clinical development program.

7.6 Additional Safety Evaluations

The safety of adalimumab in pediatric patients has been adequately evaluated in studies for Juvenile Idiopathic Arthritis and Pediatric Crohn's disease. The sponsor received orphan status designation for the current indication and therefore is exempt from conducting additional studies under PREA.

7.7 Additional Submissions / Safety Issues

The 120-day safety update includes safety data for subjects in the All Adalimumab Analysis Set who received at least 1 injection of adalimumab in Study M11-327 through the cut-off date of 31 August 2015. The Placebo-Controlled Analysis Set is not presented in this update since the placebo-controlled studies were complete at the time of the sBLA and are captured in the ISS.

MedDRA PT	ISS		Safety Update	
	Adalimumab (N = 464) (PYs = 721.43)		Adalimumab (N = 464) (PYs = 796.92)	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
All TEAEs	423 (91.2)	4290 (594.6)	432 (93.1)	4598 (577.0)
Nasopharyngitis	114 (24.6)	191 (26.5)	117 (25.2)	200 (25.1)
Uveitis	93 (20.0)	153 (21.2)	102 (22.0)	169 (21.2)
Arthralgia	81 (17.5)	110 (15.2)	83 (17.9)	115 (14.4)
Headache	73 (15.7)	104 (14.4)	74 (15.9)	106 (13.3)
Fatigue	53 (11.4)	58 (8.0)	55 (11.9)	60 (7.5)
Urinary tract infection	50 (10.8)	63 (8.7)	54 (11.6)	69 (8.7)
Upper respiratory tract infection	45 (9.7)	57 (7.9)	47 (10.1)	59 (7.4)
Cough	42 (9.1)	45 (6.2)	44 (9.5)	47 (5.9)
Cystoid macular edema	37 (8.0)	58 (8.0)	40 (8.6)	61 (7.7)
Eye pain	36 (7.8)	42 (5.8)	37 (8.0)	43 (5.4)
Bronchitis	33 (7.1)	38 (5.3)	35 (7.5)	40 (5.0)
Nausea	33 (7.1)	45 (6.2)	34 (7.3)	46 (5.8)
Back pain	31 (6.7)	36 (5.0)	34 (7.3)	40 (5.0)
Visual acuity reduced	30 (6.5)	43 (6.0)	32 (6.9)	45 (5.6)
Sinusitis Vision	29 (6.3)	38 (5.3)	31 (6.7)	42 (5.3)
blurred	28 (6.0)	32 (4.4)	32 (6.9)	35 (4.4)
Oropharyngeal pain	27 (5.8)	32 (4.4)	32 (6.9)	37 (4.6)
Pyrexia	27 (5.8)	30 (4.2)	27 (5.8)	29 (3.6)
Vitreous floaters	27 (5.8)	30 (4.2)	26 (5.6)	29 (3.6)
Hypertension	26 (5.6)	27 (3.7)	28 (6.0)	29 (3.6)
Pain in extremity	26 (5.6)	29 (4.0)	26 (5.6)	30 (3.8)
Cataract	25 (5.4)	32 (4.4)	27 (5.8)	36 (4.5)
Myalgia	25 (5.4)	30 (4.2)	25 (5.4)	31 (3.9)
Insomnia	24 (5.2)	32 (4.4)	24 (5.2)	32 (4.0)
AST increased	23 (5.0)	29 (4.0)	24 (5.2)	30 (3.8)

MedDRA PT	ISS		Safety Update	
	Adalimumab (N = 464) (PYs = 721.43)		Adalimumab (N = 464) (PYs = 796.92)	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Diarrhea	23 (5.0)	26 (3.6)	25 (5.4)	28 (3.5)
Influenza	23 (5.0)	30 (4.2)	26 (5.6)	33 (4.1)
Rash	23 (5.0)	25 (3.5)	24 (5.2)	26 (3.3)
ALT increased	22 (4.7)	29 (4.0)	22 (4.7)	29 (3.6)
Intraocular pressure increased	22 (4.7)	30 (4.2)	24 (5.2)	32 (4.0)
Muscle spasms	22 (4.7)	26 (3.6)	25 (5.4)	29 (3.6)
Alopecia	21 (4.5)	21 (2.9)	23 (5.0)	24 (3.0)
Macular edema	21 (4.5)	23 (3.2)	22 (4.7)	26 (3.3)
Pruritus	21 (4.5)	23 (3.2)	22 (4.7)	25 (3.1)
Conjunctivitis allergic	20 (4.3)	24 (3.3)	23 (5.0)	27 (3.4)
Dry eye	20 (4.3)	24 (3.3)	23 (5.0)	27 (3.4)
Injection site pain	19 (4.1)	36 (5.0)	19 (4.1)	36 (4.5)
Pharyngitis	19 (4.1)	22 (3.0)	20 (4.3)	23 (2.9)
Anxiety	18 (3.9)	23 (3.2)	18 (3.9)	24 (3.0)
Erythema Paraesthesia	18 (3.9)	18 (2.5)	20 (4.3)	21 (2.6)
Iridocyclitis	18 (3.9)	26 (3.6)	19 (4.1)	27 (3.4)
Conjunctivitis	17 (3.7)	21 (2.9)	20 (4.3)	24 (3.0)
Abdominal pain upper	16 (3.4)	16 (2.2)	17 (3.7)	17 (2.1)
Gastroenteritis	15 (3.2)	17 (2.4)	16 (3.4)	18 (2.3)
Injection site rash	15 (3.2)	17 (2.4)	15 (3.2)	17 (2.1)
Edema peripheral	15 (3.2)	17 (2.4)	16 (3.4)	18 (2.3)
Conjunctival hemorrhage	15 (3.2)	18 (2.5)	15 (3.2)	19 (2.4)
Osteoarthritis	14 (3.0)	17 (2.4)	15 (3.2)	18 (2.3)
Pain	13 (2.8)	16 (2.2)	13 (2.8)	16 (2.0)
Posterior capsule opacification	13 (2.8)	13 (1.8)	14 (3.0)	14 (1.8)
	13 (2.8)	15 (2.1)	14 (3.0)	16 (2.0)

MedDRA PT	ISS		Safety Update	
	Adalimumab (N = 464) (PYs = 721.43)		Adalimumab (N = 464) (PYs = 796.92)	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Blood triglycerides increased	12 (2.6)	13 (1.8)	12 (2.6)	13 (1.6)
Dizziness	12 (2.6)	14 (1.9)	13 (2.8)	15 (1.9)
Dyspepsia	12 (2.6)	13 (1.8)	12 (2.6)	13 (1.6)
Mycobacterium tuberculosis complex test positive	12 (2.6)	12 (1.7)	12 (2.6)	12 (1.5)
Oral herpes	12 (2.6)	14 (1.9)	13 (2.8)	15 (1.9)
Seasonal allergy	12 (2.6)	18 (2.5)	12 (2.6)	18 (2.3)
Vertigo	12 (2.6)	13 (1.8)	12 (2.6)	14 (1.8)
Abdominal pain	11 (2.4)	14 (1.9)	11 (2.4)	14 (1.8)
Dyspnea	11 (2.4)	13 (1.8)	12 (2.6)	14 (1.8)
Epistaxis	11 (2.4)	13 (1.8)	11 (2.4)	14 (1.8)
Eye inflammation	11 (2.4)	13 (1.8)	13 (2.8)	15 (1.9)
Hypercholesterolemia	11 (2.4)	11 (1.5)	11 (2.4)	11 (1.4)
Hyperhidrosis	11 (2.4)	13 (1.8)	11 (2.4)	13 (1.6)
Hypoesthesia	11 (2.4)	12 (1.7)	12 (2.6)	14 (1.8)
Injection site erythema	11 (2.4)	28 (3.9)	13 (2.8)	34 (4.3)
Joint swelling	11 (2.4)	13 (1.8)	11 (2.4)	13 (1.6)
Ocular hypertension	11 (2.4)	13 (1.8)	13 (2.8)	16 (2.0)
Palpitations	11 (2.4)	15 (2.1)	12 (2.6)	16 (2.0)
Peripheral swelling	11 (2.4)	13 (1.8)	11 (2.4)	13 (1.6)
Vomiting	11 (2.4)	19 (2.6)	11 (2.4)	20 (2.5)
Anterior chamber inflammation	10 (2.2)	19 (2.6)	11 (2.4)	23 (2.9)
Constipation	10 (2.2)	10 (1.4)	13 (2.8)	13 (1.6)
Depression	10 (2.2)	10 (1.4)	10 (2.2)	10 (1.3)
Migraine	10 (2.2)	10 (1.4)	11 (2.4)	11 (1.4)

MedDRA PT	ISS		Safety Update	
	Adalimumab (N = 464) (PYs = 721.43)		Adalimumab (N = 464) (PYs = 796.92)	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Musculoskeletal stiffness	10 (2.2)	11 (1.5)	10 (2.2)	11 (1.4)
Nasal congestion	10 (2.2)	10 (1.4)	10 (2.2)	10 (1.3)
Rash pustular	10 (2.2)	10 (1.4)	10 (2.2)	11 (1.4)
Arthritis	9 (1.9)	11 (1.5)	10 (2.2)	13 (1.6)
Blindness	9 (1.9)	14 (1.9)	10 (2.2)	15 (1.9)
Hordeolum	9 (1.9)	11 (1.5)	10 (2.2)	12 (1.5)
Influenza like illness	9 (1.9)	11 (1.5)	12 (2.6)	14 (1.8)
Ligament sprain	9 (1.9)	9 (1.2)	10 (2.2)	10 (1.3)
Tonsillitis	9 (1.9)	13 (1.8)	10 (2.2)	14 (1.8)
Hypersensitivity	8 (1.7)	8 (1.1)	10 (2.2)	12 (1.5)

Cross reference: ISS (R&D/14/0201) Table 2.4 2.1.2, Table 2.4 2.2.2; Table 2.4_2.1.2, Table 2.4_2.2.2

Reviewer's Comments: *The adverse events reported in the 120-day safety update are consistent with the ISS. There are no new safety signals in the updated safety database.*

8 Postmarket Experience

Adalimumab was first approved for the treatment of rheumatoid arthritis in the United States (US) in December 2002 and subsequently has been approved for the following indications: Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis and Plaque Psoriasis. The cumulative postmarketing patient exposure is 3.5 million patient years. All safety risks identified during the postmarketing period are included in the product labeling. No new safety risks have been identified in the uveitis program.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

(b) (4)

9.3 Advisory Committee Meeting

N/A

9.4 List of Investigators

Investigator Information for Study M10-877

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List of Investigators			
Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**
Kesen, Muge Ruken (48953) (Site did not enroll)	West Virginia University Eye Institute Box 9193 Medical Center Drive Morgantown, WV 26506 United States	Phone: 1 304 598 4814 Fax: 1 304 598 6928 Email: kesenm@wvuhealthcare.com	0
Kestelyn, Philippe (39602)	University Hospital Ghent, UZ Ghent Oogheelkunde P1 De Pintelaan 185 Ghent, 9000 Belgium	Phone: 32 9 332 25 99 Fax: 32 9 332 49 63 Email: philippe.kestelyn@ugent.be	10
Kherani, Amin (39607)	Southern Alberta Eye Center Calgary Retina Consultants 200, 5340 1st Street South West Calgary, AB T2H 0C8 Canada	Phone: 1 403 286 6802 Fax: 1 403 286 6819 Email: amin.kherani@calgaryretina.ca	1
Kim, Rosa (38927)	Retina Consultants of Houston Suite 750 6560 Fannin Houston, TX 77030 United States	Phone: 1 712 524 3434 Fax: 1 712 795 4552 Email: Rosakimmd@houstonretina.com	2
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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**
Kramer, Michal (39610)	Rabin Medical Center Ophthalmological Clinic Out patient Clinic Bldg. Campus Belinson, Rabin MC 85 Jabotinsky Street Petach Tikva, 49100 Israel	Phone: 972 3 9377199 Fax: 972 3 9377274 Email: michalkr98@gmail.com	6
Kuffova, Lucia (43780)* *This investigator is listed as Kuffova, L in the clinical database. (Replaced Forrester, John Vincent [39614])	University of Aberdeen Section of Immunology and Infection, Division of Applied Medicine Institute of Medical Sciences Foresterhill Aberdeen, AB25 2ZD United Kingdom	Phone: 44 1224 437523 Fax: 44 1224 555955 Email: l.kuffova@abdn.ac.uk	1
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Labalette, Pierre (39657) (Site did not enroll)	CHRU de Lille, Hopital Claude Huriez Service d'Ophtalmologie Rue Michel Polonovski Lille Cedex, 59037 France	Phone: 33 3 20 44 62 30 Fax: 33 3 20 44 50 47 Email: hophtalmologie@chru-lille.fr	0

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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**

Larson, Theresa* (52561) *See Stone, Donald (38790): "Larson, T" is represented in the clinical database as having enrolled subjects during this study; however, Stone was the active investigator for this site for the entire study.	Dean McGee Eye Institute 608 Stanton L. Young Boulevard Oklahoma City, OK 73104 United States	Phone: 1 405 271 6307 Fax: 1 405 271 3347 Email: theresa-larson@dmei.org	1
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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**

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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**
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Investigator Name (Investigator Number)	Investigator /Site Location	Contact Information	Number of Randomized Subjects
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Investigator Name (Investigator Number)	Investigator /Site Location	Contact Information	Number of Randomized Subjects
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Investigator Name (Investigator Number)	Investigator /Site Location	Contact Information	Number of Randomized Subjects
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Investigator Name (Investigator Number)	Investigator /Site Location	Contact Information	Number of Randomized Subjects
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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**
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Investigator Name (Investigator Number)	**Investigator /Site Location**	**Contact Information**	**Number of Randomized Subjects**
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/s/

JENNIFER D HARRIS
06/01/2016

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06/06/2016

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 125-057

Submission Date(s): 09/03/2015

Applicant: AbbVie, Inc.

Product: adalimumab

Reviewer: Jennifer D. Harris, M.D.

Date of Review: 04/26/2016

Covered Clinical Study (Name and/or Number): M10-877, M10-880, M11-327

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 129		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The development program to evaluate the safety and efficacy of adalimumab for the treatment of uveitis consisted of two phase 3 safety and efficacy trials (M10-877 and M10-880) and an open-label extension trial (M10-327). There were a total of 67 study sites for study M10-877 and 62 study sites for M10-880.

Details of the disclosable financial arrangements for the clinical investigators who participated in the development program are summarized in the following table.

Investigator	Site	Disclosure	Number of Subjects		
			Study M10-877	Study M10-880	Study M11-327
(b) (6)		Payments > $25,000			(b) (6)
		Payments > $25,000			
		Payments > $25,000			
		Payments > $25,000			
		Equity interest > $50,000			

Abbvie has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. There were five (5)

[1] See [web address].

subinvestigators who disclosed financial ties to the sponsor. A review of these arrangements do not raise questions about the integrity of the results.

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/s/

JENNIFER D HARRIS
06/01/2016

WILLIAM M BOYD
06/06/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

PRODUCT QUALITY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: January 14, 2016
To: File for STN: sBLA 125057/397
RPM: Eithu Lwin, CDER/OAP/DTOP
From: Jun Park, Ph.D., Product Reviewer, CDER/OBP/DBRR II
Through: Joel Welch, Ph.D., Team Leader, CDER/OBP/DBRR II
Applicant: AbbVie, Inc.
Product: Humira® (adalimumab)
Supplement Receipt Date: September 03, 2015
PDUFA Date: July 03, 2016

RECOMMENDATION: This sBLA submission is recommended for approval from a CMC perspective

SUMMARY:

This is an efficacy supplement for a new indication for Humira® (adalimumab) for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

No new product quality data are included with this submission. The sponsor has used the recently approved ADA assay, which was reviewed by Dr. Chikako Torigoe (DBRR II/OBP) on April 1, 2015, for immunogenicity assessment in the M10-877 and M10-880 studies.

Pursuant to 21 CFR 25.31(e) and FDA's Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (R1), dated July 1998, AbbVie requests a categorical exclusion from the requirement for environmental assessment for this sBLA. The request is considered appropriate.

This BLA efficacy supplement is approvable from a CMC perspective. There are no CMC-related PMRs recommended for this BLA efficacy supplement.

Conclusions:

I. Recommendation: **Approval from CMC perspective**
II. Sections Deferred to other reviewers: None
III. Post-marketing commitments: None
IV. Future Inspection Items: None

cc: Park/Welch HFD-123

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/s/

JUN T PARK
02/04/2016

JOEL T WELCH
02/04/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 125057/Supplement 397
Supporting document/s:	SDN 5339 (0388): New Supplement
	SDN 5390 (0401): Revised Draft Labeling
	SDN 5556 (0413): Revised Draft Labeling
	SDN 5760 (0440): Revised Draft Labeling
Applicant's letter date:	September 3, 2015
	September 23, 2015
	December 7, 2015
	March 23, 2016
CDER stamp date:	September 3, 2015
	September 23, 2015
	December 7, 2015
	March 23, 2016
Product:	Humira® (adalimumab)
Indication:	Rheumatoid Arthritis (RA); Juvenile Idiopathic Arthritis (JIA); Psoriatic Arthritis (PsA); Ankylosing Spondylitis (AS); Adult Crohn's Disease (CD); Pediatric CD; Ulcerative Colitis (UC); Plaque Psoriasis (Ps); Hidradenitis Suppurativa (HS); Uveitis (UV)
Applicant:	AbbVie Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Eleni Salicru, PhD
Supervisor/Team Leader:	Timothy Robison, PhD, DABT

Division Director: Badrul Chowdhury, MD, PhD

Project Manager: Sadaf Nabavian

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125057/Supplement 397 are owned by AbbVie Inc. or are data for which AbbVie Inc. has obtained a written right of reference.
Any information or data necessary for approval of BLA 125057/Supplement 397 that AbbVie Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125057/Supplement 397.

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1 Executive Summary

1.1 Introduction

AbbVie submitted efficacy supplement 397 (S397) for Humira® BLA 125057 to the Division of Transplant and Ophthalmology Products (DTOP) on September 3, 2015, for a new indication of non-infectious intermediate, posterior and panuveitis in adult patients. The supplement included draft labeling to conform to the Pregnancy and Lactation Labeling Rule (PLLR) implemented for applications received after June 30, 2015. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was tasked with managing the evaluation of the label with respect to the PLLR and this review evaluates the relevant nonclinical sections.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical review of the proposed Humira® label for S397 was limited to sections 8 and 13. The Division of Pediatric and Maternal Health (DPMH) was consulted for Sections 8.1 and 8.2 in order to comply with the PLLR format. Below is the recommended text for Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) after revisions to the nonclinical sections of the Sponsor's proposed Humira® label (submitted in SDN 5760 on March 23, 2016). Note, clinical labeling changes are not addressed in this review (refer to clinical review). The pharmacology review for the original BLA 125057/0 dated December 31, 2002, was referenced for the embryo-fetal perinatal development study with adalimumab in pregnant cynomolgus monkeys as information from this study is included in Section 8.1 of the label.

1.3 Recommendations

1.3.3 Labeling

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

2 Drug Information

2.1 Drug

CAS Registry Number: 331731-18-1

Trade Name: Humira®

Generic Name: Adalimumab

Molecular Weight: 148 kDa

Structure:

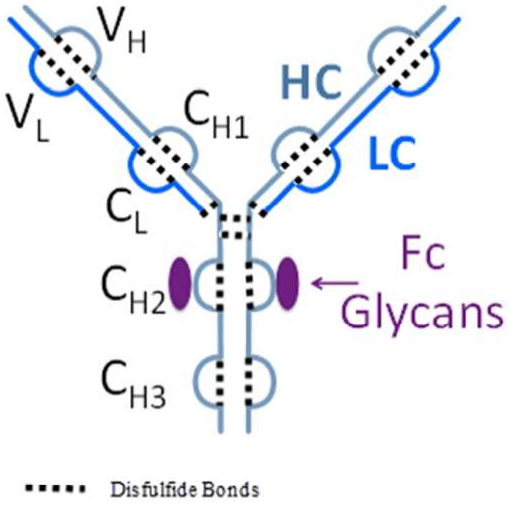

Figure 1 Schematic of Adalimumab Structure (Sponsor's Figure)

Biochemical Description: Adalimumab is a genetically engineered fully human immunoglobulin G (IgG) monoclonal antibody specific for human tumor necrosis factor

alpha (TNF-α). Adalimumab was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:κ constant regions. It consists of 1330 amino acids.

Pharmacologic Class: TNF blocker (anti-TNF alpha monoclonal antibody)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 007627 (Adalimumab by AbbVie)

2.7 Regulatory Background

The original BLA for Humira® was approved on December 31, 2002, for rheumatoid arthritis (RA) and subsequently supplements to the BLA were approved for the indications of psoriatic arthritis (PsA) in 2005, ankylosing spondylitis (AS) in 2006, adult Crohn's Disease (CD) in 2007, plaque psoriasis (Ps) and juvenile idiopathic arthritis (JIA) in 2008, ulcerative colitis in 2012, pediatric CD in 2014, and hidradenitis suppurativa (HS) in 2015. On September 3, 2015, AbbVie submitted efficacy S397 to DTOP for a new indication of non-infectious intermediate, posterior and panuveitis in adult patients. The supplement also included draft labeling to conform to the PLLR implemented for applications received after June 30, 2015. It was determined that DPARP would manage the evaluation of the draft label with respect to the PLLR.

3 Studies Submitted

There were no nonclinical studies submitted to S397 that affected the Humira® labeling changes in Sections 8.1 and 8.2 related to the PLLR format.

3.1 Studies Reviewed

One pharmacology study was submitted to S397, which was reviewed by DTOP (see nonclinical review dated December 17, 2015). Findings from this study did not impact the product insert label.

- A Role for Tumor Necrosis Factor (TNF) in a Preclinical Model of Autoimmune Uveitis (Study # 0902; non-GLP)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

The pharmacology review for the original BLA 125057/0 dated December 31, 2002 was referenced for the embryo-fetal perinatal development study with adalimumab in pregnant cynomolgus monkeys. Information from this study is included in Section 8.1 of the label.

11 Integrated Summary and Safety Evaluation

11.1 Labeling Evaluation

AbbVie submitted efficacy S397 for a new indication for Humira® for non-infectious intermediate, posterior and panuveitis in adult patients (SDN 5339 on September 3, 2015). The submission included a draft label with updated prescribing information to support the new indication. The Sponsor also updated Sections 8.1 (Pregnancy) and 8.2 (Lactation) of the label to conform to the final PLLR requirements that were implemented for applications received after June 30, 2015. Subsequently, the Sponsor submitted amended draft labels on September 23, 2015 (SDN 5390), December 7, 2015 (SDN 5556), and March 23, 2016 (SDN 5760) related to the following approvals of Humira®: for hidradenitis suppurativa (approved September 9, 2015), for the 100 mg/mL formulation in a pre-filled syringe (approved November 23, 2015), and for the 100 mg/mL formulation in a modified autoinjector (approved March 9, 2016), respectively. This nonclinical labeling evaluation focused primarily on an assessment of the PLLR language in consultation with DPMH (see March 24, 2016, maternal health review).

Below is the Sponsor's proposed labeling text (SDN 5760, March 23, 2016). The nonclinical revisions to the Sponsor's proposed labeling are also shown below along with the associated rationale for the changes. The underlined text is recommended for insertion and the ~~strikethrough~~ text is recommended for deletion from the Sponsor's proposed text. Note that changes made to "Clinical Risk Summary", "Clinical Considerations" and "Human Data" are addressed by the clinical review team and are not addressed here.

11.2 Labeling Recommendations

8 USE IN SPECIFIC POPULATIONS

Sponsor's Proposed Labeling for Section 8.1:

8.1 Pregnancy

(b) (4)

(b) (4)

Data

Human Data

In a prospective cohort pregnancy registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5% respectively. (b) (4)

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data

(b) (4)

Reviewer's Comment: Compared to the previous Humira® label, the Sponsor edited text in "Animal Data" to only reflect exposure margins relative to clinical exposures of adalimumab without methotrexate (comparisons to clinical exposures of adalimumab with methotrexate were removed). The Sponsor also added that no malformations were detected due to adalimumab treatment in the monkeys.

DPARP's Proposed Nonclinical Labeling for Section 8.1:

8.1 Pregnancy

(b) (4)

Data

Animal Data

(b) (4)

Rationale for Changes in Section 8.1:

The proposed text for Section 8.1 was discussed with DPMH and was updated to comply with the PLLR. Since the Humira® pregnancy exposure registry is no longer enrolling patients, DPMH recommended that "Pregnancy Exposure Registry" should be

removed and that the information about the pregnancy exposure registry should be included under “Human Data”. See the maternal health review dated March 24, 2016 and the clinical review, for details about the changes related specifically to the “Clinical Risk Summary”, “Clinical Considerations”, and “Human Data”.

For the embryo-fetal perinatal development study data in “Risk Summary” and “Animal Data”, details about the timing of IV adalimumab exposure were added. In addition, the exposure expressed in terms of the MRHD without methotrexate was added.

Sponsor’s Proposed Labeling for Section 8.2:

8.2 Lactation

Risk Summary

(b) (4)

DPARP Proposed Nonclinical Labeling for Section 8.2:

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature (b) (4) describe the presence of adalimumab (b) (4) in human milk (b) (4) (b) (4) at infant doses of 0.1% to 1% of the maternal serum level. (b) (4) There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. (b) (4) ised (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Rationale for Changes in Section 8.2:

The proposed text for Section 8.2 “Risk Summary” was discussed with DPMH and was updated to comply with the PLLR. No animal data is available regarding the presence

of adalimumab in milk. See the maternal health review dated March 24, 2016 and the clinical review, for details about the changes made to the "Risk Summary" and changes made to "Human Data".

13 NONCLINICAL TOXICOLOGY

Sponsor's Proposed Labeling for Section 13.1:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

DPARP's Proposed Nonclinical Labeling for Section 13.1:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Rationale for Changes in Section 13.1:

Section 13.1 was revised to remove language related to clastogenic or mutagenic effects of Humira®. This is in line with more current practices to remove information from the product insert label that is related to genetic toxicology data that is not relevant for the safety assessment of biologics produced by recombinant DNA technology.

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/s/

ELENI M SALICRU
05/23/2016

TIMOTHY W ROBISON
05/23/2016
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY sBLA REVIEW AND EVALUATION

Application number:	sBLA 125057/397 (efficacy)
Supporting document/s:	5339
Applicant's letter date:	09-03-15
CDER stamp date:	09-03-15
Product:	HUMIRA (adalimumab)
Indication:	Treatment of non-infectious intermediate, posterior and panuveitis
Applicant:	AbbVie, Inc.
Review Division:	Transplant and Ophthalmology Products
Reviewer:	Ilona G. Bebenek, PhD, DABT
Supervisor/Team Leader:	Lori E. Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Eithu Lwin

Disclaimer

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Humira® (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF)-alpha.

This efficacy supplement proposes a new indication for HUMIRA®, i.e., the treatment of non-infectious intermediate, posterior and panuveitis. This submission is based upon clinical data from the completed pivotal Studies M10-877 and M10-880 as well as interim safety data from the ongoing open-label extension Study M11-327 (as part of the integrated summary of safety) to support the proposed indication when administered as an 80 mg initial dose (subcutaneous injection), followed by 40 mg every other week starting one week after initial dose.

- The approved recommended human dose for HUMIRA is an 80 mg initial dose followed by 40 mg every other week starting one week after initial dose for *plaque psoriasis*.
- The approved recommended dose for rheumatoid *arthritis*, *psoriatic arthritis* and *ankylosing spondylitis* is 40 mg every other week.
- The approved dose for adult *Crohn's Disease* is an initial dose of 160 mg followed by a second dose of 80 mg two weeks later and a maintenance dose of 40 mg every other week, starting two weeks after the second dose.

Therefore, the applicant seeks approval of a dosing regimen within range of those previously approved by the FDA. No new toxicity studies were submitted to this supplemental BLA given that the toxicity profile of adalimumab has been well established. One pharmacology study was submitted and a review of this study is presented below. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) will address the adequacy of the PLLR conversion included in the labeling for this supplement. There were no other revisions to the nonclinical sections of the previously approved label. Accordingly, there are no new concerns/recommendations from the nonclinical perspective (DTOP).

Study Submitted/Reviewed:

A Role for Tumor Necrosis Factor (TNF) in a Preclinical Model of Autoimmune Uveitis (Study # 0902; non-GLP)

Pharmacology:

A Role for Tumor Necrosis Factor (TNF) in a Preclinical Model of Autoimmune Uveitis (Study # 0902; non-GLP)

TNF, a proinflammatory cytokine produced mainly by macrophages and T cells, has been shown to play a role in the perpetuation of inflammation in uveitis. An experimental animal uveoretinitis (EAU) model was generated by immunization of genetically-susceptible mice (B10.RIII) with subcutaneous injection of interphotoreceptor retinoid-binding peptide (IRBP). Disease pathology on Day 21 post immunization closely resembled human uveitis in this model. Two experiments were conducted using this mouse model and treatment with mouse anti-TNF antibody

(starting on the day of immunization with IRBP) to demonstrate a decrease in inflammation associated with uveoretinitis.

In the first experiment, ten B10.RIII female mice (immunized with IRBP on Day 1) per group were dosed with either 15 mg/kg (HED 73mg) anti-TNF or control IgG antibody via subcutaneous injection weekly for three weeks, starting on Day 1. Animals were sacrificed on Day 21 and both eyes were fixed for histopathological analysis. Total EAU histologic scores were based on photoreceptor damage (photoreceptor cell loss, retinal folds and detachment) and inflammatory infiltrates (vitreous, retina, retinal pigment epithelium and choroid). An additional scoring parameter was Dalen Fuchs-type nodules between the retina and the choroid which are characteristic features of chronic human uveitis. Treatment with anti-TNF reduced total EAU group mean scores (both eyes combined) by 76% compared to controls; from 3.4 (moderate/severe) in the control group (IgG antibody) to 0.8 (minimal) in the 15 mg/kg anti-TNF group.

In the second experiment, three to five female B10.RIII mice (immunized with IRBP on Day 1) were dosed with control IgG antibody, 0.15 mg/kg, 0.5 mg/kg, 1.5 mg/kg, 5 mg/kg or 15 mg/kg anti-TNF via subcutaneous injection weekly for three weeks, starting on Day 1. After 21 days, anti-TNF resulted in a dose-dependent reduction in photoreceptor damage (Table 1 and 2). Inflammation was reduced at doses ≥0.15 mg/kg anti-TNF (≥HED 0.73mg). Scores were decreased 85% and 58% at 15 mg/kg anti-TNF in left and right eyes, respectively, as compared to controls. Anti-TNF had the most drastic effect on decrease in incidence and severity of photoreceptor loss and retinal detachment, Dalen Fuchs-type nodules, non-granulomatous inflammation in the choroid and inflammatory infiltrates in the vitreous (Table 2). The high dose results from this experiment were consistent with those shown in the first experiment.

In summary, a proinflammatory role for TNF was demonstrated in this model of uveoretinitis, with anti-TNF treatment resulting in a reduction of retinal damage and inflammation in the posterior segment. The doses of anti-TNF used in this study were clinically relevant.

Table 1. Dose Response Experiment with anti-TNF antibody
Mean EAU scores

Dose (mg/kg)	Left eye	Right eye
Control IgG	3.4	3.6
0.15	3.4	2.8
0.5	2	2.2
1.5	2	2.0
5	3	2.3
15	0.5	1.5

Table 2. Dose Response Experiment with anti-TNF antibody (individual scores) Left eye

Path #SN 09091, 102809EAU										
Left eye	Photoreceptor damage			Inflammation						
					Retina		Choroid			
Animal #	Folds	Loss	Detachment	Dalen-Fuchs	Granulomatous	Non-granulomatous	Granulomatous	Non-granulomatous	Vitreous	Total score
Control IgG, weekly for 3 weeks										
1	0	++	+++	++	+	0	0	+	++	4
2	+	+	+	+	0	+	0	+++	+	4
3	+	+	++	+	0	+	0	++	++	3
4	0	+	+	++	0	+	0	+	+	3
5	+	+	+	++	+	0	0	++	+	3
									Mean	3.4
Anti-TNF, 0.15 mg/kg weekly for 3 weeks										
6	+	0	+	+	0	+	0	0	0	3
7	+	+	+	+	0	+	0	+	+	3
8	+	+	++	+	0	+	1	0	0	4
9	+	+	+	+	0	++	0	+++	+	4
10	+	0	++	0	0	0	0	+	0	3
									Mean	3.4
Anti-TNF, 0.5 mg/kg weekly for 3 weeks										
11	0	0	0	0	0	0	0	0	0	0
12	+	0	+	+	0	+	0	+	+	3
13	+	0	+	++	0	+	0	+	+	4
14	+	+	+	+	+	0	0	+	+	3
15	+	0	+	0	0	0	0	+	0	1
									Mean	2.0

(Continued) Path #SN 09091, 102809EAU										
Left eye	Photoreceptor damage			Inflammation						
					Retina		Choroid			
Animal #	Folds	Loss	Detachment	Dalen-Fuchs	Granulomatous	Non-granulomatous	Granulomatous	Non-granulomatous	Vitreous	Total score
Anti-TNF, 1.5 mg/kg weekly for 3 weeks										
16	+	+	+	+	0	+	0	+	0	3
17	0	0	0	0	0	0	0	0	0	0
18	+	0	+	+	+	0	+	0	0	3
19	+	0	+	+	0	+	0	+	0	3
20	0	0	0	0	0	0	0	0	+	1
									Mean	2.0
Anti-TNF, 5 mg/kg weekly for 3 weeks										
21	+	0	0	+	0	0	0	+	0	3
22	+	0	0	+	0	+	0	+	+	3
23	0	0	0	0	0	++	0	+	0	3
									Mean	3.0
Anti-TNF, 15 mg/kg weekly for 3 weeks										
24	+	0	0	0	0	+	0	0	0	1
25	+	0	+	0	0	0	0	+	0	1
26	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	+	0	0	0	0
									Mean	0.5

Right eye

Path #SN 09091, 102809EAU										
Right eye	Photoreceptor damage			Inflammation						
					Retina		Choroid			
Animal #	Folds	Loss	Detachment	Dalen-Fuchs	Granulomatous	Non-granulomatous	Granulomatous	Non-granulomatous	Vitreous	Total score
Control IgG, weekly for 3 weeks										
1	0	+	0	+	+	0	0	+	+	3
2	+	+	++	++	0	+	0	++	++	4
3	0	++	++	+	0	+	+	0	++	3
4	+	+	++	++	+	0	0	+	+	4
5	+	+	+	++	+	0	+	0	+	4
									Mean	3.6
Anti-TNF, 0.15 mg/kg weekly for 3 weeks										
6	+	0	0	+	0	+	0	+	+	3
7	0	+	++	++	0	+	0	++	+	4
8	+	0	+	0	0	+	0	+	0	1
9	+	0	++	+	+	0	0	+	++	3
10	+	0	+	+	+	0	0	+	0	3
									Mean	2.8
Anti-TNF, 0.5 mg/kg weekly for 3 weeks										
11	0	0	0	0	0	+	0	0	+	1
12	+	+	++	+	+	0	0	++	+	3
13	+	0	+	+	+	0	0	+	+	3
14	+	+	+	+	++	0	0	+	+	3
15	+	0	+	0	+	0	0	0	0	1
										2.2

(Continued) Path #SN 09091, 102809EAU										
Right eye	Photoreceptor damage			Inflammation						
					Retina		Choroid			
Animal #	Folds	Loss	Detachment	Dalen-Fuchs	Granulomatous	Non-granulomatous	Granulomatous	Non-granulomatous	Vitreous	Total score
Anti-TNF, 1.5 mg/kg weekly for 3 weeks										
16	+	+	++	+	0	0	0	+	+	3
17	+	0	0	0	0	0	0	0	+	1
18	+	0	+	0	0	0	0	+	0	1
19	+	+	0	0	0	0	+	0	0	2
20	0	0	0	0	0	0	0	0	++	3
									Mean	2.0
Anti-TNF, 5 mg/kg weekly for 3 weeks										
21	0	0	0	0	0	0	+	0	0	1
22	+	0	++	+	0	0	0	+	++	3
23	+	0	0	0	0	++	0	++	++	3
									Mean	2.3
Anti-TNF, 15 mg/kg weekly for 3 weeks										
24	+	0	++	+	+	0	0	+	+	3
25	+	+	++	0	0	++	0	0	+	3
26	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0
									Mean	1.5

Excerpted from the sponsor's study report, pages 16-19

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/s/

ILONA G BEBENEK
12/17/2015

LORI E KOTCH
12/17/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125057
Supplement #:	397
Drug Name:	HUMIRA® (adalimumab)
Indication(s):	Treatment of non-infectious intermediate, posterior, and panuveitis in adult patients
Applicant:	AbbVie Inc.
Date(s):	Submitted: 09/03/2015 PDUFA date: 07/03/2016
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Yunfan Deng, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D.
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Jennifer Harris, MD William Boyd, MD, Team Leader
Project Manager:	Eithu Lwin

Keywords: time-to-event, Kaplan-Meier, hazard ratio, log-rank test, non-infectious intermediate, posterior, and panuveitis

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1 EXECUTIVE SUMMARY

In this supplement Biologics License Application (sBLA), the applicant (AbbVie Inc.) seeks approval of HUMIRA® (adalimumab) for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients. The proposed dosing regimen is 80 milligrams (mg) initial dose followed by 40 mg every other week starting one week after initial does. Since December 2002, Humira® has already been approved in the US and European Union for the following indications: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Psoriasis (Ps), Juvenile Idiopathic Arthritis (JIA).

To support this sBLA approval, the applicant conducted two pivotal clinical trials – Study M10-877 and Study M10-880 (also referred to as Study 877 and Study 880 throughout this review). Both studies were prospective, multicenter, randomized, double-masked, placebo-controlled studies which were similar in study design but enrolled different study populations (adult patients with **active** disease for Study 877 versus adult patients with **inactive** disease for Study 880). For both studies, the primary efficacy endpoint was the 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) (see Table 12 for details).

In **Study 877**, the median time to treatment failure was 3 months (95% confidence interval [CI]: [2.7, 3.7]) in the placebo group, and the median time to treatment failure was 5.6 months (95% CI: [3.9, 9.2]) in the adalimumab group. The hazard ratio comparing adalimumab group to placebo group was 0.50 with a 95% CI of [0.36, 0.70]; p-value <0.001 from the log rank test.

In **Study 880**, the median time to treatment failure for subjects in the placebo group was 8.3 months (95% CI: [4.8, 12.0]) and for subjects in the adalimumab group was not estimable as more than half of the adalimumab subjects did not experience treatment failure. The hazard ratio comparing adalimumab group to placebo group was 0.57 with a 95% CI [0.39, 0.84]; p-value = 0.004 from the log rank test.

In conclusion, results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients treated with placebo.

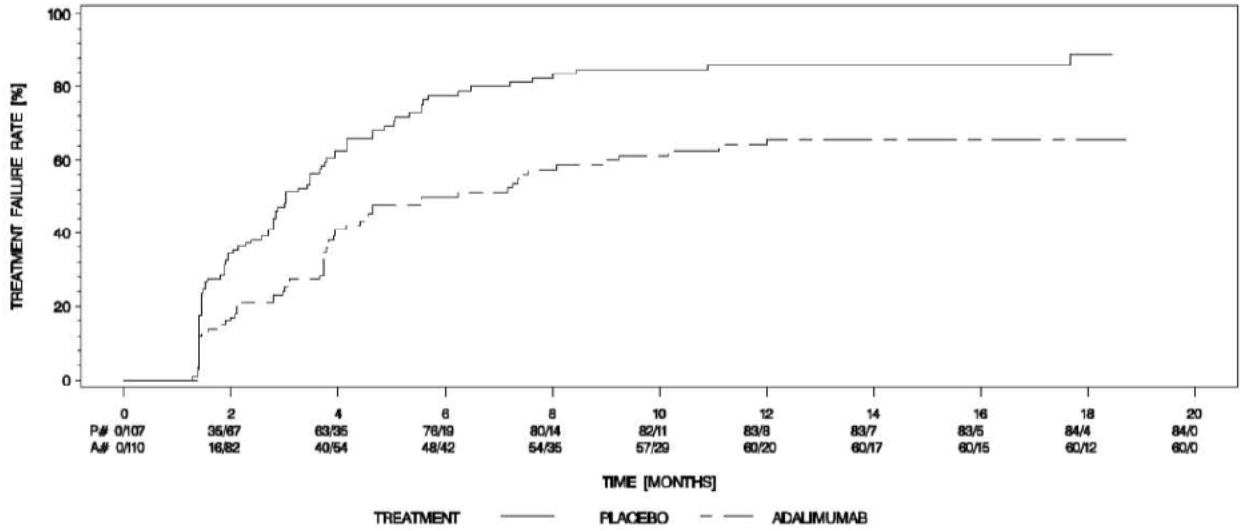
Table 1: Time to Treatment Failure (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo (N=107)	Adalimumab (N=110)	HR (95% CI)[a]	Placebo (N=111)	Adalimumab (N=115)	HR (95% CI)[a]
Failure[1] (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.57 (0.39, 0.84)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
Component of Treatment Failure						
New Active Inflammatory Lesions						
Events, n (%)	29 (27.1)	17 (15.5)	0.38 (0.21, 0.69)	17 (15.3)	12 (10.4)	0.55 (0.26, 1.15)
Anterior Chamber Cell Grade						

Events[2], n (%)	34 (31.8)	24 (21.8)	0.51 (0.30, 0.86)	30 (27.0)	27 (23.5)	0.70 (0.42, 1.18)
Vitreous Haze Grade						
Events[2], n (%)	39 (36.4)	16 (14.5)	0.32 (0.18, 0.58)	11 (9.9)	11 (9.6)	0.79 (0.34, 1.81)
Worsening of BCVA by ≥ 15 Letters Relative to Best State Achieved						
Events, n (%)	27 (25.2)	23 (20.9)	0.56 (0.32, 0.98)	23 (20.7)	10 (8.7)	0.33 (0.16, 0.70)

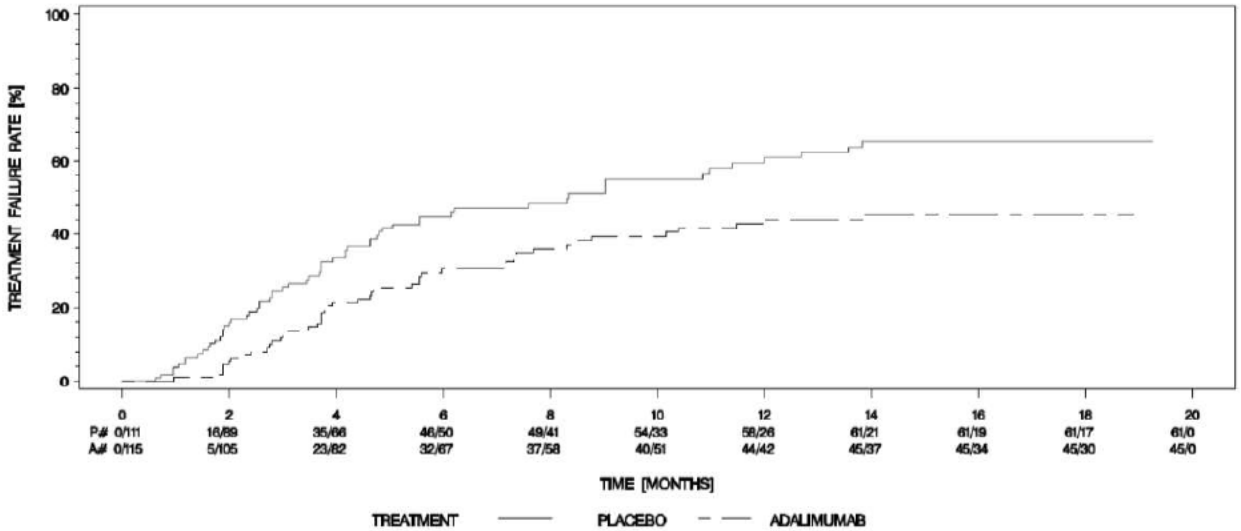
[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
[1] Treatment failure at or after Week 6 in Study 877, or at or after Week 2 in Study 880, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
[2] Study 877: Inability to achieve ≤ 0.5° at Week 6 and/or 2-step increase relative to best state achieved after Week 6; Study 880: 2-step increase relative to best state achieved at or after Week 2.
Source: Tables 22 and 25 of Study 877 Report and Tables 22 and 24 of Study 880 Report.

Figure 1: Kaplan-Meier Curve: Time to Treatment Failure (ITT; Study 877)



Note: P# - Placebo (Number of Events/Number at Risk); A# - Adalimumab (Number of Events/Number at Risk).
Source: Figure 3 of Study 877 Report.

Figure 2: Kaplan-Meier Curve: Time to Treatment Failure (ITT; Study 880)



Note: P# - Placebo (Number of Events/Number at Risk); A# - Adalimumab (Number of Events/Number at Risk).
Source: Figure 3 of Study 880 Report.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF)-α. Since December 2002, adalimumab has already been approved in the US and European Union for the following indications: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Psoriasis (Ps), Juvenile Idiopathic Arthritis (JIA).

Uveitis is a form of eye inflammation that affects uvea. The uvea is the middle layer of tissue in the wall of the eye; it consists of the iris, the ciliary body and the choroid. The uvea provides blood flow to the deep layers of the retina. The types of uveitis depend on which part(s) of the eye are affected:

- Anterior uveitis (iritis) affects the front of the eye and is the most common type
- Intermediate uveitis (cyclitis) affects the ciliary body
- Posterior uveitis (choroiditis and retinitis) affects the back of the eye
- Panuveitis occurs when all layers of the uvea are inflamed

Sometimes uveitis is caused by bacteria or a virus in the eye. This is called infectious uveitis. But other times there is no infection, and it's called noninfectious uveitis. Noninfectious uveitis can be caused by an eye injury or a disease somewhere else in one's body. People who have these conditions may be more prone to get uveitis:

- AIDS
- Behcet's syndrome
- Shingles
- Multiple sclerosis
- Psoriasis
- Rheumatoid arthritis
- Sarcoidosis
- Tuberculosis
- Ulcerative colitis

In some cases, what causes noninfectious uveitis can't be identified.

Currently, the main treatment for non-infectious uveitis is corticosteroids, which are administered in three forms: topically, locally via sub-Tenon's or intravitreal injection, and systemically. In addition, immunosuppressive agents may be added to the corticosteroid regimen to eliminate the need for high doses of systemic steroids, or used alone as steroid-sparing agents when steroids are not tolerated. So far, the only drug class approved in the US by the Food and Drug Administration (FDA) for the treatment for uveitis is corticosteroids.

2.1.2 History of Drug Development

Adalimumab was first approved in the US and EU for the treatment of rheumatoid arthritis (RA) in 2002 and 2003, respectively, and in more than 90 countries world-wide since. Additional indications have been approved in the US and EU, and globally, including PsA, AS, ulcerative colitis (UC), JIA, adult and pediatric Crohn's disease (CD), and adult and pediatric psoriasis (Ps).

Studies in adult active and inactive non-infectious intermediate uveitis, posterior uveitis, and panuveitis patients treated with adalimumab were initiated in August 2010. A pre-Phase 3 Type B Meeting was held between the FDA (Division of Anti-Infective and Ophthalmology Products) and Abbott (now AbbVie) on 18 September 2009. Further clarification and agreement were reached through a conference call held on 08 March 2010. The Agency generally agreed to the design of the studies, as well as inclusion criteria, dosing, corticosteroid tapering, and statistical analysis plan. The phase 3 study protocols were submitted to the FDA under IND 105723.

2.1.3 Studies Reviewed

HUMIRA® non-infectious unvietis clinical development plan included three clinical studies. Two of these studies (Studies 877 and 880) were pivotal, randomized, double-masked clinical studies. In addition, there is one ongoing open-label safety study – Study M11-327.

Study 877 (VISUAL I) was a multicenter, randomized, double-masked, placebo-controlled study of the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab as maintain therapy in subjects requiring high dose corticosteroids for **active** non-infectious intermediate-, posterior-, or pan-uveitis.

Study 880 (VISUAL II) was a multicenter, randomized, double-masked, placebo-controlled study of the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with **inactive** non-infectious intermediate-, posterior-, or pan-uveitis.

Study M11-327 is an ongoing open-label, multicenter, long-term safety and efficacy study of adult subjects with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who participated in Studies M10-877 or M10-880 and who either discontinued from the study for having met the endpoint of treatment failure or completed the study without treatment failure at Week 80 or remained in the study until it was stopped (completed < Week 80 but subjects had to terminate the study because the planned number of treatment failures was reached).

This statistical review focused on the two pivotal safety and efficacy studies: Studies M10-877 and M10-880 (also referred to as Study 877 and Study 880 throughout this review). Key information of the two pivotal studies is presented in the following table.

Table 2: Key Information for Studies 877 and 880

Study No Phase	Design	Objective	Treatment Groups	Study Population
Study 877	Multi-center, randomized,	to investigate the safety and efficacy of adalimumab in	adalimumab or its matching placebo 80	Adult patients who had active

	double masked, placebo-controlled	subjects who had previously shown adequate clinical response to oral corticosteroids but then had active non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least 1 eye despite at least 2 weeks of treatment with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent)	mg subcutaneous (SC) loading dose at baseline followed by 40 mg every other week (eow) starting at Week 1 Adalimumab: 112 Placebo: 111	non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least 1 eye despite at least 2 weeks of treatment with oral prednisone
Study 880	Multi-center, randomized, double masked, placebo-controlled	to demonstrate efficacy and safety of adalimumab in adult subjects with inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis whose disease had been inactive for ≥ 28 days prior to baseline and who required chronic oral corticosteroids with oral prednisone ≥ 10 mg/day (or oral corticosteroid equivalent) to maintain this inactive disease (i.e., were unable to discontinue corticosteroids without a disease flare).	adalimumab or its matching placebo 80 mg subcutaneous (SC) loading dose at baseline followed by 40 mg every other week (eow) starting at Week 1 Adalimumab: 114 Placebo: 115	Adult subjects with inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis whose disease had been inactive for ≥ 28 days prior to baseline and who were unable to discontinue corticosteroids without a disease flare.

Source: Statistical Reviewer's Summary based on Section 2.7.3.1 of Summary of Clinical Efficacy.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies 877, and 880. The study reports are available at: \\cdsesub1\evsprod\BLA125057\0388\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uveitis\5351-stud-rep-contr.

The applicant submitted SAS datasets electronically; the datasets for Study 877 are available at: \\cdsesub1\evsprod\BLA125057\0388\m5\datasets\m10-877\analysis\legacy\datasets; and for Study 880 are available at: \\cdsesub1\evsprod\BLA125057\0388\m5\datasets\m10-880\analysis\legacy\datasets.

The SAS program codes that were used to generate the results in the study reports are available at: \\cdsesub1\evsprod\BLA125057\0388\m5\datasets\m10-877\analysis\legacy\programs and \\cdsesub1\evsprod\BLA125057\0388\m5\datasets\m10-880\analysis\legacy\programs for Study 877 and Study 880 respectively.

The time to treatment failure (in month) and censored flag were included in the "tf.xpt" dataset with variable names "DIFFM" and "CENSN". The treatment variable, given both as numeric

(TRT01N) and character (TRT01), was also included in the above dataset. The variables corresponding to each component of treatment failure were included in the "ef.xpt" dataset with variable names in "PARAM" and corresponding values in "CHG". The adverse events were included in the "ae.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary and ranked secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plans (SAPs) for the two pivotal studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Both Studies 877 and 880 were multi-center (countries), randomized, double-masked, placebo-controlled pivotal studies; both has a separate sub-study of subjects in Japan only. Study 877 evaluated the efficacy and safety of adalimumab in controlling active, non-infectious intermediate uveitis, posterior uveitis, or panuveitis; while Study 880 was similarly designed but enrolled subjects with inactive non-infectious, intermediate uveitis, posterior uveitis, or panuveitis to assess the ability of adalimumab to maintain quiescence upon steroid tapering in a quiescent steroid-dependent population.

3.2.1.1 Study 877

Study 877 investigate the safety and efficacy of adalimumab in subjects who had previously shown adequate clinical response to oral corticosteroids but now had active non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least 1 eye despite at least 2 weeks of oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent).

The protocol-defined key inclusion criteria were:

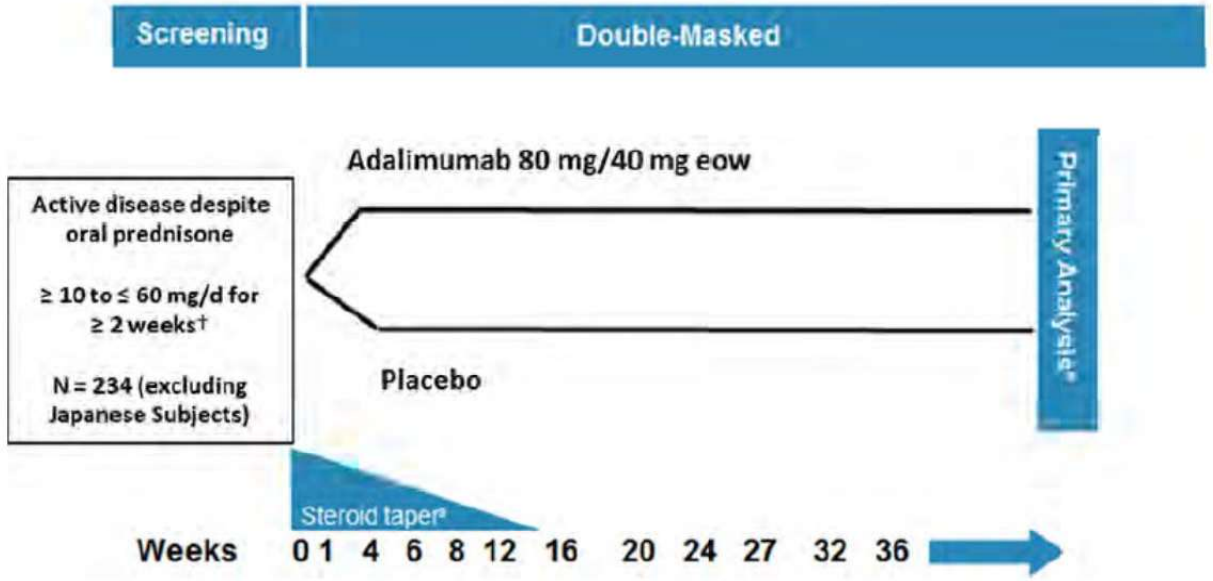
- Adult subject diagnosed with non-infectious intermediate uveitis, posterior uveitis, or panuveitis.
- Subject must have had active disease at the Baseline visit as defined by the presence of at least 1 of the following parameters in at least 1 eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent):
    - Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
    - ≥ 2+ anterior chamber (AC) cells (Standardization of Uveitis Nomenclature [SUN] criteria)

- ≥ 2+ vitreous haze (VH; National Eye Institute [NEI]/SUN criteria)

- Subject was on oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for at least 2 weeks prior to Screening and remained on the same dose from Screening to Baseline visit.

Please refer to Appendix 1 for the protocol-defined key exclusion criteria.

Figure 3: Study 877 Design Schematic



Source: Figure 1 of Study 877 Report.
* The study ended when the 138th event of treatment failure (in ex-Japan subjects only) had occurred.
† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.
a. Prednisone 60 mg per day was given at Baseline followed by a taper from Weeks 2 – 15. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Weeks 1 – 9.

Subjects were evaluated at Baseline, Weeks 1, 4, 6, and 8, and every 4 weeks thereafter except there was not a study visit at Week 28 but at Week 27 instead. Starting from Week 6, all subjects were assessed for treatment failure. According to the applicant, the Week 1 and Week 4 visits were meant to assess subjects' progress and safety. For detailed schedule of activities, please refer to Appendix 2.

The primary efficacy endpoint was the time to treatment failure. Treatment failure criteria were listed in the following table.

Table 3: Study 877 Treatment Failure Criteria by Visit

	Treatment Failure[a]	
Parameter	Week 6 Visit	All Other Visits after Week 6
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline
Anterior Chamber (AC) Cell grade (SUN Criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]

Vitreous Haze grade (NEI/SUN Criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved

[a] To be considered a treatment failure, at least one of these 4 criteria need to be present in at least 1 eye.
[b] This is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.
Source: Table 10 of Study 877 Report.

The number of AC cells observed within a 1 mm × 1 mm slit beam was recorded for each eye. The reported number was used to determine the grade according to the SUN criteria.

Table 4: SUN Criteria Grading Scale for AC Cells

Grade	Cells in Field
0	< 1
0.5+	1 – 5
1+	6 – 15
2+	16 – 25
3+	26 – 50
4+	> 50

Source: Table 4 of Study 877 Report.

The NEI/SUN criteria grading scale for vitreous haze is defined as follows.

Table 5: NEI/SUN Criteria Grading Scale for Vitreous Haze

Grade	Vitreous Haze
0	Clear
0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2+	Permits better visualization of the retinal vessels (compared to higher grades)
3+	Permits the observer to see the optic nerve head, but the borders are quite blurry
4+	Optic nerve head is obscured

Source: Table 6 of Study 877 Report.

The study did not specify "study eye"; both of the subjects' eye were evaluated to assess treatment failure. The applicant defined that at least one of the above four criteria to be present in at least one eye to be a treatment failure. In Study 877, majority (about 90%) of the randomized subjects had both eyes affected.

The ranked secondary variables included:

1. Change in AC cell grade in each eye from best state achieved prior to Week 6 to the final/early termination visit.
2. Change in VH grade (NEI/SUN criteria) in each eye from best state achieved prior to Week 6 to the final/early termination visit.
3. Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from best state achieved prior to Week 6 to the final/early termination visit.
4. Time to OCT evidence of macular edema in at least 1 eye on or after Week 6.
5. Percent change in central retinal thickness in each eye from best state achieved prior to Week 6 to the final/early termination visit.

6. Change in VFQ-25 composite score from best state achieved prior to Week 6 to the final/early termination visit.
7. Change in VFQ-25 subscore distance vision from best state achieved prior to Week 6 to the final/early termination visit.
8. Change in VFQ-25 subscore near vision from best state achieved prior to Week 6 to the final/early termination visit.
9. Change in VFQ-25 subscore ocular pain from best state achieved prior to Week 6 to the final/early termination visit

The sample size estimation of 138 events was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- The placebo treatment failure rate at 6 months was assumed to be 70%.
- The adalimumab treatment failure rate at 6 months was assumed as 50%.
- Failures would begin to occur after 2 months of study duration as the prednisone taper reached lower doses.
- A pooled dropout rate of 35% over 12 months
- 95% power.

3.2.1.2 Study 880

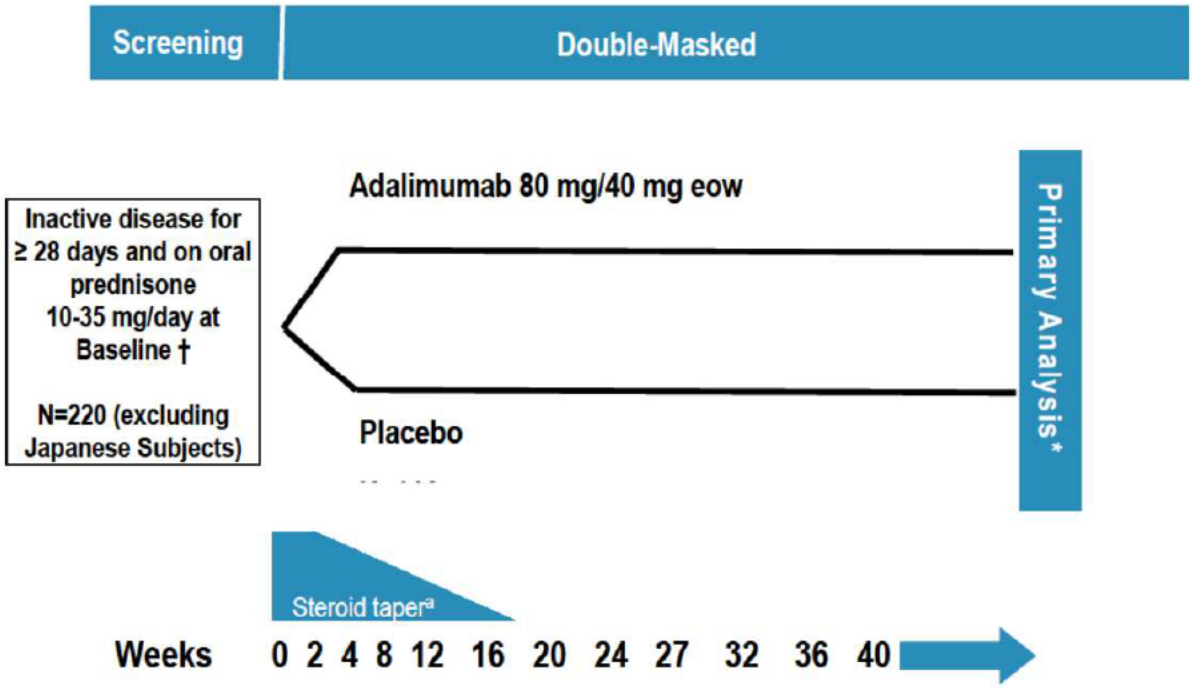
Study 880 investigated the efficacy and safety of adalimumab in with inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis in subjects whose disease had been inactive for ≥ 28 days and who required chronic oral corticosteroids with oral prednisone ≥ 10 mg/day (or oral corticosteroid equivalent) to maintain inactive disease.

The protocol-defined key inclusion criteria were:

- Adult subject diagnosed with non-infectious intermediate uveitis, posterior uveitis, or panuveitis.
- Subject had inactive disease for ≥ 28 days prior to the Baseline visit, was taking ≥ 10 mg of oral prednisone to maintain this inactive state, and fulfilled 3 of the following criteria based on the investigator's clinical judgment at the Screening and Baseline visits for both eyes:
    - Without active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
    - ≤ 0.5+ anterior chamber (AC) cells (SUN criteria)
    - ≤ 0.5+ vitreous haze (VH; National Eye Institute [NEI]/SUN criteria)
- Subject was on oral prednisone at a dose of 10 to 35 mg/day (or oral corticosteroid equivalent) at baseline and the dose had not been increased in the past 28 days or decreased in the past 14 days.
- Subject must have had a documented history of experiencing at least 1 disease flare within 18 months of the Screening visit. This flare had to occur during or up to a maximum of 28 days after tapering off the oral corticosteroid therapy.

Please refer to Appendix 1 for the protocol-defined key exclusion criteria.

Figure 4: Study 880 Design Schematic



Source: Figure 1 of Study 880 Report.
* The study ended when approximately 96 (84 to 107) treatment failures (in ex-Japan subjects only) had occurred.
a. Prednisone taper was to occur from Week 2 up to Week 19. Topical steroids were allowed at study entry, but subjects were to undergo a mandatory taper schedule from Week 1 to Week 9.
† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.

Subjects were evaluated at Baseline, Weeks 1, 4, and every 4 weeks thereafter except there was no study visit at Week 28 but at Week 27 instead. Starting from Week 2, all subjects were assessed for treatment failure. For detailed schedule of activities, please refer to Appendix 2.

The primary efficacy endpoint was the time to treatment failure. Treatment failure criteria were listed in the following table.

Table 6: Study 880 Treatment Failure Criteria by Visit

	Treatment Failure[a]
Parameter	Week 2 and all other visits after Week 2
New active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline
Anterior Chamber (AC) Cell grade (SUN Criteria)	2-step increase relative to best state achieved[b]
Vitreous Haze grade (NEI/SUN Criteria)	2-step increase relative to best state achieved[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved

[a] To be considered a treatment failure, ≥ 1 of these 4 criteria need to be present in at least 1 eye.
[b] This is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.
Source: Table 10 of Study 880 Report.

The grading of AC cells and Vitreous Haze were the same as Study 877. Study 880 did not specify "study eye"; both of the subjects' eye were evaluated to assess treatment failure. The applicant defined that at least one of the above four criteria to be present in at least one eye to be a treatment failure. In Study 880, majority (about 95%) of the randomized subjects had both eyes affected.

The ranked secondary variables included:

1. Change in AC cell grade in each eye from baseline to the final/early termination visit.
2. Change in VH grade (NEI/SUN criteria) in each eye from baseline to Week 6 to the final/early termination visit.
3. Change in logarithm of the minimum angle of resolution (logMAR) BCVA in each eye from baseline to the final/early termination visit.
4. Time to OCT evidence of macular edema in at least 1 eye at or after Week 2 (only in subjects without macular edema at baseline).
5. Percent change in central retinal thickness in each eye from baseline to the final/early termination visit.
6. Change in VFQ-25 composite score from baseline to the final/early termination visit.
7. Change in VFQ-25 subscore distance vision from baseline to Final/Early Termination visit
8. Change in VFQ-25 subscore near vision from baseline to Final/Early Termination visit.
9. Change in VFQ-25 subscore ocular pain from baseline to Final/Early Termination visit

The sample size estimation of 84 to 107 events was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- The placebo treatment failure rate at 6 months was assumed to be approximately 42.5%.
- The adalimumab treatment failure rate at 6 months was assumed as approximately 27.5%.
- Failures would begin to occur after 2 months of study duration as the prednisone taper reached lower doses.
- A pooled dropout rate of 35% over 12 months
- 80% power.

3.2.1.3 Japan Sub-Study

Both Studies 877 and 880 included Japan sub-studies that had only subjects enrolled from sites in Japan. Study 877 was planned to end at Japanese sites when either the 138th event of treatment failure had occurred in the main study or when the 19th event of treatment failure had occurred in the Japan sub-study; Study 880 was to end at sites in Japan when either approximately 96 (84 to 107) events of treatment failure had occurred in the main study or when 17 events of treatment failure had occurred in the Japan sub-study, whichever occurred later. The designs and conducts of the Japan sub-studies were almost the same as that for the main studies; the following differences in Japan sub-studies were noted:

- In both studies, subjects from Japan were randomized in a separate stratum. Due to the small sample size, no stratification by Baseline IMM usage was used for subjects from Japan.

- For both studies, Japanese subjects were excluded if they met either of the following criteria:
    - Subject had positive hepatitis C result at Screening.
    - Subject had a positive or indeterminate β-D-glucan test
- Study drug was to be administered at the investigational site at Weeks 1, 3, 5, and 7 to secure the safety of subjects. Starting at Week 9, the subject was to be allowed to self-inject study drug (placebo and adalimumab) at home or a place other than the investigation site thereafter.

Other than noted, this statistical review focuses on the main study data, which excluded the Japan sub-study data.

3.2.2 Statistical Methodologies

Both studies 877 and 880 intended to demonstrate the superiority of adalimumab to placebo based on the time to treatment failure. For Study M10-877, the sponsor stated that events during the first 6 weeks were not counted to allow time for subjects to reach a common level of quiescence following the protocol-specified prednisone burst. For Study M10-880, similarly, events were not counted until Week 2, which was the first scheduled study visit after the Baseline visit and the beginning of the protocol-specified prednisone taper.

For the primary efficacy endpoint of the time to treatment failure, the difference between treatments was tested using the log-rank test; corresponding hazard ratio with 95% confidence interval and *P*-value from the log-rank test were calculated. Treatment failures (including the use of rescue medications) were counted as events. Dropouts due to reasons other than treatment failure at any time during the study were considered as censored observations at the time of dropping out. As part of sensitivity analysis, time to treatment failure was compared between the treatment groups in a proportional hazards model with treatment and baseline IMM usage as factors.

The ranked secondary endpoints were analyzed as follows: Change in AC cell grade, change in VH grade, change in logMAR BCVA, and change in CRT were compared between treatment groups using ANOVA adjusted for clustered observations (i.e., observations from subjects with two eyes qualified for the study). Change in VFQ-25 was compared between treatment groups using ANOVA. Missing values were imputed by last observation carried forward (LOCF). The time to OCT evidence of macular edema based on CRT was compared between the treatment groups in a proportional hazards model. OCT evidence of macular edema was counted as an event. Dropouts due to reasons other than OCT evidence of macular edema were considered as censored observations at the time of dropping out.

The primary efficacy endpoint and the ranked secondary endpoints were testing hierarchically in the ranked order to control the overall family-wise Type I error rate.

For both studies, there were three different analysis populations (also known as analysis sets) defined by the applicant:

- **Intent-to-Treat (ITT) analysis set**, which included all randomized patients recruited outside Japan, with the exclusion of subjects from two investigators (Brezin, France; and Flynn, USA); the applicant's rationale for exclusion were incomplete efficacy source data (Brezin) and general compliance issues (Flynn). All the efficacy analyses were conducted using this ITT analysis set according to the treatment randomized. As presented in Section 3.2.3, the actual treatment received by all subjects in both studies was the same as their randomization assignment.
- Modified Intent-to-Treat (mITT) analysis set, which included all randomized subjects recruited outside Japan; additional sensitivity efficacy analyses were conducted using this mITT analysis set. Instead of naming this set mITT set, the statistical reviewer refers to this analysis set as the **all randomized set** throughout this review.
- **Safety analysis set**, which included all randomized subjects who received at least one dose of study treatment. All the safety analyses were conducted using the safety analysis set according to the treatment received.

For the primary efficacy endpoint, the following sensitivity analyses were conducted:

- The treatment difference in terms of time to treatment failure in the ITT set was compared using a proportional hazards model with treatment and baseline immunosuppressant usage as factors.
- The treatment difference in terms of time to treatment failure in the ITT set was compared using a proportional hazards model with treatment, baseline immunosuppressant usage, and baseline prednisone usage (> 20 mg/day, ≤ 20 mg/day) as factors.
- In addition, time to treatment failure was also analyzed using the all randomized set.

In addition, the statistical reviewer also presented the 95% CI for the estimated median time to treatment failure generated by SAS PROC LEFETEST, which was based on Brookmeyer and Crowley's publication "A Confidence Interval for the Median Survival Time" in 1982 on Biometrics.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Two hundred and twenty-three patients were randomized into Study 877, including 111 in the adalimumab group and 112 in the placebo group. The applicant stated that six subjects at two sites (one subject from Brezin, France, Investigator 39656; and five subjects from Flynn, USA, Investigator 39626) were excluded from the ITT analysis set. According to the applicant, the reasons for exclusion were due to incomplete efficacy source data (Brezin) and general compliance issues (Flynn); however, the applicant did not specify clearly whether the decision to exclude subjects from these two sites were made before the database lock or after the database lock. Due to the exclusion, there were 217 subjects (110 in the adalimumab group and 107 in the placebo group) in the ITT set in Study 877.

Upon further review of the data, the statistical reviewer discovered that six subjects from **three** sites (Brezin, France; Flynn, USA; and Kedhar, USA, Investigator 38777) were excluded from

the ITT analysis set (see Table below). These six subjects included three subjects at Flynn site; one subject at Brezin site; and two subjects at Kedhar site. According to the applicant, two subjects (subjects (b) (6) and (b) (6)) transferred from Flynn site to Kedhar site. Additional sensitivity analyses were conducted to examine the impact of the exclusion from two different aspects:

- The applicant conducted analyses included all randomized subjects without any exclusion.
- The statistical reviewer conducted analyses excluding all subjects from these three sites.

Please refer to Section 3.2.4 for detailed discussion of these sensitivity analyses.

Two hundred and twenty-nine patients were randomized into Study 880, including 115 in the adalimumab group and 114 in the placebo group. Three subjects at two sites (one from Brezin, France; and two from Flynn, USA) were excluded from the ITT analysis set due to the same reason as in Study 877. Therefore, there were 226 subjects (115 in the adalimumab group and 114 in the placebo group) in the ITT set in Study 880. The statistical reviewer did not identify any inconsistency in this dataset. Two additional sensitivity analyses the same as Study 877 were conducted to examine the impact of the exclusion. Please refer to Section 3.2.4 for results of these sensitivity analyses.

Table 7: Summary of Analysis Sets (Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Analysis Set	**Placebo**	**Adalimumab**	**Total**	**Placebo**	**Adalimumab**	**Total**
All Randomized	112	111	223	114	115	229
Safety[a]	112	111	223	114	115	229
ITT	107	110	217	111	115	226

[a] The actual treatment received by these subjects was the same as their randomization assignment.
Source: Table 13 of Study 877 Report and Table 13 of Study 880 Report.

In Study 877, among the 217 ITT subjects, 48 subjects (16 [15.0%] in placebo group and 32 [29.0%] in the adalimumab group) completed the study without experiencing a treatment failure. Among these 48 subjects, 16 subjects completed Week 80 visit; while 32 subjects did not complete Week 80 visit because the planned number of treatment failures was reached and these subjects were still considered as completers. Among the ITT subjects, 144 subjects discontinued the study due to treatment failure (84 [78.5%] in the placebo group and 60 [54.5%] in the adalimumab group). A total of 25 subjects (11.5%) discontinued from the study for reasons other than treatment failure, with more subjects in the adalimumab group (18[16.4%]) discontinuing than in the placebo group (7 [6.5%]). The most common reason for discontinuation from the study was adverse event (AE). A total of 13 subjects discontinued study with the primary reason being an AE (3 [2.8%] placebo and 10 [9.1%] adalimumab).

In Study 880, among the 226 ITT subjects, 90 subjects (34 [30.6%] in placebo group and 56 [48.7%] in the adalimumab group) completed the study without experiencing a treatment failure. Among these 90 subjects, 47 subjects completed Week 80 visit; while 43 subjects did not complete Week 80 visit because the planned number of treatment failures was reached and these subjects were still considered as completers. Among the ITT subjects, 106 subjects discontinued the study due to treatment failure (61 [55.0%] in the placebo group and 45 [39.1%] in the adalimumab group). A total of 30 subjects (13.3%) were considered to have discontinued from

the study for reasons other than treatment failure, the percentage of subjects discontinued in the placebo group (16 [14.4%]) was similar to that of subjects discontinued in the adalimumab group (14 [12.2%]). The most common reason for discontinuation from the study was AE. A total of 17 subjects discontinued study treatment with the primary reason being an AE (7 [6.3%] placebo and 10 [8.7%] adalimumab).

Table 8: Disposition of Subjects (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Subjects Who	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
Completed Week 80	4 (3.7%)	12 (10.9%)	16 (7.4%)	17 (15.3%)	30 (26.1%)	47 (20.9%)
Completed < Week 80[a]	12 (11.2%)	20 (18.2%)	32 (14.7%)	17 (15.3%)	26 (22.6%)	43 (19.0%)
Treatment Failure	84 (78.5%)	60 (54.5%)	144 (66.4%)	61 (55.0%)	45 (39.1%)	106 (46.9%)
Discontinued	7 (6.5)	18 (16.4)	25 (11.5)	16 (14.4)	14 (12.2)	30 (13.3)
Reason[b]						
AE	3 (2.8)	10 (9.1)	13 (6.0)	7 (6.3)	10 (8.7)	17 (7.5)
Lack of efficacy	2 (1.9)	1 (0.9)	3 (1.4)	3 (2.7)	0	3 (1.3)
Withdrew consent	0	2 (1.8)	2 (0.9)	3 (2.7)	2 (1.7)	5 (2.2)
Lost to follow-up	0	4 (3.6)	4 (1.8)	3 (2.7)	0	3 (1.3)
Other[c]	3 (2.8)	5 (4.5)	8 (3.7)	3 (2.7)	2 (1.7)	5 (2.2)

a. Subjects who had to terminate the study because the planned number of treatment failures was reached.
b. Subjects who discontinued were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
c. Reasons for discontinuation from the study recorded as "other" included any reason for discontinuation excluding AE, lack of efficacy, withdrew consent, and lost to follow-up.
Source: Table 11 of Study 877 Report and Table 11 of Study 880 Report.

As presented in the following table, there were no noted differences in demographic and baseline characteristics between the treatment groups for both Studies 877 and 880.

Table 9: Demographic and Baseline Characteristics (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Characteristics	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
	n (%)	**n (%)**	**n (%)**			
Gender						
Female	65 (60.7)	59 (53.6)	124 (57.1)	72 (64.9)	66 (57.4)	138 (61.1)
Male	42 (39.3)	51 (46.4)	93 (42.9)	39 (35.1)	49 (42.6)	88 (38.9)
Age						
Mean ± SD	42.6 ± 14.3	42.7 ± 15.6	42.7 ± 14.9	42.2 ± 14.0	42.9 ± 13.0	42.5 ± 13.4
Min, Max	18.0, 79.0	18.0, 81.0	18.0, 81.0	20.0, 79.0	18.0, 75.0	18.0, 79.0
Median	40.0	41.0	41.0	42.0	44.0	43.5
< 40 Years	52 (48.6)	47 (42.7)	99 (45.6)	50 (45.0)	47 (40.9)	97 (42.9)
40 – 64 Years	47 (43.9)	49 (44.5)	96 (44.2)	53 (47.7)	63 (54.8)	116 (51.3)
≥ 65 Years	8 (7.5)	14 (12.7)	22 (10.1)	8 (7.2)	5 (4.3)	13 (5.8)
Race						
White	86 (80.4)	88 (80.0)	174 (80.2)	93 (83.8)	96 (83.5)	189 (83.6)
Black	12 (11.2)	11 (10.0)	23 (10.6)	8 (7.2)	6 (5.2)	14 (6.2)
Asian	2 (1.9)	4 (3.6)	6 (2.8)	3 (2.7)	3 (2.6)	6 (2.7)
American Indian/	1 (0.9)	0	1 (0.5)	1 (0.9)	0	1 (0.4)

Characteristics	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo N=107	Adalimumab N=110	Total N=217	Placebo N=111	Adalimumab N=115	Total N=226
	n (%)	n (%)	n (%)			
Alaska Native						
Other	5 (4.7)	6 (5.5)	11 (5.1)	5 (4.5)	9 (7.8)	14 (6.2)
Multi-race	1 (0.9)	1 (0.9)	2 (0.9)	1 (0.9)	1 (0.9)	2 (0.9)
Ethnicity						
Hispanic or Latino	24 (22.4)	11 (10.0)	35 (16.1)	25 (22.5)	25 (21.7)	50 (22.1)
Non-Hispanic or Latino	83 (77.6)	99 (90.0)	182 (83.9)	86 (77.5)	90 (78.3)	176 (77.9)

Source: Table 14 of Study 877 Report and Table 14 of Study 880 Report.

As presented in the following table, there were no noted differences in uveitis diagnosis and history between the treatment groups for both Studies 877 and 880.

Table 10: Uveitis Diagnosis and History (ITT; Studies 877 and 880)

Characteristics	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo N=107	Adalimumab N=110	Total N=217	Placebo N=111	Adalimumab N=115	Total N=226
Duration of Uveitis Diagnosis (months)						
Mean ± SD	51.0 ± 72.2	40.2 ± 51.3	45.5 ± 62.5	62.9 ± 67.7	59.5 ± 64.5	61.2 ± 65.9
Median	24.1	19.0	21.2	39.3	34.6	37.4
Min, Max	1.2, 554.9	1.5, 305.9	1.2, 554.9	4.1, 393.8	2.4, 381.0	2.4, 393.8
Time Since Last Flare (months)						
Mean ± SD	10.0 ± 14.9	10.3 ± 17.2	10.2 ± 16.1	5.1 ± 3.9	5.7 ± 3.8	5.4 ± 3.9
Median	5.9	5.7	5.8	3.5	4.4	4.1
Min, Max	1.3, 107.7	0.6, 122.6	0.6, 122.6	1.0, 18.9	0.9, 18.0	0.9, 18.9
Duration of Current Flare (months)						
Mean ± SD	72.3 ± 84.4	68.6 ± 94.5	70.4 ± 89.5	N/A	N/A	N/A
Median	44.0	45.0	45.0	N/A	N/A	N/A
Min, Max	0.0, 621.0	7.0, 755.0	0.0, 755.0	N/A	N/A	N/A
Prednisone Dose at Last Flare (mg)						
Mean ± SD	9.9 ± 15.0	12.0 ± 18.0	11.0 ± 16.6	8.2 ± 9.8	8.8 ± 11.5	8.5 ± 10.7
Median	0.0	5.0	2.75	5.0	5.0	5.0
Min, Max	0.0, 60.0	0.0, 80.0	0.0, 80.0	0.0, 60.0	0.0, 60.0	0.0, 60.0
Types of Uveitis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intermediate	23 (21.5)	24 (21.8)	47 (21.7)	30 (27.0)	17 (14.8)	47 (20.8)
Posterior	37 (34.6)	36 (32.7)	73 (33.6)	34 (30.6)	39 (33.9)	73 (32.3)
Panuveitis	47 (43.9)	50 (45.5)	97 (44.7)	46 (41.4)	57 (49.6)	103 (45.6)
Intermediate/ Posterior	0	0	0	1 (0.9)	2 (1.7)	3 (1.3)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Characteristics	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
Diagnosis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Idiopathic	45 (42.1)	36 (32.7)	81 (37.3)	40 (36.0)	29 (25.2)	69 (30.5)
Birdshot choroidopathy	20 (18.7)	24 (21.8)	44 (20.3)	15 (13.5)	15 (13.0)	30 (13.3)
Multifocal choroiditis and panuveitis	3 (2.8)	8 (7.3)	11 (5.1)	2 (1.8)	5 (4.3)	7 (3.1)
Vogt Koyanagi Harada	14 (13.1)	11 (10.0)	25 (11.5)	25 (22.5)	26 (22.6)	51 (22.6)
Sarcoid	8 (7.5)	10 (9.1)	18 (8.3)	14 (12.6)	18 (15.7)	32 (14.2)
Behçet's	4 (3.7)	12 (10.9)	16 (7.4)	6 (5.4)	10 (8.7)	16 (7.1)
Other	13 (12.1)	9 (8.2)	22 (10.1)	9 (8.1)	12 (10.4)	21 (9.3)
Missing	0	0	0	0	0	0
Eye Affected	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Left	5 (4.7)	5 (4.5)	10 (4.6)	3 (2.7)	2 (1.7)	5 (2.2)
Right	3 (2.8)	7 (6.4)	10 (4.6)	4 (3.6)	1 (0.9)	5 (2.2)
Both	99 (92.5)	98 (89.1)	197 (90.8)	104 (93.7)	112 (97.4)	216 (95.6)
Number of Flares in Past 12 Months	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0 – 1	n/a	n/a	n/a	46 (41.4)	48 (41.7)	94 (41.6)
1	19 (17.8)	18 (16.4)	37 (17.1)	n/a	n/a	n/a
2	46 (43.0)	54 (49.1)	100 (46.1)	40 (36.0)	43 (37.4)	83 (36.7)
≥ 3	42 (39.3)	38 (34.5)	80 (36.9)	25 (22.5)	24 (20.9)	49 (21.7)

Source: Table 15 of Study 877 Report and Table 15 of Study 880 Report.

Baseline disease characteristics were summarized in the following table; there were no noted differences between the treatment groups for both Studies 877 and 880.

Table 11: Summary of Baseline Disease Characteristics

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Disease Characteristics	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
	n (%)	**n (%)**	**n (%)**			
AC Cell Grade						
Left Eye						
Mean ± SD	0.61 ± 0.76	0.66 ± 0.88	0.64 ± 0.82	0.10 ± 0.20	0.10 ± 0.20	0.10 ± 0.20
Right Eye						
Mean ± SD	0.65 ± 0.88	0.65 ± 0.84	0.65 ± 0.86	0.10 ± 0.20	0.11 ± 0.21	0.11 ± 0.21
≥ 2+ in at least one eye	27 (25.3)	27 (24.5)	54 (24.9)	N/A	N/A	N/A
≥ 1+ in at least one eye	42 (39.3)	44 (40.0)	86 (39.6)	N/A	N/A	N/A
VH Grade						
Left Eye						
Mean ± SD	0.95 ± 0.77	1.08 ± 0.92	1.02 ± 0.85	0.14 ± 0.23	0.16 ± 0.24	0.15 ± 0.23
Right Eye						
Mean ± SD	1.05 ± 0.86	1.00 ± 0.82	1.02 ± 0.84	0.15 ± 0.23	0.14 ± 0.23	0.14 ± 0.23

Disease Characteristics	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
	Placebo N=107	Adalimumab N=110	Total N=217	Placebo N=111	Adalimumab N=115	Total N=226
	n (%)	n (%)	n (%)			
≥ 2+ in at least one eye	52 (48.6)	55 (50.0)	107 (49.3)	N/A	N/A	N/A
≥ 1+ in at least one eye	72 (67.3)	77 (70.0)	149 (68.7)	N/A	N/A	N/A
Chorioretinal Lesions						
Left Eye	44 (41.1)	44 (40.0)	88 (40.6)	N/A	N/A	N/A
Right Eye	40 (37.4)	46 (41.8)	86 (39.6)	N/A	N/A	N/A
In at least one eye	49 (45.8)	52 (47.3)	101 (46.5)	N/A	N/A	N/A
Retinal Vascular Lesions						
Left Eye	40 (37.4)	45 (40.9)	85 (39.2)	N/A	N/A	N/A
Right Eye	35 (32.7)	39 (35.5)	74 (34.1)	N/A	N/A	N/A
In at least one eye	42 (39.3)	53 (48.2)	95 (43.8)	N/A	N/A	N/A
Log(MAR) BCVA						
Left Eye						
Mean ± SD	0.23 ± 0.29	0.24 ± 0.36	0.24 ± 0.33	0.16 ± 0.29	0.14 ± 0.26	0.15 ± 0.27
Right Eye						
Mean ± SD	0.24 ± 0.30	0.22 ± 0.28	0.23 ± 0.29	0.15 ± 0.27	0.12 ± 0.22	0.13 ± 0.25

Source: Table 14.1_5.2.M of Study 877 Report; Table 14.1_5.2.M of Study 880 Report; and Statistical Reviewer's Summary.

3.2.4 Results and Conclusions

3.2.4.1 Time to Treatment Failure

The primary endpoint was the time to treatment failure for both studies; it was defined as time from randomization to treatment failure (event) or to premature discontinuation or completion (censored observation). Because the study populations were different at baseline, definitions for treatment failure criteria and initial timepoint for measuring the primary efficacy endpoint were different for the two studies (Table 12).

Table 12: Treatment Failure[a] Criteria for Studies 877 and 880

Parameter	Study 877 (Active Disease Study)		Study 880 (Inactive Disease Study)
	Week 6 Visit	All Other Visits After Week 6	Week 2 Visit and All Subsequent Visits
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline
Anterior Chamber (AC) Cell grade (SUN Criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to best state achieved[b]
Vitreous Haze grade (NEI/SUN Criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to best state achieved[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to	Worsening of BCVA by ≥ 15 letters relative to	Worsening of BCVA by ≥ 15 letters relative to best state achieved

	best state achieved	best state achieved	

SUN = Standardization of Uveitis Nomenclature; NEI = National Eye Institute; ETDRS = Early treatment diabetic retinopathy study; BCVA = best corrected visual acuity

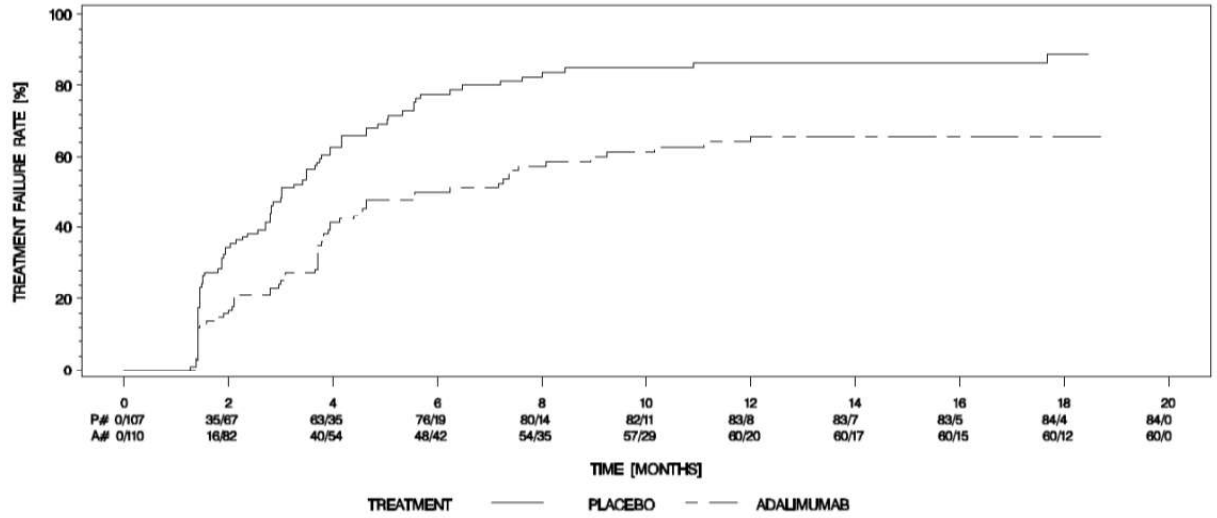
[a] To be considered a treatment failure, at least one of these 4 criteria needed to be present in at least 1 eye.

[b] A 2-step increase was represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+

Source: Table 1 of Summary of Clinical Efficacy.

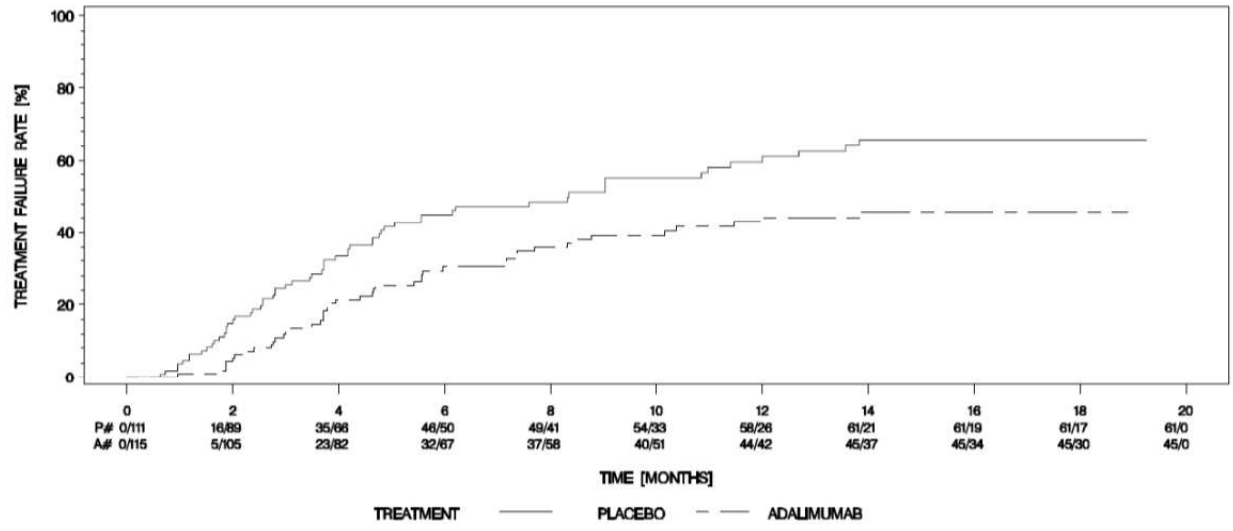
The Kaplan-Meier curves of time-to-treatment failure for both Studies 877 and 880 were presented as follows. The curves indicated a treatment effect in favor of the adalimumab group.

Figure 5: Kaplan-Meier Curve: Time to Treatment Failure (ITT; Study 877)



Note: P# - Placebo (Number of Events/Number at Risk); A# - Adalimumab (Number of Events/Number at Risk).
Source: Figure 3 of Study 877 Report.

Figure 6: Kaplan-Meier Curve: Time to Treatment Failure (ITT; Study 880)



Note: P# - Placebo (Number of Events/Number at Risk); A# - Adalimumab (Number of Events/Number at Risk).
Source: Figure 3 of Study 877 Report.

In Study 877, for the ITT analysis set, the risk of treatment failure for subjects in the adalimumab group was statistically significantly reduced compared to subjects in the placebo group (hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.36, 0.70; $P < 0.001$ from log rank test). The median time to treatment failure was 5.6 months in the adalimumab group compared to subjects in the placebo group who had a median time to treatment failure of 3 months.

In Study 880, for the ITT analysis set, the risk of treatment failure for subjects in the adalimumab group was statistically significantly reduced compared to subjects in the placebo group (HR: 0.57, 95% CI: 0.39, 0.84, $P = 0.004$ from log rank test). The median time to treatment failure for subjects in the placebo group was 8.3 months and for subjects in the adalimumab group was not estimable as more than half of the adalimumab subjects did not experience treatment failure.

Sensitivity analyses using a proportional hazards model with treatment and baseline IMM usage as factors and another hazards model with treatment and baseline IMM and prednisone usage as factors were supportive of the primary efficacy results. Sensitivity analyses based on the all randomized subjects set and all randomized subjects including the Japanese sub-study subjects were consistent with the primary efficacy analyses results.

Table 13: Time to Treatment Failure (Studies 877 and 880)

ITT; Primary						
	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			**Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2**		
	Placebo (N=107)	**Adalimumab (N=110)**	**HR (95% CI)[a]**	**Placebo (N=111)**	**Adalimumab (N=115)**	**HR (95% CI)[a]**
Failure (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.57 (0.39, 0.84)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
ITT; Adjusted for baseline IMM usage						
	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			**Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2**		
	Placebo (N=107)	**Adalimumab (N=110)**	**HR (95% CI)[c]**	**Placebo (N=111)**	**Adalimumab (N=115)**	**HR (95% CI)[c]**
Failure (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.58 (0.39, 0.85)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
ITT; Adjusted for baseline IMM and prednisone usage						
	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			**Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2**		
	Placebo (N=107)	**Adalimumab (N=110)**	**HR (95% CI)[d]**	**Placebo (N=111)**	**Adalimumab (N=115)**	**HR (95% CI)[d]**
Failure (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.56 (0.38, 0.82)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
All Randomized Subjects						
Visit	**Study 877 (Active Uveitis) Time to Treatment Failure At or After Week 6**			**Study 880 (Non-Active Uveitis) Time to Treatment Failure At or After Week 2**		

	Placebo (N=112)	Adalimumab (N=111)	HR (95% CI)[a]	Placebo (N=114)	Adalimumab (N=115)	HR (95% CI)[a]
Failure (n[%])	87 (77.7)	61 (55.5)	0.53 (0.38, 0.74)	63 (55.3)	45 (39.1)	0.56 (0.38, 0.83)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.8]	5.6 [3.9, 8.9]		8.3 [4.8, 12.0]	NE[b]	
All Randomized Including Japanese Sub-Study Subjects						
	Study 877 (Active Uveitis) Time to Treatment Failure At or After Week 6			**Study 880 (Non-Active Uveitis) Time to Treatment Failure At or After Week 2**		
Visit	**Placebo (N=120)**	**Adalimumab (N=119)**	**HR (95% CI)[a]**	**Placebo (N=130)**	**Adalimumab (N=131)**	**HR (95% CI)[a]**
Failure (n[%])	93 (77.5)	69 (58.0)	0.58 (0.42, 0.79)	77 (59.2)	57 (43.5)	0.56 (0.40, 0.80)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.8, 7.4]		5.6 [3.9, 9.0]	NE[b]	

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
[c] HR of adalimumab versus placebo from proportional hazards regression with treatment and IMM use at baseline asfactors.
[d] HR of adalimumab versus placebo from proportional hazards regression with treatment, IMM use at baseline, and prednisone use > 20 versus ≤ 20 mg at baseline as factors.
Source: Table 22 of Study 877 Report and Table 22 of Study 880 Report.

The applicant excluded six subjects at three sites in Study 877 and three subjects at two sites in Study 880 from the primary analyses set due to incomplete efficacy source data and general compliance issues, additional sensitivity analyses were conducted by the statistical reviewer excluding all subjects at three sites in Study 877 and all subjects at two sites in Study 880 without picking and selecting to examine the impact of the exclusion. The results were consistent with the primary results.

Table 14: Statistical Reviewer's Sensitivity Analyses of Time to Treatment Failure Excluding Sites with General Compliance and Source Data Issues (ITT; Studies 877 and 880)

	Study 877 (Active Disease Study) Excluding All Subjects from Investigators 39626, 39656, and 38777 Time to Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Excluding All Subjects from Investigators 39626, and 39656 Time to Treatment Failure At or After Week 2		
Visit	**Placebo (N=104)**	**Adalimumab (N=107)**	**HR (95% CI)[a]**	**Placebo (N=111)**	**Adalimumab (N=114)**	**HR (95% CI)[a]**
Failure (n[%])	81 (77.9)	59 (55.1)	0.52 (0.37, 0.73)	61 (55.0)	45 (39.5)	0.58 (0.39, 0.85)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.8]	5.6 [3.9, 8.9]		8.3 [4.8, 12.0]	NE[b]	

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.

For the analysis of the primary efficacy endpoint, the outcomes for subjects who discontinued the study early were considered as censored regardless the reasons for discontinuation in the applicant's primary analysis.

As presented in Table 15, there were three subjects in Study 877 (two subjects from Placebo group; and one subject from Adalimumab group) and three subjects in Study 880 (all from

Placebo group) who discontinued the study early due to lack of efficacy. The statistical reviewer examined each of the components (active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA) of the primary endpoint. It seemed that these subjects did not satisfy any treatment failure criteria defined in the protocol. For subjects discontinued due to AE in Studies 877 and 880, detailed listings were presented in Table 23 and Table 24 respectively.

Table 15: Summary of Subjects Discontinued Study (ITT; Studies 877 and 880)

	Study 877 (Active Uveitis)			Study 880 (Non-Active Uveitis)		
Subjects Who	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
Discontinued	7 (6.5)	18 (16.4)	25 (11.5)	16 (14.4)	14 (12.2)	30 (13.3)
	Before Week 6 Visit			Before Week 2 Visit		
	1 (0.9)	7 (6.4)	8 (3.7)	1 (0.9)	0	1 (0.4)
Reason[a]						
AE	0	5 (4.5)	5 (2.3)	1 (0.9)	0	1 (0.9)
Lack of Efficacy	0	0	0	1 (0.9)	0	1 (0.9)
Withdrew consent	0	0	0	0	0	0
Lost to follow-up	0	2 (1.8)	2 (0.9)	0	0	0
Other[b]	1 (0.9)	1 (0.9)	2 (0.9)	0	0	0
	On or After Week 6 Visit			On or After Week 2 Visit		
	6 (5.6)	11 (10.0)	17 (7.8)	15 (13.5)	14 (12.2)	29 (12.8)
Reason[a]						
AE	3 (2.8)	5 (4.5)	8 (3.7)	6 (5.4)	10 (8.7)	16 (7.1)
Lack of Efficacy	1 (0.9)	1 (0.9)	2 (0.9)	2 (1.8)	0	2 (0.9)
Withdrew consent	0	0	0	3 (2.7)	2 (1.7)	5 (2.2)
Lost to follow-up	0	2 (1.8)	2 (0.9)	3 (2.7)	0	3 (1.3)
Other[b]	2 (1.9)	4 (3.6)	8 (2.8)	3 (2.7)	2 (1.7)	5 (2.2)

[a] Subjects were counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
[b] Reasons for discontinuation from the study recorded as "other" included any reason for discontinuation excluding AE, lack of efficacy, withdrew consent, and lost to follow-up.
Source: Table 11 of Study 877 Report and Table 11 of Study 880 Report; Statistical Reviewer's Summary.

In the applicant primary analysis, the outcomes for subjects who discontinued the study early were considered as censored; (b) (4) the applicant assumed the dropouts were not related with the efficacy outcomes. Although this assumption could not be verified, to examine the impact of the discontinuation on the primary efficacy endpoint, three additional sensitivity analyses were conducted by the statistical reviewer based on the following imputation strategy for subjects who discontinued study early:

- Sensitivity Analysis 1:
  - For subjects (in both placebo and adalimumab groups) discontinued due to lack of efficacy, "treatment failures" (events) were imputed for their primary efficacy outcomes; time to treatment failure were imputed as time to event/censored recorded.
  - For subjects discontinued due to reasons other than lack of efficacy, the following "worst case" imputation was utilized:
    - Placebo-treated subjects were imputed as censored, time to censor were imputed as time to event/censored recorded.

    - For adalimumab-treated subjects, "treatment failures" (events) were imputed for their primary efficacy outcomes; time to treatment failure were imputed as time to event/censored recorded.
- Sensitivity Analysis 2: subjects who discontinued study were all considered as treatment failure (events) for both treatment groups; time to treatment failure were imputed as time to event/censored recorded.
- Sensitivity Analysis 3:
    - All discontinued subjects in the placebo group were imputed as censored for their primary efficacy outcomes; time to censor were imputed as time to event/censored recorded.
    - "Treatment failures" (events) were imputed for all discontinued subjects in the adalimumab group as their primary efficacy outcomes; time to treatment failure were imputed as time to event/censored recorded.

The results of this sensitivity analysis were supportive of the primary efficacy results (Table 16).

Table 16: Statistical Reviewer's Sensitivity Analyses of Time to Treatment Failure (ITT; Studies 877 and 880)

	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2		
Visit	**Placebo (N=107)**	**Adalimumab (N=110)**	**HR (95% CI)[a]**	**Placebo (N=111)**	**Adalimumab (N=115)**	**HR (95% CI)[a]**
Sensitivity Analysis 1						
Failure (n[%])	86 (80.4)	78 (70.9)	0.63 (0.46, 0.86)	64 (57.7)	59 (51.3)	0.71 (0.50, 1.00)
Median Time to Failure (Months) [95% CI]	3.0 [2.6, 3.7]	4.5 [3.7, 7.3]		7.6 [4.8, 11.4]	13.1 [7.7, NE[b]]	
Sensitivity Analysis 2						
Failure (n[%])	91 (85.0)	78 (70.9)	0.59 (0.44, 0.81)	77 (69.4)	59 (51.3)	0.58 (0.42, 0.82)
Median Time to Failure (Months) [95% CI]	3.0 [2.5, 3.7]	4.5 [3.7, 7.3]		5.6 [4.6, 9.0]	13.1 [7.7, NE[b]]	
Sensitivity Analysis 3						
Failure (n[%])	84 (78.5)	78 (70.9)	0.65 (0.47, 0.88)	61 (55.0)	59 (51.3)	0.74 (0.52, 1.06)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	4.5 [3.7, 7.3]		7.6 [4.8, 11.4]	13.1 [7.7, NE[b]]	

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable.
Source: Statistical reviewer's calculation.

The applicant also presented the proportions of subjects who met at least 1 of the 4 pre-specified reasons for treatment failure, in both studies these proportions were higher in the placebo group compared to adalimumab.

Table 17: Number of Reasons Met for Treatment Failure (ITT; Studies 877 and 880)

	Study 877 (Active Disease Study) Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Treatment Failure At or After Week 2		
Number of Reasons Met	**Placebo N=107**	**Adalimumab N=110**	**Total N=217**	**Placebo N=111**	**Adalimumab N=115**	**Total N=226**
0	23 (21.5)	50 (45.5)	73 (33.6)	50 (45.0)	70 (60.9)	120 (53.1)
1	53 (49.5)	43 (39.1)	96 (44.2)	44 (39.6)	32 (27.8)	76 (33.6)

Number of Reasons Met	Study 877 (Active Disease Study) Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Treatment Failure At or After Week 2		
	Placebo N=107	Adalimumab N=110	Total N=217	Placebo N=111	Adalimumab N=115	Total N=226
2	19 (17.8)	14 (12.7)	33 (15.2)	14 (12.6)	11 (9.6)	25 (11.1)
3	10 (9.3)	3 (2.7)	13 (6.0)	3 (2.7)	2 (1.7)	5 (2.2)
4	2 (1.9)	0	2 (0.9)	0	0	0

Source: Table 23 of Study 877 Report and Table 23 of Study 880 Report.

In addition, time to treatment failure was analyzed for each of the components (active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA) of the primary endpoint. These results were supportive of the primary efficacy results.

Table 18: Time to Treatment Failure for Components of the Primary Endpoint (ITT; Studies 877 and 880)

Component	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2		
	Placebo	Adalimumab	HR (95% CI)[a]	Placebo	Adalimumab	HR (95% CI)[a]
Active Inflammatory Lesions						
All ITT Subjects (N=217)				All ITT Subjects (N=226)		
Median Time to Failure (Months)	8	NE[b]	0.38 (0.21, 0.69)	NE[b]	NE[b]	0.55 (0.26, 1.15)
Failure (n/N [%])	29/107 (27.1)	17/110 (15.5)		17/111 (15.3)	12/115 (10.4)	
Subjects with active inflammatory lesions at Baseline (N = 143)						
Median Time to Failure (Months)	5.3	NE[b]	0.36 (0.19, 0.68)			
Failure (n/N [%])	25/63 (39.7)	17/80 (21.3)				
AC Cell Grade						
All ITT Subjects (N=217)				All ITT Subjects (N=226)		
Median Time to Failure (Months)	NE[b]	NE[b]		NE[b]	NE[b]	
Failure (n/N [%])	34/107 (31.8)	24/110 (21.8)	0.51 (0.30, 0.86)	30/111 (27.0)	27/115 (23.5)	0.70 (0.42, 1.18)
Subjects with AC cell grade ≥ 1 at Baseline (N = 86)						
Median Time to Failure (Months)	4.2	7.4				
Failure (n/N [%])	20/42 (47.6)	19/44 (43.2)	0.50 (0.26, 0.96)			
VH Grade						
All ITT Subjects (N=217)				All ITT Subjects (N=226)		
Median Time to Failure (Months)	6.2	NE[b]		NE[b]	NE[b]	
Failure (n/N [%])	39/107 (36.4)	16/110 (14.5)	0.32 (0.18, 0.58)	11/111 (9.9)	11/115 (9.6)	0.79 (0.34, 1.81)
Subjects with VH grade ≥ 1 at Baseline (N = 149)						
Median Time to Failure (Months)	5.7	NE[b]				
Failure (n/N [%])	33/72 (45.8)	15/77 (19.5)	0.36 (0.19, 0.66)			
Subjects with VH grade ≥ 2 at Baseline (N = 107)						
Median Time to Failure (Months)	5.6	NE[b]				
Failure (n/N [%])	26/52 (50.0%)	11/55 (20.0%)	0.32 (0.15, 0.64)			
logMAR BCVA						

Component	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2		
	Placebo	Adalimumab	HR (95% CI)[a]	Placebo	Adalimumab	HR (95% CI)[a]
All ITT Subjects (N=217)				All ITT Subjects (N=226)		
Median Time to Failure (Months)	10.9	NE[b]		NE[b]	NE[b]	
Failure (n/N [%])	27/107 (25.2)	23/110 (20.9)	0.56 (0.32, 0.98)	23/111 (20.7)	10/115 (8.7)	0.33 (0.16, 0.70)

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
Source: Table 25 of Study 877 Report and Table 24 of Study 880 Report.

In conclusion, both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients treated with placebo.

3.2.4.2 Ranked Secondary Efficacy Variables

In Study 877, among the nine ranked secondary efficacy variables, statistical significance in favor of adalimumab versus placebo for the following first three secondary efficacy endpoints was observed:

- Change in AC cell grade from best state achieved to Final/Early Termination visit
- Change in VH grade from best state achieved to Final/Early Termination visit
- Change in logMAR BCVA from best state achieved to Final/Early Termination visit

In Study 880, none of the nine ranked secondary efficacy endpoints achieved statistical significance.

Table 19: Summary of Efficacy Results for Ranked Secondary Efficacy Endpoints (ITT; Studies 877 and 880)

Secondary Endpoint	Study 877 (Active Disease Study)				Study 880 (Inactive Disease Study)			
	Placebo		Adalimumab		Placebo		Adalimumab	
	n[a]	Mean	n	Mean	n	Mean	n	Mean
1. Change in AC cell grade in each eye from best state achieved prior to Week 6 to the final/early termination visit					1. Change in AC cell grade in each eye from baseline to Final/Early Termination visit (LOCF)			
Left Eye	102	0.59	101	0.35	110	0.57	115	0.41
Right Eye	102	0.69	101	0.36	110	0.53	115	0.40
Diff (Adalimumab –Placebo) (95% CI)[b]		-0.29 (-0.51, -0.07)				–0.14 (–0.37, 0.08)		
2. Change in VH grade in each eye from best state achieved prior to Week 6 to the final/early termination visit					2. Change in VH grade in each eye from baseline to Final/Early Termination visit (LOCF)			
Left Eye	103	0.33	101	0.11	110	0.33	115	0.16
Right Eye	103	0.45	101	0.13	110	0.27	115	0.18
Diff (Adalimumab –Placebo) (95% CI)[b]		-0.27 (-0.43, -0.11)				–0.13 (–0.28, 0.01)		
3. Change in logMAR BCVA in each eye from best state achieved prior to Week 6 to the final/early termination visit					3. Change in logMAR BCVA in each eye from baseline to Final/Early Termination visit (LOCF)			
Left Eye	103	0.12	101	0.07	110	0.06	115	0.01
Right Eye	103	0.13	101	0.04	110	0.02	115	-0.01

Secondary Endpoint	Study 877 (Active Disease Study)				Study 880 (Inactive Disease Study)			
	Placebo		Adalimumab		Placebo		Adalimumab	
	n[a]	Mean	n	Mean	n	Mean	n	Mean
Diff (Adalimumab –Placebo) (95% CI)[b]	-0.07 (-0.11, -0.02)				–0.04 (–0.08, 0.01)			
4. Time to OCT evidence of macular edema (months) in at least 1 eye on or after Week 6 (only in subjects without macular edema at Baseline)					4. Time to OCT evidence of macular edema based on CRT (months; median) in at least 1 eye at or after Week 2 (only in subjects without macular edema at baseline)			
	45	6.2	55	11.1	95	NE[c]	90	NE
HR (95% CI)[1]	0.70 (0.39, 1.26)				0.75 (0.34, 1.69)			
5. Percent change in central retinal thickness in each eye from best state achieved prior to Week 6 to the final/early termination visit					5. Percent change in CRT in each eye from baseline to Final/Early Termination visit (LOCF)			
Left Eye	100	20.2	100	9.6	107	6.4	114	4.5
Right Eye	102	22.0	101	8.2	108	7.7	113	5.4
Diff (Adalimumab –Placebo) (95% CI)[b]	-11.4 (-20.9, -1.8)				–2.3 (–8.5, 3.8)			
6. Change in VFQ-25 total score from best state achieved prior to Week 6 to the final/early termination visit					6. Change in VFQ-25 total score from baseline to Final/Early Termination visit (LOCF)			
	102	-5.50	101	-1.30	109	1.24	115	3.36
Diff (Adalimumab –Placebo) (95% CI)[2]	4.20 (1.02, 7.38)				2.12 (–0.84, 5.08)			
7. Change in VFQ-25 subscore distance vision from best state achieved prior to Week 6 to the final/early termination visit					7. Change in VFQ-25 subscore distance vision from baseline to Final/Early Termination visit (LOCF)			
	102	-5.64	101	-3.77	109	0.76	115	2.64
Diff (Adalimumab –Placebo) (95% CI)[2]	1.86 (-2.03, 5.75)				1.88 (–2.53, 6.29)			
8. Change in VFQ-25 subscore near vision from best state achieved prior to Week 6 to the final/early termination visit					8. Change in VFQ-25 subscore near vision from baseline to Final/Early Termination visit (LOCF)			
	102	-8.09	101	-2.97	109	3.98	115	3.88
Diff (Adalimumab –Placebo) (95% CI)[2]	5.12 (0.34, 9.90)				–0.10 (–4.81, 4.61)			
9. Change in VFQ-25 subscore ocular pain from best state achieved prior to Week 6 to the final/early termination visit					9. Change in VFQ-25 subscore ocular pain from baseline to Final/Early Termination visit (LOCF)			
	102	-12.62	101	2.60	109	2.87	115	3.42
Diff (Adalimumab –Placebo) (95% CI)[2]	10.02 (4.86, 15.19)				0.56 (–4.56, 5.68)			

[a] For each endpoint, n = number of subjects with non-missing value.
[b] From ANOVA of change from baseline to Final/Early Termination visit with treatment as factor adjusted for clustered observations.
[c] Median time to macular edema was not estimable. Fewer than half of at-risk subjects had an event.
[1] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor; and 95% confidence interval for HR.
[2] From ANOVA of change from baseline to Final/Early Termination visit with treatment as factor
Source: Table 26 of Study 877 Report and Table 25 of Study 880 Report.

Since the change from best state achieved to Final/Early Termination visit was not straightforward to understand, the statistical reviewer also analyzed the following endpoints in Study 877 post-hocly:

- Change in AC cell grade from baseline to Final/Early Termination visit
- Change in VH grade from baseline to Final/Early Termination visit
- Change in BCVA in letters at 4 meters from baseline to Final/Early Termination visit

These results were supportive of the analyses results of the first three secondary endpoints in Study 877.

Table 20: Efficacy Results for Change from Baseline in AC Cell Grades, VH Grades, and BCVA in letters at 4 Meters (ITT; Studies 877)

	Study 877 (Active Disease Study)			
	Placebo		Adalimumab	
Endpoint	**n[a]**	**Mean**	**n**	**Mean**
1. Change in AC cell grade in each eye from baseline to Week 6 to the final/early termination visit				
Left Eye (Mean ± SD)	102	0.11 ± 0.95	101	-0.21 ± 0.94
Right Eye (Mean ± SD)	102	0.18 ± 1.18	101	-0.17 ± 0.82
Diff (Adalimumab –Placebo) (95% CI)[b]		-0.34 (-0.58, -0.10)		
2. Change in VH grade in each eye from baseline to Week 6 to the final/early termination visit				
Left Eye (Mean ± SD)	103	-0.22 ± 0.83	101	-0.65 ± 0.92
Right Eye (Mean ± SD)	103	-0.27 ± 0.93	101	-0.56 ± 0.93
Diff (Adalimumab –Placebo) (95% CI)[b]		-0.36 (-0.57, -0.16)		
3. Change in BCVA in letters at 4 meters in each eye from baseline to the final/early termination visit				
Left Eye	102	-0.13 ± 8.30	101	1.55 ± 9.52
Right Eye	102	0.32 ± 9.05	101	3.51 ± 7.13
Diff (Adalimumab –Placebo) (95% CI)[b]		2.43 (0.55, 4.32)		

[a] For each endpoint, n = number of subjects with non-missing value.
[b] From ANOVA of change from baseline to Final/Early Termination visit with treatment as factor adjusted for clustered observations.
Source: Statistical Reviewer's Analyses.

In summary, analyses results of these ranked secondary efficacy endpoints and statistical reviewer's post-hoc analyses were supportive of the primary efficacy results.

3.3 Evaluation of Safety

For both Studies 877 and 880, mean and median durations of treatment were higher in the adalimumab group compared to the placebo group. According to the applicant, the interpretation of the safety data should take this difference into consideration. The statistical reviewer agreed with the applicant that mean and median durations of treatment were higher in the adalimumab group in both studies; however the statistical reviewer deferred to the clinical review team regarding the clinical meaning of this difference on the safety data.

Table 21: Extent of Exposure (Safety Set; Studies 877 and 880)

	Study 877 (Active Disease Study)		Study 880 (Inactive Disease Study)	
	Placebo	Adalimumab	Placebo	Adalimumab
Exposure to Study Drug	**N=112**	**N=111**	**N=114**	**N=115**
Total number of doses received				
Mean ± SD	11.7 ± 9.93	15.9 ± 12.46	17.6 ± 13.00	22.7 ± 14.08
Median (min – max)	8 (2 – 42)	11 (2 – 43)	12.0 (2 – 42)	19.0 (2 – 42)
Duration of treatment (days)				
Mean ± SD	144.3 ± 139.21	205.4 ± 175.80	227.4 ± 184.07	300.2 ± 198.88
Median (min – max)	91.0 (14 – 567)	133.0 (14 – 570)	155.0 (14 – 591)	245.0 (14 – 576)
Duration of exposure (days) (n[%])				
1 – 28	4 (3.6)	5 (4.5)	6 (5.3)	2 (1.7)
29 – 56	22 (19.6)	17 (15.3)	11 (9.6)	4 (3.5)

Exposure to Study Drug	Study 877 (Active Disease Study)		Study 880 (Inactive Disease Study)	
	Placebo	Adalimumab	Placebo	Adalimumab
	N=112	N=111	N=114	N=115
57 – 112	39 (34.8)	22 (19.8)	23 (20.2)	18 (15.7)
113 – 168	21 (18.8)	20 (18.0)	19 (16.7)	19 (16.5)
169 – 224	7 (6.3)	8 (7.2)	12 (10.5)	10 (8.7)
225 – 280	6 (5.4)	9 (8.1)	8 (7.0)	9 (7.8)
281 – 336	2 (1.8)	4 (3.6)	4 (3.5)	6 (5.2)
337 – 392	1 (0.9)	7 (6.3)	7 (6.1)	7 (6.1)
393 – 448	1 (0.9)	2 (1.8)	4 (3.5)	3 (2.6)
449 – 504	2 (1.8)	2 (1.8)	1 (0.9)	3 (2.6)
≥ 505	7 (6.3)	15 (13.5)	19 (16.7)	34 (29.6)

Source: Table 36 of Study 877 Report and Table 34 of Study 880 Report.

In Study 877, one death due to chronic renal failure was reported in a subject randomized to adalimumab; the investigator considered the event not related to study drug. In Study 880, one death due to aortic dissection and cardiac tamponade was reported post-treatment (Day 54 [18 days after last dose]) in a subject randomized to adalimumab; the investigator considered the events to be not related to study drug.

In both studies, a higher percentage of subjects in the adalimumab group (9.9% in Study 877; and 8.7% in Study 880) experienced treatment-emergent adverse events (TEAEs) leading to the discontinuation of study treatment (adalimumab) compared with the placebo group (3.6% in Study 877; and 6.1% in Study 880).

Table 22: Summary of Deaths and Adverse Events of Studies 877 and 880 (Safety Analysis Set)

	Study 877 (Active Disease Study)		Study 880 (Inactive Disease Study)	
	Placebo	Adalimumab	Placebo	Adalimumab
	N=112 n (%)	N=111 n (%)	N=114 n (%)	N=115 n (%)
Death due to AE	0	1 (0.9)	0	1 (0.9)
Patients discontinued due to treatment-emergent adverse event (TEAE)	4 (3.6)	11 (9.9)	7 (6.1)	10 (8.7)
Patients with at least 1 treatment-emergent adverse event	88 (78.6)	94 (84.7)	96 (84.2)	105 (91.3)
Most frequent treatment-emergent adverse events (reported by 5% or more of the patients in either treatment group)				
Nasopharyngitis	8 (7.1)	21 (18.9)	19 (16.7)	18 (15.7)
Fatigue	7 (6.3)	12 (10.8)	9 (7.9)	14 (12.2)
Headache	15 (13.4)	12 (10.8)	17 (14.9)	17 (14.8)
Uveitis[b]	8 (7.1)	11 (9.9)	9 (7.9)	6 (5.2)
Arthralgia	11 (9.8)	10 (9.0)	12 (10.5)	27 (23.5)
Back pain	2 (1.8)	9 (8.1)	7 (6.1)	9 (7.8)
Eye pain	2 (1.8)	9 (8.1)	6 (5.3)	9 (7.8)
Vision blurred	2 (1.8)	8 (7.2)	6 (5.3)	4 (3.5)
Bronchitis	4 (3.6)	7 (6.3)	6 (5.3)	3 (2.6)
Cough	4 (3.6)	7 (6.3)	6 (5.3)	11 (9.6)
Hyperhidrosis	3 (2.7)	7 (6.3)	0	2 (1.7)
Muscle spasms	4 (3.6)	7 (6.3)	1 (0.9)	2 (1.7)
Urinary tract infection	0	7 (6.3)	10 (8.8)	13 (11.3)

	Study 877 (Active Disease Study)		Study 880 (Inactive Disease Study)	
	Placebo	Adalimumab	Placebo	Adalimumab
	N=112 n (%)	N=111 n (%)	N=114 n (%)	N=115 n (%)
Nausea	7 (6.3)	6 (5.4)	9 (7.9)	4 (3.5)
Paraesthesia	0	6 (5.4)	1 (0.9)	4 (3.5)
Pain in extremity	2 (1.8)	3 (2.7)	3 (2.6)	10 (8.7)
Upper respiratory tract infection	4 (3.6)	5 (4.5)	3 (2.6)	10 (8.7)
Alanine aminotransferase increased	2 (1.8)	1 (0.9)	1 (0.9)	8 (7.0)
Injection site pain	4 (3.6)	2 (1.8)	9 (7.9)	8 (7.0)
Insomnia	8(7.1)	5 (4.5)	3 (2.6)	8 (7.0)
Sinusitis	1 (0.9)	4 (3.6)	4 (3.5)	8 (7.0)
Cystoid macular oedema	6 (5.4)	3 (2.7)	7 (6.1)	7 (6.1)
Hypertension	1 (0.9)	4 (3.6)	5 (4.4)	7 (6.1)
Aspartate aminotransferase increased	1 (0.9)	1 (0.9)	1 (0.9)	6 (5.2)
Myalgia	2 (1.8)	5 (4.5)	2 (1.8)	6 (5.2)
Visual acuity reduced	3 (2.7)	4 (3.6)	10 (8.8)	6 (5.2)

[b] Worsening of a pre-existing condition or illness was considered an AE.
Source: Tables 37, 38, and 14.3_1.3.1.M of Study 877 Report; Tables 35, 36, and of Study 880 Report.

In Study 877, 4 (3.6%) subjects in placebo group and 11 (9.9%) subjects in adalimumab group discontinued study treatment (adalimumab or placebo) due to a TEAE. The list of these subjects was presented as follows.

Table 23: List of Subjects with TEAEs Leading to Study Treatment Discontinuation (Study 877; Safety Set)

Subject Number	AE	Severity	Serious (Y/N)	Relationship to Study Treatment per the Investigator
Adalimumab				
(b) (6)	Lupus-like syndrome	Severe	Y	Probably related
	Demyelination	Severe	Y	Probably related
	Tuberculosis	Severe	Y	Possibly related
	Fatigue	Mild	N	Possibly related
	Malaise	Mild	N	Possibly related
	Mycobacterium TB complex test positive	Mild	N	Probably related
	Suicidal ideation	Severe	N	Probably not related
	Vision blurred	Moderate	N	Possibly related
	Visual acuity reduced	Moderate	N	Possibly related
	Light chain analysis increased	Mild	N	Not related
	Renal failure chronic	Severe	Y	Not related
	Glioblastoma multiforme	Mild	Y	Probably related
	Choroidal neovascularization	Moderate	N	Probably not related
Placebo				
(b) (6)	Hepatitis acute	Moderate	Y	Probably related
	Cystoid macular edema	Moderate	N	Not related
	Drug intolerance	Moderate	N	Not related
	Deposit eye	Moderate	N	Not related
	Vitreous detachment	Moderate	N	Not related

Source: Table 46 of Study 877 Report.

In Study 880, 7 (6.1%) subjects in placebo group and 10 (8.7%) subjects in adalimumab group discontinued study treatment (adalimumab or placebo) due to a TEAE. The list of these subjects was presented in the following table.

Table 24: List of Subjects with TEAEs Leading to Study Treatment Discontinuation (Study 880; Safety Set)

Subject Number	AE	Severity	Serious (Y/N)	Relationship to Study Treatment per the Investigator
Adalimumab				
(b) (6)	Mycobacterium TB complex test positive	Mild	N	Not related
	Bronchitis	Moderate	Y	Probably not related
	Mycobacterium TB complex test positive	Mild	N	Probably related
	Status migrainosus	Severe	Y	Probably not related
	Neutropenia	Moderate	Y	Probably related
	Hepatic steatosis	Moderate	Y	Possibly related
	Mycobacterium TB complex test positive	Mild	N	Not related
	Dermatitis	Moderate	N	Probably related
	Aortic dissection	Severe	Y	Not related
	Cardiac tamponade			
	Pulmonary sarcoidosis	Moderate	N	Probably not related
Placebo				
(b) (6)	Pulmonary sarcoidosis	Moderate	N	Probably not related
	Mycobacterium TB complex test positive	Moderate	N	Probably related
	Macular oedema	Moderate	N	Not related
	Colon adenoma	Moderate	N	Not related
	Rash macular	Mild	N	Probably related
	Color blindness acquired	Moderate	N	Possibly related
	Dermatitis allergic	Moderate	N	Probably related

Source: Table 43 of Study 880 Report.

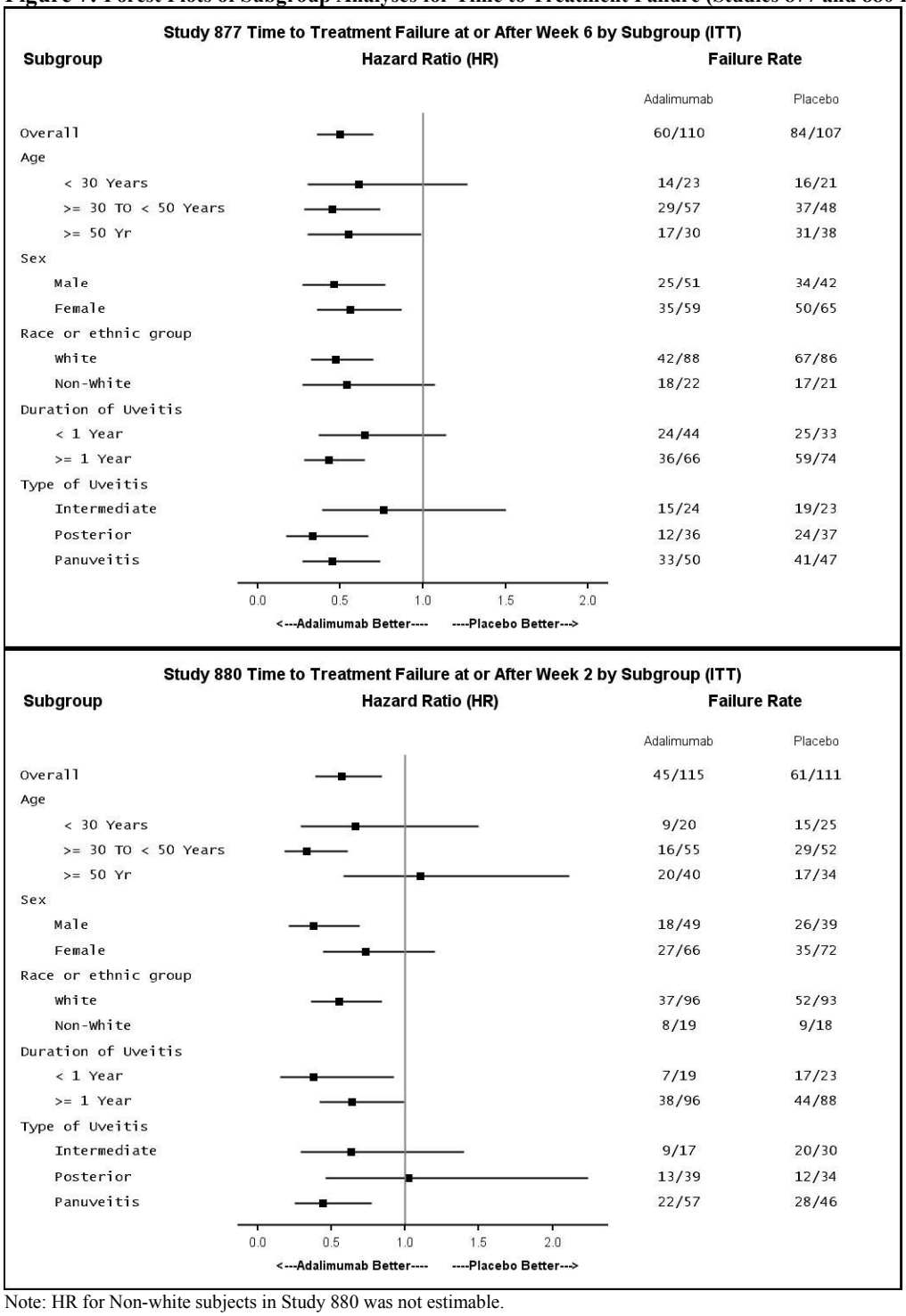
According to the applicant, no new safety signals were identified in both studies; and the AE profile was consistent with the safety profile established across the approved indications of adalimumab. Please refer to the review of the medical reviewer for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Duration of Uveitis, and Type of Uveitis

Subgroup analyses based on gender, race, age, duration of uveitis, and type of uveitis were performed. In Study 880, adalimumab-treated subjects had similar risk of treatment failure compared to placebo subjects for those who were 50 years or older and for those who had posterior uveitis. Other than these two sub-groups in Study 880, in general, there were no marked differences in the efficacy results among the various subpopulations.

Figure 7: Forest Plots of Subgroup Analyses for Time to Treatment Failure (Studies 877 and 880 ITT)



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the two pivotal studies submitted.

For the analysis of the primary efficacy endpoint, the outcomes for subjects who discontinued the study early were considered as censored. In Study 877, 25 subjects (11.5%) discontinued from the study early, with more subjects in the adalimumab group (18[16.4%]) discontinuing than in the placebo group (7 [6.5%]). In Study 880, 30 subjects (13.3%) discontinued from the study early; the percentage of subjects discontinued in the placebo group (16 [14.4%]) was similar to that of subjects discontinued in the adalimumab group (14 [12.2%]). The most common reason for discontinuation from the studies was AE (see Table 8: Disposition of Subjects (ITT; Studies 877 and 880) for details).

(b) (4)

the applicant assumed the dropouts were not related with the efficacy outcomes. Although this assumption could not be verified, to examine the impact of the discontinuation (dropouts) on the primary efficacy endpoint, additional sensitivity analyses were conducted by the statistical reviewer based on the different imputation strategy for subjects who discontinued study early (see Section 3.2.4 for detailed discussion). The results of these additional sensitivity analyses were supportive of the primary efficacy results. Therefore, the statistical reviewer did not consider it had any major impact on the final conclusion.

5.2 Collective Evidence

In Study 877, the median time to treatment failure was 3 months (95% CI: [2.7, 3.7]) in the placebo group, and the median time to treatment failure was 5.6 months (95% CI: [3.9, 9.2]) in the adalimumab group. The hazard ratio comparing adalimumab group to placebo group was 0.50, 95% CI: [0.36, 0.70] with p-value < 0.001 from the log-rank test.

In Study 880, the median time to treatment failure for subjects in the placebo group was 8.3 months (95% CI: [4.8, 12.0]) and for subjects in the adalimumab group was not estimable as more than half of the adalimumab subjects did not experience treatment failure. The hazard ratio comparing adalimumab group to placebo group was 0.57 with a 95% CI [0.39, 0.84] with p-value = 0.004 from the log rank test.

Time to treatment failure was analyzed for each of the components (active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA) of the primary endpoint; the results were supportive of the primary efficacy results (See Table 18 in Section 3.2.4).

Sensitivity analyses based on the all randomized analysis set and all randomized subjects including the Japanese sub-study subjects were consistent with the primary efficacy analyses results.

Table 25: Time to Treatment Failure (Studies 877 and 880)

ITT						
	Study 877 (Active Disease Study) Time to Treatment Failure At or After Week 6			Study 880 (Inactive Disease Study) Time to Treatment Failure At or After Week 2		
Visit	Placebo (N=107)	Adalimumab (N=110)	HR (95% CI)[a]	Placebo (N=111)	Adalimumab (N=115)	HR (95% CI)[a]
Median Time to Failure (Months)	3.0	5.6	0.50 (0.36, 0.70)	8.3	NE[b]	0.57 (0.39, 0.84)
Failure (n[%])	84 (78.5)	60 (54.5)		61 (55.0)	45 (39.1)	
All Randomized Subjects						
	Study 877 (Active Uveitis) Time to Treatment Failure At or After Week 6			Study 880 (Non-Active Uveitis) Time to Treatment Failure At or After Week 2		
Visit	Placebo (N=112)	Adalimumab (N=111)	HR (95% CI)[a]	Placebo (N=114)	Adalimumab (N=115)	HR (95% CI)[a]
Median Time to Failure (Months)	3.0	5.6	0.53 (0.38, 0.74)	8.3	NE[b]	0.56 (0.38, 0.83)
Failure (n[%])	87 (77.7)	61 (55.5)		63 (55.3)	45 (39.1)	
All Randomized Including Japanese Sub-Study Subjects						
	Study 877 (Active Uveitis) Time to Treatment Failure At or After Week 6			Study 880 (Non-Active Uveitis) Time to Treatment Failure At or After Week 2		
Visit	Placebo (N=120)	Adalimumab (N=119)	HR (95% CI)[a]	Placebo (N=130)	Adalimumab (N=131)	HR (95% CI)[a]
Median Time to Failure (Months)	3.0	4.6	0.58 (0.42, 0.79)	5.4	NE[b]	0.56 (0.40, 0.80)
Failure (n[%])	93 (77.5)	69 (58.0)		77 (59.2)	57 (43.5)	

[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.
Source: Table 22 of Study 877 Report and Table 22 of Study 880 Report; and statistical reviewer's analyses.

5.3 Conclusions and Recommendations

In conclusion, results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients treated with placebo for active disease subjects (Study 877) and inactive disease subjects (Study 880).

5.4 Labeling Recommendations

The applicant proposed to include the four components of the treatment failure in the label. The statistical reviewer considered it was acceptable; (b) (4) these components be not included in the label and 95% CI for the HR be presented. The statistical reviewer proposes that Table 17 and Table 18 in the clinical studies section are combined and presented in the following mock-up table.

Treatment Failure and Its Components in Study UV I and UV II

	UV I			UV II		
	Placebo (N=107)	**Adalimumab (N=110)**	**HR (95% CI)[a]**	**Placebo (N=111)**	**Adalimumab (N=115)**	**HR (95% CI)[a]**
Failure[1] (n[%])	84 (78.5)	60 (54.5)	0.50 (0.36, 0.70)	61 (55.0)	45 (39.1)	0.57 (0.39, 0.84)
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]		8.3 [4.8, 12.0]	NE[b]	
Component of Treatment Failure						
New Active Inflammatory Lesions						
Events, n (%)	29 (27.1)	17 (15.5)	0.38 (0.21, 0.69)	17 (15.3)	12 (10.4)	0.55 (0.26, 1.15)
Anterior Chamber Cell Grade						
Events[2], n (%)	34 (31.8)	24 (21.8)	0.51 (0.30, 0.86)	30 (27.0)	27 (23.5)	0.70 (0.42, 1.18)
Vitreous Haze Grade						
Events[2], n (%)	39 (36.4)	16 (14.5)	0.32 (0.18, 0.58)	11 (9.9)	11 (9.6)	0.79 (0.34, 1.81)
Worsening of BCVA by ≥ 15 Letters Relative to Best State Achieved						
Events, n (%)	27 (25.2)	23 (20.9)	0.56 (0.32, 0.98)	23 (20.7)	10 (8.7)	0.33 (0.16, 0.70)

[1] Treatment failure at or after Week 6 in Study 877, or at or after Week 2 in Study 880, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
[2] Study 877: Inability to achieve ≤ 0.5[+] at Week 6 and/or 2-step increase relative to best state achieved after Week 6; Study 880: 2-step increase relative to best state achieved at or after Week 2.
[a] HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
[b] NE = not estimable. Fewer than half of at-risk subjects had an event.

(b) (4)

[redacted]

Without supporting evidence from Study 880, the statistical reviewer recommended to delete this paragraph from the labeling.

Appendix 1: Protocol Defined Exclusion Criteria

For Study 877, the protocol-defined key exclusion criteria were:

- Subject had isolated anterior uveitis.
- Subject had prior inadequate response to high-dose oral corticosteroids.
- Subject had confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to tuberculosis (TB), cytomegalovirus, Lyme disease, toxoplasmosis, human T-lymphotropic virus type 1 infection, Whipple's disease, herpes zoster virus, and herpes simplex virus.
- Subject had presumed ocular histoplasmosis syndrome.
- Subject had ocular masquerade syndromes, such as ocular lymphoma.
- Subject had serpiginous choroidopathy.
- Subject had a contraindication to pupil dilation with mydriatic eyedrops.
- Subject had corneal or lens opacity that precluded visualization of the fundus or that likely required cataract surgery during the duration of the study.
- Subject had intraocular pressure of $\geq$ 25 mmHg and on $\geq$ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
- Subject had Best Corrected Visual Acuity (BCVA) less than 20 letters (Early Treatment Diabetic Retinopathy Study [ETDRS]) in at least 1 eye at the Baseline visit.
- Subject had intermediate uveitis or panuveitis with signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) and symptoms and/or magnetic resonance imaging (MRI) findings suggestive of a demyelinating diseasesuch as multiple sclerosis. All subjects with intermediate uveitis or panuveitis who had signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) must have had a brain MRI within 90 days prior to the Baseline visit.
- Subject had previous exposure to anti-TNF therapy or any biologic therapy (except intravitreal anti-vascular endothelial growth factor [VEGF] therapy [See Exclusion Criterion No. 43]) with a potential therapeutic impact on non-infectious uveitis.
- Subject was on more than 1 immunosuppressive therapy (not including corticosteroids) at Baseline.
- Subject was on concomitant immunosuppressive therapy other than MTX, cyclosporine, mycophenolate mofetil, or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid), azathioprine, or tacrolimus at Baseline.
- Subject, if entering the study on 1 concomitant immunosuppressive therapy, was on a dose that had been increased within the last 28 days prior to Baseline visit or was not within the following allowable doses at the Baseline visit:
    - MTX $\leq$ 25 mg per week
    - Cyclosporine $\leq$ 4 mg/kg per day
    - Mycophenolate mofetil $\leq$ 2 grams per day or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid) at an equivalent dose approved by the medical monitor
    - Azathioprine $\leq$ 175 mg per day
    - Tacrolimus (oral formulation) $\leq$ 8 mg per day
- Subject had prior or current use of chlorambucil.

- Subject had received Retisert® (glucocorticosteroid implant) within 3 years prior to the Baseline visit or had had complications related to the device. Subject had had Retisert® (glucocorticosteroid implant) removed within 90 days prior to the Baseline visit or had had complications related to the removal of the device.

For Study 880, the protocol-defined key exclusion criteria were:

- Subject had isolated anterior uveitis.
- Subject had confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to TB, cytomegalovirus, Lyme disease, toxoplasmosis, human T-lymphotropic virus type 1 infection, Whipple's disease, herpes zoster virus, and herpes simplex virus.
- Subject had presumed ocular histoplasmosis syndrome.
- Subject had ocular masquerade syndromes, such as ocular lymphoma.
- Subject had serpiginous choroidopathy.
- Subject had a contraindication to pupil dilation with mydriatic eyedrops.
- Subject had corneal or lens opacity that precluded visualization of the fundus or that likely required cataract surgery during the duration of the study.
- Subject had intraocular pressure of $\geq$ 25 mmHg and on $\geq$ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
- Subject had Best Corrected Visual Acuity (BCVA) less than 20 letters (Early Treatment Diabetic Retinopathy Study [ETDRS]) in at least 1 eye at the Baseline visit.
- Subject had intermediate uveitis or panuveitis with signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) and symptoms and/or magnetic resonance imaging (MRI) findings suggestive of a demyelinating disease such as multiple sclerosis. All subjects with intermediate uveitis or panuveitis who had signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) must have had a brain MRI within 90 days prior to the Baseline visit.
- Subject had previous exposure to anti-TNF therapy or any biologic therapy (except intravitreal anti-vascular endothelial growth factor [VEGF] therapy [See Exclusion Criterion No. 43]) with a potential therapeutic impact on non-infectious uveitis.
- Subject was on more than 1 immunosuppressive therapy (not including corticosteroids) at Baseline.
- Subject was on concomitant immunosuppressive therapy other than MTX, cyclosporine, mycophenolate mofetil, or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid), azathioprine, or tacrolimus at Baseline.
- Subject, if entering the study on 1 concomitant immunosuppressive therapy, was on a dose that had been increased within the last 28 days prior to Baseline visit or was not within the following allowable doses at the Baseline visit:
    - MTX $\leq$ 25 mg per week
    - Cyclosporine $\leq$ 4 mg/kg per day
    - Mycophenolate mofetil $\leq$ 2 grams per day or an equivalent drug to mycophenolate mofetil (e.g., mycophenolic acid) at an equivalent dose approved by the medical monitor
    - Azathioprine $\leq$ 175 mg per day
    - Tacrolimus (oral formulation) $\leq$ 8 mg per day

- Subject had prior or current use of chlorambucil.
- Subject had received Retisert® (glucocorticosteroid implant) within 3 years prior to the Baseline visit or had had complications related to the device. Subject had had Retisert® (glucocorticosteroid implant) removed within 90 days prior to the Baseline visit or had had complications related to the removal of the device.

Enrolled patients were randomized at 1:1 ratio to receive adalimumab or placebo administered subcutaneously (SC) as an 80 mg loading dose at Baseline followed by a 40 mg dose every other week (eow) at approximately the same time of day starting at Week 1. Randomization was stratified using baseline immunosuppressant usage as the stratification factor (Yes or No). The study design schematic is as follows.

Appendix 2: Schedule of Activities

Table 26: Study 877 Schedule of Activities

Activity	Screening	Baseline	Week 1	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Informed consent	X												
Inclusion/exclusion criteria	X	X											
12-lead ECG[a]	X												
CXR[b]	X												
MRI[c]	X												
TB screening[d] (PPD skin test or QuantiFERON®-TB Gold [or IGRA equivalent])	X												
Serum pregnancy test[e]	X												
Hepatitis B screen	X												
Syphilis testing (FTA)	X												
Lyme IgG/immunoglobulin M [IgM] antibody serology[f]	X												
Antinuclear antibody (ANA)/ anti-dsDNA[g]	X												
HIV (Argentina, Mexico, and Japan only)	X												
Visual Functioning Questionnaire (VFQ-25)[h]		X	X	X	X	X	X	X	X	X	X	X	X
EuroQol-5D™ Questionnaire (EQ-5D)[i]		X	X	X	X	X	X	X	X	X	X	X	X
Hospital Anxiety and Depression Scale (HADS)[j]		X			X								

Activity	Screening	Baseline	Week 1	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)[i]		X			X								
SF-36® Health Status Survey (SF-36)[i]		X											
Health Resource Utilization Questionnaire (HRU)[h]		X	X	X	X	X	X	X	X	X	X	X	X
Medical/surgical history[j]	X	X											
Uveitis history[j]	X												
Alcohol and nicotine use	X												
Vital signs/weight/height[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
ETDRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated indirect ophthalmoscopy (DIO)	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photography[l]	X	X											
Physical examination	X	X					X			X			
Symptom-directed physical examination			X	X	X	X		X	X		X	X	X
Urine pregnancy test[m]		X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]
PK[n,o]		X	X			X	X				X		X

Activity	Screening	Baseline	Week 1	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Anti-adalimumab antibody (AAA)[o,p]		X					X				X		X
Hematology/chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X								X			
Monitor AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral prednisone taper[s]				X	X	X	X						
Corticosteroid eye drop taper[t]			X	X	X	X							
Monitor compliance		X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X											
Dispense adalimumab/placebo study drug (Contact IVRS/IWRS)		X	X	X		X	X	X	X	X[u]	X	X	X
Dispense prednisone study drug[v,w,x] (Contact IVRS/IWRS)		X[y]		X[z]		X[aa]							
Perform drug accountability[y]			X	X		X	X	X	X	X	X	X	X

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
Informed consent													
Inclusion/exclusion criteria													
12-lead ECG[a]												X	
CXR[b]				X								X	
MRI[c]													
TB screening[d] (PPD skin test or QuantiFERON®-TB Gold [or IGRA equivalent])				X								X	
Serum pregnancy test[e]													
Hepatitis B screen													
Syphilis testing (FTA)													
Lyme IgG/IgM antibody serology[f]													
ANA/anti dsDNA[g]												X	
HIV (Japan, Mexico, and Argentina only)													
VFQ-25[h]	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D[i]	X	X	X	X	X	X	X	X	X	X	X	X	
HADS[i]											X	X	
WPAI-SHP[j]											X	X	

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
SF-36[i]													
HRU Questionnaire[h]	X	X	X	X	X	X	X	X	X	X	X	X	
Medical/surgical history[j]											X[m]		
Uveitis history[j]													
Alcohol and nicotine use													
Vital signs/weight/height[k]	X	X	X	X	X	X	X	X	X	X	X	X	
ETDRS	X	X	X	X	X	X	X	X	X	X	X	X	
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	
OCT	X	X	X	X	X	X	X	X	X	X	X	X	
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	
DIO	X	X	X	X	X	X	X	X	X	X	X	X	
Fundus photography[l]											X	X	
Physical examination			X						X		X	X	
Symptom-directed physical examination	X	X		X	X	X	X	X		X			
Urine pregnancy test[m]	X	X	X	X	X	X	X	X	X	X	X	X	
PK[n,o]				X							X	X	
AAA[o,p]				X							X	X	

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
Hematology/chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[q]				X							X	X	
Monitor AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Oral prednisone taper[s]													
Corticosteroid eye drop taper[t]													
Monitor compliance	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization													
Dispense adalimumab/placebo (Contact IVRS/IWRS)	X	X	X	X	X	X	X	X	X	X			
Dispense prednisone[v,w,x] (Contact IVRS/IWRS)													
Perform drug accountability[y]	X	X	X	X	X	X	X	X	X	X	X	X	

a. Resting 12-lead ECG. For subjects with a normal ECG taken within 90 days of the Screening visit, a repeat ECG at Screening was not required, provided all protocol required documentation was available. If there were other findings that were clinically significant, the investigator was to contact the AbbVie medical monitor before enrolling the subject. Subjects could have a repeat ECG at any time during the study as warranted by the investigator.

b. To include a posterior-anterior and lateral view. If a subject had a CXR performed within 90 days of the Screening visit, the test did not need to be repeated provided all protocol required documentation listed in Section 5.3.1.1 of the protocol (Appendix 16.1.1) was available. A CXR could be repeated at any time during the study as warranted based on the opinion of the investigator. Other diagnostic imaging tests may have been performed as needed if pulmonary involvement was suspected based on the investigator's clinical assessment. At Week 52, if TB test was positive, subject was to undergo additional CXR. If Week 52 TB test was positive, a CXR was to be completed.

c. Subjects with intermediate uveitis or panuveitis who had signs of intermediate uveitis (e.g., presence of snowbanking or snowballs) were required to have an MRI of the brain with and without Gadolinium within 90 days prior to Baseline visit that revealed no hint of demyelinating disease such as multiple sclerosis. In countries where Gadolinium is not routinely used, a country's regional procedures for ruling out demyelinating disease could be used once the AbbVie medical monitor was consulted and in agreement with the procedure. In addition, the site was to notify the assigned monitor.

d. See Section 5.3.1.1 of the protocol (Appendix 16.1__1) for screening TB information, including country-specific requirements for the Czech Republic. For subjects with a negative test at Screening, an annual repeat PPD skin test (alternatively, also known as tuberculin skin test) or QuantiFERON®-TB Gold test (or IGRA equivalent) was required for any subject participating in the study at the Week 52 visit. The same type of TB test should have been used at Week 52 that was used for the initial TB screening for the study. However, for subjects with a positive PPD skin test at Screening (for those subjects entering the study prior to Amendment 7), a QuantiFERON®-TB Gold test (or IGRA equivalent) was to have been performed at the Week 52 visit. If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) was positive or if there was a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting at the Week 52 visit, the subject was to be discontinued and it was to be reported as an AE in the source documents and eCRFs. PPD skin test or QuantiFERON®-TB Gold (or IGRA equivalent) could have been repeated at any time if clinically warranted based on investigators' judgment.

e. A serum pregnancy test was to be performed at Screening on all female subjects.

f. The Lyme IgG/IgM antibody serology test was optional. See Section 5.3.1.1 of the protocol (Appendix 16.1__1).

g. Collection of ANA/dsDNA samples was required at the Screening visit. These tests are markers and the results are not exclusionary, therefore they were not to delay randomization. If a subject developed signs and symptoms of lupus, an ANA test could be repeated based on the investigator's clinical judgment. If a subject was screened prior to IEC/IRB approval of Global Protocol Amendment 4, the ANA/dsDNA sample was to be collected at the subject's next scheduled visit.

h. Questionnaire was to be administered by site staff (interview administered) prior to any other study procedure or examination.

i. Questionnaire was to be completed by the subject prior to any other study procedure or examination. Site staff were to complete the questionnaire with the subject if the subject had impaired vision that precluded him/her from reading and completing the questionnaire. The HADS questionnaire was not to be completed by subjects in Germany and Austria nor by German-speaking subjects in Switzerland.

Table 27: Study 880 Schedule of Activities

Activity	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Informed consent	X												
Inclusion/exclusion criteria	X	X											
12-lead ECG[a]	X												
CXR[b]	X												
MRI[c]	X												
TB screening[d] (PPD skin test or QuantiFERON-TB Gold [or IGRA equivalent])	X												
Serum pregnancy test[e]	X												
Hepatitis B screen	X												
Syphilis testing (FTA)	X												
Lyme IgG/immunoglobulin M [IgM] antibody serology[f]	X												
Antinuclear antibody (ANA)/ anti-dsDNA[g]	X												
HIV (Argentina, Mexico, and Japan only)	X												
Visual Functioning Questionnaire (VFQ-25)[h]		X	X	X	X	X	X	X	X	X	X	X	X
EuroQol-5D™ Questionnaire (EQ-5D)[i]		X	X	X	X	X	X	X	X	X	X	X	X
Hospital Anxiety and Depression Scale (HADS)[i]		X											

Activity	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)[i]		X										
SF-36® Health Status Survey (SF-36)[i]		X										
Health Resource Utilization (HRU) questionnaire[h]		X	X	X	X	X	X	X	X	X	X	X
Medical/surgical history[j]	X	X										
Uveitis history[j]	X											
Alcohol and nicotine use	X											
Vital signs/weight/height[k]	X	X	X	X	X	X	X	X	X	X	X	X
ETDRS	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X
Dilated indirect ophthalmoscopy (DIO)	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photography[l]	X	X										
Physical examination	X	X				X			X			
Symptom-directed physical examination			X	X	X		X	X		X	X	X
Urine pregnancy test[m]		X	X	X	X	X	X	X	X	X	X	X
PK[n,o]		X	X		X	X				X		X

Activity	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 27	Week 32	Week 36
Anti-adalimumab antibody (AAA)[o,p]		X				X				X		X
Hematology/chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X							X			
Monitor AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Oral prednisone taper[s]			X	X	X	X	X					
Corticosteroid eye drop taper[t]			X	X	X							
Monitor compliance		X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
Dispense adalimumab/placebo study drug (Contact IVRS/IWRS)		X		X	X	X	X	X	X[u]	X	X	X
Dispense prednisone study drug[v,w,x] (Contact IVRS/IWRS)		X		X	X	X						
Perform drug accountability[y]			X	X	X	X	X	X	X	X	X	X

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
Informed consent													
Inclusion/exclusion criteria													
12-lead ECG[a]												X	
CXR[b]				X								X	
MRI[c]													
TB screening[d] (PPD skin test or QuantiFERON-TB Gold [or IGRA equivalent])				X								X	
Serum pregnancy test[e]													
Hepatitis B screen													
Syphilis testing (FTA)													
Lyme IgG/IgM antibody serology[f]													
ANA/anti-dsDNA[g]												X	
HIV (Argentina, Mexico, and Japan only)													
VFQ-25[h]	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D[i]	X	X	X	X	X	X	X	X	X	X	X	X	
HADS[i]											X	X	
WPAI-SHP[i]											X	X	

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
SF-36[i]													
HRU questionnaire[h]	X	X	X	X	X	X	X	X	X	X	X	X	
Medical/surgical history[j]											X		
Uveitis history[j]													
Alcohol and nicotine use													
Vital signs/weight/height[k]	X	X	X	X	X	X	X	X	X	X	X	X	
ETDRS	X	X	X	X	X	X	X	X	X	X	X	X	
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	
OCT	X	X	X	X	X	X	X	X	X	X	X	X	
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	
DIO	X	X	X	X	X	X	X	X	X	X	X	X	
Fundus photography[l]											X	X	
Physical examination			X						X		X	X	
Symptom-directed physical examination	X	X		X	X	X	X	X		X			
Urine pregnancy test[m]	X	X	X	X	X	X	X	X	X	X	X	X	
PK[n,o]				X							X	X	
AAA[o,p]				X							X	X	

Activity	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Final/Early Termination Visit	Unscheduled Visit[z]	70-Day Follow-up[aa]
Hematology/chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[q]				X							X	X	
Monitor AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Oral prednisone taper[s]													
Corticosteroid eye drop taper[t]													
Monitor compliance	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization													
Dispense adalimumab/placebo (Contact IVRS/IWRS)	X	X	X	X	X	X	X	X	X	X			
Dispense prednisone[v,w,x] (Contact IVRS/IWRS)													
Perform drug accountability[y]	X	X	X	X	X	X	X	X	X	X	X	X	

a. Resting 12-lead ECG. For subjects with a normal ECG taken within 90 days of the Screening visit, a repeat ECG at screening was not required, provided all protocol-required documentation was available. If there were other findings that were clinically significant, the investigator was to contact the AbbVie medical monitor before enrolling the subject. Subjects could have a repeat ECG at any time during the study as warranted by the investigator.

b. To include a posterior-anterior and lateral view. If a subject had a CXR performed within 90 days of the Screening visit, the test did not need to be repeated provided all protocol-required documentation listed in Section 5.3.1.1 of the protocol (Appendix 16.1__1) was available. A CXR could be repeated at any time during the study as warranted based on the opinion of the investigator. Other diagnostic imaging tests may have been performed as needed if pulmonary involvement was suspected based on the investigator's clinical assessment. At Week 52, a CXR was to be completed if the Week 52 TB test was positive.

c. Subjects with intermediate uveitis or panuveitis who had signs of intermediate uveitis (e.g., presence of snowbanking or snowballs) were required to have an MRI of the brain with and without gadolinium within 90 days prior to Baseline visit that revealed no hint of demyelinating disease such as multiple sclerosis. In countries where gadolinium is not routinely used, a country's regional procedures for ruling out demyelinating disease could be used once the AbbVie medical monitor was consulted and in agreement with the procedure. In addition, the site was to notify the assigned monitor.

d. See Section 5.3.1.1 of the protocol (Appendix 16.1__1) for screening TB information, including country-specific requirements for the Czech Republic. For subjects with a negative test at screening, an annual repeat PPD skin test (alternatively, also known as tuberculin skin test) or QuantiFERON-TB Gold test (or IGRA equivalent) was required for any subject participating in the study at the Week 52 visit. The same type of TB test should have been used at Week 52 that was used for the initial TB screening for the study. However, for subjects with a positive PPD skin test at screening (for those subjects entering the study prior to Amendment No. 8), a QuantiFERON-TB Gold test (or IGRA equivalent) was required to be performed at the Week 52 visit. If PPD and/or the QuantiFERON-TB Gold test (or IGRA equivalent) was positive or if there was a repeat indeterminate QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting at the Week 52 visit, the subject was to be discontinued and it was to be reported as an AE in the source documents and eCRFs. PPD skin test or QuantiFERON-TB Gold (or IGRA equivalent) could have been repeated at any time if clinically warranted based on investigators' judgment.

e. A serum pregnancy test was to be performed at screening on all female subjects.

f. The Lyme IgG/IgM antibody serology test was optional. See Section 5.3.1.1 of the protocol (Appendix 16.1__1).

g. Collection of ANA/dsDNA samples was required at the Screening visit. These tests are markers and the results are not exclusionary; therefore, they were not to delay randomization. If a subject developed signs and symptoms of lupus, an ANA test could be repeated based on the investigator's clinical judgment. If a subject was screened prior to IEC/IRB approval of Global Protocol Amendment No. 4, the ANA/dsDNA sample was to be collected at the subject's next scheduled visit.

h. Questionnaire was to be administered by site staff (interview administered) prior to any other study procedure or examination.

i. Questionnaire was to be completed by the subject prior to any other study procedure or examination. Site staff was to complete the questionnaire with the subject if the subject had impaired vision that precluded him/her from reading and completing the questionnaire. The HADS questionnaire was not to be completed by subjects in Germany and Austria nor by German-speaking subjects in Switzerland.

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/s/

YUNFAN DENG
05/26/2016

YAN WANG
05/26/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

sBLA:	STN 125057/397
Submission Type:	Efficacy supplement
Brand Name:	HUMIRA®
Drug Name:	Adalimumab
Submission Date:	09/03/2015
PDUFA Goal Date:	07/03/2016
Priority:	Standard
Proposed Indication:	Treatment of non-infectious uveitis in adults
Proposed Dosing Regimen:	Initial dose of 80 mg administered by subcutaneous injection, followed by 40 mg given subcutaneously every other week starting 1 week after the initial dose
Dosage Forms and Strength:	A single-use pen, containing a 1 mL prefilled glass syringe providing 40 mg/0.4 mL or 40 mg/0.8 mL of adalimumab
Applicant:	AbbVie Inc.
Clinical Pharmacology Reviewer:	Abhay Joshi, Ph.D.
Pharmacometrics Team Leader:	Jeffry Florian, Ph.D.
Clinical Pharmacology Team Leader:	Philip Colangelo, Pharm. D., Ph.D.
OCP Division:	Division of Clinical Pharmacology IV (DCP-IV)
OND Division:	OAP/DTOP

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1. EXECUTIVE SUMMARY

Adalimumab (HUMIRA®) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNFα). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Adalimumab was initially approved for the treatment of rheumatoid arthritis (RA) in December 2002. At present, adalimumab is approved for multiple indications, including Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult and Pediatric Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps) and Hidradenitis Suppurativa (HS).

This submission is an efficacy supplement that is intended to support an indication for adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

The proposed dosing regimen for adalimumab is 80 mg subcutaneous (SQ) loading dose at baseline, followed by 40 mg SQ dose every other week (eow) starting at Week 1. The proposed dosing regimen is same as the dosage regiment approved for Ps.

The submission package contains two phase 3 clinical study reports, i.e. for Study M10-877 and Study M10-880. The overall study design for both studies was similar except for the study population. Study M10-877 enrolled patients who had active uveitis at baseline, whereas, Study M10-880 enrolled patients with inactive uveitis. The submission also contains the selected preliminary efficacy and safety data from ongoing open-label extension Study M11-327, with a data cutoff date 30 April 2015. In Study M11-327, the enrolled uveitis patients were from Study M10-877 or Study M10-880, who met one of the three possible outcomes: met the endpoint of treatment failure, completed the study, or remained in the study until the study was stopped. In a subsequent submission, the Sponsor has also provided an additional pharmacokinetic report (R&D/15/1161), which assesses the impact of immunogenicity on pharmacokinetic (PK), efficacy, and safety in two phase 3 studies, i.e. Study M10-877 and Study M10-880. The re-analysis of immunogenicity samples was performed using the new improved Anti-Adalimumab Antibodies (AAA) assay.

1.1. Recommendations

The Clinical Pharmacology information provided by the Applicant in the sBLA submission is acceptable, and the Clinical Pharmacology review team recommends that this sBLA for adalimumab (Humira) be approved for treatment of non-infectious uveitis in adults.

The Reviewer's proposed label changes in Section 3 will be forwarded to the sponsor.

1.2. Phase 4 Commitments

None.

1.3. Summary of important Clinical Pharmacology and Biopharmaceutics findings

1.3.1. Pharmacokinetics and Exposure-Response Relationships

The proposed SQ dosing regimen for adalimumab is the same as the approved dosing regimen for the Ps indication. In addition, the proposed maintenance dose of 40 mg eow, is the maximum approved maintenance dose amongst all the approved indications. The observed adalimumab systemic PK exposures were consistent between the two Phase 3 studies i.e., Study M10-877 and Study M10-880. The mean steady-state serum adalimumab concentration range was 8.34 - 10.00 μg/mL in uveitis patients, which is comparable to the range observed in patients with CD, UC, RA, and Ps, following the same maintenance SQ regimen of adalimumab.

The mean serum adalimumab concentrations were slightly higher in uveitis patients who did not have treatment failure compared to those patients who had treatment failure in both studies, however, the observed serum concentration ranges were mostly overlapping between the groups and an exposure-response relationship for efficacy was not apparent.

1.3.2. Immunogenicity and Its Impact on PK and Efficacy / Safety

The submission also contains the study results on the impact of immunogenicity on adalimumab PK, efficacy, and safety in uveitis patients based on the detection of Anti-Adalimumab Antibodies (AAA) with the newly validated drug-tolerant assay. The mean adalimumab concentrations appeared lower in uveitis patients with detected serum levels of AAA (AAA+) compared to patients without any serum levels of AAA (AAA-). In addition, the serum adalimumab concentrations remained lower in AAA+ patients throughout the study. These results are in agreement with the previously observed relationship between formation of AAA and reduced serum adalimumab concentrations in AAA+ patients with other indications. However, there was no clear impact of immunogenicity on adalimumab efficacy in non-infectious uveitis patients. Additionally, in non-infectious uveitis patients, no new safety risks were identified that are associated with the adalimumab immunogenicity.

2. QUESTION BASED REVIEW

This submission is an efficacy supplement (sBLA) for an already approved drug product; therefore, only questions that pertain to this uveitis supplement are addressed in this section.

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Adalimumab (HUMIRA) is a specific recombinant human Immunoglobulin G1 (IgG1) monoclonal antibody (mAb) to human Tumor necrosis factor alpha (TNF-α). It is produced by fermentation in a Chinese hamster ovary (CHO) cell line. Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It is formulated as injectable solution for subcutaneous administration in a pre-filled autoinjectior or a single-use institutional use vial. Each prefilled autoinjector contains 40 mg/0.4 mL or 40 mg/0.8 mL of adalimumab solution.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed therapeutic indication is non-infectious uveitis, which is an inflammatory condition. Given that TNF-α plays a pivotal role in the inflammatory process, the anti-TNF activity of adalimumab is proposed for treatment of non-infectious uveitis.

2.2. General Clinical Pharmacology

2.2.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug

Adalimumab was initially approved for treatment of rheumatoid arthritis (RA) in 2002. At present, in addition to RA, approved indications are Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult and Pediatric Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), and Hidradenitis Suppurativa (HS). The highest approved maintenance dose amongst the all indications is 40 mg every other week (eow).

Following is the list of relevant intrinsic/extrinsic factors that are known to have an impact on the adalimumab exposures:

1) *Body Weight:* Higher body weight is associated with higher adalimumab clearance
2) *Methotrexate Co-medication:* Methotrexate Co-medication is associated with lower adalimumab clearance
3) *Presence of Anti-Adalimumab Antibodies:* Presence of AAA is associated with higher adalimumab clearance

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

For both phase 3 studies, the primary efficacy endpoint was the time to treatment failure with adalimumab therapy in comparison to the placebo arm. Due to the different baseline criteria of the enrolled patients between two studies; i.e., active versus inactive noninfectious uveitis, there were different criteria for the assessment of treatment failure. Treatment failure criteria as well as time lines for the primary efficacy endpoints for both studies are listed in Table 1. Beginning at the Week 6 visit, and at subsequent visits thereafter for Study M10-877, or beginning at the Week 2 visit and at subsequent visits thereafter for Study M10-880, patients were considered to be treatment failures in the presence of 1 of the following 4 parameters in at least 1 eye (Table 1).

Table 1: Treatment Failure Criteria and Assessment Timeline for Study M10-877 and M10-880 (source: Report R&D/15/0264 Table 1)

	Treatment Failure[a]		
	Study M10-877		Study M10-880
Parameter	Week 6 Visit	All Other Visits After Week 6	Week 2 Visit and all Subsequent Visits
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to baseline	New active, inflammatory lesions relative to baseline	New active, inflammatory lesions relative to baseline
Anterior Chamber (AC) Cell grade (SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to baseline[b]
Vitreous Haze (VH) grade (NEI/SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]	2-step increase relative to Baseline[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to baseline

a. To be considered a treatment failure, ≥ 1 of these 4 criteria needed to be present in at least 1 eye.

b. A 2-step increase was represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

BCVA = Best Corrected Visual Acuity

ETDRS = Early Treatment Diabetic Retinopathy Study

NEI = National Eye Institute

SUN = Standardization of Uveitis Nomenclature

2.2.3. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The proposed dosing regimen is same as the approved dosing regimen for the Ps indication. In addition, the proposed maintenance dose; i.e. 40 mg eow, is the same as the maximum approved maintenance dose. With the above mentioned dosing recommendations, the sponsor seeks to add a new indication "treatment of non-infectious intermediate, posterior and panuveitis in adult patients" to the currently approved product labeling. The Sponsor has submitted the clinical study reports for two pivotal phase 3, randomized, double-masked, placebo-controlled studies; i.e., Study M10-877 and M10-880, in support of the efficacy claim. Both studies have assessed the pharmacokinetics and immunogenicity of proposed adalimumab treatment in Uveitis patients:

Study M10-877: Active Uveitis Patients

Study M10-877 was conducted in 217 subjects with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least one eye despite at least 2 weeks of oral prednisone at a dose of $\geq$ 10 mg/day to $\leq$ 60 mg/day (or oral corticosteroid equivalent).

Study M10-880: Inactive Uveitis Patients

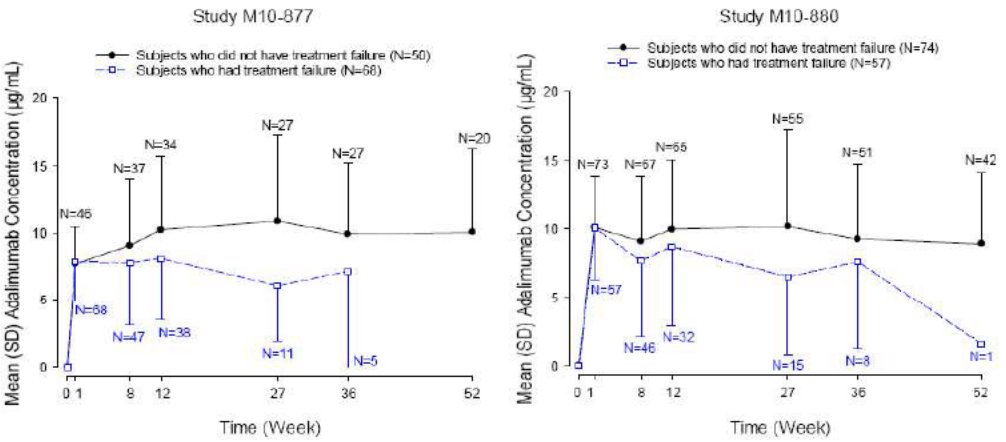
Study M10-880 was conducted in 226 subjects with inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis whose disease had been inactive for $\geq$ 28 days and who required chronic oral corticosteroids with oral prednisone $\geq$ 10 mg/day (or oral corticosteroid equivalent) to maintain inactive disease.

2.2.4. Exposure-response

Overall, in both studies, the risk of treatment failure for uveitis patients in the adalimumab treatment group was lower in comparison to uveitis patients in the placebo group. In comparison to the patients in placebo group, the risk of treatment failure was reduced by 50% and 43% in the adalimumab treatment group patients in Study M10-877 and M10-880, respectively. In Study M10-877, estimated hazard ratio (HR) was 0.50 (95% CI: 0.36 - 0.70) and patients in the adalimumab group had a longer median time to treatment failure of 5.6 months compared to 3 months in the placebo group patients. In Study M10-880, estimated HR was 0.57 (95% CI: 0.39, 0.84) and the median time to treatment failure for the adalimumab group exceeds 18 months; i.e., total duration of study, compared to 8.3 months in the placebo group patients.

However, with regard to drug exposures and efficacy relationship in the both studies, the mean serum adalimumab concentrations were only slightly higher in patients who did not have treatment failure compared to those who had treatment failure (Figure 1 and Table 2). Additionally, as discussed in the PK and immunogenicity result sections i.e., Section 2.2.5 & Section 2.2.6, there is no apparent relationship between adalimumab exposures and time-to-treatment failure in uveitis patients.

Figure 1: Mean (SD) Serum Adalimumab Concentrations Versus Time by Occurrence of Treatment Failure (source: Report R&D/15/0300 Figure 2)



Note: The numbers next to the standard deviation bars are total N at that time point. For the treatment failure subjects, none had Week 52 samples for Study M10-877.

Table 2: Summary of Serum Adalimumab Concentrations (µg/mL) by Treatment Failure (source: Report R&D/15/0300 Table 3)

Study/ Treatment Failure	Mean ± SD (Range), N						
	Week						
	0	1 or 2[a]	8	12	27	36	52
M10-877 No (N = 50)	0 ± 0 (0 – 0), 50	7.69 ± 2.76 (2.49 – 18.4), 46	9.04 ± 5.00 (0.592 – 21.2), 37	10.2 ± 5.49 (0.050 – 23.0), 34	10.8 ± 6.48 (0 – 31.4), 27	9.88 ± 5.37 (1.07 – 21.3), 27	10.0 ± 6.25 (0 – 22.0), 20
M10-877 Yes (N = 68)	0 ± 0 (0 – 0), 67	7.87 ± 2.96 (1.47 – 17.6), 68	7.80 ± 4.72 (0 – 18.0), 47	8.10 ± 4.62 (0 – 19.4), 38	6.09 ± 4.19 (0.533 – 13.1), 11	7.15 ± 8.65 (0 – 18.1), 5	NS
M10-880 No (N = 74)	0 ± 0 (0 – 0), 74	10.1 ± 3.85 (0.311 – 21.0), 73	9.09 ± 4.82 (0 – 25.0), 67	9.94 ± 5.11 (0.461 – 22.4), 65	10.1 ± 7.15 (0 – 46.8), 55	9.23 ± 5.55 (0 – 28.8), 51	8.89 ± 5.23 (0 – 27.1), 42
M10-880 Yes (N = 57)	0 ± 0 (0 – 0), 57	10.1 ± 3.74 (0.859 – 17.7), 57	7.65 ± 5.59 (0 – 21.6), 46	8.69 ± 5.82 (0 – 23.9), 32	6.50 ± 5.78 (0 – 19.5), 15	7.60 ± 6.38 (1.62 – 20.5), 8	1.58, 1

NS = No sample

a. Week 1 for Study M10-877 and Week 2 for Study M10-880.

The Sponsor also submitted a population pharmacokinetic-pharmacodynamic (popPK-PD) study report: RD150547, which characterized the exposure-response relationship for adalimumab in this population. For the development of the popPK-PD model, the popPK model was determined using the combined PK dataset of Study M10-877 and M10-880. Individual popPK model parameters were estimated and used to simulate individual adalimumab exposures over the treatment duration. Then, simulated exposures were linked with efficacy using time-to-event analyses, conducted separately for both the studies. The Sponsor concludes that the results from the popPK-PD analysis support the proposed dosing regimen for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

An independent analysis of the popPK-PD analysis was not conducted during the review as: i) only one dosage regimen was tested, ii) no apparent exposure-response relationship was observed in the provided report; iii) the efficacy results from the two provided studies support utilization of the proposed regimen for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients; and iv) information from the report was not planned to be included in product labeling.

2.2.5. Pharmacokinetic characteristics

The pharmacokinetics (PK) of adalimumab was assessed in two Phase 3 Studies (Study M10-877 and M10-880) following the proposed dosing regimen for patients with non-infectious uveitis. Adalimumab exposures were comparable between the two phase 3 studies (Table 3, Figure 2).

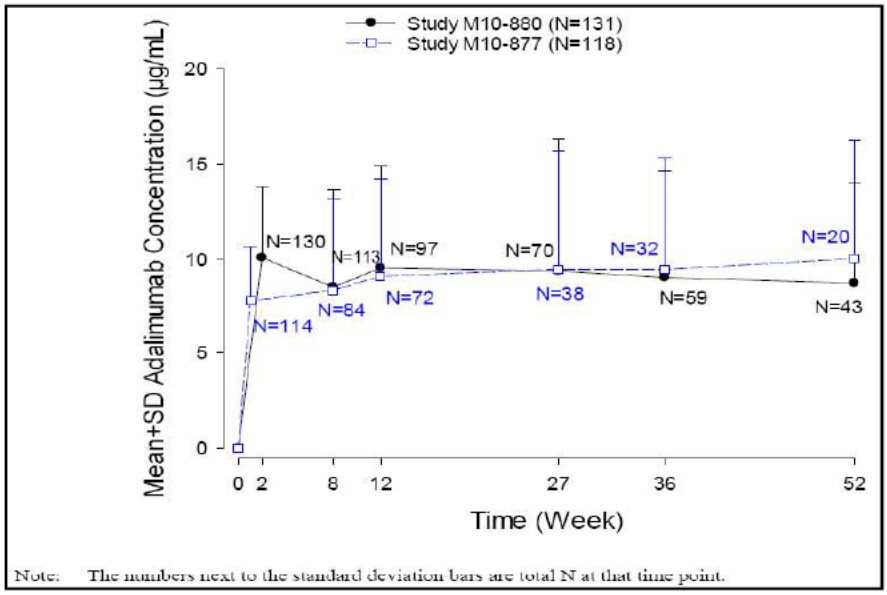
Table 3: Mean Serum Adalimumab Concentrations (µg/mL) for Patients with Uveitis (source: Report R&D/15/0300 Table 2)

	Mean ± SD (Range), N						
	Week						
Study	0	1 or 2[a]	8	12	27	36	52
M10-877 (N = 118)	0 ± 0 (0 – 0), 117	7.80 ± 2.87 (1.47 – 18.4), 114	8.34 ± 4.86 (0 – 21.2), 84	9.09 ± 5.12 (0 – 23.0), 72	9.46 ± 6.25 (0 – 31.4), 38	9.45 ± 5.90 (0 – 21.3), 32	10.0 ± 6.25 (0 – 22.0), 20
M10-880 (N = 131)	0 ± 0 (0 – 0), 131	10.1 ± 3.79 (0.311 – 21.0), 130	8.50 ± 5.17 (0 – 25.0), 113	9.53 ± 5.36 (0 – 23.9), 97	9.36 ± 7.00 (0 – 46.8), 70	9.01 ± 5.63 (0 – 28.8), 59	8.72 ± 5.28 (0 – 27.1), 43

a. Week 1 for Study M10-877 and Week 2 for Study M10-880.

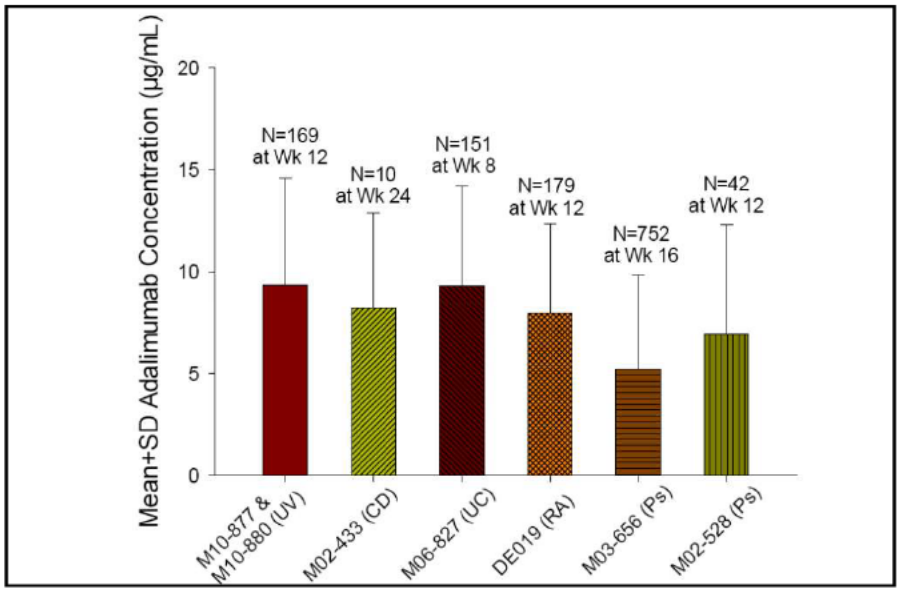
All subjects (non-Japanese and Japanese) included in the analysis.

Figure 2: Mean (+SD) Serum Adalimumab Concentrations Versus Time in Patients with Uveitis (source: Report R&D/15/0300 Figure 1)



Mean steady state concentration range was 8.34 - 10.00 µg/mL. Additionally, the observed mean steady-state serum adalimumab concentrations following the maintenance regimen of 40 mg adalimumab SQ treatment eow, in patients with uveitis were found comparable to those observed in patients with CD (Study M02-433), UC (Study M06-827), RA (Study DE019), and Ps (Studies M02-528 and M03-656), that used the same maintenance regimen (Figure 3).

Figure 3: Comparison of Mean (+SD) Steady-State Serum Adalimumab Concentrations in Patients with Uveitis (Studies M10-877 and M10-880) and Patients with CD, UC, RA and Ps During Maintenance Dosing (Adalimumab 40 mg eow) (source: Report R&D/15/0300 Figure 3)



2.2.6. *Immunogenicity*

2.2.6.1. *Impact of immunogenicity on adalimumab concentrations*

As per the agreement during the pre-sBLA meeting, the Sponsor submitted an amendment (SDN-5583) to this efficacy supplement, which consists of the immunogenicity report based on the new Anti-Adalimumab Antibodies (AAA) assay in patients with non-infectious uveitis. The previous AAA assay was a double antigen sandwich ELISA method, which detected AAA only when adalimumab concentration in a sample was ≤2 µg/mL, because of the drug interference issue. The new improved drug-tolerant assay is an electrochemiluminescence (ECL)-based assay, which has reduced sensitivity to adalimumab interference.

With the improved ECL assay, detected immunogenicity (AAA+) rates were 39.8%, 24.9%, and 8.4% at the AAA titer cut-offs ≥10, ≥100, and ≥1000, respectively (Table 4). These AAA+ rates were higher than the previously reported rates based on the current ELISA AAA assay.

Table 4: Rates of Titer Measurement Using New Drug-Tolerant ECL AAA Assay (source: Report R&D/15/1161 Table 2)

	Current AAA Assay	New Drug-Tolerant AAA Assay		
Study	AAA+ Rate	Titer ≥ 10	Titer ≥ 100	Titer ≥ 1000
M10-877[a]	3.4% (4/118)	35.6% (42/118)	23.7% (28/118)	6.8% (8/118)
M10-880	6.1% (8/131)	43.5% (57/131)	26.0% (34/131)	9.9% (13/131)
Total	4.8% (12/249)	39.8% (99/249)	24.9% (62/249)	8.4% (21/249)

Titer ≥ 10: Subjects had any AAA samples with AAA titer ≥ 10.

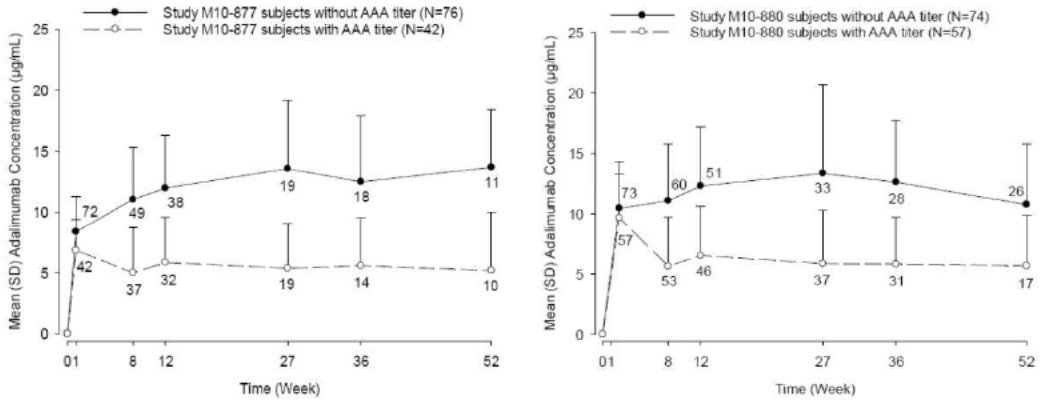
Titer ≥ 100: Subjects had any AAA samples with AAA titer ≥ 100.

Titer ≥ 1000: Subjects had any AAA samples with AAA titer ≥ 1000.

a. One adalimumab subject (Subject (b) (6) was excluded from the PK and immunogenicity summary analysis due

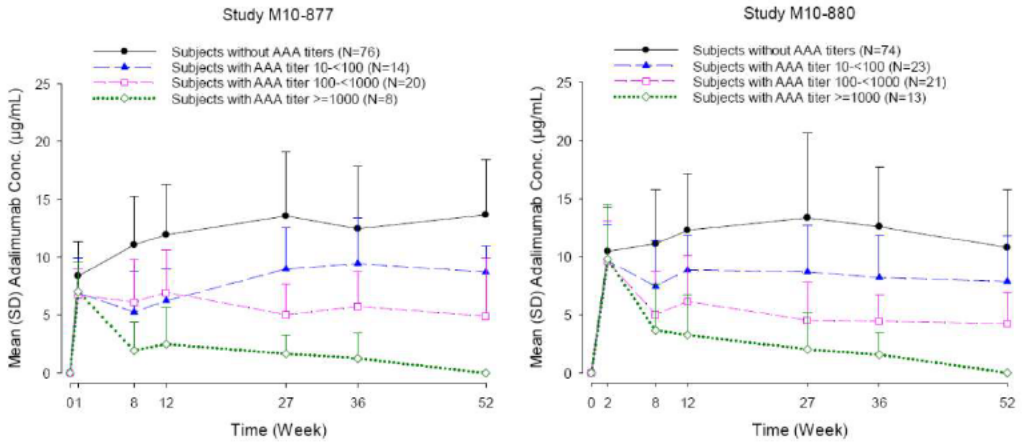
Overall, mean serum adalimumab concentrations appeared lower in AAA+ patients with any measurable titer (AAA titer ≥ 10) compared to the AAA- patients, and remained lower throughout the study (Figure 4). Additionally, the observed decline was proportional to the AAA titer values (Figure 5).

Figure 4: Comparison of Mean (+SD) Steady-State Serum Adalimumab Concentrations by AAA Titer Measurement Status (source: Report R&D/15/1161 Figure 1)



Note: The numbers at each time point in the figures represent the total N.

Figure 5: Comparison of Mean (SD) Adalimumab Concentration in Patients Developing Different AAA Titer Levels (source: Report R&D/15/1161 Figure 2)



Additionally, as per the popPK report in uveitis patients, mean adalimumab clearance (CL) value was about 3-fold higher in the AAA+ patients when compared to the AAA– patients. Similar inferences were made in HS patients, where mean clearance values were 6.1-fold higher in "on-treatment" AAA+ patients when compared to AAA- patients.

2.2.6.2. Impact of Immunogenicity on efficacy

Despite of the clear impact of immunogenicity on adalimumab concentrations in Study M10-877 and M10-880, the observed impact of immunogenicity on efficacy was not apparent. In Study M10-877, the time to treatment failure mostly appeared to be longer in the AAA+ patients compared to AAA- patients, however, the failure rate was similar between both groups (Figure 6, Table 4). In Study M10-880, the time to treatment failure appeared to be longer in the AAA- patients when compared to AAA+ patients. Additionally, contrary to Study M10-877, the failure rate was higher in AAA+ patients (47%) compared to patients without AAA titers (41%) (Figure 6, Table 4). Therefore, the combined results from both studies indicate the lack of clear relationship between immunogenicity and efficacy.

Figure 6: Comparison of Time-to-Treatment Failure in Patients Developing Different AAA Titer Levels (source: Report R&D/15/1161 Figure 4)

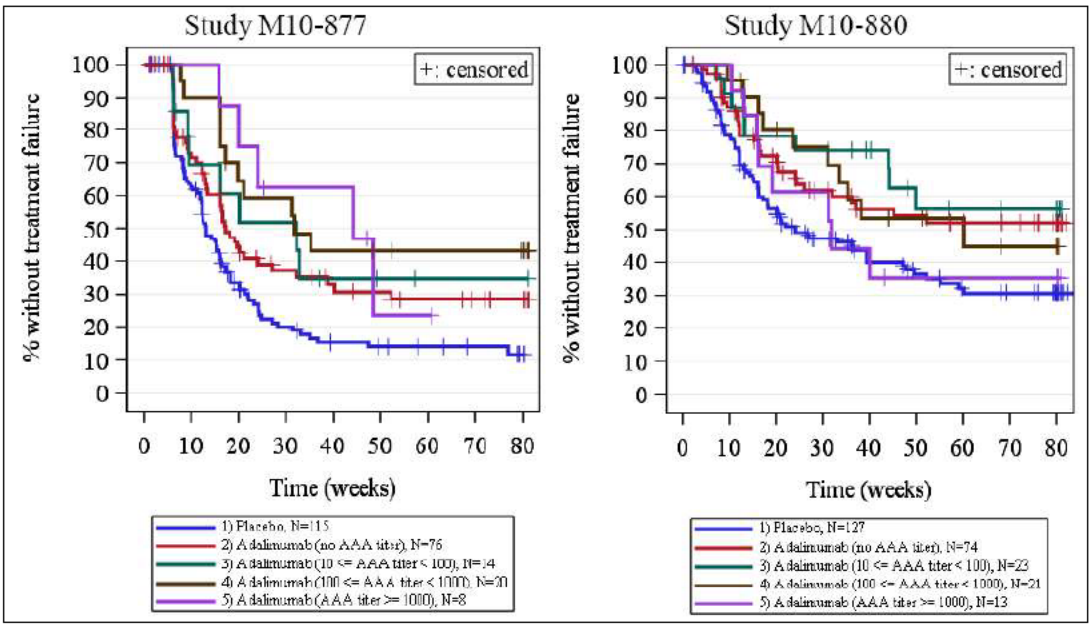


Table 4: Time to Treatment Failure by AAA Titer Status (source: Report R&D/15/1161 Table 10.4_1)

Study	AAA Titer Group	N	Failure N (%)	Median Time to Failure (Weeks)
M10-877	Placebo	115	90 (78.3)	13.1
	Adalimumab (Without AAA titer)	76	44 (57.9)	17.1
	Adalimumab (With AAA titer ≥ 10)	42	24 (57.1)	32.1
M10-880	Placebo	127	75 (59.1)	24.1
	Adalimumab (Without AAA titer)	74	30 (40.5)	NE
	Adalimumab (With AAA titer ≥ 10)	57	27 (47.3)	60.1

Note: Treatment failure at or after Week 6 (M10-877) and Week 2 (M10-880) was counted as event.
NE= Not estimable; Fewer than half of at-risk subjects had an event

2.3. Intrinsic factors

As per the popPK analysis results, which utilized the pharmacokinetic data from both studies: M10-877 and M10-880, higher baseline body weight and the presence of AAA was associated with higher adalimumab clearance. Additionally, baseline body weight was also identified as a significant covariate for apparent volume of distribution. These observations are consistent with reported covariates from other indications as described in Question 2.2.1.

2.4. Extrinsic factors

No specific drug interaction study(ies) was conducted in uveitis patients, however, as per the popPK analysis results, which utilized the pharmacokinetic data from both studies: M10-877 and M10-880, baseline methotrexate and mycophenolate mofetil co-medication was associated with the lower clearance. These observations are consistent with reported covariates from other indications as described in Question 2.2.1

2.5. General Biopharmaceutics

No new biopharmaceutics studies were submitted as part of this application. However, the sponsor has provided an amendment to this sBLA to update the previously submitted labeling (USPI), Medication Guide and Instructions for Use to accommodate the approval of the Humira 100 mg/mL (40 mg/0.4 mL) formulation in a prefilled syringe (sBLA 125057/394). The new 100 mg/mL formulation was approved by the Division of Pulmonary, Allergy, and Rheumatology Products DPARP) and the Sponsor plans to use the same for all currently approved indications, as well as for the indication of uveitis, if approved.

2.6. Analytical section

2.6.1. How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Adalimumab and Anti-Adalimumab antibodies (AAA) were quantified in serum using validated assays. Refer to Section 2.6.2. for further information.

2.6.2. What bioanalytical methods are used to assess concentrations?

Adalimumab concentrations in serum were determined using a validated enzyme-linked immunosorbent assay (ELISA) method. Anti-Adalimumab antibodies (AAA) were quantified in approximate relative amount (titer) by an electrochemiluminescence bridging assay.

2.6.3. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Adalimumab

The human serum samples were analyzed by using a validated ELISA method over an analytical range of 3.125 ng/mL to 50.0 ng/mL. Without the minimum required dilution of 10-fold, the LLOQ was 31.25 ng/mL and the ULOQ was 500 ng/mL. The following 5 parameter function was used for the standard curve fitting with a uniform weighting factor (1/y):

$$y = \frac{(A - D)}{\left(1 + \left(\frac{x}{C}\right)^{B}\right)^{M}} + D$$

Where:
y = response variable
x = dose variable
A = response at zero concentration
B = slope factor
C = initial estimate for mid-range concentration
D = response at infinite concentration
M = asymmetry parameter

2.6.3.1. What are the accuracy, precision, and selectivity at these limits?

Adalimumab

Inter-run precision measured as % CV was less than or equal to 3.9% and 5.8% for Study M10-877 and M10-880, respectively. Inter-run accuracy measured as mean bias in both the studies varied between -2.4% and 2.9%.

2.6.3.2. What is the sample stability under the conditions used in the study?

Adalimumab

The short-term stability of adalimumab in human serum was 120 hours at 37°C and the long-term stability was at least 6.5 years (2480 days) at -20ºC and at -80ºC.

2.6.3.3. What is the QC sample plan?

Adalimumab

The quality control (QC) samples were prepared in human serum with the concentrations of 40, 240 and 380 ng/mL and were used after 10-fold dilution.

3. DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

Recommended Clinical Pharmacology revsions are provided below with the annotation to the Sponsor's proposed labeling that was submitted with SDN-5760 on March 23, 2016:

6.1 Clinical Trials Experience

Immunogenicity

(b) (4)

4. APPENDICES

4.1. Clinical Pharmacology and Biopharmaceutics individual study review

The initial submission comprised the study reports for Study M10-877 and Study M10-880, which assessed the Pharmacokinetic (PK) and Immunogenicity of Adalimumab in Active and Inactive Non-infectious Uveitis patients, respectively. However, the ELISA assay method utilized to detect Anti-Adalimumab Antibodies (AAA) in the both studies had a drug interference issue. As per the Pre-sBLA meeting agreement, in a subsequent submission, the Sponsor has provided additional analyses for the assessment of the impact of immunogenicity on PK, efficacy, and safety using the new drug-tolerant AAA assay for both of the studies in a single study report. Therefore, these new immunogenicity relevant assessments and findings from both studies, are summarized in the separate subsequent section 4.1.4.

4.1.1. Study M10-877

Title:

Pharmacokinetic and Immunogenicity Assessments from the Phase 3 Trial: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-Study in Japanese Patients

Sample Analysis Dates: November 28, 2011 to September 10, 2014.
PK Analytical site: (b) (4)

Objectives:
The primary objective of this study was to assess the pharmacokinetics and immunogenicity of adalimumab treatment in patients that are requiring high dose corticosteroids for active non-infectious intermediate uveitis, posterior uveitis or panuveitis.

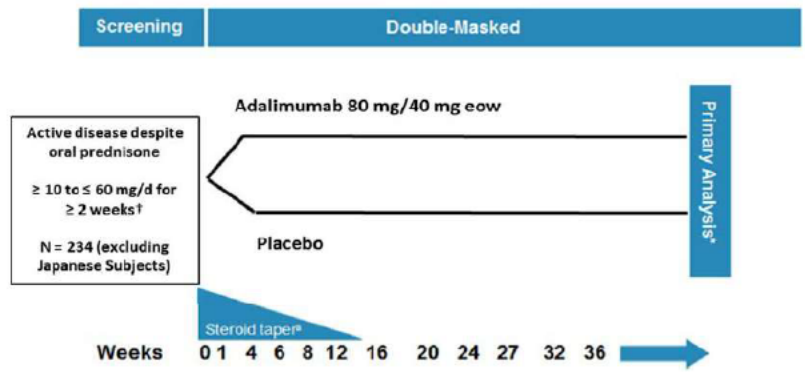
Formulation & Administration:
Adalimumab subcutaneous (SQ) injection, 80 mg (50 mg/mL) dose at baseline followed by 40 mg doses every other week (eow) starting at Week 1 using Pre-filled syringes.

Study Design:
This was a phase 3, randomized, double-masked, placebo-controlled, multicenter study to investigate the safety and efficacy of adalimumab as maintenance therapy. Efficacy was assessed in patients who had previously shown adequate clinical response to oral corticosteroids but now had active non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least one eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent). The study design is provided in Figure 1.

A total of 239 patients including 223 patients in Australia, Canada, Europe, Israel, Latin America, and the US (main study) and 16 Japanese patients (Japan sub-study) were enrolled in the study. Six patients from the main study were excluded from the pharmacokinetic analysis due to the followings:

- One placebo patient (Subject (b) (6)) due to incomplete efficacy source data
- Four placebo patients (Subjects (b) (6), (b) (6), (b) (6), and (b) (6)) and one adalimumab subject (Subject (b) (6)) due to general compliance issues

Figure 1: Study Design: Study M10-877 (source: Report R&D/14/1026 Figure 1)



† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.
* The study ended when the 138th event of Treatment Failure (in non-Japanese subjects only) had occurred.
a. Prednisone 60 mg per day was given at baseline followed by a taper from Weeks 2 – 15.

Patients were randomized 1:1 to receive either adalimumab treatment or placebo. Both arms also received a standardized prednisone burst of 60 mg/day at study entry followed by a protocol-defined mandatory taper schedule. In total, 119 patients received adalimumab treatment and 18 of them terminated early. In

total 120 patients were randomized to placebo and 7 of them terminated early from the study. Overall, patients' disposition is shown in Table 1.

Table 1: All Patients Disposition: Study M10-877 (source: Report R&D/14/1026 Table 3)

	Study M10-877		
	Adalimumab	**Placebo**	**Total**
Randomized and treated	119	120	239
Included in pharmacokinetic analysis	118	115	233
Excluded	1[a]	5	6
Subjects early termination	18	7	25
Completed Week 80	12	5	17
Completed < Week 80[b]	20	13	33
Treatment failure	68	90	158

a. One adalimumab treated subject was excluded from the adalimumab concentration summary analysis due to general compliance issues.
b. Subjects who had to terminate the study because the planned number of treatment failures was reached.

Starting at Week 6 and every visit thereafter, all patients were assessed for Treatment Failure based on the criteria described in Table 2. Demographic summary for patients included in the PK analysis is provided in Table 3.

Table 2: Treatment Failure Criteria by Study Visit: Study M10-877 (source: Report R&D/14/1026 Table 1)

	Treatment Failure[a]	
Parameter	**Week 6 Visit**	**All Other Visits After Week 6**
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline	New active, inflammatory lesions relative to Baseline
Anterior Chamber Cell grade (SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]
Vitreous Haze grade (NEI/SUN criteria)	Inability to achieve ≤ 0.5+	2-step increase relative to best state achieved[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature
a. To be considered a treatment failure, ≥ 1 of these 4 criteria need to be present in at least 1 eye.
b. A 2-step increase is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

For the pharmacokinetic and immunogenicity assessments, blood samples were obtained at baseline, and at Weeks 1, 8, 12, 27, 36, and, 52 or at the final/early termination visit. Amongst these sampling time points, baseline, Week 1, and Week 27 blood samples were drawn prior to dosing.

Table 3: Baseline Demographic Summary for Subjects Included in the Pharmacokinetic Analysis: Study M10-877 (source: Report R&D/14/1026 Table 4)

		Mean ± SD (Range)		
		Total (N = 233)	Adalimumab (N = 118)	Placebo (N = 115)
Age (yr)		43.2 ± 15.0 (18 – 81)	43.5 ± 15.5 (18 – 81)	43.0 ± 14.5 (18 – 79)
Weight (kg)		81.1 ± 22.8 (38 – 222)	80.0 ± 21.0 (38 – 174)	82.3 ± 24.5 (44 – 222)
Height (cm)		168 ± 10.2 (145 – 200)	169 ± 10.2 (145 – 191)	168 ± 10.2 (147 – 200)
			N (%)	
Sex	Male	98 (42.1)	53 (44.9)	45 (39.1)
	Female	135 (57.9)	65 (55.1)	70 (60.9)
Race	White	174 (74.7)	88 (74.6)	86 (74.8)
	Black	23 (9.9)	11 (9.3)	12 (10.4)
	Other	36 (15.4)	19 (16.1)	17 (14.8)

Other = Asian, American Indian/Alaska native, multi race and other

Assay Method:
Adalimumab concentrations in serum were determined using a validated enzyme –linked immunosorbent assay (ELISA) method. The validated analytical range of the assay was 3.125 to 50 ng/mL. The lower limit of quantitation (LLOQ) for adalimumab was 31.3 ng/mL in undiluted human serum and 3.125 ng/mL in diluted serum. In-study quality control sample concentrations were 40, 240 and 380 ng/mL of adalimumab. The accuracy and precision was satisfactory (CV ≤ 9.7%).

Results:
The mean serum adalimumab concentrations ranged from 8.34 to 10 µg/mL. In some patients, serum adalimumab concentrations were below detectable level after Week 8. Overall, summary of serum adalimumab concentrations from all patients who received adalimumab treatment is presented in Table 4.

Table 4: Summary of Serum Adalimumab Concentrations (µg/mL) for Patients with Uveitis: Study M10-877 (source: Report R&D/14/1026 Table 5)

Mean ± SD (Range), N						
Week						
0	1	8	12	27	36	52
Non-Japanese Subjects in the Main Study (N = 110)						
0 ± 0 (0 – 0), 109	7.85 ± 2.84 (2.49 – 18.4), 106	8.59 ± 4.80 (0 – 21.2), 79	9.20 ± 5.05 (0 – 23.0), 69	9.46 ± 6.25 (0 – 31.4), 38	9.45 ± 5.90 (0 – 21.3), 32	10.0 ± 6.25 (0 – 22.0), 20
All Subjects in the Study (N = 118)						
0 ± 0 (0 – 0), 117	7.80 ± 2.87 (1.47 – 18.4), 114	8.34 ± 4.86 (0 – 21.2), 84	9.09 ± 5.12 (0 – 23.0), 72	9.46 ± 6.25 (0 – 31.4), 38	9.45 ± 5.90 (0 – 21.3), 32	10.0 ± 6.25 (0 – 22.0), 20
Japanese Subjects in the Sub-Study (N = 8)						
0 ± 0 (0 – 0), 8	7.12 ± 3.45 (1.47 – 10.8), 8	4.41 ± 4.49 (0 – 11.9), 5	6.54 ± 7.48 (0 – 14.7), 3	NS	NS	NS

NS = No sample

When stratified by incidence of treatment failure, the mean serum adalimumab concentrations after Week 8 ranged from 6.09 to 8.1µg/mL and from 9.04 to 10.8µg/mL, in patients with and without treatment failure, respectively. Overall, summary of serum adalimumab concentrations stratified by treatment failure is presented in Table 5.

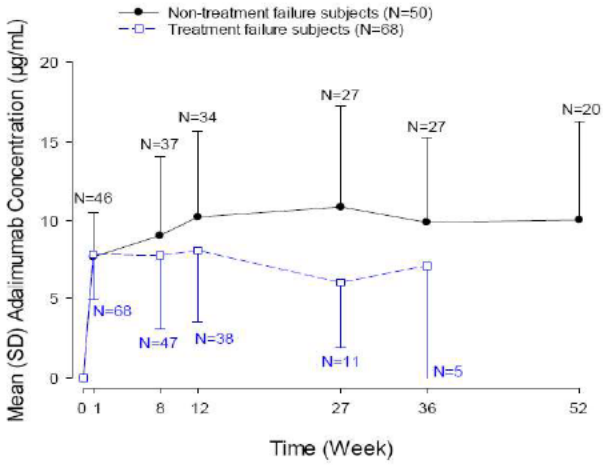
Table 5: Summary of Serum Adalimumab Concentrations (µg/mL) by Treatment Failure: Study M10-877 (source: Report R&D/14/1026 Table 6)

Treatment Failure[a]	Mean ± SD (Range), N						
	Week						
	0	1	8	12	27	36	52
All Subjects in the Study (N = 118)							
No (N = 50)	0 ± 0 (0 – 0), 50	7.69 ± 2.76 (2.49 – 18.4), 46	9.04 ± 5.00 (0.592 – 21.2), 37	10.2 ± 5.49 (0.050 – 23.0), 34	10.8 ± 6.48 (0 – 31.4), 27	9.88 ± 5.37 (1.07 – 21.3), 27	10.0 ± 6.25 (0 – 22.0), 20
Yes (N = 68)	0 ± 0 (0 – 0), 67	7.87 ± 2.96 (1.47 – 17.6), 68	7.80 ± 4.72 (0 – 18.0), 47	8.10 ± 4.62 (0 – 19.4), 38	6.09 ± 4.19 (0.533 – 13.1), 11	7.15 ± 8.65 (0 – 18.1), 5	NS

NS = No sample

a. For subjects who had treatment failure, they only had Treatment failure samples at different weeks.

Figure 2: Mean (SD) Serum Adalimumab Concentrations Versus Time by Occurrence of Treatment Failure: Study M10-877 (source: Report R&D/14/1026 Figure 3)



Note: For the subjects who had treatment failure, none had Week 52 samples.

The comparison of mean serum adalimumab concentrations between patients with and without treatment failure is shown in Figure 2.

Sponsor's conclusions:
Following 80 mg SQ dose of adalimumab at baseline and 40 mg eow at Week 1, the mean serum adalimumab concentrations reached steady state levels by Week 1 (8 – 10 μg/mL), which were maintained constant through Week 52. The mean serum adalimumab concentrations were slightly higher in patients who did not have treatment failure compared to those who had treatment failure.

Reviewer's Assessment:
Even though, the mean serum adalimumab concentrations were slightly higher in patients who did not have treatment failure, due to the observed variability, concentration rage was overlapping in patients with and without treatment failure. Additionally, in some patients with successful outcome, observed serum adalimumab concentrations were undetectable. These findings indicate of a weak exposure-response relationship in the study population.

4.1.2. Study M10-880

Title:
Pharmacokinetic and Immunogenicity Assessments from the Phase 3 Trial: A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Inactive Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients

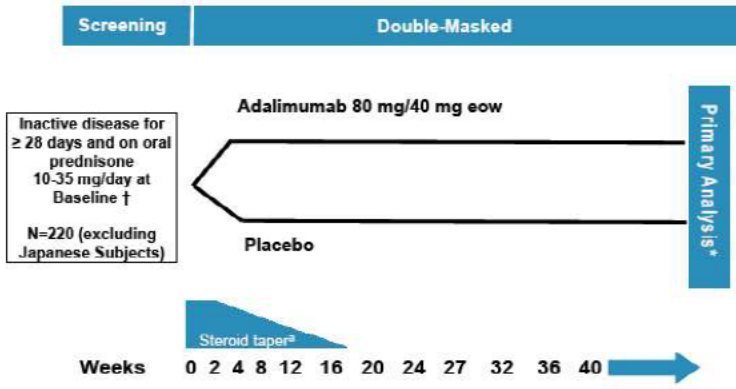
Sample Analysis Dates: December 7, 2011 to May 11, 2015.
PK Analytical site: (b) (4)

Objectives:
The primary objective of this study was to assess the pharmacokinetics and immunogenicity of adalimumab in patients requiring systemic corticosteroids for inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Formulation & Administration:
Adalimumab subcutaneous (SQ) injection, 80 mg (50 mg/mL) dose at baseline followed by 40 mg doses every other week (eow) starting at Week 1 using Pre-filled syringes.

Study Design:
This was a phase 3, randomized, double-masked, placebo-controlled, multicenter study to investigate the efficacy and safety of adalimumab. Efficacy was assessed in patients with inactive non-infectious intermediate, posterior or pan-uveitis for ≥ 28 days and who required chronic oral corticosteroids with oral prednisone ≥ 10 mg/day (or oral corticosteroid equivalent) to maintain this inactive disease. Overall study design is provided in Figure 1.

Figure 1: Study Design: Study M10-880 (source: Report R&D/15/0207 Figure 1)



* The study was to end when approximately 96 (84 to 107) treatment failures (in ex-Japan subjects only) had occurred.
a. Corticosteroid taper occurred from Weeks 2 up to Week 19.
† May have been on 1 immunosuppressive therapy and/or topical steroids at pre-defined stable doses.

A total of 261 patients including 229 patients in Australia, Canada, Europe, Israel, Latin America, and the US (main study) and 32 Japanese patients (Japan sub-study) were enrolled in the study. Overall, patients' disposition is shown in Table 1. Three patients from the main study were excluded from the pharmacokinetic analysis due to the followings:

- One placebo subject (Subject [redacted]) due to incomplete efficacy source data
- Two placebo patients (Subjects [redacted] and [redacted]) due to general compliance issues

Patients were randomized 1:1 to receive either adalimumab treatment or placebo. Baseline immunosuppressant (IMM) criteria was also used as the stratification factor. In total, 131 patients were randomized to adalimumab treatment and 15 of them terminated early; 130 patients were randomized to placebo and 17 of them discontinued the study. Patients' disposition is shown in Table 3. Patients were also on oral prednisone 10 to 35 mg/day at Baseline (or oral corticosteroid equivalent) to ensure that such patients were dependent on their current corticosteroid usage to maintain disease control and now required systemic immunosuppressive therapy to allow further reduction of their corticosteroids.

Table 1: All Patietns Disposition: Study M10-880 (source: Report R&D/15/0207 Table 3)

	Study M10-880		
	Adalimumab	**Placebo**	**Total**
Enrolled	131	130	261
Included in Pharmacokinetic Analysis	131	127	258
Excluded	0	3	3
Subjects early termination	15	17	32
Completed Week 80	31	17	48
Completed < Week 80[a]	28	18	46
Treatment failure	57	75	132

a. Subjects who had to terminate the study because the planned number of treatment failures was reached.

Starting at Week 2 and every visit thereafter, all patients were assessed for Treatment Failure based on the criteria described in Table 2. Patients from both arms were to follow a protocol-defined mandatory prednisone taper schedule. Demographic summary for patients included in the PK analysis is provided in Table 3.

Table 2: Treatment Failure Criteria by Study Visit: Study M10-880 (source: Report R&D/15/0207 Table 1)

Parameter	Treatment Failure[a] Week 2 Visit and All Other Visits After Week 2
Inflammatory, chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Baseline
Anterior Chamber Cell grade (SUN criteria)	2-step increase in AC cell grade relative to Baseline[b]
Vitreous Haze grade (NEI/SUN criteria)	2-step increasein VH grade relative to Baseline[b]
Visual Acuity (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI = National Eye Institute; SUN = Standardization of Uveitis Nomenclature

a. To be considered a treatment failure, ≥ 1 of these 4 criteria need to be present in at least 1 eye.

b. A 2-step increase is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

Table 3: Baseline Demographic Summary for Patients Included in the Pharmacokinetic Analysis: Study M10-880 (source: Report R&D/15/0207 Table 4)

		Mean ± SD (Range)		
		Total (N = 258)	Adalimumab (N = 131)	Placebo (N = 127)
Age (yr)		43.1 ± 13.4 (18 – 79)	43.2 ± 12.7 (18 – 75)	43.0 ± 14.0 (20 – 79)
Weight (kg)		76.9 ± 19.7 (42 – 183)[a]	76.8 ± 17.4 (45 – 153)[b]	76.9 ± 21.9 (42 – 183)[c]
Height (cm)		167 ± 10.2 (138 – 207)[a]	168 ± 10.5 (142 – 207)[b]	166 ± 9.86 (138 – 190)[c]
			N (%)	
Sex	Male	98 (42.1)	53 (44.9)	45 (35.4)
	Female	157 (60.9)	75 (57.3)	82 (64.6)
Race	White	189 (73.3)	96 (73.3)	93 (73.2)
	Black	38 (14.7)	19 (14.5)	8 (6.3)
	Other	31 (12.0)	16 (12.2)	26 (20.5)

Other = Asian, American Indian/Alaska native, multi race and other

a. N = 256.

For the pharmacokinetic and immunogenicity assessments, blood samples were obtained at baseline, and at Weeks, 8, 12, 27, 36, and 52 or at the final/early termination visit. Amongst these sampling time points, baseline, and Week 27 blood samples were drawn prior to dosing.

Assay Method:

Adalimumab concentrations in serum were determined using a validated enzyme –linked immunosorbent assay (ELISA) method. The validated analytical range of the assay was 3.125 to 50 ng/mL. The lower limit of quantitation (LLOQ) for adalimumab was 31.3 ng/mL in undiluted human serum and 3.125 ng/mL in diluted serum. In-study quality control sample concentrations were 40, 240 and 380 ng/mL of adalimumab. The accuracy and precision was satisfactory (CV ≤ 10.7%).

Results:

The mean serum adalimumab concentrations ranged from 8.5 to 9.53 µg/mL. In some patients, serum adalimumab concentrations were below detectable level after Week 8. Overall, summary of serum adalimumab concentrations from all patients who received adalimumab treatment is presented in Table 4.

Table 4: Summary of Serum Adalimumab Concentrations (µg/mL) for Patients with Uveitis: Study M10-880 (source: Report R&D/15/0207 Table 5)

Mean ± SD (Range), N						
Week						
0	2	8	12	27	36	52
Non-Japanese Subjects in the Main Study (N = 115)						
0 ± 0 (0 – 0), 115	9.85 ± 3.74 (0.311 – 21.0), 114	8.68 ± 5.08 (0 – 25.0), 100	9.68 ± 5.39 (0 – 23.9), 90	9.48 ± 7.11 (0 – 46.8), 63	9.24 ± 5.62 (0 – 28.8), 54	8.93 ± 5.23 (0 – 27.1), 41
All Subjects in the Study (N = 131)						
0 ± 0 (0 – 0), 131	10.1 ± 3.79 (0.311 – 21.0), 130	8.50 ± 5.17 (0 – 25.0), 113	9.53 ± 5.36 (0 – 23.9), 97	9.36 ± 7.00 (0 – 46.8), 70	9.01 ± 5.63 (0 – 28.8), 59	8.72 ± 5.28 (0 – 27.1), 43
Japanese Subjects in the Sub-Study (N = 16)						
0 ± 0 (0 – 0), 16	11.7 ± 3.90 (0.859 – 17.7), 16	7.45 ± 5.93 (0.097 – 19.0), 13	7.53 ± 4.94 (1.50 – 16.2), 7	8.26 ± 6.32 (0 – 14.9), 7	6.53 ± 5.76 (0 – 13.1), 5	4.58 ± 6.47 (0 – 9.15), 2

Table 5: Summary of Serum Adalimumab Concentrations (µg/mL) by Treatment Failure: Study M10-880 (source: Report R&D/15/0207 Table 6)

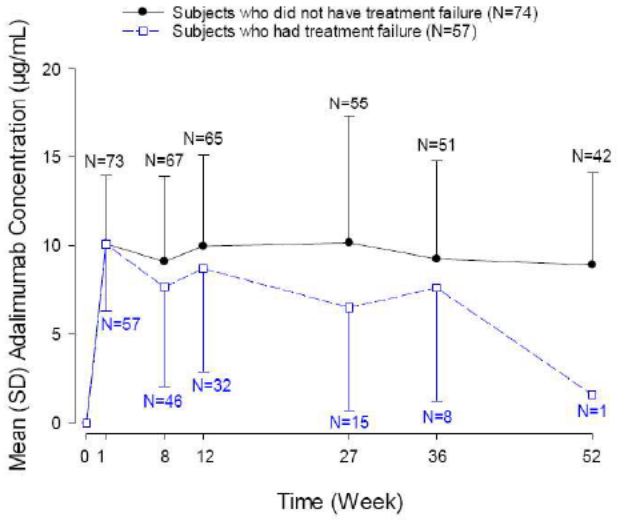
Treatment Failure[a]	Mean ± SD (Range), N						
	Week						
	0	2	8	12	27	36	52
All Subjects in the Study (N = 131)							
No (N = 74)	0 ± 0 (0 – 0), 74	10.1 ± 3.85 (0.311 – 21.0), 73	9.09 ± 4.82 (0 – 25.0), 67	9.94 ± 5.11 (0.461 – 22.4), 65	10.1 ± 7.15 (0 – 46.8), 55	9.23 ± 5.55 (0 – 28.8), 51	8.89 ± 5.23 (0 – 27.1), 42
Yes (N = 57)	0 ± 0 (0 – 0), 57	10.1 ± 3.74 (0.859 – 17.7), 57	7.65 ± 5.59 (0 – 21.6), 46	8.69 ± 5.82 (0 – 23.9), 32	6.50 ± 5.78 (0 – 19.5), 15	7.60 ± 6.38 (1.62 – 20.5), 8	1.58 1

a. For subjects who had treatment failure, their treatment failure samples were at different weeks.

When stratified by incidence of treatment failure, the mean serum adalimumab concentrations after Week 8 ranged from 6.5 to 8.69 µg/mL and from 8.89 to 10.1 µg/mL, in patients with and without treatment failure, respectively. Overall, summary of serum adalimumab concentrations stratified by treatment failure is presented in Table 5.

The comparison of mean serum adalimumab concentrations between patients with and without treatment failure is shown in Figure 2.

Figure 2: Mean (SD) Serum Adalimumab Concentrations Versus Time by Occurrence of Treatment Failure: Study M10-880 (source: Report R&D/15/0207 Figure 3)



Sponsor's conclusions:
Following 80 mg SQ dose of adalimumab at baseline and 40 mg eow at Week 1, the mean serum adalimumab concentrations reached steady state levels by Week 2 (8 – 10 µg/mL) and were maintained constant through Week 52. The mean serum adalimumab concentrations were slightly higher in patients who did not have treatment failure compared to those who had treatment failure, starting from Week 8.

Reviewer's Assessment:
Similar to the findings of M10-877, the mean serum adalimumab concentrations were slightly higher in patients who did not have treatment failure. However, due to the observed variability, concentration rage was overlapping in patients with and without treatment failure, except at Week 52. Additionally, in this study also, some patients with successful outcome had undetectable levels of adalimumab concentrations in serum. These findings support the previously indicated weak exposure-response relationship.

4.1.3. Study M11-327

This phase 3 Open-label multicenter study is ongoing and is scheduled to be completed in 2018. Patients enrolled in this study were either, enrolled in Study M10-877 or Study M10-880 and also, either met the endpoint of treatment failure, completed the study, or remained in the study until the study was stopped. Primary objective of this study is to assess long-term safety and efficacy of 40 mg SQ adalimumab maintenance dose given eow in patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis. To Reviewer's knowledge, this study does not include any Clinical Pharmacology relevant assessments.

4.1.4. Impact of Adalimumab Immunogenicity on Pharmacokinetics, Efficacy, and Safety in Study M10-877 and Study M10-880

As per the pre-sBLA meeting agreement on 07 July 2015, the Sponsor has provided this study report on impact of immunogenicity on adalimumab PK, efficacy, and safety using the new drug-tolerant Anti-Adalimumab Antibody (AAA) assay.

Report Title:

Immunogenicity Assessment of Adalimumab Using New Drug-Tolerant Anti-Adalimumab Antibody (AAA) Assay in Patients with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis Based on Phase 3 Studies M10-877 and M10-880

Objectives:

To assess the impact of immunogenicity on the pharmacokinetics, efficacy, and safety of adalimumab treatment: 80 mg SQ loading dose followed by 40 mg SQ dose given eow starting at Week 1, using the new drug-tolerant AAA assay in the 2 pivotal Phase 3 studies i.e., Studies M10-877 and M10-880.

Methodology for Evaluation:

In Study M10-877, out of 239 enrolled patients, 119 patients received adalimumab treatment and 118 were included in this assessment. In Study M10-880, out of 261 enrolled patients, 131 patients received adalimumab treatment and all were included in this assessment.

Following the adalimumab treatment, blood samples were collected previously during these studies at the following time points:

For PK assessment:

Study M10-877- at baseline, and at Weeks 1, 8, 12, 27, 36, and, 52 or at the final/early termination visit

Study M10-880- at baseline, and at Weeks, 8, 12, 27, 36, and 52 or at the final/early termination visit

For Immunogenicity assessments:

At Baseline, Weeks 12, 27, 36, and 52; and at the final/early termination visit when the patient terminated prior to Week 52, an unscheduled visit before Week 52 if applicable. Baseline and Week 27 samples for serum AAA concentration were drawn prior to dosing.

Further details regarding patients' disposition and study design for Studies M10-877 and M10-880 can be found in section 4.1.1 and 4.1.2.

New Drug Tolerant AAA assay:

With the new drug-tolerant tittering AAA assay, the determination of AAA in human serum samples was carried out using a combination of screening and confirmatory assays to determine the presence of AAA and, using a titer assay to approximate their relative amounts. The detection method was developed and validated using a bridging immunoassay, which employs electrochemiluminescence (ECL) detection technology base on the Mesoscale Discovery™ assay platform.

Results:

Immunogenicity rates:

The AAA rates determined using the previously utilized assay method, which is referred as "current assay", and the rates based on new drug-tolerant AAA assay are summarized in Table 1.

Table 1: Rates of Titer Measurement Using Current and New Drug-Tolerant AAA Assay (source: Report R&D/15/1161 Table 2)

	Current AAA Assay	New Drug-Tolerant AAA Assay		
Study	AAA+ Rate	Titer ≥ 10	Titer ≥ 100	Titer ≥ 1000
M10-877[a]	3.4% (4/118)	35.6% (42/118)	23.7% (28/118)	6.8% (8/118)
M10-880	6.1% (8/131)	43.5% (57/131)	26.0% (34/131)	9.9% (13/131)
Total	4.8% (12/249)	39.8% (99/249)	24.9% (62/249)	8.4% (21/249)

Titer ≥ 10: Subjects had any AAA samples with AAA titer ≥ 10.

Titer ≥ 100: Subjects had any AAA samples with AAA titer ≥ 100.

Titer ≥ 1000: Subjects had any AAA samples with AAA titer ≥ 1000.

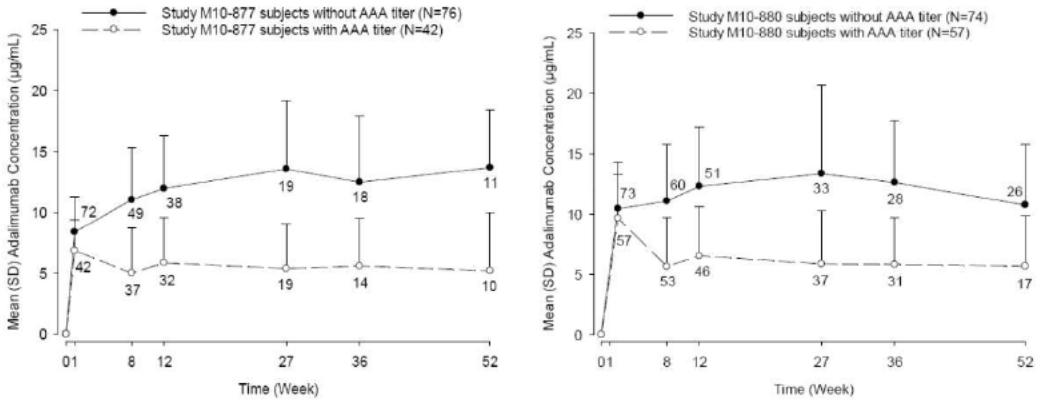
a. One adalimumab subject (Subject (b) (6)) was excluded from the PK and immunogenicity summary analysis due to general compliance issues.

In all patients treated with adalimumab 80 mg at baseline followed by 40 mg eow starting at Week 1, the percentage of patients with any titer ≥ 10, ≥ 100, or ≥ 1000 in Studies M10-877 and M10-880 (combined) was 39.8% (99/249), 24.9% (62/249) and 8.4% (21/249), respectively.

Impact of Immunogenicity on Pharmacokinetics:

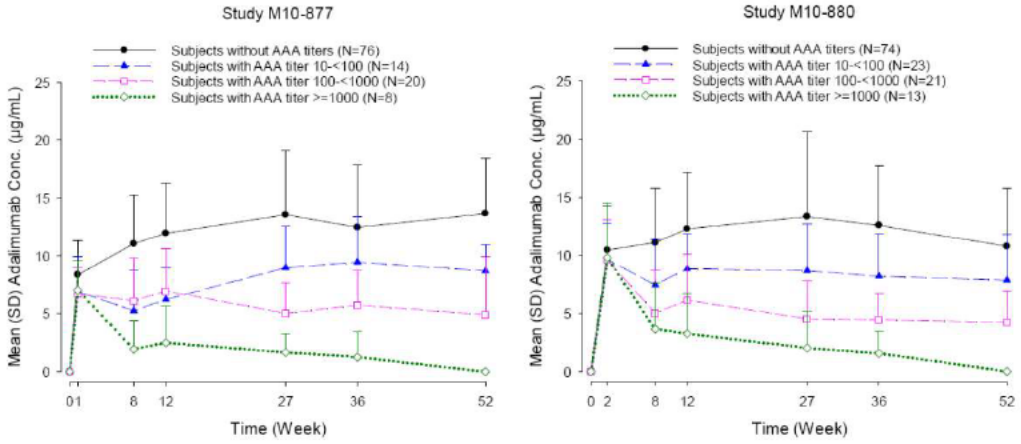
The mean and standard deviation (SD) adalimumab concentration over time comparison in patients with any measurable AAA titer (AAA+) and those without any measurable AAA titer (AAA-) using the new drug-tolerant AAA say in Studies M10-877 and M10-880 is shown in Figure 1. Overall, mean adalimumab concentrations appeared lower in AAA+ patients compared to AAA- patients, and the concentrations remained lower throughout the study in AAA+ patients. In order to further explore the impact of different levels of AAA titers measured on the serum concentrations of adalimumab, patients were grouped into the three AAA titer category: no titer, a titer of 10 – <100, a titer of 100 – < 1000, and a titer of ≥ 1000; and mean serum adalimumab concentrations were compared.

Figure 1: Comparison of Mean (SD) Adalimumab Concentration by AAA Titer Measurement Status with New Drug-Tolerant AAA Assay (source: Report R&D/15/1161 Figure 1)



Note: The numbers at each time point in the figures represent the total N.

Figure 2: Comparison of Mean (SD) Adalimumab Concentration in Subjects Developing Different AAA Titer Levels (source: Report R&D/15/1161 Figure 2)



Impact of Immunogenicity on Efficacy:

The primary efficacy endpoint was time to treatment failure, which was assessed at or after Week 6 for Study M10-877 and at or after Week 2 for Study M10-880. Even though the mean adalimumab serum concentrations appeared lower in AAA+ patients, the estimate of time-to-treatment failure appeared to be comparable (Table 2).

In Study M10-877, the estimate of time to treatment failure appeared to be longer in AAA+ patients compared to AAA- , however, the failure rate was similar between both the titer groups (Table 2). Overall, there was no clear impact of AAA titers measured using the new drug-tolerant assay on the efficacy of adalimumab in patients with non-infectious uveitis (Figure3).

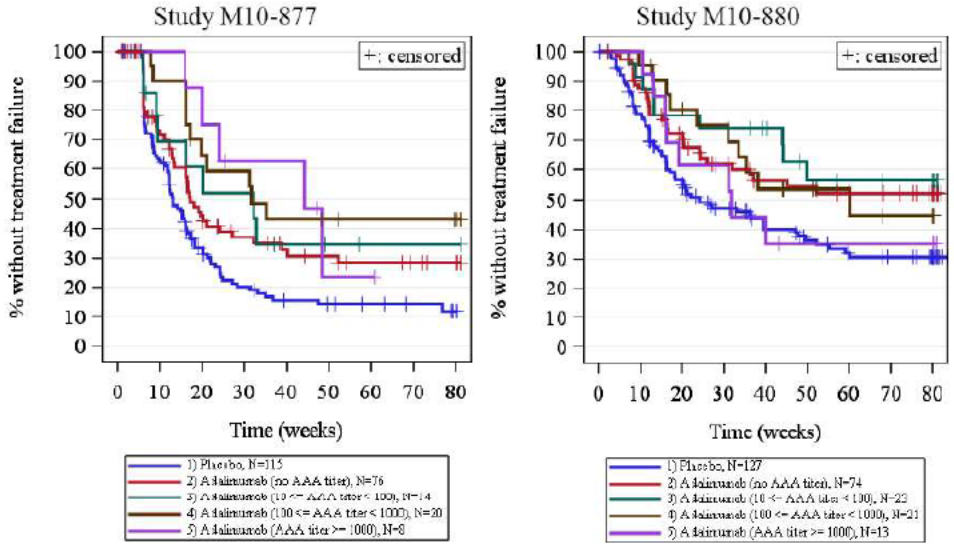
Table 2: Time to Treatment Failure by AAA Titer Status (Using AAA Titer Cutoff of 10) with New Drug-Tolerant AAA Assay (source: Report R&D/15/1161 Table 10.4 1)

Study	AAA Titer Group	N	Failure N (%)	Median Time to Failure (Weeks)
M10-877	Placebo	115	90 (78.3)	13.1
	Adalimumab (Without AAA titer)	76	44 (57.9)	17.1
	Adalimumab (With AAA titer ≥ 10)	42	24 (57.1)	32.1
M10-880	Placebo	127	75 (59.1)	24.1
	Adalimumab (Without AAA titer)	74	30 (40.5)	NE
	Adalimumab (With AAA titer ≥ 10)	57	27 (47.3)	60.1

Note: Treatment failure at or after Week 6 (M10-877) and Week 2 (M10-880) was counted as event.
NE= Not estimable; Fewer than half of at-risk subjects had an event

In Study M10-880, the time to treatment failure appeared to be shorter in AAA+ when compared to AAA- patients, and the failure rate was higher in patients with higher AAA titer values (Table 2). Additionally, the risk of treatment failure appeared to be similar in patients with AAA titer levels greater than 1000 and in patients who received placebo (Figure3).

Figure 3: Comparison of Time-to-Treatment Failure in Subjects Developing Different AAA Titer Levels Measured with New Drug-Tolerant AAA Assay (source: Report R&D/15/1161 Figure 4)



Impact of Immunogenicity on Safety:

An overview of the safety for all patients who received adalimumab treatment stratified by AAA status using different titer cut-off from the new drug-tolerant AAA assay in Study M10-877 and Study M10-880 is provided in Table 3 and Table 4.

Table 3: Overview of Number and Percentage of All Subjects with Treatment Emergent AEs Stratified by New Drug-Tolerant AAA Assay Titer Cutoff: Study M10-877 (source: Report R&D/15/1161 Table 3)

	Titer Cutoff 10		Titer Cutoff 100		Titer Cutoff 1000	
	No AAA Titer	AAA ≥ 10	AAA < 100	AAA ≥ 100	AAA < 1000	AAA ≥ 1000
Subjects with:	(N = 77) n (%)	(N = 42) n (%)	(N = 91) n (%)	(N = 28) n (%)	(N = 111) n (%)	(N = 8) n (%)
Any AE	65 (84.4)	36 (85.7)	76 (83.5)	25 (89.3)	93 (83.8)	8 (100)
Any serious AE	9 (11.7)	7 (16.7)	13 (14.3)	3 (10.7)	15 (13.5)	1 (12.5)
Any AE leading to discontinuation of study drug	7 (9.1)	4 (9.5)	8 (8.8)	3 (10.7)	10 (9.0)	1 (12.5)
Any severe AE	8 (10.4)	6 (14.3)	11 (12.1)	3 (10.7)	14 (12.6)	0
Any AE at least possibly drug related[a]	25 (32.5)	21 (50.0)	31 (34.1)	15 (53.6)	41 (36.9)	5 (62.5)
Any SAE at least possibly drug related[a]	3 (3.9)	3 (7.1)	4 (4.4)	2 (7.1)	6 (5.4)	0
Any infectious AE	31 (40.3)	21 (50.0)	36 (39.6)	16 (57.1)	46 (41.4)	6 (75.0)
Any serious infectious AE	2 (2.6)	3 (7.1)	3 (3.3)	2 (7.1)	4 (3.6)	1 (12.5)
Any oral candidiasis	1 (1.3)	0	1 (1.1)	0	1 (0.9)	0
Any tuberculosis (active or latent)	0	2 (4.8)	1 (1.1)	1 (3.6)	2 (1.8)	0
Any malignancy	1 (1.3)	1 (2.4)	2 (2.2)	0	2 (1.8)	0
Any malignancy other than lymphoma, hepatosplenic T-cell lymphoma, leukaemia, non-melanoma skin cancer or melanoma	1 (1.3)	1 (2.4)	2 (2.2)	0	2 (1.8)	0
Any allergic reaction including angioedema/anaphylaxis	6 (7.8)	4 (9.5)	7 (7.7)	3 (10.7)	10 (9.0)	0
Any lupus-like reactions and systemic lupus erythematosus	0	1 (2.4)	0	1 (3.6)	1 (0.9)	0
Any sarcoidosis	0	1 (2.4)	0	1 (3.6)	1 (0.9)	0
Any demyelinating disorder	1 (1.3)	0	1 (1.1)	0	1 (0.9)	0
Any hematologic disorders including pancytopenia	2 (2.6)	0	2 (2.2)	0	2 (1.8)	0
Any injection site reaction related AE	5 (6.5)	2 (4.8)	5 (5.5)	2 (7.1)	6 (5.4)	1 (12.5)
Any AE leading to death	1 (1.3)	0	1 (1.1)	0	1 (0.9)	0

SAE = Serious adverse event

a. As assessed by investigator.

In the safety analysis for all patients, the rate of any AEs and any serious AEs was comparable between AAA+ patients and AAA- patients. However, the Sponsor notes that the number of patients with a titer ≥ 1000 (N = 8 for Study M10-877, N = 13 for Study M10-880) is too small to make a definitive conclusion on the impact of immunogenicity on safety.

Table 4: Overview of Number and Percentage of All Subjects with Treatment Emergent AEs Stratified by New Drug-Tolerant AAA Assay Titer Cutoff: Study M10-880 (source: Report R&D/15/1161 Table 4)

	Titer Cutoff 10		Titer Cutoff 100		Titer Cutoff 1000	
	No AAA Titer	AAA ≥ 10	AAA < 100	AAA ≥ 100	AAA < 1000	AAA ≥ 1000
Subjects with:	(N = 74) n (%)	(N = 57) n (%)	(N = 97) n (%)	(N = 34) n (%)	(N = 118) n (%)	(N = 13) n (%)
Any AE	67 (90.5)	50 (87.7)	88 (90.7)	29 (85.3)	106 (89.8)	11 (84.6)
Any serious AE	5 (6.8)	3 (5.3)	6 (6.2)	2 (5.9)	8 (6.8)	0
Any AE leading to discontinuation of study drug	8 (10.8)	3 (5.3)	10 (10.3)	1 (2.9)	11 (9.3)	0
Any severe AE	5 (6.8)	7 (12.3)	8 (8.2)	4 (11.8)	12 (10.2)	0
Any AE at least possibly drug related[a]	40 (54.1)	27 (47.4)	53 (54.6)	14 (41.2)	63 (53.4)	4 (30.8)
Any SAE at least possibly drug related[a]	1 (1.4)	2 (3.5)	2 (2.1)	1 (2.9)	3 (2.5)	0
Any infectious AE	39 (52.7)	31 (54.4)	51 (52.6)	19 (55.9)	62 (52.5)	8 (61.5)
Any serious infectious AE	1 (1.4)	1 (1.8)	1 (1.0)	1 (2.9)	2 (1.7)	0
Any oral candidiasis	1 (1.4)	0	1 (1.0)	0	1 (0.8)	0
Any tuberculosis (active or latent)	2 (2.7)	1 (1.8)	3 (3.1)	0	3 (2.5)	0
Any non-melanoma skin cancer (NMSC)	1 (1.4)	0	1 (1.0)	0	1 (0.8)	0
Any malignancy	1 (1.4)	1 (1.8)	2 (2.1)	0	2 (1.7)	0
Any malignancy other than lymphoma, hepatosplenic T-cell lymphoma, leukaemia, non-melanoma skin cancer or melanoma	0	1 (1.8)	1 (1.0)	0	1 (0.8)	0
Any allergic reaction including angioedema/anaphylaxis	4 (5.4)	1 (1.8)	5 (5.2)	0	5 (4.2)	0
Any vasculitis	0	1 (1.8)	0	1 (2.9)	1 (0.8)	0
Any sarcoidosis	4 (5.4)	1 (1.8)	5 (5.2)	0	5 (4.2)	0
Any hematologic disorders including pancytopenia	2 (2.7)	0	2 (2.1)	0	2 (1.7)	0
Any liver failure and other liver event	2 (2.7)	0	2 (2.1)	0	2 (1.7)	0
Any injection site reaction related AE	13 (17.6)	11 (19.3)	16 (16.5)	8 (23.5)	20 (16.9)	4 (30.8)
Any AE leading to death	1 (1.4)	0	1 (1.0)	0	1 (0.8)	0

SAE = Serious adverse event

a. As assessed by investigator.

Overall, immunogenicity did not appear to have a significant impact on the safety of adalimumab in non-infectious uveitis patients.

Sponsor's Conclusion:

Adalimumab concentrations trended lower in AAA+ patients compared to AAA- patients, with the greatest impact observed at AAA titers ≥ 1000. Even though adalimumab serum concentrations appeared lower in AAA+ patients, the estimate of time-to-treatment failure appeared to be comparable. No new safety risks were identified. Despite the observed higher rates immunogenicity in the phase 3 studies using the new drug-tolerant AAA assay, compared to rates determined by the current assay, titer measurement did not seem to have an impact on the efficacy of adalimumab. Compared to the current assay, the results of analyses using the new drug – tolerant AAA assay suggest that the titers measured have limited clinical relevance.

Reviewer's Assessment:
Results obtained with the new drug-tolerant assay supports the previously noted impact of immunogenicity on adalimumab pharmacokinetics. However, no new safety risks were identified and this new information on immunogenicity does not appear to have any robust clinical relevance in uveitis patients.

The previously reported combined immunogenicity rate for both phase 3 studies: M10-877and M10-880 was 4.8%. This rate was determined based on the current AAA assay, which had a drug interference issue; therefore, 4.8 % immunogenicity rate was assumed to be an underestimate. The revised immunogenicity rate for both phase 3 studies is 39.8%, and at maximum titer level (≥1000), immunogenicity rate is 8.4%. Therefore, these findings indicate that the current assay may not capture all the immunogenicity incidences, even at the highest titer level (≥1000).

Given the clear and proportional impact of presence of AAA on the PK of adalimumab, any further PK characterization efforts should accommodate the immunogenicity rate that is determined with the new drug-tolerant AAA assay.

4.2. Cover sheet and ocpb filing/review form

(Excerpts from the filing form submitted on October 10, 2015)

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125057	**SDN**	5339
Applicant	AbbVie Inc.	**Submission Date**	09/03/2015
Generic Name	Adalimumab	**Brand Name**	Humira™
Drug Class	anti-TNF monoclonal antibody		
Indication	For the treatment of non-infectious uveitis (efficacy supplement)		
Dosage Regimen	Initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose		
Dosage Form	Adalimumab injection	**Route of Administration**	Subcutaneous
OCP Division	IV	**OND Division**	DTOP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Abhay Joshi, Ph.D.	Philip Colangelo Pharm. D., Ph.D.	
Pharmacometrics	TBD	Jeffry Florian, Pharm.D	
Genomics	-		
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	11/2/2015	**74-Day Letter Date**	11/16/2015
Review Due Date	5/29/2016	**PDUFA Goal Date**	7/3/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		

1

Reference ID: 3837103

In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	2	M10-877 and M10-880 were similar in the study design but differed in the study populations due to key eligibility and baseline disease severity criteria (Refer to Table 1 below for specific selection criteria)
☐ Mass Balance Study			
☑ Immunogenicity		2	M10-877 and M10-880
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		2	Active non-infectious uveitis patients in M10-877 and inactive non-infectious uveitis patients in M10-880 (Refer to Table 1 below for specific selection criteria)
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		1	Combined population pharmacokinetic analysis for pharmacokinetic data for M10-877 and M10-880
☑ Exposure-Efficacy		2	Separate Exposure-Response analysis for M10-877 and M10-880
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	2
Total Number of Studies to be Reviewed				2

2

Reference ID: 3837103

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Pharmacokinetic data submitted for both M10-877 and M10-880
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Refer note section below for additional information regarding anti-adalimumab antibody (AAA) assay
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	Refer note section below for additional information
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	☑Yes ☐No ☐N/A	

3

previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	Exposure–response analysis is submitted for the desired effect
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	Refer note section below for additional information on dose selection rationale
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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/s/

ABHAY JOSHI
10/22/2015

PHILIP M COLANGELO
10/22/2015

Reference ID: 3837103

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/s/

ABHAY JOSHI
05/26/2016

JEFFRY FLORIAN
05/26/2016

PHILIP M COLANGELO
05/26/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s397

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 8, 2016

To: Ei Thu Z. Lwin, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Humira® (adalimumab) Injection, for subcutaneous use
BLA 125057/S-397

On November 24, 2015, DTOP consulted OPDP to review the draft Package Insert (PI), Medication Guide (MG) and Instructions for Use (IFU) for Humira® (adalimumab), for subcutaneous use (Humira) for the supplemental BLA submission (supplement 397), which provides for a proposed new indication for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

OPDP conducted a focused review of the proposed substantially complete version of the PI, MG, and IFU provided by DTOP via e-mail on June 1, 2016 titled "BLA 125057_s397_uveitis_Draft Labeling CLEAN.doc". OPDP has no comments on the PI, MG or IFU.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/

MEENA RAMACHANDRA
06/08/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	June 7, 2016
To:	Renata Albrecht, MD Director **Division of Transplant and Ophthalmology Products (DTOP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	HUMIRA (adalimumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 125057
Supplement Number:	S-397
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On September 3, 2015, AbbVie, Inc. submitted for the Agency's review an Efficacy Supplement for HUMIRA (adalimumab) injection, for subcutaneous use. The purpose of this submission is to support the use of HUMIRA for the following indication:

- *The treatment of non-infectious intermediate, posterior and panuveitis in adult patients*.

HUMIRA was originally approved on December 31, 2001 and is indicated for the treatment of:

- **Rheumatoid Arthritis (RA)**: Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA)**: Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- **Psoriatic Arthritis (PsA)**: Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS)**: Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD)**: Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- **Pediatric Crohn's Disease**: Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC)**: Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps)**: The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or

phototherapy, and when other systemic therapies are medically less appropriate.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on November 24, 2015 for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for HUMIRA (adalimumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft HUMIRA (adalimumab) injection, for subcutaneous use MG and IFU received on September 3, 2015 and received by DMPP on June 1, 2016.
- Draft HUMIRA (adalimumab) injection, for subcutaneous use Prescribing Information (PI) received on September 3, 2015 and received by DMPP on June 1, 2016.

3 REVIEW METHODS

In our focused review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFUs is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
06/07/2016

MARCIA B WILLIAMS
06/07/2016

LABEL, LABELING, AND PACKAGING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 23, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125057/S-397
Product Name and Strength:	Humira (adalimumab) Injection 40 mg/0.8 ml and 40 mg/0.4 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Abbvie
Submission Date:	September 3, 2015 and March 23, 2016
OSE RCM #:	2015-2588
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This memorandum evaluates the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton labeling for BLA 125057/S-397, Humira (Adalimumab), submitted on September 3, 2015 (initial submission) and March 23, 2016 [submitted updated carton labeling based upon the March 9, 2016 approval of the Humira (adalimumab) 40 mg/0.4 mL (100 mg/mL) modified autoinjector (Pen)] . Abbvie is proposing a new indication for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients (Uveitis).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Abbvie is proposing a new indication for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients (Uveitis). The proposed dose and frequency for Uveitis is 80 mg initial dose, followed by 40 mg every other week starting one week after the initial dose. Abbvie is also proposing to add this indication to the currently approved Plaque Psoriasis starter pack. The currently approved Humira dosage forms and strengths support the proposed Uveitis dose and frequency. We find the addition of the Uveitis indication to the Plaque Psoriasis starter pack acceptable because both indications require the same dose and frequency.

In addition, Abbvie did not propose any significant changes to the IFU and DMEPA did not identify any issues. Also, the Prescribing Information adequately reflects the proposed Uveitis dose and frequency.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the proposed labeling acceptable and do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Humira (adalimumab) that Abbvie submitted on September 3, 2015 and March 23, 2016.

Table 2. Relevant Product Information for Humira	
Initial Approval Date	December 31, 2002
Active Ingredient	Adalimumab
Indication	Treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis, Ulcerative Colitis, and Hidradenitis Suppurativa
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	20 mg/0.4 mL, 40 mg/0.4 mL, 40 mg/0.8 mL
Dose and Frequency	Dose ranges from 10 mg to 160 mg depending on the indication
How Supplied	Single-use Prefilled syringe, Single-use Pen, Single-use vial for institutional use only
Storage	Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F) and should be protected from exposure to light.
Proposed Additions to Humira (Adalimumab)	Indication-Uveitis

APPENDIX B. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Prednisone Tablets, USP labels and labeling submitted by Abbvie on September 3, 2015 and March 23, 2016.

- Carton labeling

G.2 Label and Labeling Images

Carton labeling

40 mg/0.4 mL

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
05/23/2016

MISHALE P MISTRY
05/24/2016

Clinical Inspection Summary

Date	5/11/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, GCPAB/DCCE/OSI Janice Pohlman, M.D., M.P.H., Team Leader, GCPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB/DCCE/OSI
To	Eithu Lwin Pharm.D., Regulatory Project Manager DTOP Jennifer Harris M.D., Medical Officer DTOP William Boyd M.D., Team Leader DTOP
BLA #	BLA 125057 S-397
Applicant	AbbVie, Inc.
Drug	Humira (adalimumab)
NME	No
Therapeutic Classification	Standard
Proposed Indication(s)	Treatment of non-infectious intermediate, posterior and panuveitis in adults
Consultation Request Date	11/19/2015
Summary Goal Date	5/11/2016
Action Goal Date	6/20/2016
PDUFA Date	7/3/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 125057, S-397, three clinical investigator sites were inspected. These inspections did not reveal significant regulatory violations and no Form FDA 483s were issued. Based on results of these clinical investigator inspections, it appears that the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies appear to have been conducted adequately.

These inspections are preliminarily classified as No Action Indicated (NAI). Establishment Inspection Reports (EIRs) have been received and reviewed for two of the clinical sites, the EIR for the third site is pending. Classification will be finalized when the inspection correspondence is issued to the inspected entity.

Observations noted above are based on communications with the field, an inspection summary addendum will be generated if conclusions change upon completion of review of the third outstanding EIR.

II. BACKGROUND

HUMIRA (adalimumab) for subcutaneous use was approved in the U.S. in 2002. HUMIRA is a tumor necrosis factor blocker and is indicated for the treatment of arthritis (rheumatoid, juvenile

idiopathic (JIA), psoriatic (PsA)), ankylosing spondylitis (AS), Crohn's disease, ulcerative colitis and plaque psoriasis. The sponsor, AbbVie, submitted an efficacy supplement (S- 397) to BLA 125057 in support of the efficacy and safety of HUMIRA in the treatment of non-infectious intermediate, posterior and panuveitis in adults. The sponsor submitted two Phase 3 studies in support of the safety and efficacy of adalimumab for the treatment of non-infectious uveitis. Study M10-877 was performed in subjects with active uveitis and Study M10-880 was performed in subjects with inactive uveitis.

Protocol M10-877: A multicenter study of the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab as maintenance therapy in subjects requiring high dose corticosteroids for active non-infectious intermediate uveitis, posterior uveitis, or panuveitis – including a sub-study in Japanese patients

Treatment Groups: adalumumab, placebo

Subjects: 223 subjects in North America (30 sites, including 22 in the United States), Europe (30 sites), Asia (9 sites), Australia (2 sites) and South America (3 sites).

Study Initiation/Completion: August 10, 2010 – August 29, 2014

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to investigate the safety and efficacy of adalimumab in subjects who had previously shown adequate clinical response to oral corticosteroids but now had active non-infectious intermediate uveitis, posterior uveitis, or panuveitis in at least one eye despite at least 2 weeks of oral prednisone or oral corticosteroid equivalent. The study included a screening period, a double-blind treatment period and a follow-up period. After the screening period, subjects were randomized 1:1 to adalimumab or matching placebo and randomization was stratified by baseline immunosuppressant usage. The maximum double-blind treatment period was to end after 80 weeks or when the 138th treatment failure occurred.

Study drug was administered subcutaneously. Subjects received adalimumab as an 80 mg loading dose at baseline followed by 40 mg doses every other week starting at Week 1 or placebo. Both treatment arms received a standardized open-label prednisone dose of 60 mg/day at study entry followed by a protocol-defined mandatory taper schedule in which all subjects were to discontinue prednisone no later than Week 15.

Included were subjects with non-infectious uveitis, posterior uveitis, or panuveitis with active disease at baseline and on oral prednisone for at least two weeks prior to screening. Subjects were allowed to continue on one ongoing non-biologic immunosuppressant if the dose had not been increased within 28 days prior to baseline, the dose was to remain unchanged throughout the study and doses were to be within limits indicated in protocol.

The primary efficacy endpoint was the time to treatment failure comparing the adalimumab and placebo arms. 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). The sponsor reported a statistically significant reduction in the risk of treatment failure in subjects treated with adalimumab compared to subjects receiving placebo. The median time to treatment failure was 5.6 months for subjects treated with adalimumab and 3 months for subjects receiving placebo (Hazard ratio 0.50; 95% CI 0.36, 0.70; $p < 0.001$). One of the secondary efficacy endpoints was time to optical coherence tomography (OCT) evidence of

macular edema.

Protocol M10-880: A multicenter study of the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis – including a sub-study in Japanese patients

Treatment Groups: adalumumab, placebo

Subjects: 229 subjects in North America (28 sites; including 22 sites in the US), Europe (27 sites), South America (4 sites), Australia (2 sites) and Asia (2 sites)

Study Initiation/Completion: August 10, 2010 - May 14, 2015

The study design for Protocol M10-880 was very similar to Protocol M10-877. Protocol M10-880 was conducted in subjects with inactive uveitis requiring chronic corticosteroid treatment at baseline. Per protocol, subjects followed a mandatory prednisone taper in which all subjects were to discontinue prednisone no later than Week 19. The primary efficacy endpoint was the time to treatment failure comparing the adalimumab and placebo arms.

The sponsor reported a statistically significant reduction of the risk of treatment failure in subjects treated with adalimumab compared to subjects receiving placebo. The median time to treatment failure was not estimable (fewer than half of the subjects had an event) for subjects treated with adalimumab and 8.3 months for subjects receiving placebo (Hazard ratio 0.57; 95% CI 0.39, 0.84; $p < 0.004$). One of the secondary efficacy endpoints was time to optical coherence tomography (OCT) evidence of macular edema.

Inspections of clinical sites were considered essential to verify the quality of conduct of the studies for this BLA application. Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site, prior inspectional history, protocol violations and enrollment of subjects into both clinical trials (the site selection tool was not available for this application). The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events and verification of the primary endpoint.

III. RESULTS (by site)

Site #, Name of CI, Address	Protocol # and # of Subjects	Inspection Date	Classification
Site #2016 David Scales, MD Foresight Studies, LLC Suite 101 9623 Huebner Road San Antonio, TX	M10-877: 19 subjects M10-880: 8 subjects	1/25/2016 – 2/2/2016	Pending Interim classification = NAI

Site #, Name of CI, Address	Protocol # and # of Subjects	Inspection Date	Classification
Site #2012 Pauline Merrill, MD Illinois Retina Associates Suite 945 1725 West Harrison Chicago, IL	M10-877: 2 subjects M10-880: 6 subjects	3/21/2016 – 4/19/2016 (7 days)	Pending Interim classification = NAI
Site #2030 Pouya Dayani, MD Retina Vitreous Associates Medical Group Suite 301 9001 Wilshire Boulevard Beverly Hills, CA	M10-877: 11 subjects M10-880: 3 subjects	3/14/2016 – 4/20/2016	Pending Interim classification = NAI

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Clinical Investigator:** David Scales, MD; San Antonio, TX; Site #2016

For Protocol M10-877, twenty-one subjects were consented and screened, nineteen subjects were enrolled and seven subjects completed the study. Of the twelve subjects discontinuing the study, nine met criteria for treatment failure (primary efficacy endpoint), two were lost to follow-up and one discontinued due to an adverse event. For Protocol M10-880, eight subjects were consented, screened and enrolled and one subject completed the study. Of the seven subjects discontinuing the study, five met criteria for treatment failure, one was lost to follow-up and one withdrew consent. An audit of the study records for ten subjects, six for Protocol M10-877 and four for Protocol M10-880, was conducted.

Signed consent forms were on file for each subject reviewed. Additional records reviewed included, but were not limited to, source documents, adverse event reports, drug accountability, subject dosing diaries, IRB communications, financial disclosure, protocol deviations, certifications as required by protocol (e.g. approved optical coherence tomography [OCT] machine, photographer and system certification for fundus photography), primary and secondary efficacy endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. Minor discrepancies were noted for site values obtained for central retinal thickness derived from the OCT machine and values recorded on the corresponding CRF. A Form FDA 483 was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately at this site and the data submitted by this site appear acceptable in support of the pending

application.

2. **Clinical Investigator:** Pauline Merrill, MD; Chicago IL; Site #2012

For Protocol M10-877, four subjects were consented and screened, two subjects were enrolled and no subjects completed the study. The two subjects who discontinued the study met criteria for treatment failure (primary efficacy endpoint). For Protocol M10-880, seven subjects were consented and screened, six subjects were enrolled and two subjects completed the study. Of the four subjects who discontinued the study, two met criteria for treatment failure and two discontinued due to an adverse event. Disposition of subjects was difficult to determine based on the screening/enrollment logs at this site; disposition was confirmed via data listings. An audit of the study records for eight subjects, two for Protocol M10-877 and six for Protocol M10-880, was conducted.

Signed consent forms were on file for each subject reviewed. Additional records reviewed included, but were not limited to, source documents, inclusion/exclusion criteria, adverse event reports, drug accountability, IRB/sponsor communications, financial disclosure, protocol deviations, primary and secondary efficacy endpoints.

Review of records noted discrepancies between source documents (OCT machine report) and corresponding site-recorded central retinal thickness values on the CRF/OCT site-recorded data listings.

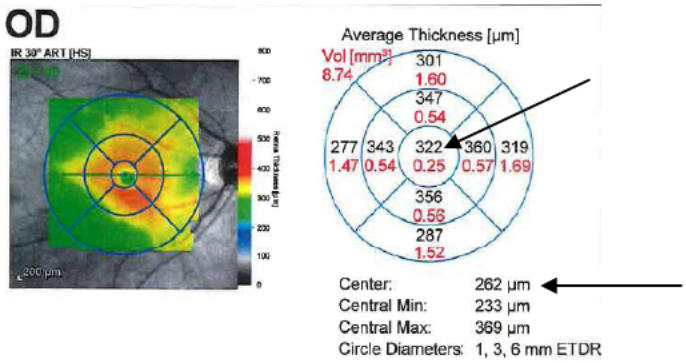
Discrepancies were noted for Protocol M10-880 for OCT readings by site for three of five subjects reviewed. OCT readings to assess central retinal thickness were obtained using an approved OCT machine (Spectralis). The largest discrepancies were noted for subject (b) (6) (see table below). For this subject, values for central retinal thickness recorded on the worksheet (paper CRF) were ~60 microns lower than values obtained/reported by the Spectralis machine. Values recorded manually on the worksheet were entered into the eCRF and are included in the OCT site-recorded data listings. Discrepancies for subject (b) (6) ranged from 11 – 28 microns and discrepancies for subject (b) (6) ranged from 17 – 35 microns, the number recorded on the CRF always a lower value than that noted by the OCT machine.

Subject (b) (6)

	Right Eye (OD)			Left Eye (OS)		
Visit	Source (Spectralis)	CRF*	Difference	Source (Spectralis)	CRF*	Difference
Screening	322	262	60	282	215	67
Baseline	321	259	62	281	215	66
Week 2	323	267	56	285	218	67
Week 4	323	261	62	285	221	64
Week 8	327	259	68	280	214	66
Week 12	321	268	53	280	218	62
Week 16	319	253	66	283	218	65
Week 20	328	254	74	288	217	71

Source: Establishment Inspection Report
*CRF reading recorded by site

The reason for this error was that the study coordinator was recording the value for the most central point in the retina instead of the average thickness of the center circle (1 mm subfield) of the diagram of the retina. For example, in the figure shown below, the study coordinator entered the value of 262 µm rather than 322 µm. OCTs were used to assess retina thickness as a measure of macular edema, a secondary endpoint in the trial.



The site had noted some discrepancies and had previously corrected them for some subjects but the site did not extend their review of this issue to all subjects. The study protocol also included an OCT assessment by a central reader for consistency. The protocol states "OCT measurements at every visit will be captured and sent to the central reader. The central reader will evaluate the OCT images and record these findings". It is unclear how, or if, this site's OCT readings/measurements were used in any efficacy or safety assessments for the study.

During the inspection, Dr. Merrill educated her staff and developed a checklist tracking form for reviewing the transfer of machine generated data to case report forms for future clinical trials. This form includes verification by the investigator (e.g. Dr. Merrill).

Another protocol deviation was noted in which subject (b) (6) was enrolled in M10-880 but did not appear to meet inclusion criterion 5 "subject must have a documented history of experiencing at least one disease flare within 18 months of the screening visits; this flare has to occur during or up to a maximum of 28 days after tapering off the oral corticosteroid therapy". There was no documentation that the subject experienced a flare during or up to 28 days after tapering off of prednisone. This protocol deviation was noted by the sponsor's monitor and was reflected in the data listings for this application.

A Form FDA 483 was not issued at the conclusion of the inspection.

In general, although discrepancies existed for OCT readings by site, it does not appear that these discrepancies would have significant impact on the results of this

secondary endpoint for this clinical trial because of the central OCT assessment. Otherwise, the studies appear to have been conducted adequately and the data submitted by this site appear acceptable in support of the pending application.

3. **Clinical Investigator:** Pouya Dayani, MD; Beverly Hills, CA; Site #2030

For Protocol M10-877, fifteen subjects were consented and screened, eleven subjects were enrolled and no subjects completed the study. All eleven subjects who discontinued this study met criteria for treatment failure (primary efficacy endpoint). For Protocol M10-880, seven subjects were consented and screened, three subjects were enrolled and two subjects completed the study. The subject who discontinued the study met criteria for treatment failure. An audit of the study records for all fourteen enrolled subjects was conducted.

Signed consent forms were on file for each of the fourteen subjects enrolled in these studies. Additional records reviewed included, but were not limited to, source documents, inclusion/exclusion criteria, concomitant medications, adverse event reports, laboratory reports, drug accountability, training documents (e.g. electronic capture, CGP, protocol), certifications as required by protocol (e.g. approved optical coherence tomography [OCT] machine, photographer and system certification for fundus photography), IRB/sponsor communications, subject dosing diaries, financial disclosure, protocol deviations, primary and secondary efficacy endpoints.

Review of records noted above revealed some discrepancies but no regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection.

The primary endpoint for these clinical trials was time to treatment failure as defined in the protocol. The protocol states "if a subject meets treatment failure criteria but is not withdrawn (Final/Early Termination visit completed) within 14 days following confirmation of treatment failure at a visit, this will be considered a protocol deviation. Subject (b) (6), enrolled in M10-877, met treatment failure at Week 20 ((b) (6)), but was not discontinued until 21 days later ((b) (6)). It appears that personnel at the site misunderstood the best-corrected visual acuity (BCVA) treatment failure criterion. The treatment failure definition for this particular assessment is "worsening by $\geq$ 15 letters relative to best state achieved" while personnel thought the worsening was compared to baseline. The subject's dosing diary indicated that the subject took one dose of study drug ((b) (6)) after meeting treatment failure. It is unclear how this error was detected such that the subject could be discontinued 21 days later; the next scheduled study visit would have been Week 24. The sponsor's monitor had noted this deviation and it is included in protocol deviations in the submission. The IRB was also notified of this deviation. One other subject enrolled in M10-877 ((b) (6)) was discontinued ~ 14 days after meeting treatment failure criteria. The reason for the delayed discontinuation was that the subject could not remain in the clinic to complete all assessments for early termination and could not return until two weeks later.

Protocol deviations were also noted for the storage temperature of the prednisone tablets. Per protocol, prednisone was to be stored at 15-25°C. Temperature excursions occurred from 4/2012 to 9/2013 and were slightly higher (26-27°C) than the protocol-defined range. It is unknown how significant this deviation is to the stability of the prednisone tablets. The sponsor noted this deviation and the IRB was also notified. There were no storage temperature deviations noted for study drug (adalimumab or placebo).

In general, the studies appear to have been conducted adequately at this site and the data submitted by this site appear acceptable in support of the pending application. The two subjects enrolled in M10-877 who were withdrawn ~14 and 21 days after meeting criteria for treatment failure were receiving the active study drug, adalimumab. Since the primary endpoint is the time to treatment failure, it is not known if these deviations would impact the overall efficacy results. These deviations were reported in Appendix 16.2_2.2.M (Protocol Deviations) of the BLA submission.

{See appended electronic signature page}

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Memo for Proposed Pregnancy and Lactation Labeling Rule Language

Date:	4/18/2016
Reviewer(s):	Efe Eworuke, PhD, Epidemiologist Division of Epidemiology II
Team Leader	Margie R. Goulding, PhD, Epidemiologist Acting Deputy Director Division of Epidemiology II
Division Director	CDR David Moeny, M.P.H, R.Ph., USPHS, Acting Director Division of Epidemiology II
Subject	Pregnancy and Lactation Labeling Rule (PLLR) Language
Drug Name(s):	Adalimumab (Humira®)
Application Type/Number:	IND 007627
Applicant/sponsor:	Abbvie
OSE RCM #:	2016-274

1 INTRODUCTION

Humira® (adalimumab) is a tumor necrosis factor blocker (anti-TNF) approved in December 2002 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults. Subsequent approved indications include psoriatic arthritis (2005), ankylosing spondylitis (2006), Crohn's disease (2007), plaque psoriasis (2008), juvenile idiopathic arthritis (2008) and ulcerative colitis (2012). At the first approval in 2002, the sponsor committed to conduct a pregnancy registry study of adalimumab-exposed women with RA. The registry was initially planned to run for three years, from June 2003 through June 2006. However, in 2009 the pregnancy registry was expanded to include women with Crohn's disease (CD), due to low recruitment of RA patients. The registry enrollment period was also extended to 2015 to accommodate recruitment efforts.

The objectives of the pregnancy registry include estimating the risk of birth defects and other adverse pregnancy outcomes in children born to women with RA who were exposed to adalimumab (ADA) during pregnancy; identifying patterns of these outcomes compared to RA ADA-unexposed women and non-RA controls and comparing the rate of birth defects to a cohort from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) population based birth defects surveillance program.

On March 17, 2016 DPARP held a meeting to assess the proposed pregnancy lactation labeling (PLL) language for adalimumab with the Divisions of Epidemiology II (DEPI), Gastroenterology and Inborn Errors Products (DGEIP) and Pediatric and Maternal Health (DPMH). At that meeting, it was decided that major malformation incidence rates for only the RA cohort should be included in the language since data collection for the CD arm of the registry has yet to be concluded. DEPI recommended that the previous DEPI reviews be re-examined to assure that there is agreement between the proposed PLL language and data reported. (b) (4)

(b) (4)

1.1 REPORT REVIEW HISTORY

Following the initiation of the pregnancy registry (in 2003), the Division of Epidemiology II (DEPI) reviewed the 9th (dated February, 2012)[1] and 10th interim (dated January, 27 2014)[2] reports. For both reports, the study had met the pre-planned recruitment goals for the RA cohort analysis. Therefore both DEPI reviews focused on the RA arm of the analysis, and not the CD analysis. From the 10th interim report, the DEPI reviewer concluded that the RA registry is not statistically powered to identify risks of major birth defects less than 9-fold with adalimumab exposure. The reviewer further stated that the higher incidence of spontaneous abortion and small for gestation age observed among RA patients may be due to confounding by indication, since the

[1] Cynthia Kornegay. Epidemiology: Assessment of preliminary data for completed adalimumab pregnancy registry (OSE RCM#: 2012:2222)

[2] Jie Li: Review of the Revised Annual (10th Interim) Report of the Humira pregnancy registry (OSE RCM#: 2014-381)

registry did not control for RA disease severity during the pregnancy. Based on this review, several recommendations were communicated to the sponsor on October 30, 2014. The 11th interim report dated February 13, 2015 addressed these recommendations, the two most important of which were to: 1) define study outcomes and revisions to the denominator population for each outcome and 2) present incidence rates by disease state - RA and CD. The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) asked DEPI to determine whether a review of the 11th report was necessary, given that the 10th annual report was reviewed on September, 15 2014. DEPI examined the report and determined that only 2 patients in the CD-exposed group and 5 patients in the CD-unexposed group had been recruited since the last report and there was no change in the number of patients in the RA arm of the study. In addition, there was no formal statistical analysis in the report.[3] Therefore DEPI concluded that no formal review of the 11th interim report was warranted. DEPI recommended conducting a formal review of the final report that is due in January 2017.

2 DEPI'S ASSESSMENT OF PROPOSED PREGNANCY LACTATION LABELING RULE (PLLR) LANGUAGE

2.1 RELEVANT SECTION OF THE LABELING LANGUAGE

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab- exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. (b) (4)

(b) (4)

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[3] Efe Eworuke: Memorandum to File: Response to 11th annual interim clinical study report for Humira pregnancy registry

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4 REFERENCES

1. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54(1):26-37.
2. Heiberg MS, Rodevand E, Mikkelsen K, et al. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. *Ann Rheum Dis.* 2006;65(10):1379-1383.
3. Carvalheiras G, Faria R, Braga J, Vasconcelos C. Fetal outcome in autoimmune diseases. *Autoimmun Rev.* 2012;11(6-7):A520-530.
4. Barnabe C, Faris PD, Quan H. Canadian Pregnancy Outcomes in Rheumatoid Arthritis and Systemic Lupus Erythematosus. *International Journal of Rheumatology.* 2011;2011:6.
5. de Man YA, Hazes JM, van der Heide H, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum.* 2009;60(11):3196-3206.
6. Bowden AP, Barrett JH, Fallow W, Silman AJ. Women with inflammatory polyarthritis have babies of lower birth weight. *J Rheumatol.* 2001;28(2):355-359.

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/s/

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Division of Pediatric and Maternal Health Memorandum

Date: March 18, 2016 **Date consulted:** October 26, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Drug: Humira (adalimumab)

BLA: 125057/S-397

Applicant: AbbVie

Subject: Pregnancy and Lactation Labeling

Current Indications: For the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing arthritis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps) and Hidradenitis Suppurativa.

Proposed Indication: For the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

Materials Reviewed:

- DPMH consult request dated October 26, 2015, DARRTS Reference ID 3838181
- Applicant's submitted background package for Humira (adalimumab), BLA 125057/S-397
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Jeanine Best, MSN, RN, PNP. March 13, 2013. DARRTS Reference ID 3275320
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Miriam Dinatale, DO. March 25, 2014. DARRTS Reference ID 3476883
- Division of Pediatric and Maternal Health review of 9th interim report of the adalimumab pregnancy registry report 2012, IND 7627. Carrie Ceresa, PharmD, MPH. December 26, 2012. DARRTS Reference ID 3236313
- Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679
- Division of Pediatric and Maternal Health review of 11th interim report of the adalimumab pregnancy registry report, IND 7627. Miriam Dinatale, D.O. July 15, 2015. DARRTS Reference ID 3791839

Consult Question:

DPARP would like to seek DPMH input on the PLLR language for the draft label submitted to BLA 125057 Humira (adalimumab)/S-397.

INTRODUCTION

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 26, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Humira (adalimumab) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF) and is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing arthritis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps) and Hidradenitis Suppurativa. Humira was approved in the US on December 31, 2002. On September 3, 2015, AbbVie submitted an efficacy supplement for Humira (adalimumab), BLA 125057/S-397, for a new indication for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients. AbbVie also updated labeling to comply with the PLLR format.

BACKGROUND

Adalimumab and Drug Characteristics

Adalimumab binds to TNF-alpha (α) and blocks its interaction with p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF is increased in patients with RA, JIA, PsA, and

AS. The exact mechanism of action of adalimumab is unknown. Adalimumab has a molecular weight of 148,000 Daltons and a mean terminal half-life of two weeks. [1]

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

LITERATURE REVIEW

Nonclinical Experience

Current Humira labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of Humira in 2002. No additional nonclinical studies were submitted with this NDA. In perinatal development studies, there was no evidence of embryofetal toxicity in pregnant cynomolgus monkeys administered adalimumab during organogenesis at doses 373 times the maximum recommended human dose (MRHD). There are no studies with adalimumab that evaluate its carcinogenic potential or its effects on fertility. The reader is referred to the Nonclinical Review by Eleni Salicru, Ph.D. for further details.

Adalimumab and Pregnancy

In addition to providing results of the Humira Pregnancy Exposure Registry and internal clinical trials data, the applicant performed a literature review in BIOSIS Previews, Derwent Drug File, Embase, Embase Alert, International Pharmaceutical Abstracts, MEDLINE, and SciSearch to obtain any new information on adalimumab use during pregnancy. DPMH also conducted a search in PubMed, Embase, ReproTox[4], and TERIS[5] to evaluate the use of adalimumab in pregnant women. A review of the available published literature conducted by the applicant and DPMH to support changes to adalimumab labeling is provided below.

The TERIS database notes that there are no adequate and well-controlled studies with adalimumab in pregnant women. However, in studies that have been performed with adalimumab use during pregnancy there was no increased risk of fetal anomalies compared with women not treated with adalimumab.

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[1] Humira (adalimumab) labeling. Section 12: Clinical Pharmacology. Drugs @FDA. Accessed 11/2/2015.
[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[3] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[4] ReproTox database, Truven Health analytics, Micromedex solutions, 2016
[5] TERIS database, Truven Health Analytics, Micromedex Solutions, 2016.

In a prospective comparative observational study (Diav-Citrin, *et al*.) performed at the Israeli Information Service between 2002 and 2011, 83 pregnancies exposed to anti-TNF-α drugs during the first trimester of pregnancy (35 on infliximab, 25 on etanercept, 23 on adalimumab) were compared to 86 disease-matched pregnancies (not on treatment) and 341 non-teratogenic-exposed pregnancies. Out of the 23 patients taking adalimumab, there was one major congenital malformation (ventricular septal defect that spontaneously closed at six months of age) that occurred. Overall, the rate of major congenital malformations included the following: 4.6% in the anti-TNF-α group, 6.4% in the disease-matched group and 2.4% in the non-teratogenic-exposed group. The authors concluded that anti-TNF-α treatment does not appear to increase the risk of major congenital malformations but noted that the number of pregnancies exposed to anti-TNF-α treatment was small and larger studies are needed. [6]

Reviewer comments:
DPMH agrees with the authors' conclusions.

In an observational study (Schnitzler, *et al*.), 212 women with inflammatory bowel disease (IBD) were studied. Out of 196 pregnancies that were identified, seven pregnancies had exposure to adalimumab. Of the seven pregnancies, five pregnancies resulted in live births of healthy infants and two pregnancies resulted in elective terminations. In one elective termination, a 37 year-old patient with CD terminated her pregnancy at gestational week 13 due to a diagnosis of trisomy 18. The patient had been receiving adalimumab (40mg) weekly during the first trimester of pregnancy. In another pregnancy, the patient was diagnosed with an empty amniotic sac, and the pregnancy was terminated (gestational age not provided). The authors noted that the study is limited by the small number of pregnancies and that larger prospective studies are needed to determine the effects of anti-TNF agents, such as adalimumab, on fetal development. [7]

Reviewer comments:
DPMH agrees with the authors' conclusions.

In a prospective study conducted between 2006 and 2011 (Zelinkova, *et al*.), 31 pregnant women with IBD, who were treated with anti-TNF agents (infliximab (n=18) and adalimumab (n=13)), were followed. Enzyme-linked immunosorbent assays were used to measure the levels of anti-TNF-α agents in cord blood collected six infants whose mothers took adalimumab. Among women taking adalimumab, there were two spontaneous abortions (6 weeks gestation and 8 weeks gestation) and no congenital malformations were observed. Adalimumab was detected in five samples (mothers discontinued adalimumab between gestational weeks 21 to 26) of cord blood (mean concentration, 1.7± 0.4 microgram/mL); in

[6] Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol. 2014;43:78-84.
[7] Schnitzler F, Fidder H, Ferrante M, et al: Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflamm Bowel Dis 2011; 17(9):1846-1854.

one cord blood sample (mother discontinued adalimumab at 22 weeks gestation), there was no detectable level of adalimumab. [8]

In a prospective observational study conducted in three centers in the Czech Republic between 2007 and 2012 (Bortilik, *et al*.), 41 pregnancies (27 CD patients; 14 UC patients) were exposed to either infliximab (n=32) or adalimumab (n=9). Of the patients treated with adalimumab, one SAB occurred in a woman with CD with a history of multiple abortions prior to anti-TNF-α treatment and one elective abortion occurred in a patient due to personal circumstances. The authors noted that the pregnancy course and outcomes with anti-TNF-α treatment did not demonstrate an increased risk of fetal malformations (no major fetal malformations were noted), spontaneous abortions (12% rate) and low birth weight (3%) compared to the general population. However, the authors noted that the study is limited by the lack of a control group of IBD patients not exposed to anti-TNF-α treatment and a small number of patients in the study. [9]

Reviewer comments:
DPMH agrees with the authors' conclusions.

In a cohort study of 154,976 performed between 2004 and 2007 (Viktil, *et al*.), pregnancies registered in the Medical Birth Registry of Norway were linked to the Norwegian Prescription Database. There were 1461 women exposed to anti-rheumatic drugs; three women out of the 1461 women were exposed to adalimumab. None of the children born to women who had received adalimumab during pregnancy was born with a major congenital malformation. The authors noted that it is difficult to draw any conclusion about fetal risk with adalimumab use during pregnancy due to the small numbers of pregnant women exposed to adalimumab in the study. [10]

Reviewer comments:
DPMH agrees with the authors' conclusions.

In a prospective observational multi-center cohort study (Weber-Schoendorfer, *et al*.) conducted from 1998 to 2013, data from exposed pregnant women (women exposed to more than one dose of one of the five approved anti-TNF-α drugs: adalimumab, infliximab, certolizumab, etanercept, golimumab) from 11 institutions from nine countries within the European Network of Teratology Information Services were compared to data from unexposed pregnant women (healthy patients not taking any teratogenic drugs). Pregnancy outcomes were available for 495 exposed women (adalimumab (n=172), infliximab (n= 168), etanercept (n= 140), certolizumab (n= 7), golimumab (n= 3). Five patients had double exposure: adalimumab + etanercept (n=3) and adalimumab + infliximab (n=2)) and 1532

[8] Zelinkova A et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clinical Gastroenterology and Hepatology. 2013 11:318-321.
[9] Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. Scand J Gastroenterol. 2013; 48(8):951-8.
[10] Viktil et al. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150 000 pregnant women and expectant fathers. 2012 Scand J Rheumatol 41:196-201.

unexposed women. There rate of birth defects[11] were as follows: 6% (n=9) in the adalimumab group, 4.5% in the infliximab group, and 5.4% in the etanercept group. The overall rate of major congenital malformations was 5% in the anti-TNF-α exposed group compared to 1.5% in the unexposed group. In addition, there was in increase in preterm births and lower birth weights in the anti-TNF-α exposed group compared to the unexposed groups. The authors noted that although the rate of fetal malformations was higher in the anti-TNF-α exposed group, there was no distinct pattern of malformations. In addition, the authors noted that the results of their study may be due to either the drug toxicity during pregnancy or to the underlying disease and its activity.[12]

Review comment:
Although the study above demonstrates an increased rate of birth defects in pregnant women treated with anti-TNF-α drugs, the exposed pregnancies were compared to a healthy population and not to diseased comparison group. Therefore, it is difficult to attribute the increase in birth defects to the anti-TNF-α drugs since disease activity and flares during pregnancy may have affected pregnancy outcomes.

In three review articles (Grunewald, *et al*., Leung, *et al*., and Ostensen, M.), the authors note there are over 300 reports of pregnancies (case reports, cohort studies, case-control studies) in women taking adalimumab. There is no evidence of increased rates of fetal malformations or spontaneous abortions that have been reported after the administration of adalimumab in the first trimester of pregnancy. Since adalimumab passes into fetal circulation in the second and third trimester of pregnancy, infants born to mothers who took adalimumab during pregnancy are at an increased risk of infection. However, there are no current reports of infection observed in infants exposed to adalimumab *in utero.* [13,14,15]

Summary:
Overall, published literature, regarding the use of adalimumab during pregnancy, does not show an increase in adverse events (fetal malformations, reduced birth weight, spontaneous abortions). Since the transport of monoclonal antibodies into fetal circulation increases in the second and third trimester of pregnancy, there is a theoretical concern that the infant of a mother exposed to adalimumab is at an increased risk for infection. However, publications evaluating children who have been exposed to adalimumab in utero have not reported evidence of a consistent pattern of adverse events, including an increased incidence of infection.

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[11] Observed birth defects included the following: hexadactyly of both feet, atrial septal defect, esophageal atresia with tracheo-esophageal fistula, ventricular septal defect, syndactyly, pulmonary stenosis, cavum septum pellucidum, hip dysplasia, imperforate anus, hemangioma, amniotic band sequence with talipes and amputation of four fingers of the right hand, and cystic adenomatoid malformation of the right lung

[12] Weber-Schoendorfer, et al. Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study. British Journal of Clinical Pharmacology. 2015; 80 (4): 727-739.

[13] Grunewald S, Jank A. New systemic agents in dermatology w with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015;13(4):277-89.

[14] Ostensen, M. Safety issues of biologics in pregnant patients with rheumatic diseases. Annals of the New York Academy of Sciences. 2014. 1317: 32-38.

[15] Leung YPY, Panaccione R, Ghosh S, et al. Management of the pregnant inflammatory bowel disease patient on antitumour necrosis factor therapy: state of the art and future directions. Can J Gastroenterol Hepatol. 2014;28(9):505-9.

Humira Pregnancy Exposure Registry[16,17]

The applicant updated the text in the "Human Data" subsection of section 8.1 based on the results of their pregnancy registry. The Organization of Teratology Information Specialists (OTIS)[18] Collaborative Research Group conducted a prospective cohort study in the U.S. and Canada between 2004 and 2013 OTIS (Chambers, *et al*.), comparing the pregnancy outcomes of 74 adalimumab-exposed women with RA, 80 women with RA but without adalimumab exposure, and 218 non-diseased women (control). DPMH has reviewed interim reports of the adalimumab pregnancy exposure registry, and the reader is referred to the DPMH reviews by Carrie Ceresa, PharmD, MPH and Miriam Dinatale, D.O. for further details.[19,20,21]

Women in the adalimumab-exposed group had at least one dose of adalimumab in the first trimester of pregnancy with 43% of patients continuing adalimumab throughout the entire pregnancy. The disease severity was similar between both disease-matched groups. The rate of major birth defects in the adalimumab-exposed, the disease-matched (adalimumab-unexposed), and non-diseased comparison group were 5.6%, 7.8% and 5.5%, respectively. There was no difference in the rate of minor malformations among the three groups.

The applicant noted that in women with RA, the adalimumab-exposed group had a higher percentage of spontaneous abortions (SAB) compared to adalimumab -unexposed women (9% vs. 3.8%). The rate of SAB of clinically recognized pregnancies in the general population is between 15 to 20%. However, the number of SABs was small with seven events in the adalimumab -exposed cohort and three events in the adalimumab -unexposed cohort. The rate of preterm delivery and small-for-gestational age infants did not differ among the three groups.

Summary

The applicant concluded that pregnant women with RA who used adalimumab in the first trimester of pregnancy compared to women with RA who were not treated with adalimumab, did not appear to be at an increased risk for adverse fetal outcomes and included the results of the Humira Pregnancy Exposure Registry in the "Human Data" subsection of adalimumab labeling. DPMH reviewed the published literature and the results of the Humira Pregnancy Exposure Registry provided by the applicant, and agrees that the rates of fetal malformations observed in the Humira Pregnancy Exposure Registry should be included in the "Human Data" section of Humira labeling.

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[16] Chambers, et al. Pregnancy Outcome in Women Treated with Adalimumab for the Treatment of Rheumatoid Arthritis: An Update on the OTIS Autoimmune Disease in Pregnancy Project. Gastroenterology. 2015; 148(4): S405.

[17] Chambers, et al. Pregnancy Outcome in Women Treated with Adalimumab for the Treatment of Rheumatoid Arthritis: An Update on the OTIS Autoimmune Disease in Pregnancy Project. Arthritis Rheumatol. 2014; 66: S361.

[18] OTIS is a network of teratogen information centers serving pregnant women and health care providers throughout North America.

[19] Division of Pediatric and Maternal Health review of 9th interim report of the adalimumab pregnancy registry report 2012, IND 7627. Carrie Ceresa, PharmD, MPH. DARRTS Reference ID 3236313

[20] Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679.

[21] Division of Pediatric and Maternal Health review of 11th interim report of the adalimumab pregnancy registry report, IND 7627. Miriam Dinatale, D.O. July 15, 2015. DARRTS Reference ID 3791839.

Placental Transfer of Adalimumab

Current Humira labeling has the following statement regarding the placental transfer of monoclonal antibodies in "Clinical Considerations":

> *In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.*

The applicant updated the text in the "Clinical Considerations" subsection of section 8.1 based on a review of published literature, which showed an exponential increase in fetal IgG1 exposure with gestational age.[22,23] The applicant noted that the published literature[24,25] used to support the current statement in "Clinical Considerations" does not have supporting data to justify the description. Therefore, the applicant proposed modifications of the statement as noted below:

> *Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester.*

Transplacental immunoglobulin G (IgG) slowly disappears from infant circulation and is generally completely cleared by six months of age.[26] Section 5.10 of Humira labeling notes that "patients on HUMIRA may receive concurrent vaccinations, except for live vaccines." Section 8.4 of Humira labeling notes that "the clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants."[27] Therefore, infants who have been exposed to Humira *in utero* should not receive live vaccines until six months of age.

DPMH proposes that the following statement appear in Humira labeling:

> *Fetal/Neonatal Adverse Reactions*
> *Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [see Data]. Avoid administering live vaccines to infants exposed to HUMIRA in utero up to six months of age [see Warnings and Precautions (5.10] and Use in Specific Populations (8.4)).*

Adalimumab and Lactation

In addition to searching through internal clinical trials data, the applicant performed a literature review in BIOSIS Previews, Derwent Drug File, Embase, Embase Alert,

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[22] Malek, et al. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol. 1996; 36(5): 248.55.

[23] Gitlin, D. Serum alpha-fetoprotein, albumin, and gamm-G-globulin in the human conceptus. J Clin Invest. 1966: 45(11): 1826-38.

[24] Mahadevan, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterology Hepatology. 2013; 11(3): 286-92.

[25] Palmeira, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012; 2012: 985646.

[26] www.primaryimmune.org. Accessed 3/4/2016.

[27] Current Humira (adalimumab) labeling. Warnings and Precautions, Section 5.10 and Use in Specific Populations(8.4)

International Pharmaceutical Abstracts, MEDLINE, and SciSearch to obtain information on adalimumab use during breastfeeding. DPMH also conducted a review of published literature in PubMed and Embase, using the search terms "adalimumab," and "lactation/breastfeeding," and also reviewed data related to adalimumab use during lactation in *Medications and Mother's Milk*[28] and the Drugs and Lactation Database (LactMed).[29] A review of the available published literature is provided below.

In one case report (Ben-Horin, *et al*.) a 26-year-old female with CD was taking adalimumab during pregnancy until week 30 of gestation. She gave birth to a healthy infant at 38 weeks gestation and experienced a flare-up of CD at four weeks post-partum. The mother decided to restart adalimumab and to continue breastfeeding; the patient consented to testing for adalimumab in her breastmilk. Maternal blood and breast milk sample were obtained before and every two days for eight days after adalimumab (40mg) administration. Sample collection stopped at day eight when the patient decided to stop breastfeeding (no reason provided). Following injection of adalimumab, adalimumab level rose in the maternal serum peaking at day three at 4300 ng/mL and declining after day three. The adalimumab milk:plasma (M/P) ratio was <1%. The level of drug in the maternal breast milk rose from undetectable (pre-adalimumab injection) to 31 ng/mL of post-injection day six. No infant serum samples were drawn, and there were no reported adverse effects on the infant. The authors noted that small quantities of adalimumab would be present in breast milk and would be further broken down in the infant after ingestion. However, the authors noted that further studies would be needed to determine if even low levels of adalimumab would have an effect on an infant. [30]

Reviewer comment:
DPMH agrees with the authors' conclusion in the study reviewed above.

In another case report (Fritzsche, *et al*.) [31], the authors reported on two patients who were treated with adalimumab 40mg for treatment of inflammatory bowel disease at unstated intervals. The detection limit of the assay for adalimumab in breast milk was 40ng/ml.

- One patient was treated with adalimumab throughout pregnancy with the last injection 3.5 weeks prior to delivery. The mother resumed adalimumab after delivery and started breastfeeding. Twenty-one weeks postpartum and seven days after the last adalimumab injection, adalimumab concentration in the maternal serum was found to be 6700 ng/mL (6.7 microgram/mL) and M/P ratio was < 0.1%

[28] Hale, T. Medications and Mother's Milk. Hale Publishing, 2012.
[29] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[30] Ben-Horin S, Yavzori M, Katz L et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010;8:475-6
[31] Fritzsche J, Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46:718-9

(4.83 ng/mL). The corresponding infant's serum could not be analyzed (reason not provided). Besides developing acute spasmodic laryngitis (a common disease in young infants) at 10 months of age, the infant had normal growth and development at the time of evaluation at 14.5 months of age.

- In another patient taking adalimumab while breastfeeding, maternal serum and breastmilk samples were taken eight weeks postpartum and nine days after the last adalimumab injection. The maternal serum concentration of adalimumab was 5500 ng/mL (5.5 microgram/mL) and the breast milk concentration of adalimumab was 4.88ng/mL (M/P: 0.08%). Adalimumab was undetectable in the infant's serum. The infant had no reported adverse events and had normal growth and development at the time of physician evaluation at 15 months of age.

Overall, the authors noted that adalimumab is present in breastmilk, but adalimumab was not detectable in the serum of one of the infants studied (<0.65 mcg/L). The authors determined that long-term consequences of adalimumab exposure during breastfeeding are unknown and further studies are needed.

Reviewer comment:
According to current labeling, the maximum serum concentration (Cmax) and the time to reach the maximum concentration (Tmax) are 4.7 ±1.6 microgram/mL (range 3.1 to 6.3 microgram/mL) and 131 ±56 hours (b) (4) *respectively, following a single 40mg subcutaneous does of adalimumab to healthy adult volunteers.*[32] *Although the first case report described by Fritzsche, et al. appears to have captured the peak adalimumab concentration, the second case report may have missed the peak adalimumab concentration. Therefore, although adalimumab was not detectable in the serum of infant in the second case report, this may be due to the timing when the maternal serum and breastmilk and infant serum samples were taken.*

LactMed notes that there are low levels of adalimumab in breast milk and no evidence of adverse effects of the drug on the breastfeeding infant. Since the molecular weight of adalimumab is large (148,000 Daltons), the amount of drug in the milk is likely to be low and absorption is unlikely since the infants' gastrointestinal tract destroys the drug. Since there is minimal information of adalimumab use during breastfeeding, LactMed recommends that "caution should be used while nursing a newborn or preterm infant." [33]

In Hale's Medication and Mother's Milk, Dr. Thomas Hale, a breastfeeding expert, notes that IgG transfer into breast milk is highest in the first four days postpartum and is minimal afterwards. Immunoglobulins are transferred into breast milk by carrier protein, with IgA as the primary immunoglobulin seen in human milk. The transfer of IgG-like products is limited, and it is unlikely that adalimumab will be transferred into breast milk in clinically relevant amounts after the first week postpartum. However, data are limited.[34]

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[32] Current Humira (adalimumab) labeling, Section 12: Clinical Pharmacology.
[33] Lactmed. Adalimumab. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~nfjwSG:1. Accessed 11/4/2015
[34] Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15th edition. Hale Publishing, L.P. 2012

Summary

Current adalimumab labeling recommends that caution be exercised when adalimumab is administered to a nursing woman and notes the adalimumab is present in human milk at low levels. The applicant added details of case reports in the "Data" subsection of section 8.2, Lactation and added the following risk/benefit statement to the "Risk Summary":

> *The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.*

DPMH agrees with the applicant's assessment of published literature and recommends that the relative infant doses be included in section 8.2, "Risk Summary." Data from case reports should not be included in the "Data" section, but the relative infant doses and M/P from case reports can be placed in the "Risk Summary" section of 8.2. DPMH agrees with the addition of the risk/benefit statement proposed by the applicant. The reader is referred to the previous DPMH review by Jeanine Best, MSN, RN, PNP for a complete review of published literature related to adalimumab and lactation.[35]

Adalimumab and Females and Males of Reproductive Potential

Long-term animal studies with adalimumab have not been conducted to evaluate the carcinogenic potential or effect on fertility. Although clinical data is limited, adalimumab does not appear to affect female or male fertility. In men, sperm appear to be unchanged with adalimumab use, and in women, a decrease in inflammation due to adalimumab has improved fertility. Adalimumab is not genotoxic.[36]

In addition to searching through internal clinical trials data, the applicant performed a literature review in BIOSIS Previews, Derwent Drug File, Embase, Embase Alert, International Pharmaceutical Abstracts, MEDLINE, and SciSearch to obtain information regarding adalimumab and fertility. DPMH also performed a literature review in PubMed using the key search words "adalimumab and fertility" and "adalimumab and sperm" Three relevant articles were found and are presented below.

In a prospective study (Micu, *et al*.), 20 male patients (average age 34) with AS and taking anti-TNF therapy (adalimumab 40mg every 2 weeks (n=14), infliximab 5mg/kg every 8 weeks (n=4), etanercept 50mg every week (n=2)) were compared to 42 controls of healthy males (average age 34). The patients in the treatment group gave semen samples once before the start of anti-TNF therapy. The second semen analysis occurred three to six months after the start of anti-TNF therapy (n=20 patients) and a third semen analysis was performed at 12-months after the start of anti-TNF therapy (n=6 patients). At baseline and at 3-6 months, 91% of the males in the treatment group had normospermia and 9% had oligospermia. At the 12-month follow-up, 100% of the patients had normospermia and none of the patients had oligospermia; out of the six patients who followed up at 12-months, five were on adalimumab and one was one infliximab. There was no statistically significant difference

[35] DPMH Review. Humira (adalimumab) Injection, BLA 125057. Jeanine Best, MSN, RN, PNP. March 13, 2013. DARRTS Reference ID 3275320.

[36] Grunewald S, Jank A. New systemic agents in dermatology with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015;13(4):277 -89.

between the semen analysis performed in patients in the treatment group and the control group. The authors concluded that the disease process of AS and exposure to anti-TNF therapy does not appears to adversely affect sperm quality during active phases of AS.[37]

In a prospective case-control study (Ramonda, *et al*.), 10 male patients with spondyloarthritis (SpA) were compared to 20 healthy control subjects. The treatment group had a semen evaluation before and after one year of treatment with adalimumab 40mg every two weeks for 12-months). The average age of patients was 28 (age 27 in controls). At baseline, the subjects in the treatment group had reduced sperm motility (30% versus 52% in the control group) and a higher percentage of aneuploides (0.97% versus 0.75% in the control group), high luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels and lower testosterone levels. After treatment with adalimumab, there was a statistically significant decrease in sperm aneuploidies (0.46%) and an increase in sperm motility (66%) and a normalization of hormone levels. The authors concluded that the study hypothesizes that inflammatory diseases, such as SpA, can affect sperm quality and sex hormone levels and that anti-TNF therapy does not appear to adversely affect testicular function or spermatogenesis.[38]

In a prospective cohort (Villiger, *et al*.), the semen samples of 26 male patients with SpA (11 patients not currently on anti-TNF therapy and 15 patients on long-standing TNF therapy, including infliximab, Etanercept or adalimumab) were compared to the semen samples of 102 healthy male subjects. The authors founds that the 11 patients with SpA who were untreated had poorer sperm motility and vitality (p=0.001) compared to the 15 patients with SpA who were on treatment. There was no difference in sperm quality between healthy controls and the anti-TNF treated patients.[39]

Summary
DPMH agrees with the authors' conclusions in the three published studies reviewed above. Overall, it does not appear that adalimumab affects male fertility. There were no studies that evaluated the effects of adalimumab on female fertility. Since there is no evidence that adalimumab impacts fertility, section 8.3, Females and Males of Reproductive Potential will be omitted from labeling.

CONCLUSIONS
Humira labeling has been updated to comply with the PLLR. DPMH has the following recommendations for Humira labeling:

[37] Micu, et al. TNF-a inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology. 2014; 53(7):1250-5.
[38] Ramonda, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014: 101(2): 359-365.
[39] Villiger, et al. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Annals of Rheumatic Disease. 2010. 69(10): 1842-4.

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Humira labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" subsections[40].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Humira labeling was formatted in the PLLR format to include the "Risk Summary" subsection[41].
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of Humira labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 in Humira labeling for compliance with the PLLR (see below). See Appendix A for the applicant's proposed pregnancy and lactation labeling. DPMH refers to the final NDA action for final labeling.

[40] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[41] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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