

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125057Orig1s393

Trade Name: HUMIRA

Generic or Proper Name: adalimumab

Sponsor: AbbVie Inc.

Approval Date: September 9, 2015

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.

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APPROVAL LETTER



BLA 125057/S-393

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Mary Konkowski
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-1
North Chicago, Illinois 60064

Dear Ms. Konkowski:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received November 10, 2014, submitted under section 351(a) of the Public Health Service Act for HUMIRA (adalimumab) solution, 40mg/0.8mL.

We acknowledge receipt of your amendments dated December 9, 2014, and January 13, February 9, March 10 and 26, July 10, August 3, 14 and 19, and September 2 and 8, 2015.

This Prior Approval supplemental biologics application proposes an indication for the treatment of hidradenitis suppurativa.

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.

We note that your August 19, 2015, submission includes final printed labeling (FPL) for your package insert, Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 include the labeling changes proposed in any pending “Changes Being Effectuated” (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 Effectuated” (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

We acknowledge your February 9, 2015, submission containing final printed carton and container labels.

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, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since HUMIRA (adalimumab) solution was approved on December 31, 2002, we have become aware of a signal of an unexpected increased risk of serious adverse events related to the development of anti-adalimumab antibodies that could affect the assessment of risks relative to

benefits in subjects with hidradenitis suppurativa. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of immunogenicity through its effect on the pharmacokinetics, efficacy, and safety of HUMIRA (adalimumab) solution in subjects with hidradenitis suppurativa.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2936-1 Utilize the validated anti-adalimumab antibody (AAA) assay developed under PMR 2517-3 (as described in the FDA Fulfillment of Postmarketing Requirement Letter dated April 1, 2015) to analyze the immunogenicity profile of adalimumab using banked patient samples from Phase 3 trials M11-810 and M11-313. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with hidradenitis suppurativa based on the AAA data generated with the newly validated assay.

The timetable you submitted on September 8, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	01/2016
Final Report Submission:	03/2016

Submit the final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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 Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Acting Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

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/

JILL A LINDSTROM
09/09/2015

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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, Juvenile Idiopathic Arthritis (1.2)	9/2014
Indications and Usage, Pediatric Crohn's Disease (1.6)	9/2014
Indications and Usage, Hidradenitis Suppurativa (1.9)	9/2015
Dosage and Administration, Juvenile Idiopathic Arthritis (2.2)	9/2014
Dosage and Administration, Pediatric Crohn's Disease (2.4)	9/2014
Dosage and Administration, Hidradenitis Suppurativa (2.7)	9/2015
Dosage and Administration, General Considerations for Administration (2.9)	12/2014
Warnings and Precautions, Malignancies (5.2)	9/2015

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.

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 (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/0.8 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: 09/2015

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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.

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)	<ul style="list-style-type: none">• 80 mg on Day 1 (administered as two 40 mg injections in one day); and• 40 mg two weeks later (on Day 15)	<ul style="list-style-type: none">• 20 mg every other week
≥ 40 kg (88 lbs)	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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

The recommended dose of HUMIRA for adult patients with plaque psoriasis (Ps) 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 needle cover of the syringe because it contains dry rubber (latex).

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: A single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg/0.8 mL of HUMIRA.

• Prefilled Syringe

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg/0.8 mL of HUMIRA.

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 20 mg/0.4 mL of HUMIRA.

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 10 mg/0.2 mL of HUMIRA.

- **Single-Use Institutional Use Vial**

Injection: A single-use, glass vial, providing 40 mg/0.8 mL of HUMIRA 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 37 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) and hidradenitis suppurativa (HS), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.45, 1.01) per 100 patient-years among 7723 HUMIRA-treated patients versus a rate of 0.8 (0.48, 1.31) per 100 patient-years among 4598 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 50 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps and HS, 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 37 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps and HS, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.11) per 100 patient-years among HUMIRA-treated patients and 0.3 (0.11, 0.63) 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 37 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps and HS, 2 lymphomas occurred among 7723 HUMIRA-treated patients versus 1 among 4598 control-treated patients. In 50 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps and HS with a median duration of approximately 0.7 years, including 24,135 patients and over 39,000 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 \leq 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.

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.

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 37 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps and HS, the rate of serious infections was 4.4 per 100 patient-years in 7723 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4598 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 50 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps and HS that included 24,135 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.10 per 100 patient-years. In a subgroup of 9959 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 0.08 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ 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 $\geq 3 \times$ ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects.

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%.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. 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 $\geq 5\%$ 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	Placebo

	Every Other Week	
	(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 $\geq 25\%$ 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.

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 and HS. 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., TNF α , 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

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (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 blood, and 0-16.1 µg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had 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

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab.

8.3 Nursing Mothers

Limited data from published literature indicate that adalimumab is present in low levels in human milk and is not likely to be absorbed by a breastfed infant. However, no data is available on the absorption of adalimumab from breastmilk in newborn or preterm infants. Caution should be exercised when HUMIRA is administered to a nursing woman.

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 TNF α , 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/0.8 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 $1-2 \times 10^{-10}M$).

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 $4.7 \pm 1.6 \mu\text{g/mL}$ 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 $5 \mu\text{g/mL}$ and 8 to $9 \mu\text{g/mL}$, 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 $10 \mu\text{g/mL}$ and 8.5 to $12 \mu\text{g/mL}$, 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 $12 \mu\text{g/mL}$ at Week 2 and Week 4. Mean steady-state trough levels of approximately $7 \mu\text{g/mL}$ 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.

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. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

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-naïve or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study 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)

Response	Study RA-II Monotherapy (26 weeks)			Study RA-III Methotrexate Combination (24 and 52 weeks)	
	Placebo	HUMIRA 40 mg every other week	HUMIRA 40 mg weekly	Placebo/MTX	HUMIRA/MTX 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

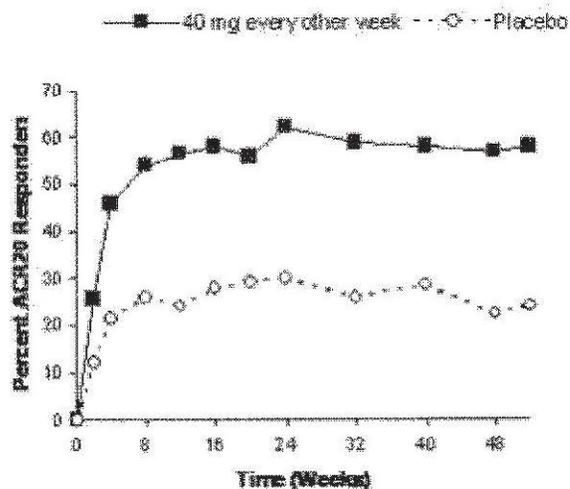
Parameter (median)	Study RA-II				Study RA-III			
	Placebo N=110		HUMIRA ^a N=113		Placebo/MTX N=200		HUMIRA ^a /MTX N=207	
	Baseline	Wk 26	Baseline	Wk 26	Baseline	Wk 24	Baseline	Wk 24
Number of tender	35	26	31	16*	26	15	24	8*

joints (0-68)								
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/m² 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 $\geq 30\%$ 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/m² 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

Parameter: median	Placebo N=162		HUMIRA* N=151	
	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.

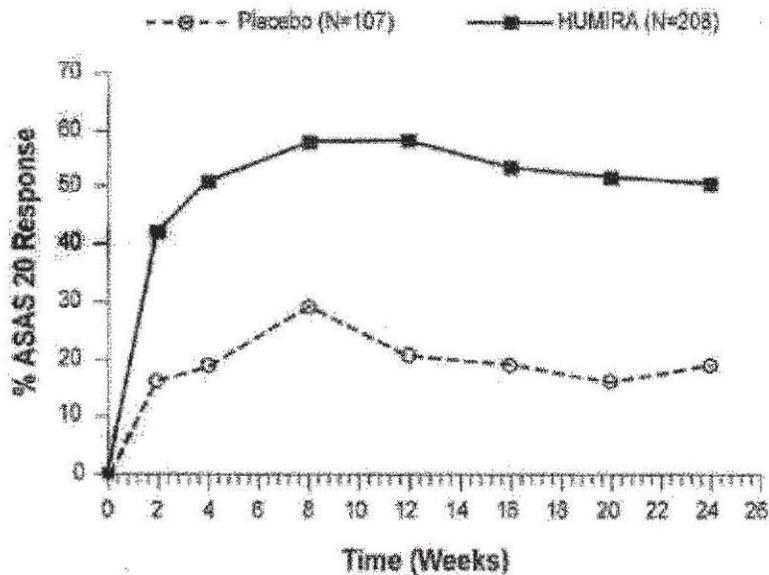
14.4 Ankylosing Spondylitis

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) \geq 220 and \leq 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 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 \geq 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 $\geq 10\%$ 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 $\geq 10\%$ 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 $\geq 25\%$ 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.

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**
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 NDC number is 0074-4339-02.
- **HUMIRA Pen - 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 NDC number is 0074-4339-06.
- **HUMIRA Prefilled Syringe - 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 NDC number is 0074-3799-06.

- HUMIRA Prefilled Syringe - 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 NDC number is 0074-3799-03.
- HUMIRA Pen - Psoriasis Starter Package**
 HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis 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 NDC number is 0074-4339-07.
- Prefilled Syringe Carton - 40 mg**
 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 NDC number is 0074-3799-02.
- Prefilled Syringe Carton - 20 mg**
 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 NDC number is 0074-9374-02.
- Prefilled Syringe Carton - 10 mg**
 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 NDC number is 0074-6347-02.
- Single-Use Institutional Use Vial Carton - 40 mg**
 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 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 needle cap of the prefilled syringe contains latex.

- **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).

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. The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to 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.
- 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 the FDA at 1-800-FDA-1088.

How should I store HUMIRA?

- Store HUMIRA in the refrigerator at 36°F to 46°F (2°C to 8°C). 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

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.

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.

03-B166

Revised: 09/2015

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

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 has 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**”.

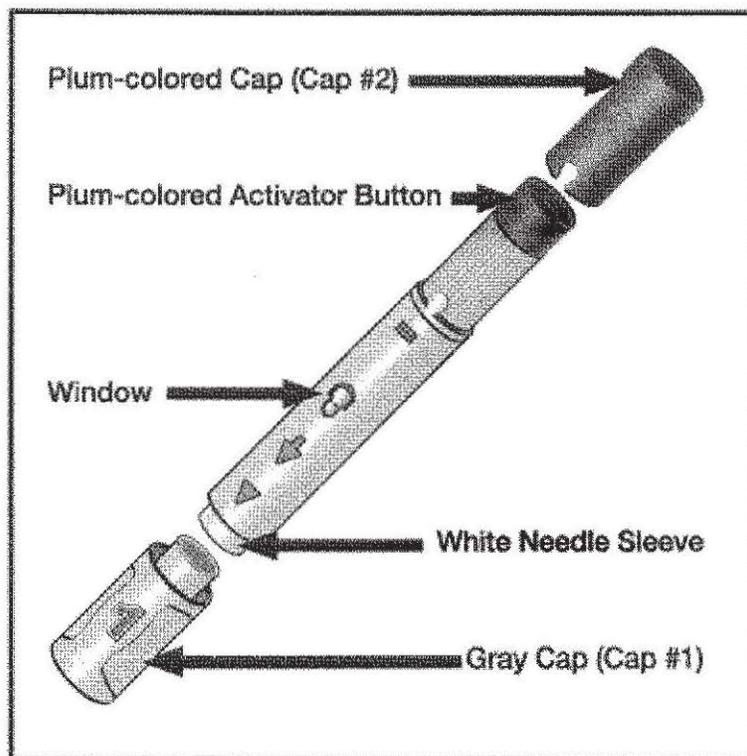
Gather the Supplies for Your Injection

- 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



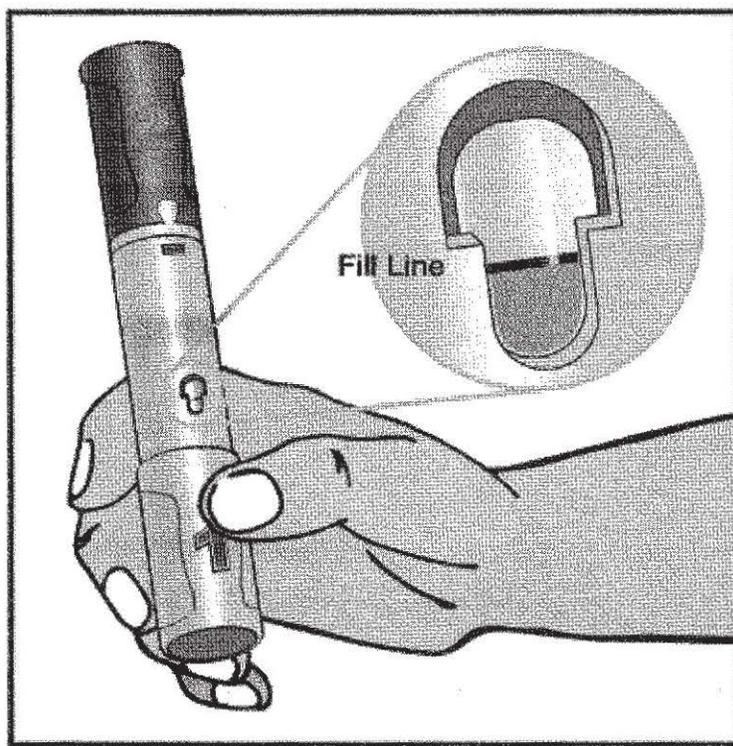
Check the carton, dose tray, and HUMIRA Pen.

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.

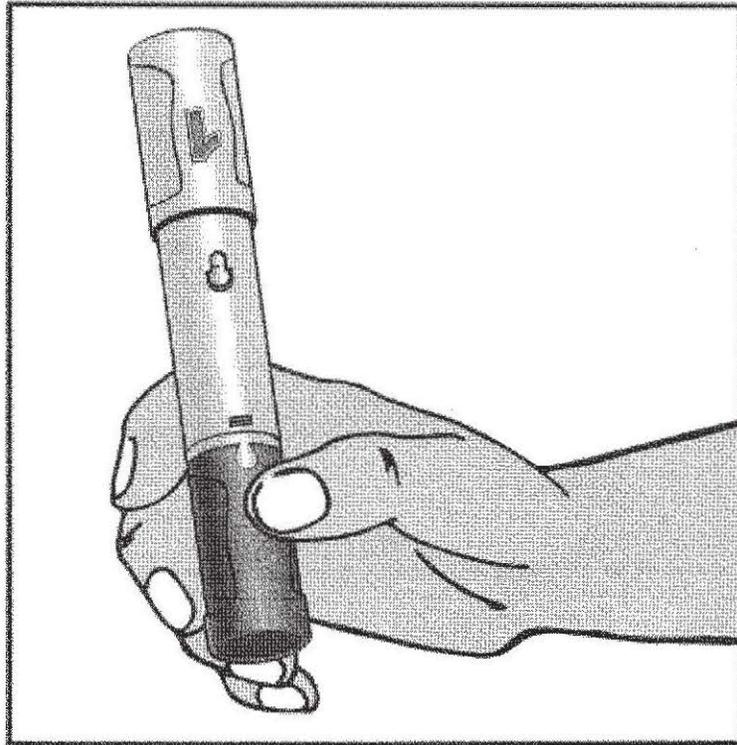
Figure B



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.

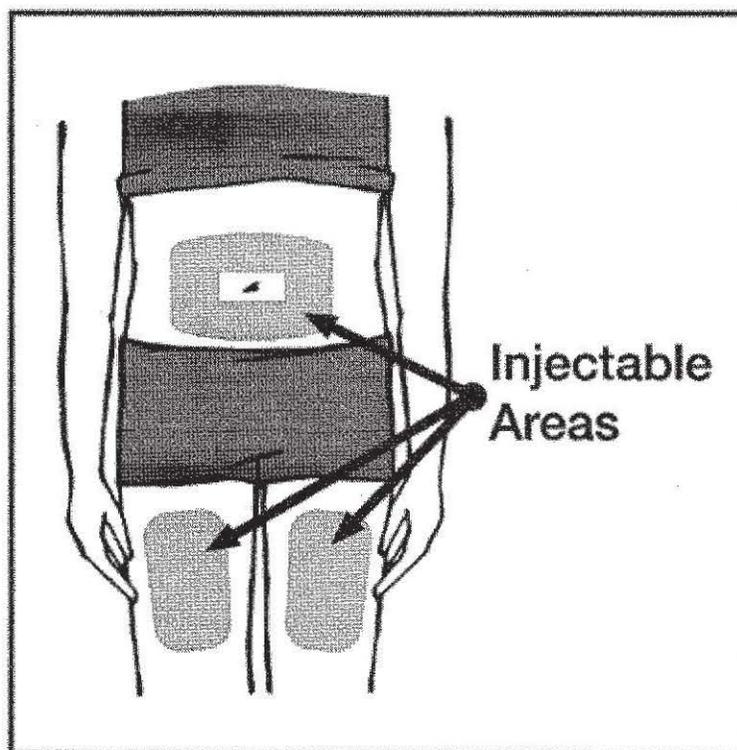
Figure C



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

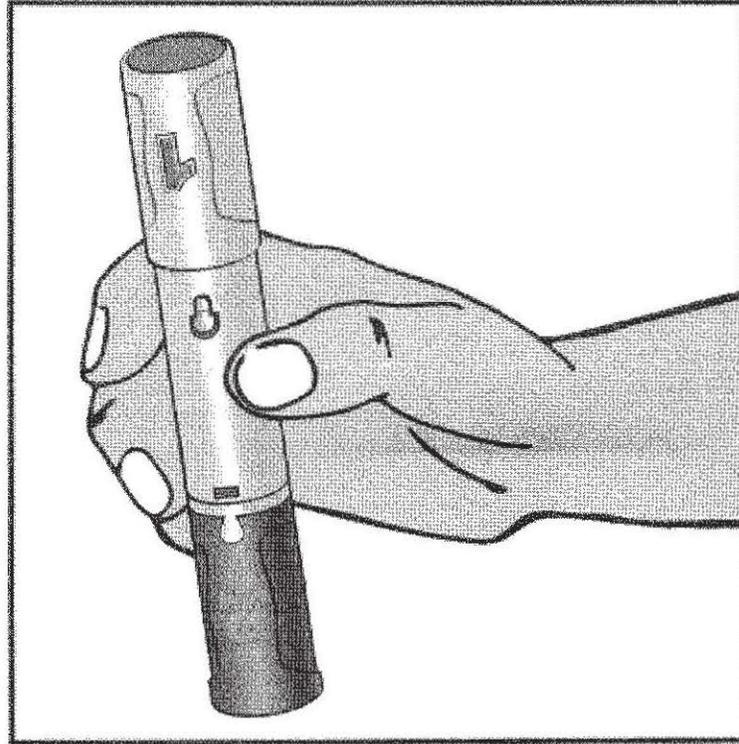
10. Wipe the injection site with an alcohol prep (swab) using a circular motion.
 - **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

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.

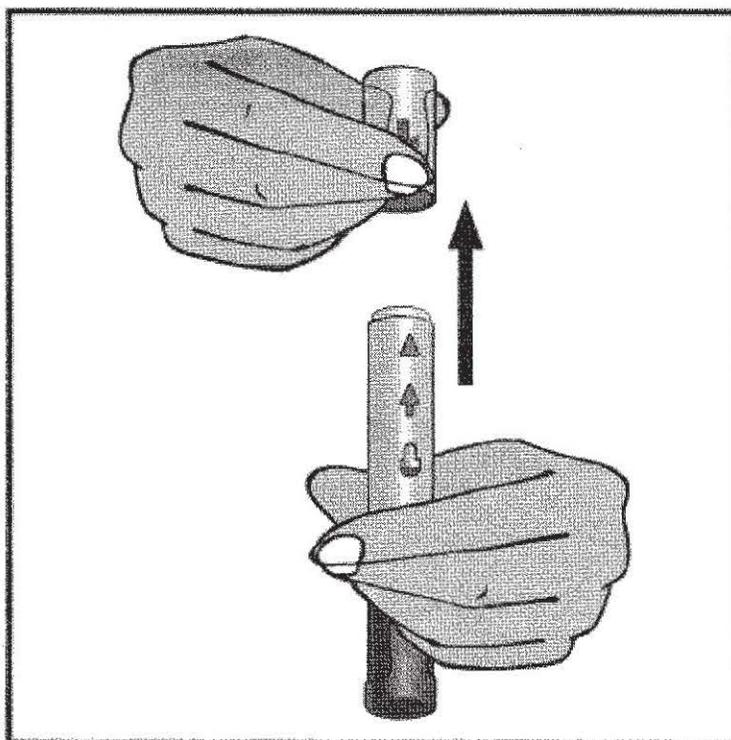
Figure E



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.

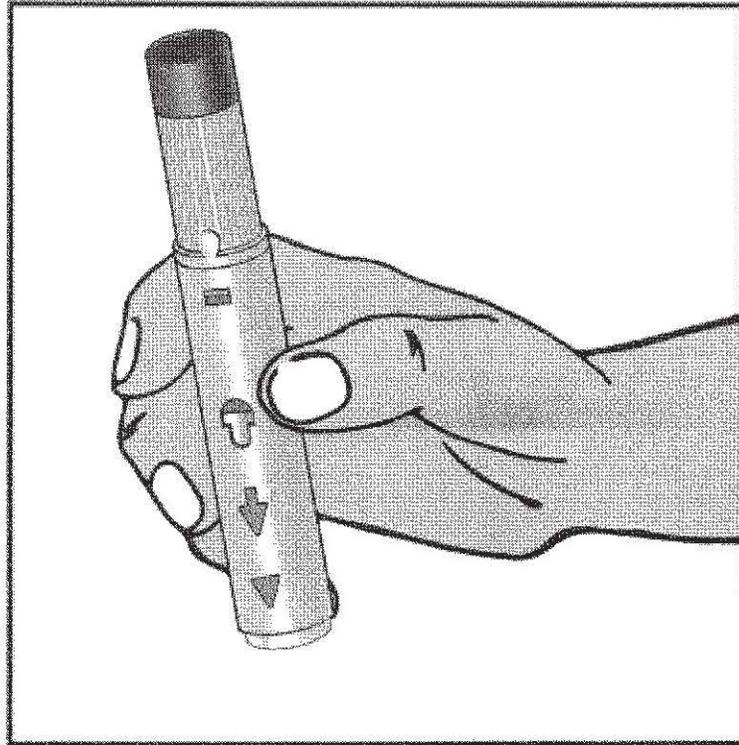
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- 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:

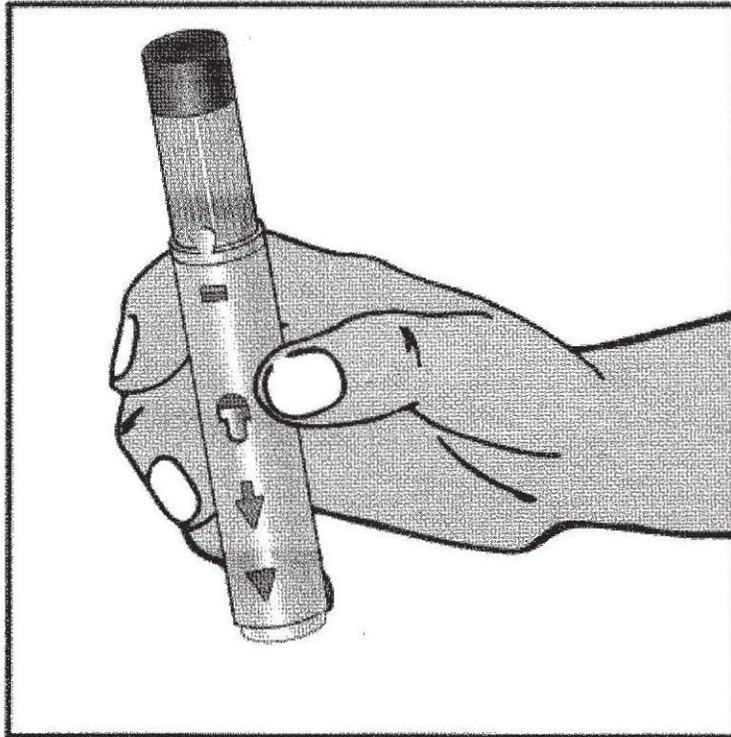
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

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:

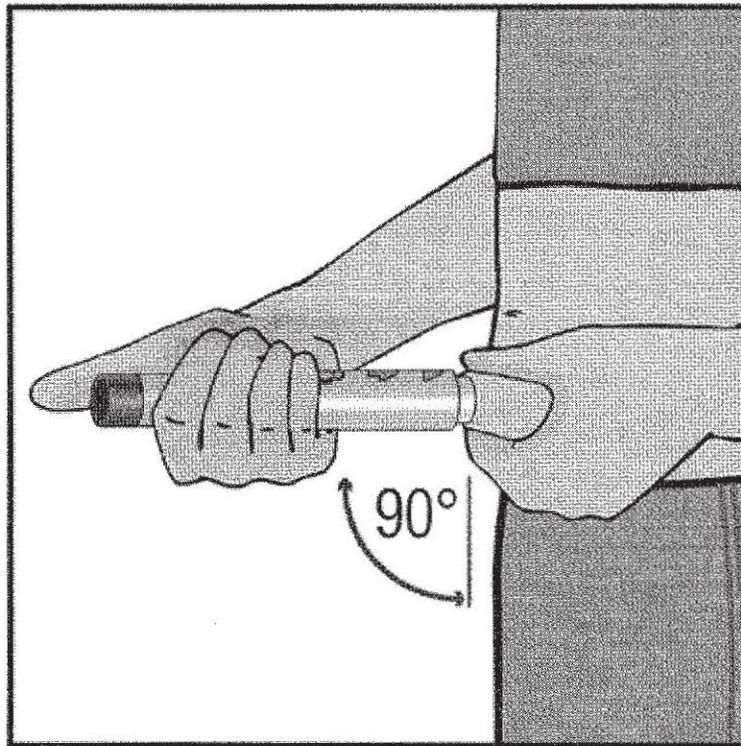
- Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

Figure I



17. Place the white end of the Pen straight (at a 90° 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.

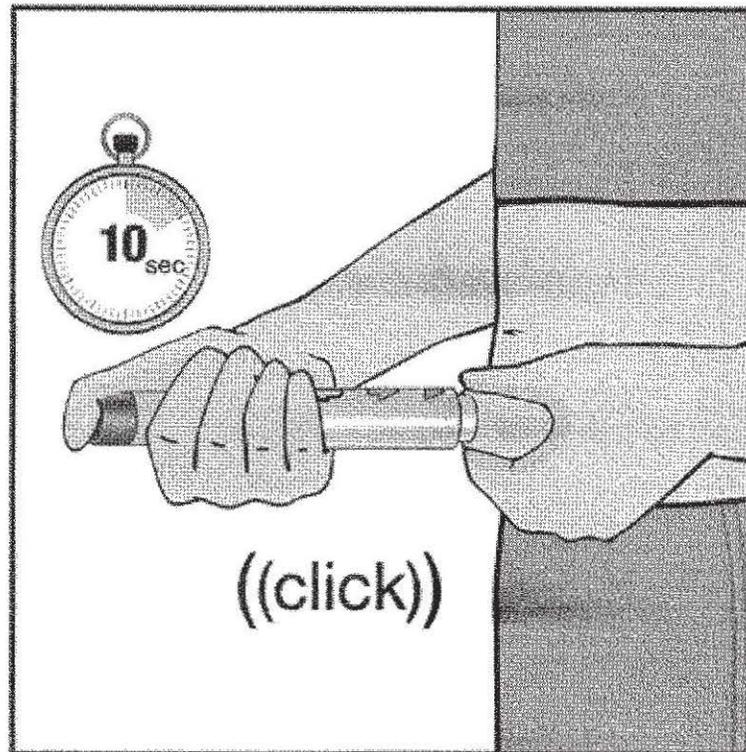
Figure J



18. Inject HUMIRA

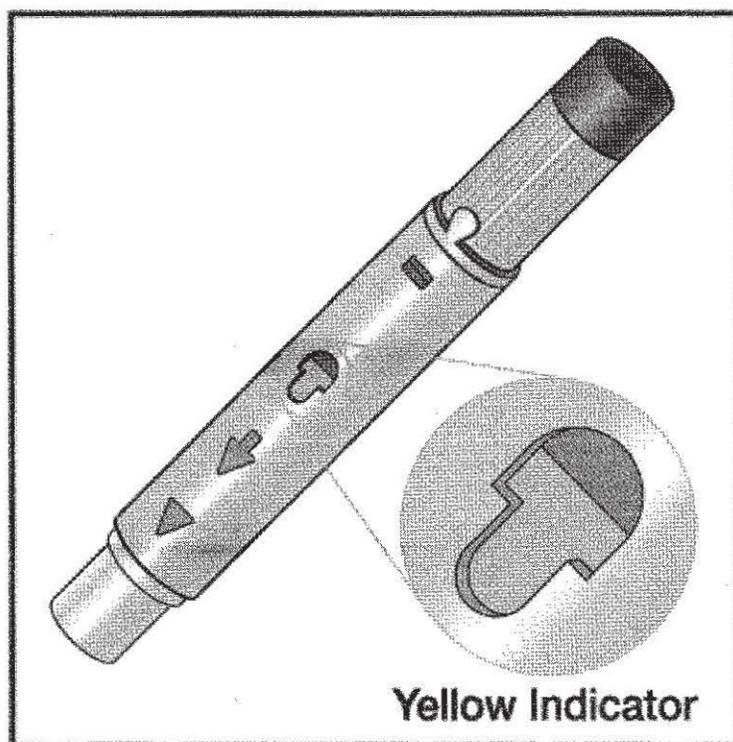
- With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

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.

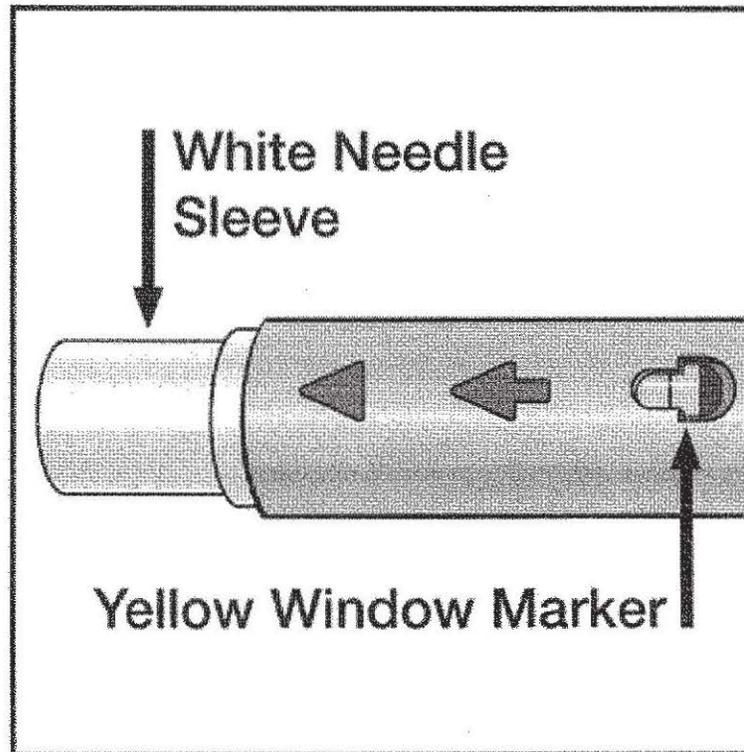
Figure L



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.

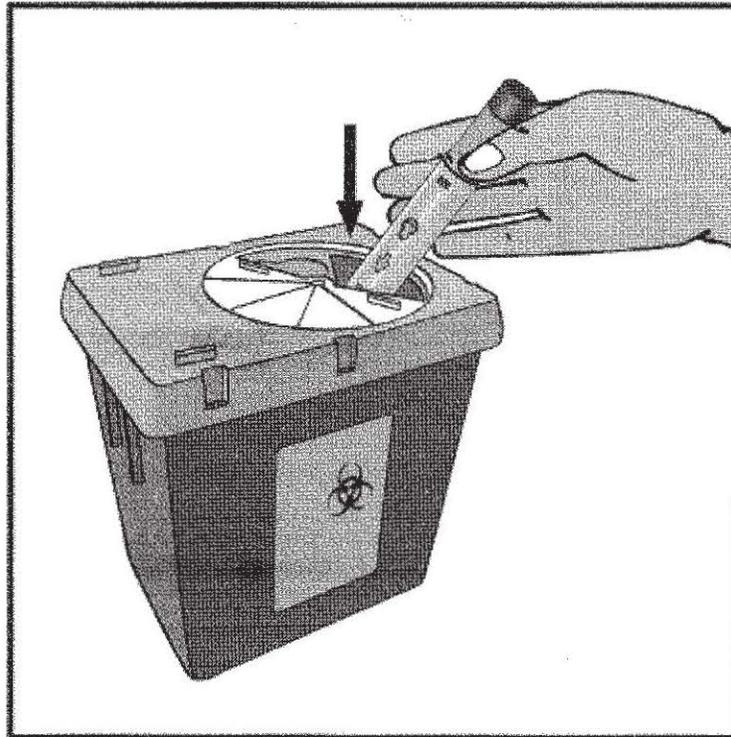
20. Dispose of your used HUMIRA Pen. See the section “**How should I dispose of the used HUMIRA Pen?**”

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 36°F to 46°F (2°C to 8°C). 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-B195

Revised: 09/2015

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

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 has any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

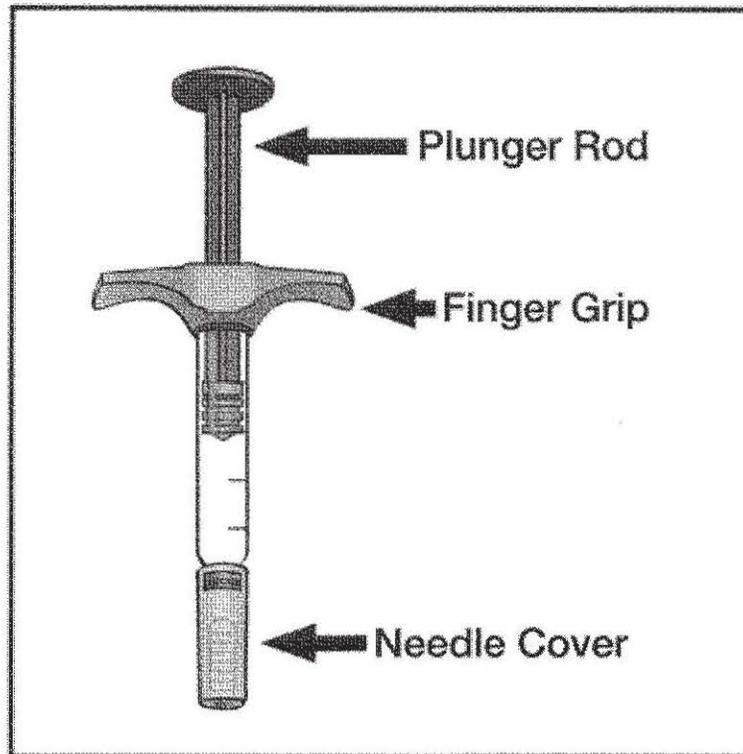
- You will need the following supplies for each injection of HUMIRA.
Find a clean, flat surface to place the supplies on.
 - 1 alcohol swab
 - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
 - 1 HUMIRA prefilled syringe (See Figure A)
 - FDA-cleared sharps disposal container for HUMIRA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

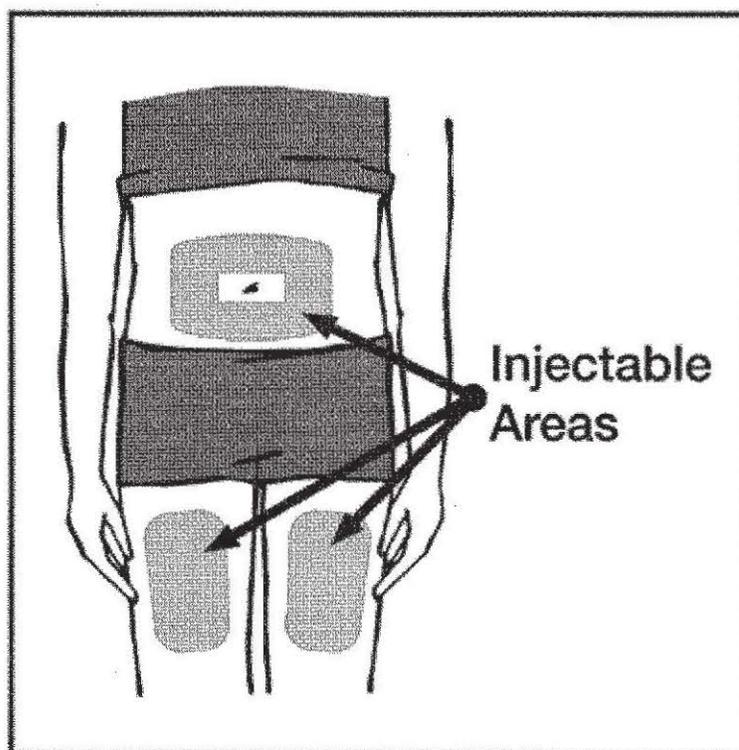
1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.
2. **Do not use** and **do call** your doctor or pharmacist if:
 - the seals on top or bottom of the carton are broken or missing.
 - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton 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.

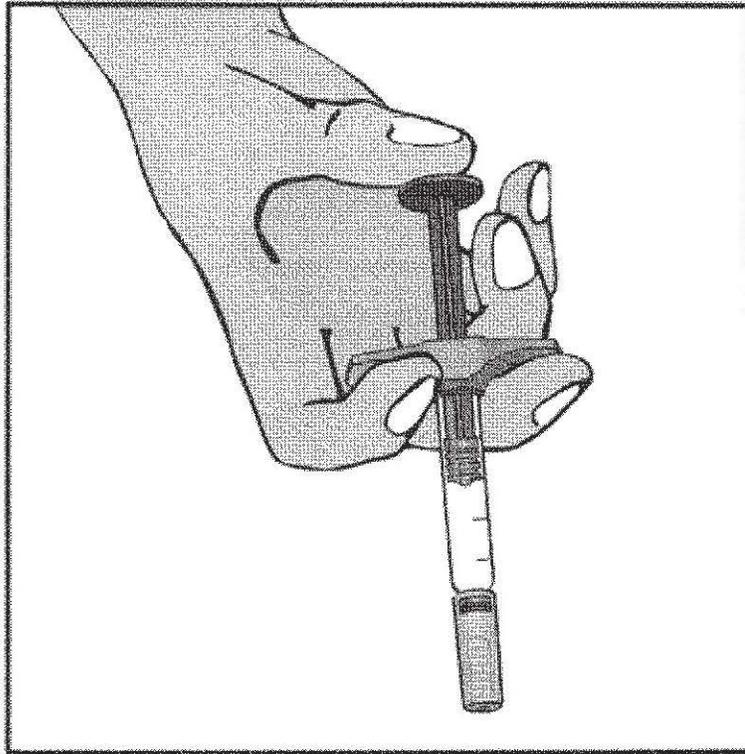
Prepare the Injection Site

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

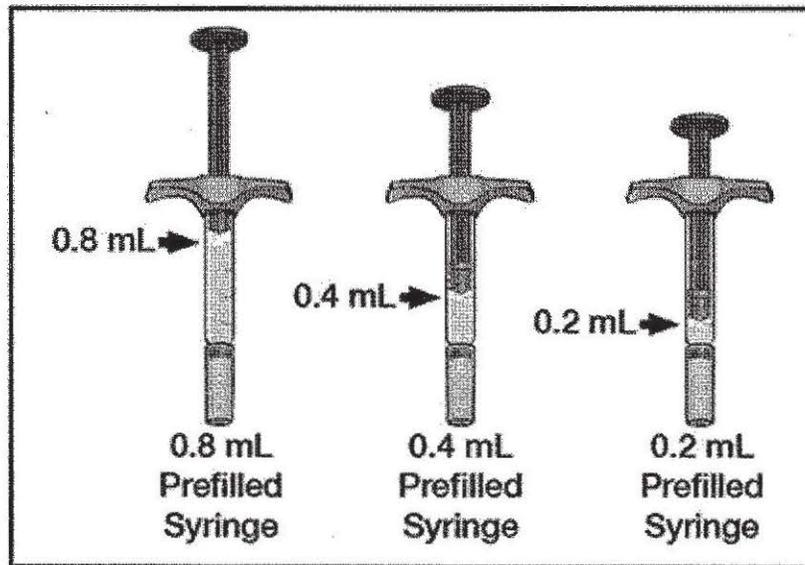
7. Check the fluid level in the syringe:
 - Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

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

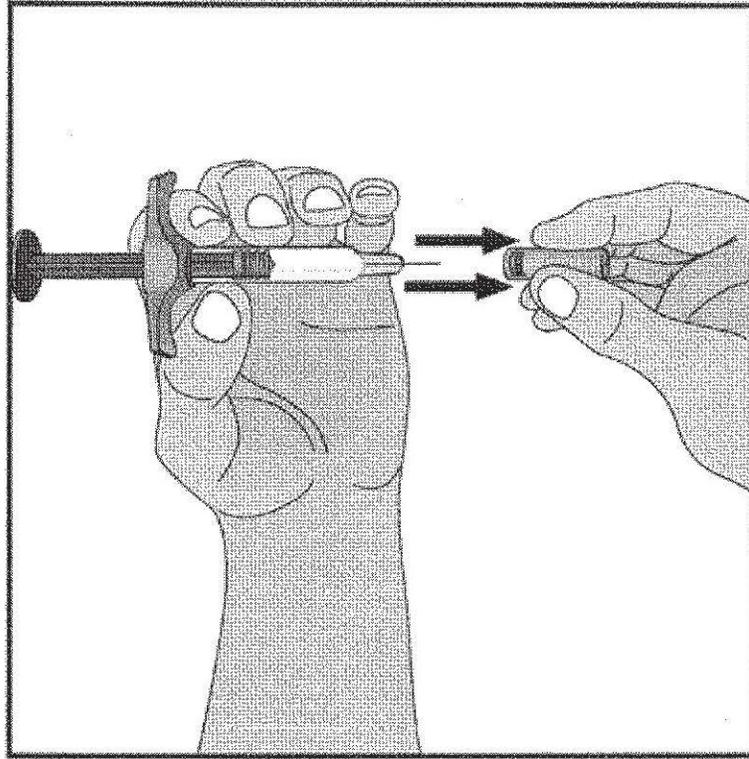


8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

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.

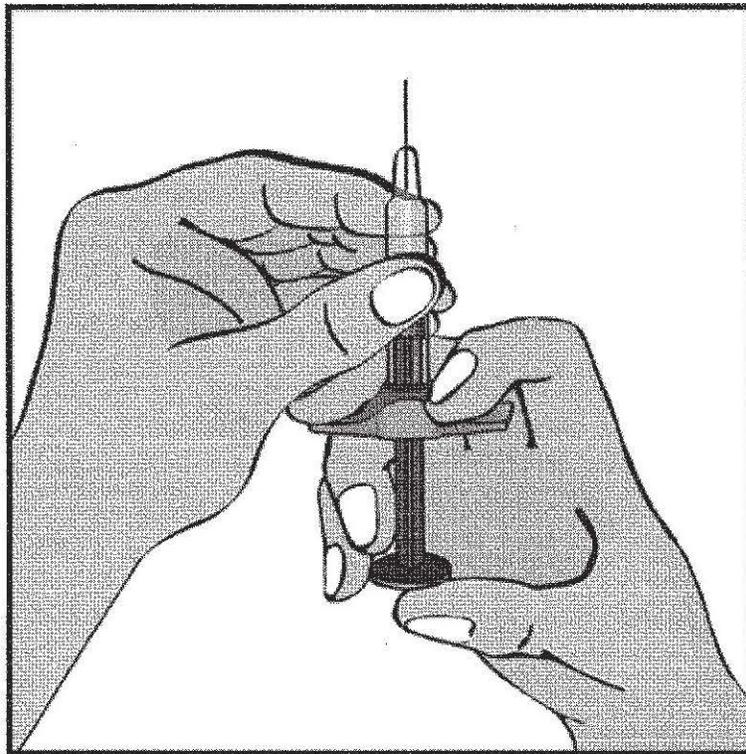
Figure E



- 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



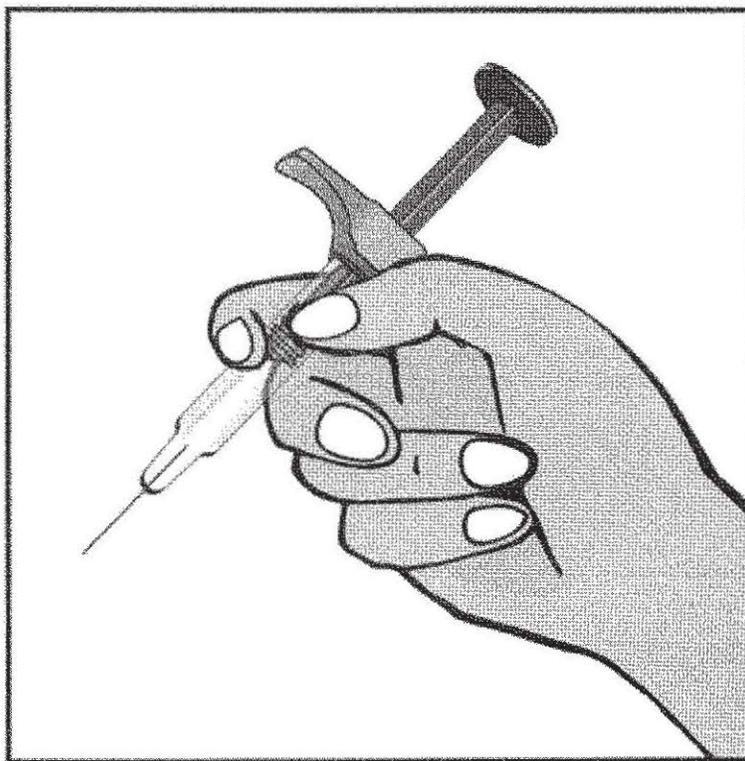
- You may see a drop of liquid at the end of the needle. This is normal.

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.

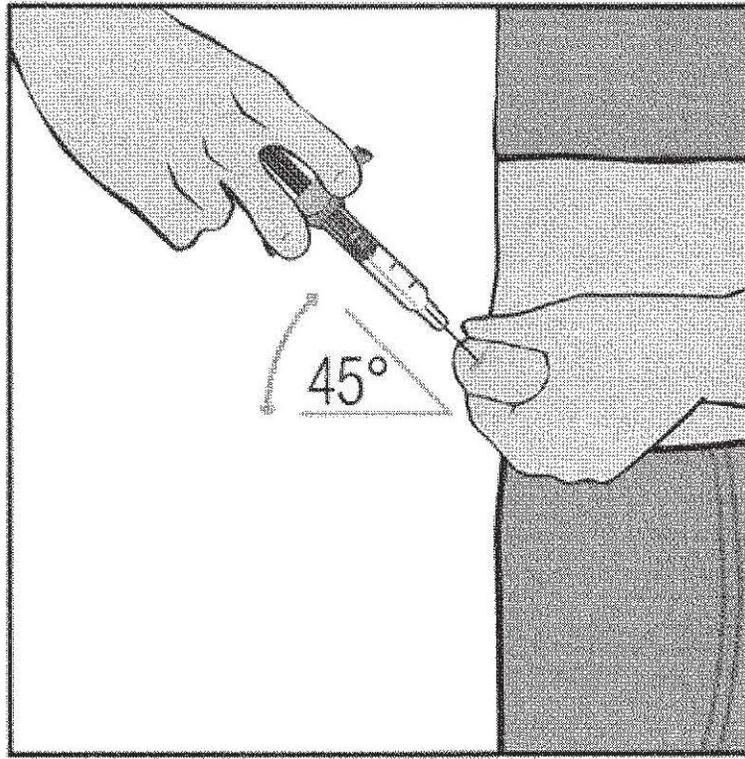
Figure H



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

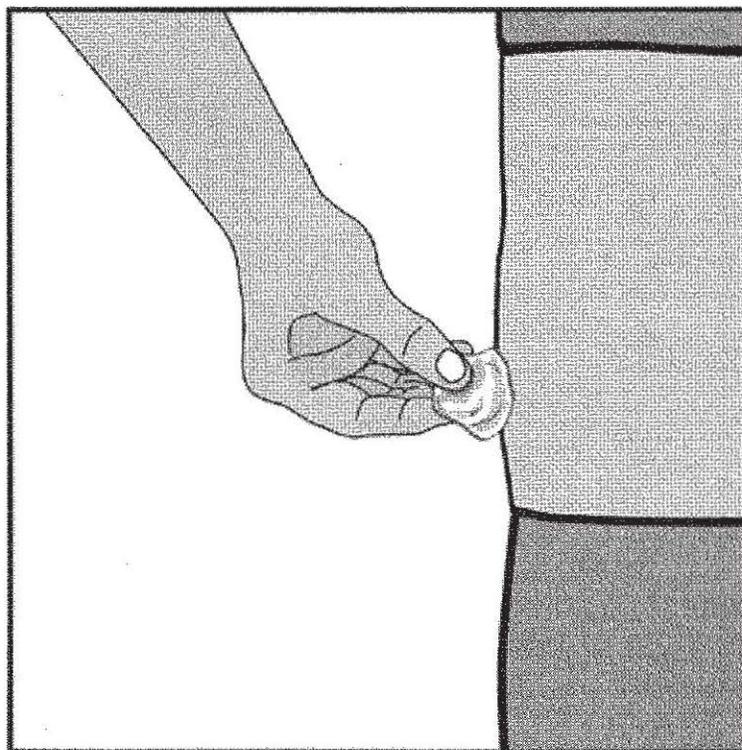


- After the needle is in, let go of the skin. Pull back gently on the plunger.

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.

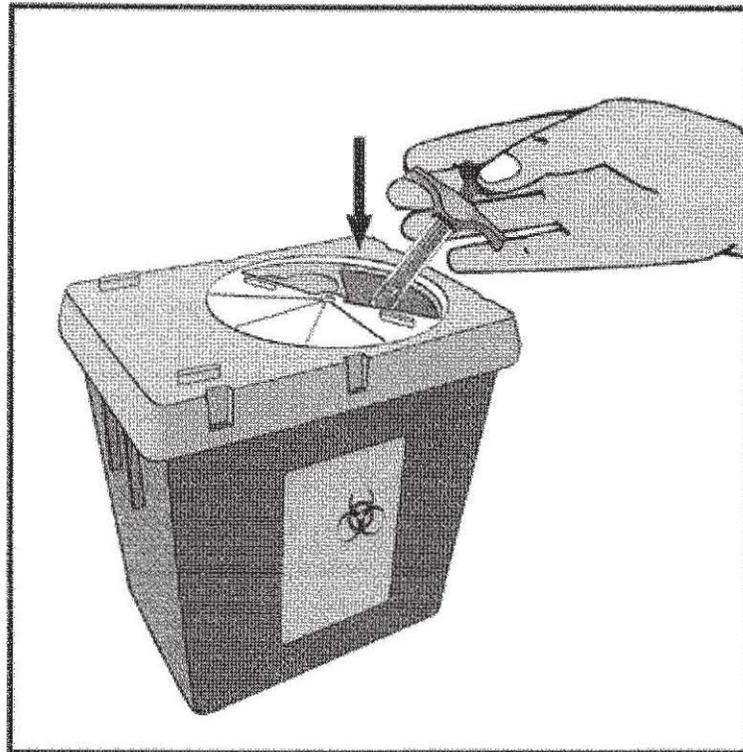
13. Throw away the used prefilled syringe and needle. See “**How should I dispose of used prefilled syringes and needles?**”

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 36°F to 46°F (2°C to 8°C). 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:

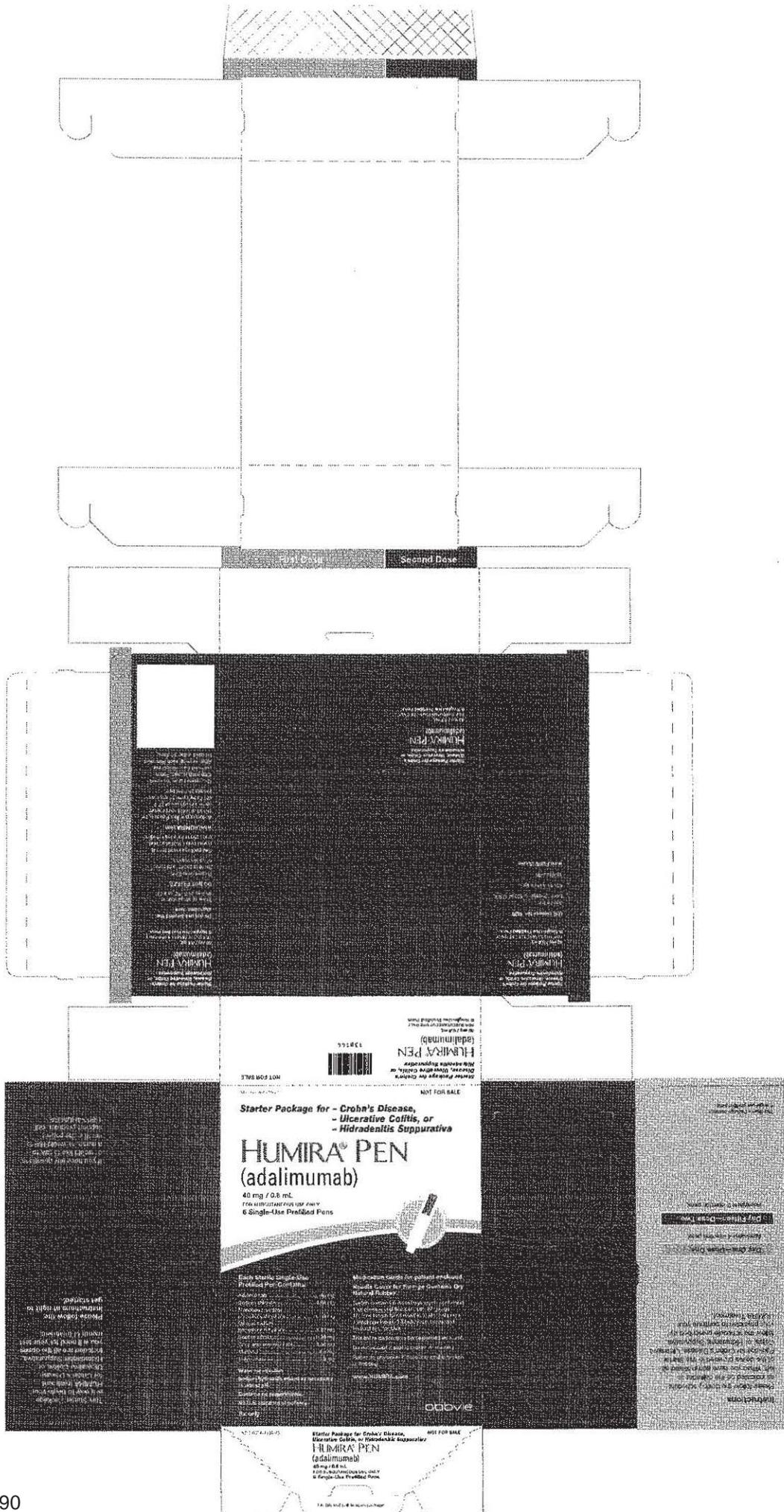
AbbVie Inc.

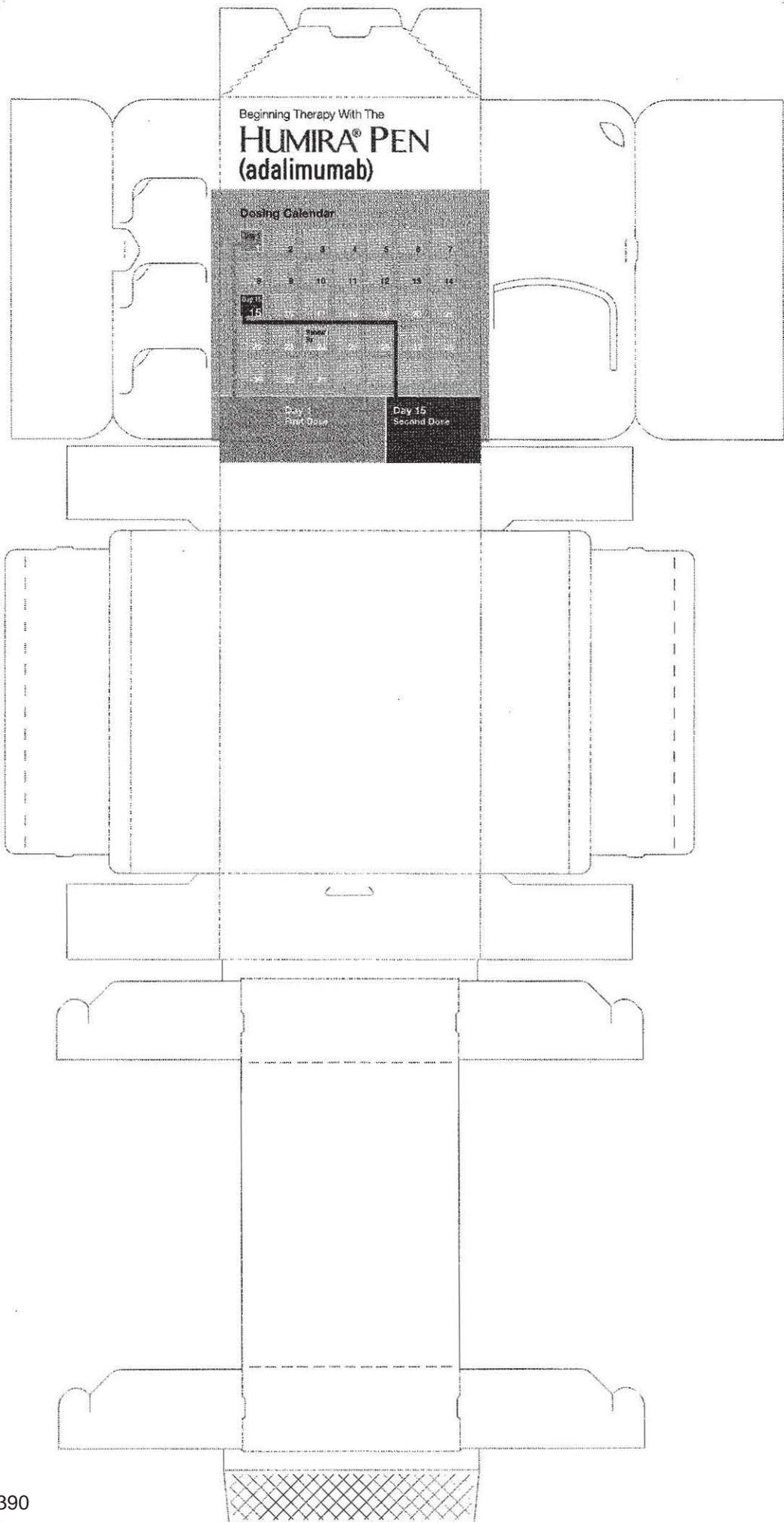
North Chicago, IL 60064, U.S.A.

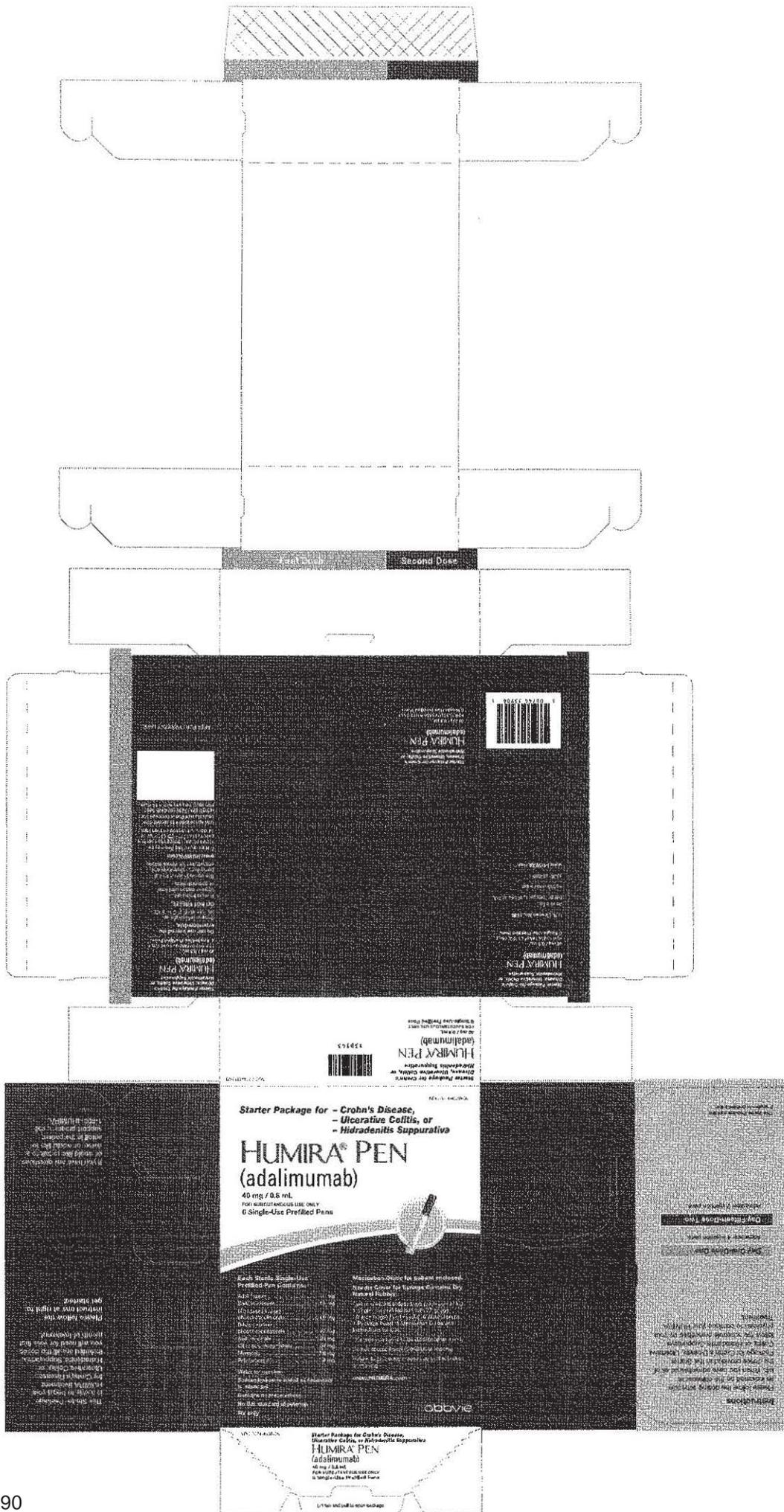
US License Number 1889

03-B196

Revised: 09/2015







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/s/

JILL A LINDSTROM
09/09/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: BLA 125057/393 for Humira (adalimumab) injection, 40 mg

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Abdus-Samad, Jibril
Ayalew, Kassa
Florian, Jeffry
Fuller, Barbara
Griffiths, LaShawn
Hill, Barbara
Liedtka, Jane
Lindstrom, Jill
Liu, Juhong
Marcus, Kendall
Mena-Grillasca, Carlos
Park, Jun
Pohlman, Janice
Turner, Tara
Walker, Morgan
Wang, Jie
Wang, Yow-Ming
Welch, Joel

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL and Summary Review for Regulatory Action

Date	9 September 2015
From	Jill A Lindstrom, MD
Subject	CDTL and Acting Deputy Division Director Summary Review
BLA #	125057
Applicant Name	AbbVie, Inc.
Date of Submission	10 November 2014
PDUFA Goal Date	10 September 2015
Proprietary Name	Humira
Established (USAN) Name	adalimumab
Dosage Forms	injection
Presentations	Pen, prefilled syringe, vial
Strengths	40mg/0.8mL, 20mg/0.4mL, 10mg/0.2mL
Proposed Indication(s)	Treatment of moderate to severe hidradenitis suppurativa
Action	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Snezana Trajkovic, MD
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Barbara Hill, PhD
CMC Review	Jun Park, PhD
CMC Labeling	Jabril Abdus-Samad, PharmD
Clinical Pharmacology Review	Jie Wang, PhD
OSI	Roy Blay, PhD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
PLT	Morgan Walker, PharmD, MBA

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

PLT=Patient Labeling Team

1. Introduction

HUMIRA (adalimumab) injection for subcutaneous use is a marketed product for which the applicant seeks approval of an efficacy supplement for the new indication of moderate to severe hidradenitis suppurativa (HS). Humira was initially approved in 2002 for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Approval of additional

supplements expanded the indication to include improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs (2004), psoriatic arthritis (2005), recently diagnosed patients with moderately to severely active rheumatoid arthritis who have not received methotrexate (2005), inhibiting the progression of structural damage and improving physical function in patients with psoriatic arthritis (2005), 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; and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant of infliximab (2007), long-term maintenance of efficacy with respect to clinical response, physical function and radiographic response in patients with rheumatoid arthritis (2007), 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 (2008), treatment of juvenile idiopathic arthritis (2008), 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 (2012), pediatric Crohn's disease patients aged 6 years or older (2014), and treatment of polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 to less than 4 years of age (2014).

Humira is a recombinant human IgG1 monoclonal antibody specific for tumor necrosis factor (TNF), a human cytokine involved in inflammatory and immune responses. Humira binds to TNF- alpha but not TNF-beta.

This memo, which serves as my summary review as well as the cross-discipline team leader review (a role which I fulfilled during the review cycle), will summarize the findings of the multi-disciplinary review team and provide the rationale for my decision.

2. Background

Hidradenitis suppurativa (HS) is chronic, recurrent suppurative disease that occurs in adolescents and adults, and with higher incidence in women and blacks. Clinical manifestations include nodules, cysts, draining sinuses and scarring in the apocrine gland-bearing areas such as the axillary, inguinal and anogenital regions. Lesions may be painful and pruritic; the psychological burden of the disease, measured as impairment in quality of life, is significant. There are no approved drugs or biologic products for the treatment of HS. Treatment approaches include topical and systemic antibiotics, oral retinoids, incision and drainage of cysts, intralesional corticosteroids, surgical excision, grafting, and laser ablation.

Humira (adalimumab) injection was approved for marketing on December 31, 2002. In this supplemental application, the applicant seeks approval for treatment of moderate to severe HS, a novel indication for which there are no approved drug or biologic products. To support the safety and efficacy of their product, the applicant included data from a phase 2 study, two randomized placebo-controlled phase 3 trials, and an open label phase 3 study (ongoing at the time of close of this review). The applicant received orphan drug designation for adalimumab for the treatment of moderate to severe HS on May 13, 2015.

3. CMC

No new product quality data were included in this efficacy supplement. The marketed presentations will support the proposed dosing. Carton and container labeling, which were reviewed by Dr. Jabril Abdus-Sabad, will be revised to reflect the new indication and dose.

The CMC reviewer, Dr. Jun Park, recommended *Approval* of this application from a CMC perspective. I concur with the conclusion reached by the CMC reviewer that there are no outstanding CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in this efficacy supplement.

The pharmacology/toxicology reviewer, Dr. Barbara Hill, recommended *Approval* of this application from a pharmacology/toxicology perspective.

I concur with the conclusion reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Humira (adalimumab) for injection is a recombinant human IgG1 monoclonal antibody specific for tumor necrosis factor (TNF), a human cytokine involved in inflammatory and immune responses. Humira binds to TNF- alpha but not TNF-beta. For the treatment of HS, it is intended to be administered by subcutaneous injection at a dose of 160mg for the first dose, 80mg two weeks later, and 40mg weekly beginning two weeks after that (week 4).

The marketed formulation was used in the clinical trials. Other than additional labeling content, no changes are proposed to the marketed drug product. The existing presentations can accommodate the new dose regimen for HS.

In the pivotal trials, subjects had mean serum trough adalimumab concentrations of 7 to 8 mcg/L at weeks 2 and 4 following initial doses of 160 and 80mg at days 0 and 15, and 8 to 9 mcg/L at weeks 8 and 12 following doses of 40mg weekly starting at week 4. These trough concentrations are lower than those seen in other disease states at the same doses, and comparable to the exposures seen with the approved doses in populations with rheumatoid arthritis, psoriatic arthritis, Crohns disease, and ulcerative colitis. The mean \pm SD clearance of adalimumab in subjects with HS was 0.77 \pm 0.58L/day, based on population PK analyses

The clinical pharmacology reviewer, Dr. Jie Wang, found that the dose-/exposure-response relationships for efficacy and safety supported the proposed dosing regimen. He noted that higher body weight and higher CRP level correlated with lower response on the primary endpoint (HiSCR), but that neither body weight nor baseline CRP level was a significant

covariate for explaining differences in the primary endpoint based on exposure-response analysis. Thus no dose adjustment was recommended.

In the HS pivotal trials, the incidence of anti-adalimumab antibody (AAA) development in subjects exposed to adalimumab was 12.6% (58/461). Formation of AAA was associated with lower serum adalimumab concentrations and decreased efficacy. Assay limitations preclude detection of AAA when drug levels exceed 2mcg/mL.

The Clinical Pharmacology/Biopharmaceutics reviewer, Dr. Jie Wang, found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended *Approval* from a clinical pharmacology/biopharmaceutics perspective.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

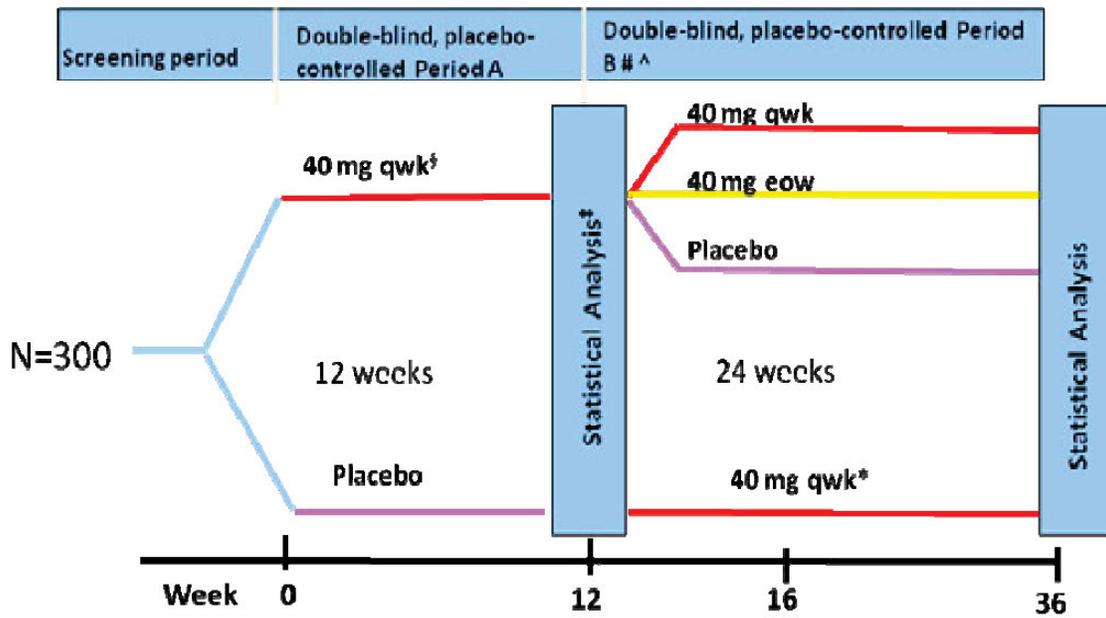
6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted data from two pivotal trials, M11-810 and M11-313, to establish the effectiveness of their product in the treatment of moderate to severe HS. The trials, which were similar in design, were randomized, double-blind and placebo-controlled, with parallel groups and two phases. In the first phase (period A), subjects received either adalimumab 40mg every week (following initial doses of 160mg at week 0 and 80mg at week 2) or placebo. In the second phase (period B), subjects who had received adalimumab in the first phase were re-randomized to receive either adalimumab 40mg every week, adalimumab 40mg every other week, or placebo, and subjects who had received placebo in the first phase were either continued on placebo (M11-810) or crossed-over to receive adalimumab 40mg every week (M11-313). Subjects in M11-810 were allowed to continue concomitant baseline oral antibiotics.

Schematic for Study M11-313



= Primary Endpoint: Week 12 HiSCR Response Rate

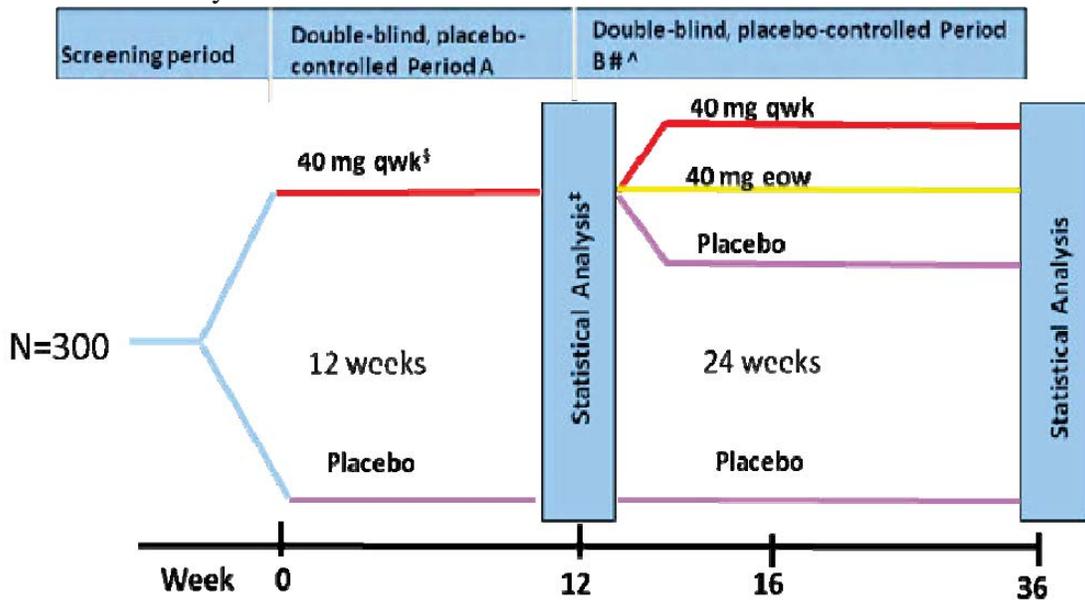
§ Starting at Week 4 after 160 mg at Week 0, 80 mg at Week 2

¶ Week 12 responders will continue in Period B through Week 36 or until loss of response (LOR).

^ Week 12 non-responders will continue in Period B through at least Week 16 (and up to Week 36).

* Blinded adalimumab load of 160 mg at Week 12, 80 mg at Week 14

Schematic for Study M11-810



= Primary Endpoint: Week 12 HiSCR Response Rate

§ Starting at Week 4 after 160 mg at Week 0, 80 mg at Week 2

¶ Week 12 responders will continue in Period B through Week 36 or until loss of response (LOR).

^ Week 12 non-responders will continue in Period B through at least Week 16 (and up to Week 36).

Enrolled subjects were 18 years of age or older with chronic, refractory but stable HS affecting two or more distinct anatomic sites one of which was Hurley Stage II or III, with a total abscess and inflammatory nodule count of ≥ 3 . Randomization was stratified by baseline Hurley Stage (both trials, Hurley III not to exceed 50%) and baseline concomitant antibiotic use (M11-810 only, antibiotic use not to exceed 30%). The primary time point was twelve weeks. The primary efficacy measure was lesion count. The primary efficacy endpoint was the proportion of subjects achieving hidradenitis suppurativa clinical response (HiSCR) at week twelve, defined as at least 50% reduction in the inflammatory lesion count and no increase in abscess or draining fistula counts.

The applicant was granted a Special Protocol Assessment, and a letter with agreements was issued on 4 August 2011. Agreements included:

- General trial design with a 12-week placebo-controlled period followed by a 24-week re-randomized treatment period
- Primary endpoint of proportion of subjects achieving HiSCR at week 12, defined as at least 50% reduction in inflammatory lesion count and no increase in either abscess or draining fistula count
- ITT population as the primary analysis population
- Primary endpoint analysis and method including the stratification variables
- Analysis of efficacy results from period B as exploratory

The results for the primary endpoint are presented in the following table:

Trial M11-313			Trial M11-810		
	Humira N=153	Placebo N=154		Humira N=163	Placebo N=163
Primary endpoint	64 (42%)	40 (26%)	Primary endpoint	96 (59%)	45 (28%)
p-value	0.003		p-value	>0.001	

Source: adapted from Statistical Review and Evaluation sBLA 125057/393, Carin Kim, PhD; archived 9 July 2015, p 14.

In both trials, Humira was superior to placebo for the primary endpoint of proportion of subjects achieving HiSCR at week 12, defined as at least 50% reduction in inflammatory lesion count and no increase in either abscess or draining fistula count.

Ranked secondary endpoints included i) the proportion of subjects with Hurley Stage II disease at baseline who achieved AN count of 0, 1 or 2 at weeks 12, ii) proportion of subjects with baseline NRS ≥ 3 who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30), and iii) change in modified Sartorius score from baseline at Week 12. Statistical significance was not achieved for any of these endpoints in Study M11-313, and the results were not included in labeling.

The reader is referred to the biostatistics and clinical reviews by Carin Kim, PhD, and Snezana Trajkovic, MD, respectively, for detailed review of the pivotal trials and additional analyses, including post hoc explorations of the data and sensitivity analysis.

I concur with Drs. Kim and Trajkovic that the clinical trial data support a determination of efficacy.

8. Safety

Seven hundred twenty seven subjects with HS were exposed to adalimumab during the development program. Of these, 549 subjects were exposed for at least 6 months, and 281 subjects for at least one year. The median duration of adalimumab exposure was 321 days.

Three deaths were reported in the development program for HS. In Study M11-810, a 35-year-old male subject experienced a fatal cardiac arrest on day 234, 42 days after receipt of his last dose of study drug. The investigator considered the death to be probably not related to study drug. In Study M12-555, a 62-year-old female subject experienced autoimmune pancreatitis on Day 214 and cardiac arrest/respiratory failure on day 241, 30 days after receipt of her last dose of study drug. The investigator considered the death to be not related to study drug. Also in Study M12-555, a 49-year-old male subject was hospitalized for dyspnea on day 423, 9 days after his final dose of adalimumab. On day 424, he was admitted to the intensive care unit where he died of fulminant pulmonary edema. The investigator considered the death to be probably not related to study drug.

In the primary safety analysis pool (placebo-controlled analysis pool), treatment-emergent serious adverse events (SAE) occurred in 3.1% of subjects in the adalimumab group and 3.6% of subjects in the placebo group. Other than the SAEs of hidradenitis suppurativa (2 subjects in adalimumab group and 5 in placebo group), no other SAEs occurred in more than one subject in the adalimumab group.

In the placebo-controlled analysis pool, the frequency of commonly-occurring ($\geq 2\%$ of subjects) treatment-emergent adverse events was slightly higher in the placebo group than the adalimumab group. Adverse events that occurred in greater than 2% of subjects in the placebo-controlled analysis pool and at greater frequency in adalimumab subjects dosed every week than placebo are presented in the table below:

MedDRA PT	placebo		adalimumab 40mg ew	
	%	Events/100 person-years	%	Events/100 person-years
Any TEAE	64	744.8	58	669.3
Headache	10	57.1	12	67.7
Upper respiratory tract infection	4	17.5	5	20.7
Nausea	3	12.8	4	16.1
Diarrhea	2	9.3	3	13.8
Dizziness	2	7.0	3	16.1
Arthralgia	1	3.5	3	10.3

Source: adapted from BLA 125057 Section 2.7.4.2.1.1 p26.

In period B, following re-randomization at week 12, subjects who were re-randomized to a lower dose of adalimumab or to placebo reported “hidradenitis” as an adverse event in 18 and 20% of subjects, respectively, versus 5% of subjects who were randomized to continue to receive the same dose of adalimumab and 9% of subjects who continued to receive placebo (study M11-810 only). The applicant assessed “risk of flare” defined as $\geq 25\%$ increase in AN counts, with a minimum increase in two lesions; using this definition, flare occurred in approximately 22% of subjects upon decrease in dose or discontinuation of adalimumab. When assessed by individual lesion counts of inflammatory nodules or draining fistulas, the rate of flare was slightly greater. The issue of flare upon reduction or discontinuation of adalimumab is addressed in labeling.

Analysis of special safety concerns including infection and malignancy did not identify new signals not already addressed in product labeling.

The reader is referred to the clinical review by Dr. Snezana Trajkovic for a full review of the safety database, as well as to the biostatistics review by Dr. Caren Kim.

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

The supplemental application included data from studies of Humira in the treatment of hidradenitis suppurativa conducted in adults. Orphan product designation was granted to the applicant for the treatment of moderate to severe hidradenitis on May 13, 2015; this supplemental application is therefore exempt from the Pediatric Research Equity Act of 2007.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

All components of labeling were reviewed, and agreement reached with the applicant.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: *Approval*

I concur with the recommendations of the multi-disciplinary review team regarding approval of BLA 125057 Humira (adalimumab) for injection for the treatment of moderate to severe hidradenitis suppurativa.

Risk-benefit assessment: The applicant established the efficacy and safety of Humira (adalimumab) for injection in the treatment of moderate to severe hidradenitis suppurativa in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product.

Postmarketing requirements (PMR) and commitments (PMC):

Utilize the validated anti-adalimumab antibody (AAA) assay developed under PMR 2517-3 (as described in the FDA Fulfillment of Postmarketing Requirement Letter dated April 1, 2015) to analyze the immunogenicity profile of adalimumab using banked patient samples from Phase 3 trials M11-810 and M11-313. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with hidradenitis suppurativa based on the AAA data generated with the newly validated assay.

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/s/

JILL A LINDSTROM
09/09/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type: Efficacy Supplement
Application Number(s): 125057, S-393
Priority or Standard: Standard

Submit Date(s): November 10, 2014
Received Date(s): November 10, 2014
PDUFA Goal Date
Division / Office: DDDP/OND

Reviewer Name(s): Snezana Trajkovic
Review Completion Date: July 17, 2015

Established Name: Adalimumab
(Proposed) Trade Name: Humira
Therapeutic Class: Monoclonal antibody
Applicant: AbbVie Inc.

Formulation(s): Solution for subcutaneous injection
Dosing Regimen: 40mg subcutaneous injection once weekly
Indication(s): Moderate to severe hidradenitis suppurativa
Intended Population(s): Adults 18 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that adalimumab 40mg dose administered by subcutaneous injection once weekly is approved for the treatment of moderated to severe hidradenitis suppurativa.

1.2 Risk Benefit Assessment

In this BLA supplement, the applicant requested approval for their product, adalimumab 40mg subcutaneous injection, for the treatment of moderated to severe hidradenitis suppurativa. In support of this indication, the applicant conducted two well controlled Phase 3 trials.

The primary evidence of efficacy was based on two well-controlled Phase 3 trials of similar design, M11-313 and M11-810. These two Phase 3 trials were randomized, multicenter, double-blind, placebo-controlled, 36-week trials that evaluated the safety and efficacy of adalimumab 40mg administered subcutaneously once weekly, for the treatment of adult subjects with moderate to severe hidradenitis suppurativa. Two trials enrolled 633 subjects, 18 years of age and older, who had hidradenitis suppurativa of Hurley Stage II or Hurley Stage III, and total abscess and inflammatory nodules count of equal/greater than 3 at Baseline. Subjects administered adalimumab 40mg subcutaneously once weekly; adalimumab 40mg subcutaneously every other week; or placebo, for 36 consecutive weeks.

The primary efficacy endpoint was the proportion of subjects who achieved Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least 50% reduction in Abscess and inflammatory Nodule (AN) count with no increase in abscess count and no increase in draining fistula count, relative to Baseline, at Week 12. After 12 weeks of treatment, in M11-313, 41.8% of adalimumab treated subjects achieved HiSCR, compared to 26% of placebo treated subjects, a treatment effect of 15.9% ($p < 0.003$). In M11-810, 58.9% of adalimumab treated subjects achieved HiSCR, compared to 27.6% of placebo treated subjects, a treatment effect of 31.5% ($p < 0.001$).

Major secondary endpoints were:

- Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline.

- Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst, at Week 12, among subjects with Baseline NRS \geq 3.
- Change in modified Sartorius score from Baseline to Week 12.

The results of ranked secondary endpoints showed that the difference between adalimumab and placebo group were statistically significant in Study M11-811 but did not reach statistical significance in Study M11-313. Because the results of secondary endpoints were not replicated in the second trial, these results will not be included in product labeling.

The data from these two Phase 3 trials provided evidence of efficacy for 40mg adalimumab subcutaneous injection in the target patient population. Efficacy, although modest, was consistent across sub-groups (by age, gender, race, BMI, baseline disease severity) and across study centers.

The assessment of safety for the adalimumab 40mg administered once weekly was primarily based on analysis of data from two Phase 3 trials (M11-313 and M11-810), Phase 3 open-label extension trial M12-555 and one Phase 2 trial, M10-467. The safety population included 688 subjects exposed to repeat dosing of adalimumab at the proposed dose of 40mg once weekly. The target population, number of subjects, duration of exposure at the proposed dose and dosing frequency, was adequate for evaluation of safety in subjects with moderate to severe hidradenitis suppurativa.

During adalimumab development program for the hidradenitis indication, although three deaths were reported, analysis of these events revealed that causality could not be definitely attributed to the treatment. Review of serious adverse events (SAEs) did not reveal new or increased safety signals. Analysis of adverse events of special interest (AESI) did not reveal new or increased safety signals.

Evaluation of the effect of a decrease of dosing frequency or discontinuation of dosing, revealed that 21% and 22% of subjects experienced HS rebound, respectively. The potential for rebound will be included into product labeling.

In this reviewer's opinion, the applicant provided adequate evidence of safety of adalimumab 40mg administered once weekly. Review of the safety database did not identify a safety signal that would preclude an approval of adalimumab for the indication of treatment of hidradenitis suppurativa. The overall safety profile of adalimumab in hidradenitis patients appears to be similar to safety profile of adalimumab in other approved indications.

This reviewer concludes that 40mg subcutaneous injection, administered once weekly, has acceptable risk/benefit profile for the treatment of subjects with moderate to severe hidradenitis suppurativa. An approval action for this sBLA is recommended, pending final labeling negotiations with the applicant.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The following post-marketing commitments/requirements are recommended:

- PMR: Utilize the validated anti-adalimumab antibody (AAA) assay (as described in the FDA Fulfillment of Postmarketing Requirement Letter dated April 1, 2015) to analyze the immunogenicity profile of adalimumab using banked subject's samples from Phase 3 trials M11-810 and M11-313. The Applicant should evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety based on the AAA data generated with the newly validated assay.
- PMC: To conduct a clinical drug-drug interaction (DDI) study to evaluate whether adalimumab alters the PK or metabolism of CYP substrates in HS patients treated with adalimumab. The DDI study should use a "cocktail" approach to simultaneously evaluate the effect of adalimumab on the PK of probe substrates metabolized by CYP enzymes including but not limited to CYP3A4, CYP2C19, CYP2C9, CYP2D6 and CYP1A2.

2 Introduction and Regulatory Background

2.1 Product Information

Adalimumab is an approved product indicated for the treatment of:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Pediatric Crohn's Disease
- Ulcerative Colitis (UC)
- Plaques Psoriasis (Ps)

Adalimumab (HUMIRA) is a recombinant human immunoglobulin (IgG1) monoclonal antibody that binds with high affinity and specificity to soluble TNF- α and neutralizes the biological function of TNF- α by blocking its interaction with the p55 and p75 cell surface TNF- α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF- α .

Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It is comprised of human heavy and light chain variable regions which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF- α but not to lymphotoxin (TNF- β).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no approved products for the treatment of hidradenitis suppurativa.

2.3 Availability of Proposed Active Ingredient in the United States

Humira is widely available in the United States; the product is approved for several indications.

2.4 Important Safety Issues With Consideration to Related Drugs

HUMIRA's labeling carries boxed warning that includes the risk of serious infections leading to hospitalization or death from tuberculosis, bacterial sepsis, invasive fungal infections and infections due to opportunistic pathogens. In addition, lymphoma and other malignancies, some fatal, in children and adolescent patients, as well as hepatosplenic T-cell lymphomas, a rare type of T-cell lymphoma, in adolescent and young adults with inflammatory bowel disease, have been reported. Similar boxed warnings have been included in labeling of other approved TNF inhibitor biologic products, including infliximab (REMICADE); etanercept (Enbrel); golimumab (SIPMPONI); certolizumab (CIMZIA).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for the hidradenitis indication was conducted under IND 102320 submitted on August 15, 2008. Key pre-submission regulatory activities include the following:

- End-of-Phase 2 meeting (January 19, 2011)
- SPA-1 and SPA-2 agreement letter (August 4, 2011)
- Deny Breakthrough Therapy Designation letter (September 20, 2013)
- Pre-sBLA meeting (July 30, 2014)

End-of-Phase 2 meeting was held on January 19, 2011

The following advice was conveyed to the sponsor:

- The Agency did not agree with proposed study population as it would not truly represent the population of subjects with moderate to severe hidradenitis suppurativa (HS).

- The Agency did not agree with sponsor's proposed efficacy endpoint of AN50 (50% reduction in number of inflammatory nodules and abscesses) because without assessment of other components (erythema, fistulas, scarring, tracks) it would be difficult to conclude that an improvement in the AN would be meaningful and sufficient for establishing and efficacy claim.

Request for SPA of two clinical protocols (SPA-1 and SPA-2) request were submitted on **June 23, 2011**.

Two Phase 3 protocols were reviewed and the SPA letter dated August 4, 2011 was sent to the sponsor. The following agreements/disagreements were communicated to the sponsor.

The agency agreed with proposed:

- Study design
- Primary endpoint of "Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12" (HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess count and no increase of draining fistula count).
- Dosing of 40mg every week.

The agency did not agree with proposed:

- Subject population in regard to inclusion criterion of baseline inflammatory lesion count of 3 as it would not adequately represent the population of subjects with moderate to severe HS.

Deny Breakthrough Therapy Designation Letter (September 20, 2013)

The sponsor submitted a request for Breakthrough Therapy under Section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA). In accordance with definition of breakthrough therapy in the legislation, the company stated that adalimumab would treat a serious condition (hidradenitis suppurativa) and would demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The agency reviewed the preliminary clinical evidence supporting sponsor's request and it was decided that designation as a Breakthrough Therapy could not be granted for the following reason:

"The magnitude of the treatment effect was modest in both study periods, particularly in the subgroup of subjects with severe disease or compared to historical experience with surgical approaches".

Pre-sBLA meeting was held on July 30, 2014.

The content and format of the proposed sBLA submission was discussed.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Office of Scientific Investigations (OSI) inspections were requested for 3 Phase 3 study sites, selected because they had some of the largest enrollments and greatest treatment effects.

Study M11-810

Investigators:

- Seth Forman M.D., Site #37884
- Alma Cruz-Santana M.D., Site # 42801

Study M11-313

Investigator:

- Jamie Weisman M.D., Site# 36627

Inspection of all three investigation sites was conducted and the following conclusion was reached by Roy Blay Ph.D. of Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation:

“The clinical sites of Drs. Weisman, Forman, and Cruz-Santana were inspected in support of this sBLA. None of these sites were issued a Form FDA 483, and the final classification of the inspections of each of these sites was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by each of these sites appear acceptable in support of the respective indication.”

After reviewing the inspection report, this reviewer agrees with findings and the conclusion by Dr. Blay.

3.2 Compliance with Good Clinical Practices

The applicant stated that studies were designed, monitored, and conducted in accordance with Good Clinical Practice (GCP) requirements and ethical principles. Trial protocols, the subject information and informed consent forms, and subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The applicant obtained an approval from IRB prior to trial initiation.

3.3 Financial Disclosures

The applicant certified (Form FDA 3454) that they had not entered into any financial arrangements with any of the clinical investigators. In addition, form FDA 3455 (Disclosure: Financial Interests and Arrangement of Investigators), for 30 investigators

who participated in Study M10-467; Stud M11-810; Study M11-313 and Study M12-555, was provided by the applicant. The applicant provided details on investigator's disclosable financial arrangements, along with steps taken to minimize the potential bias of study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was included in this efficacy supplement.

4.2 Clinical Microbiology

This section of the review is not applicable to this product.

4.3 Preclinical Pharmacology/Toxicology

The applicant has not included any new Pharmacology/Toxicology studies.

4.4 Clinical Pharmacology

The pharmacokinetics and immunogenicity of adalimumab were evaluated in subjects with moderate to severe hidradenitis suppurativa in a single Phase 2 study (M10-467) and two Phase 3 studies (M11-313 and M11-810). In this section, pharmacokinetics of adalimumab in subjects with HS will be discussed. Immunogenicity will be presented in Section 7.4.6 of this review.

4.4.1 Mechanism of Action

Adalimumab binds specifically to TNF- α and blocks its interaction with cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1; VCAM-1 and ICAM-1).

4.4.2 Pharmacodynamics

Following treatment with adalimumab, there are decreased levels of acute phase reactants [C-reactive protein; erythrocyte sedimentation rate, IL-6 and serum levels of matrix metalloproteinase (MMP-1 and MMP-3)].

4.4.3 Pharmacokinetics

The pharmacokinetic of adalimumab was evaluated in subjects with moderate to severe HS in Phase 2 Study M10-467 and two Phase 3 Studies M11-313 and M11-810. In addition, the applicant compared pharmacokinetics results in subjects with HS with results from previous studies in subjects with Crohn's disease (CD), ulcerative colitis (UC) and plaque psoriasis (Ps).

Study M10-467

Study Title: A Phase 2 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Chronic Hidradenitis Suppurativa

Study Period: April 22, 2009 to November 9, 2010.

Study Objective: To evaluate safety, efficacy, PK and immunogenicity of adalimumab in subjects with HS.

Study Design: This was double-blind, placebo-controlled, randomized study with open label phase.

Number of Centers: 26 sites in Germany, United States, Denmark, and The Netherlands.

Number of Subjects: 154

Study Population: Adult subjects with HS of ≥ 6 months duration involving ≥ 2 distinct anatomic areas, Unresponsive or intolerant to oral antibiotics for treatment of HS and with HS PGA of ≥ 3 at baseline.

Study procedures:

This was a 52-week, multicenter, Phase 2 study conducted to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of adalimumab in adult subjects with moderate to severe HS. Study consisted of two treatment periods:

- **Period 1:** A 16-week, double-blind, placebo-controlled treatment period where subjects were randomized to one of 3 treatment arms, in 1:1:1 ratio, to receive adalimumab 40 mg every week (ew) or 40 mg every other week (eow) or matching placebo.

Subjects randomized to adalimumab 40 mg ew were to receive the following regimen:

- Loading dose of 160 mg adalimumab SC at Baseline (Day 1) administered as four 40 mg SC injections;

- One 0.8 ml placebo injection on Day 8;
- 80 mg adalimumab at Day 15 administered as two 40 mg injections;
- One 0.8 mL placebo injection on Day 22;
- 40 mg ew starting at Day 29 administered as one 40 mg injection.

Subjects randomized to adalimumab 40 mg eow were to receive the following regimen:

- 80 mg adalimumab SC at Baseline (Day 1) administered as two 40 mg injections and two placebo (0.8 mL) injections
- 40 mg adalimumab eow starting at Day 8 through Week 15 administered as one 40 mg injection
- 0.8 mL placebo injections will be administered eow starting on Week 2 through Week 14 (2 placebo injections at Week 2)

Subjects randomized to placebo were to receive the following regimen:

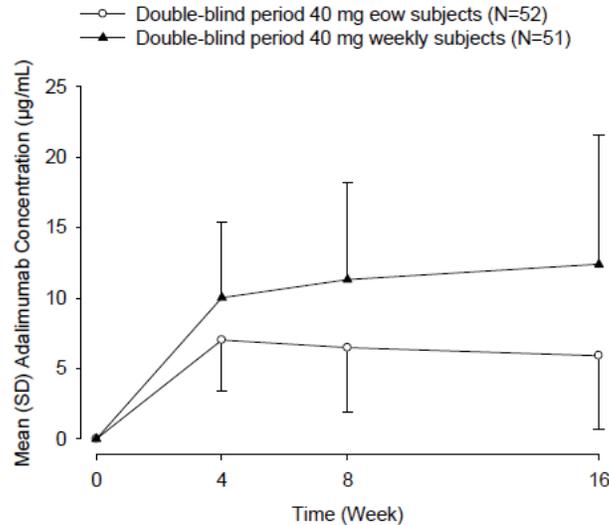
- Four 0.8 mL placebo injections at Baseline (Day 1)
 - One 0.8 mL placebo injection at Week 1 (Day 8)
 - Two 0.8 mL placebo injections at Week 2 (Day 15)
 - One 0.8 mL placebo injection ew from Week 3 (Day 22) through Week 15.
- **Period 2:** A 36-week, open-label treatment period. During Period 2 all subjects received open-label adalimumab 40 mg eow with the option to escalate to ew at Week 28 if the subject failed to achieve PGA <3.

Serum adalimumab concentrations were measured at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45, and Week 52. Serum measurements of anti-adalimumab antibodies (AAA) were obtained at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45, and Week 52/ end of trial (ET).

A total of 154 subjects were randomized in the double-blind, placebo-controlled period. A total of 11 subjects discontinued this portion of the study. One hundred and three subjects completed the study.

At the end of Period 1, the mean adalimumab concentration following 40mg ew was 10-12µg/ml, about 2-fold of that observed with 40mg eow (6-7µg/ml). See Figure below.

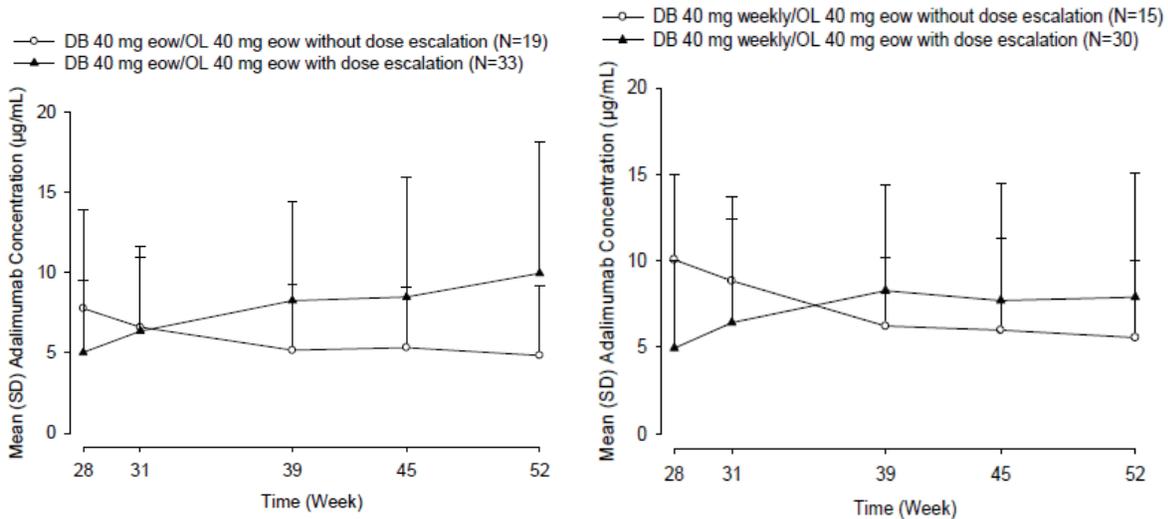
Figure 1: Median (SD) Serum Adalimumab Concentrations vs. Time in Double-Blind Period; Study M10-467

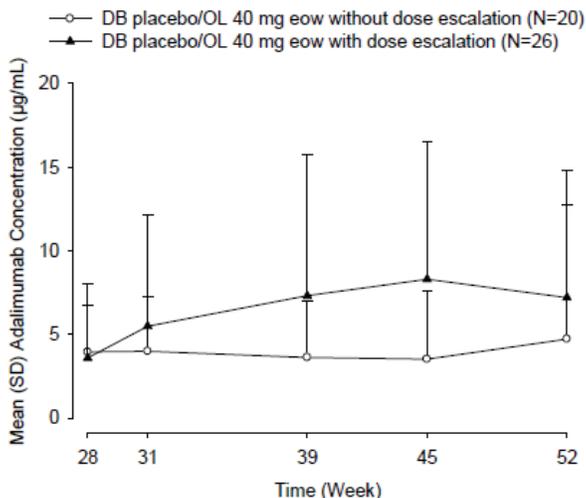


Source: Summary of Clinical Pharmacology Studies; Figure 1; page 6.

Serum adalimumab concentrations in the Period 2, separately by treatment group in the Period 1, are presented in Figure below.

Figure 2: Mean (SD) Serum Adalimumab Concentrations vs. Time in Open-Label Period by Treatment Groups (Week 28 to 52) Study M10-467



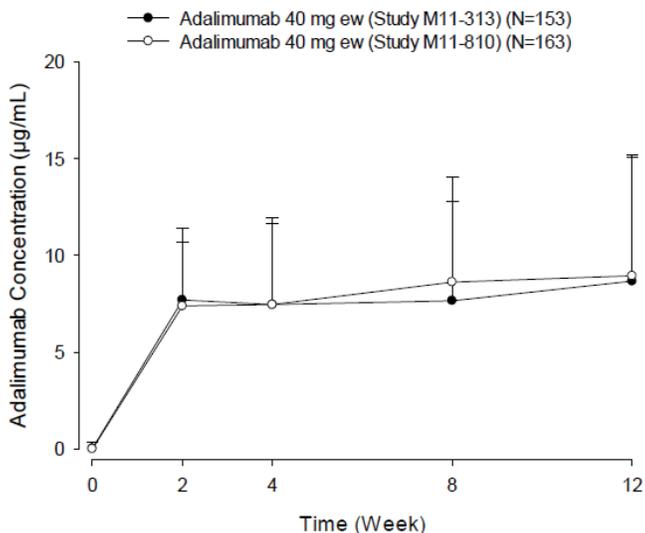


DB = Double-blind (Week 0 – 16); OL = Open-label (Week 17 – 52); Dose escalation = In the open-label period at Week 28 or Week 31, adalimumab 40 mg ew treatment could dose escalate to 40 mg ew based on PGA score
 Source: Summary of Clinical Pharmacology Studies; Figure 2; page 8.

Pharmacokinetics Results from Study M11-313 and M11-810

Following initial dosing with adalimumab 160mg at Week 0 and 80mg at Week 2, and continuation with adalimumab 40mg ew dosing, the mean steady state concentration reached steady state (7-9µg/mL) by Week 2, and was maintained through Week 12. Adalimumab concentrations were similar in both studies M11-313 and M11-810. Mean serum adalimumab concentration during Period A of studies M11-313 and M11-810 are presented in Figure below.

Figure 3: Mean Serum Adalimumab Concentration Over time in Subjects with HS during Period A; Study M11-313 and M11-810



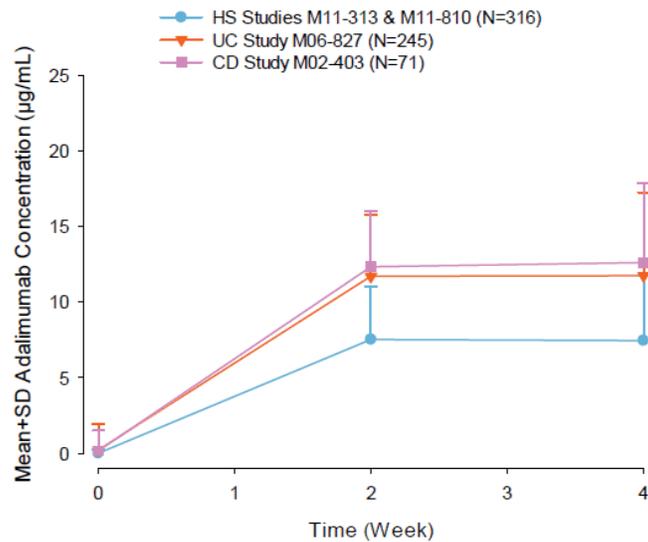
Source: Summary of Clinical Pharmacology Studies; Figure 3; page 13.

Comparison and Analysis of Results Across Indications

Initial Dosing Regimen

Following initial dosing with adalimumab 160mg at Week 0 and 80mg at Week 2 in subjects with HS, Crohn's disease and ulcerative colitis, adalimumab concentrations were lower in subjects HS compared to subjects with CD and UC.

Figure 4: Mean Serum Adalimumab Concentrations During Initial Dosing Regimen (Adalimumab 160mg at Week 0 and 80mg at Week 2) in Subjects with HS, UC and CD (Week 0-4)

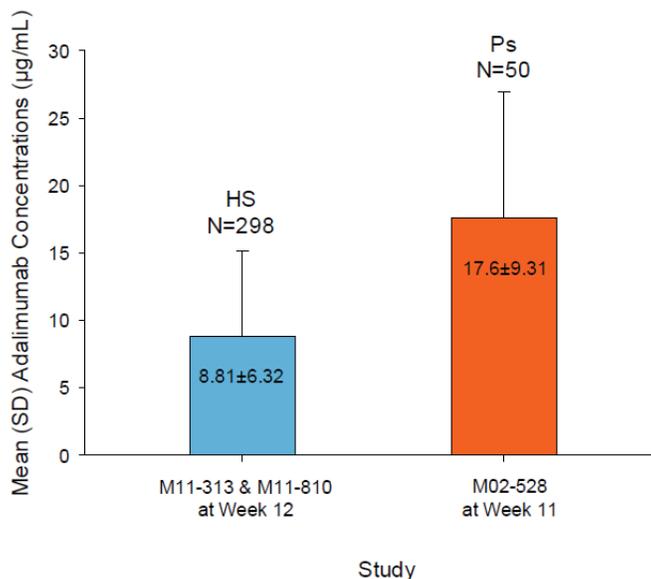


Source: Summary of Clinical Pharmacology Studies; Figure 6; page 17.

Maintenance Period Dosing Regimen

Adalimumab concentrations were compared in subjects with HS and Ps, treated with adalimumab 40mg ew during maintenance period. Adalimumab concentrations were lower in subjects with HS (8.8µg/mL at Week 12) compared to subjects with Ps (17.6µg/mL at Week 11).

Figure 5: Mean Serum Adalimumab Concentrations Following Adalimumab 40mg Weekly Treatment in Subjects with HS and Ps



Source: Applicant's submission, Summary of Clinical Pharmacology Studies; Figure 7; page 18.

Reviewer's comments: Adalimumab serum concentrations were lower in subjects with HS compared to subjects with UC, CD or PS given at the same loading doses and with repeated dosing regimens of ew in HS and Ps. Despite the increased dosing frequency of adalimumab in HS, the exposure did not appear to be increased. Therefore, it should be expected that safety profile of adalimumab in HS patients be similar to that of other adalimumab indications.

5 Sources of Clinical Data

The applicant conducted 4 clinical trials in the development program for hidradenitis suppurativa.

5.1 Tables of Studies/Clinical Trials

Table 1: Trials Supporting the Application

Trial number	Objective	Study design	Test product; dosage; regimen	Number of subjects	Study subjects	Duration of treatment
Phase 3 M11-313 (11/29/11-01/28/14)	Efficacy and safety	Randomized, double blind, placebo controlled	Period A: <ul style="list-style-type: none"> Adalimumab 40mg ew Placebo Period B: <ul style="list-style-type: none"> Adalimumab 40mg ew Adalimumab 40mg eow Placebo 	307	Moderate to severe HS	Period A: 12 weeks Period B: 24 weeks
Phase 3 M11-810 (12/28/11-4/28/14)	Efficacy and safety	Randomized, double blind, placebo controlled	Period A: <ul style="list-style-type: none"> Adalimumab 40mg ew Placebo Period B: <ul style="list-style-type: none"> Adalimumab 40mg ew Adalimumab 40mg eow Placebo 	326	Moderate to severe HS	Period A: 12 weeks Period B: 24 weeks
Phase 3 M12-555 (04/12/12-04/29/14)	Long term safety	Open label	Adalimumab 40mg ew with possible reduction to 40mg eow	497	Moderate to severe HS	≥60 weeks
Phase 2 M10-467 (4/22/09 - 11/09/10)	Efficacy and safety; PK and immunogenicity	Randomized, double blind, placebo controlled with open label phase	Period A: <ul style="list-style-type: none"> Adalimumab 40mg ew Adalimumab 40mg eow Placebo Period B: Adalimumab 40mg eow with possible escalation to 40mg ew	154	Moderate to severe HS	Period A: 16 weeks Period B: 36 weeks

5.2 Review Strategy

For efficacy, two Phase 3 trials (M11-313 and M11-810) will be reviewed separately and pooled, and discussed in **Section 6** of this review.

For safety, trials M10-467; M11-313; M11-810; M12-555 will be reviewed as pooled data and discussed in section 7 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Three Phase 3 trials (M11-313; M11-810; M12-555) and one Phase 2 trial (M10-467), support this BLA efficacy supplement.

Phase 3 trial: M11-313

Study Title: A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa- PIONEER I

Study Period: November 29, 2011 to January 28, 2014

Number of Centers: 48 centers in Canada, United States, Czech Republic, Hungary, Germany, and Australia.

Study Objective: To evaluate safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS.

Study Design: This was multicenter, randomized, placebo-controlled trial.

Number of Centers: 48 (24 in the US; 5 in Check Republic; 7 in Germany; 3 in Australia; 5 in Canada and 4 in Hungary).

Number of Subjects: 307

Study Population

Key Inclusion Criteria

1. Male and female subjects \geq 18 years of age.
2. Subject had a diagnosis of HS for at least 1 year (365 days) prior to Baseline.
3. HS lesions were present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which was Hurley Stage II or Hurley Stage III.
4. Subject had an inadequate response to at least a 3-month (90 days) trial of oral antibiotics for treatment of HS (or demonstrated intolerance to, or had a contraindication to, oral antibiotics for treatment of their HS).
5. Subject had stable HS for at least 2 months (60 days) prior to Screening and also at the Baseline visit as determined by the investigator through subject interview and review of the medical history.
6. Subject had a total abscess and inflammatory nodules (AN) count of greater than or equal to 3 at the Baseline visit.

A minimum of 3 and a maximum of 6 representative lesions (3 inflammatory nodules, 1 abscess if present, up to 2 fistulas if present) were to be identified in the 4 recommended anatomic regions (left axilla, right axilla, left inguino-crural fold, and right

inguino-crural fold), evaluated at Baseline and followed over time for progression or resolution. A representative lesion was an inflammatory nodule, abscess, or fistula which was typical of its group. It was not necessary to include the largest or worst lesion, or one that was progressing, or expected to progress.

Key Exclusion Criteria

1. Subject had a draining fistula count of greater than 20 at the Baseline visit;

Study Visits and Procedures

The study consisted of two periods: a 12-week double-blind treatment period (Period A) and subsequent 24-week double-blind period (Period B).

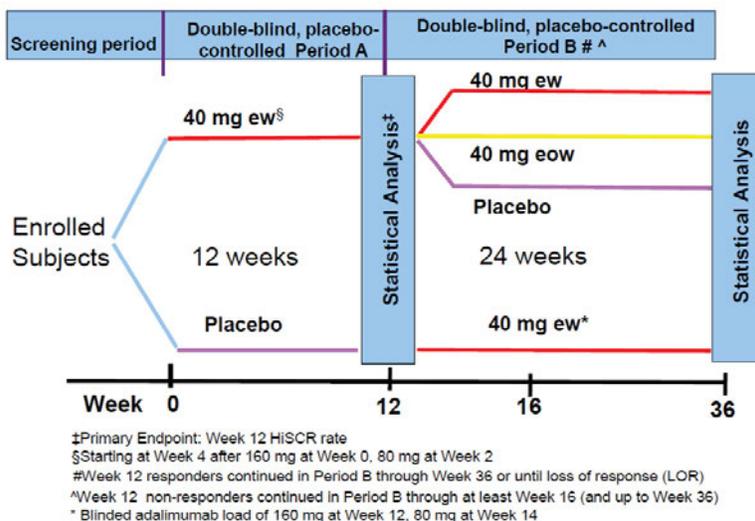
Period A

This was a 12-week, double-blind, placebo-controlled treatment period during which subjects were randomized in 1:1 ratio to receive adalimumab 160mg at Week 0; 80mg at Week 2; and 40mg every week (ew) or placebo starting at Week 4. The randomization was stratified by Baseline Hurley Stage (II vs. III).

Period B

This was a 24-week, double-blind, placebo-controlled treatment period. All subjects from period A were re-randomized at Week 12. Subjects randomized to adalimumab in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40mg ew, adalimumab 40mg eow, or placebo. Subjects randomized to placebo in Period A were to receive adalimumab 160mg at Week 12, 80mg at Week 14, placebo at Week 13 and Week 15, and adalimumab 40mg ew from Week 16 to Week 35. Schematic of study design is presented in Figure 3 below.

Figure 6: Study Design Schematic (M11-313)



All subjects from Period A, who achieved Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12, were to continue in Period B through Week 36. Subjects who experienced a loss of response (LOR) in Period B (AN count greater than the average of AN counts at Baseline and Week 12) were to be discontinued from the study and had the opportunity to enter into OLE M12-555.

All subjects from Period A who did not achieve HiSCR at Week 12 were to continue in Period B through Week 36. Starting at Week 16, subjects who experienced worsening or absence of improvement (AN count greater than or equal to the AN count at Baseline or 2 consecutive visits that occurred at least 14 days apart), were to be discontinued from the study and had the opportunity to enter into OLE M12-555.

At Week 36, all subjects had the opportunity to enter the Open-Label Extension (OLE) Study M12-555 during which they were to receive adalimumab 40mg ew. The schedule of study procedures is presented in Table below.

Table 2: Schedule of Study Procedures

Activity	Period A						Period B						Wk 36 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call	
	Screening (Day -30 to Day -1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32				
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X ^a														
Prior and Concomitant Therapy Assessment ^b	X	X ^a	X	X	X	X	X	X	X	X	X	X	X	X		
Medical/Surgical History	X	X ^a														
Alcohol Use	X															
Nicotine Use	X					X							X			
Physical Exam	X	X	X ^c	X	X ^c											
Chest X-Ray/ECG	X												X ^d			
TB Screening	X															
Vital Signs	X ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist Circumference		X				X							X			
Pregnancy Tests	X ^f	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	
General Labs: Chemistry and Hematology	X	X ^h		X		X ^h		X		X	X	X	X ^h			

Table 2: Schedule of Study Procedures (continues)

Activity	Period A						Period B						Wk 36 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call	
	Screening (Day -30 to Day -1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32				
Urinalysis ⁱ	X	X		X		X		X		X	X	X	X			
Urine Nicotine Metabolite Screening	X					X							X			
hsCRP		X				X							X			
Hepatitis B Screen	X															
HbA1c		X				X							X			
Advanced Lipid Testing		X ^h				X ^h							X ^h			
PK Measurements ^j		X	X	X	X	X	X	X	X	X		X	X			
AAA Measurements ^j		X		X		X		X		X			X			
ANA/dsDNA ^k	X															
Pharmacogenetic Sample ^l		X														
Serum and Plasma Biomarkers		X		X		X							X			
Pharmacogenomic Sample		X				X										

Source: Applicant's submission, Module 5.3.5.1. Study report body M11-313, Section 9.5.1, page 281.

Concomitant Medication

Antiseptic Therapy: Subjects were required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes were limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.

Wound Care: Concomitant use of wound care dressings on HS wounds was allowed; however, options were limited to alginates, hydrocolloids, and hydrogels.

Antibiotic Therapy: Starting at Week 4 or Week 8 (Period A), if AN counts were greater than or equal to 150% of Baseline AN counts, antibiotic rescue medication (minocycline or doxycycline up to 100mg bid) was permitted. The dosing regimen was to remain stable throughout study participation. Otherwise, concomitant use of oral antibiotic therapy for treatment of HS was not allowed. Rescue antibiotic therapy was to be captured in the source and on the appropriate eCRF. Permitted oral concomitant antibiotics included: doxycycline (up to 100 mg b.i.d.) and minocycline (up to 100 mg b.i.d.). *If a subject received antibiotic rescue medication, the subject was counted as a non-responder from the start of rescue medication, and had the last observation obtained prior to the start of rescue medication carried forward for continuous variables.*

Analgesic Therapy: if a subject was on a stable dose of a non-opioid analgesic for a non-HS medical condition the subject was allowed to continue the analgesic, provided the dose was stable for 14 days prior to Baseline and was to remain stable throughout study. If a subject's **HS-related pain** worsened after Baseline, the subject was allowed to initiate analgesic therapy on PRN basis at any time as follows:

- Ibuprofen not to exceed 3.2gr/24 hours
- Acetaminophen as per labeling
- Tramadol not to exceed 400mg/24 hours

All analgesics and dose adjustments were to be captured in the source documentation and on the appropriate eCRF.

For **Non-HS-related pain** opioid analgesics were prohibited. All other analgesics, including tramadol, were allowed at the recommended or prescribed dose.

Lesion Intervention: In the event that an acutely painful lesion occurred that required an immediate intervention only two types of interventions were allowed:

- Injection with intralesional triamcinolone acetonide suspension (at a concentration up to 5 mg/mL and a volume up to 1 mL) and
- Incision and drainage.

New systemic and topical therapies following incision and drainage (including antibiotics), were prohibited. Concomitant use of wound care dressings was allowed, however options were limited to alginates, hydrocolloids, and hydrogels. Subjects were to continue to use any ongoing oral and topical therapies (including antibiotics, with the exception of prohibited therapies) Concomitant medications associated with the lesion interventions were to be captured in eCRF. A total of 2 protocol-allowed interventions were permissible during Period A. An intervention could have occurred on maximally 2

different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion could not be treated 2 times at the same visit. If a subject required more than 2 interventions within the first 12 weeks, then that subject was to be discontinued from the study. During Period B, a maximum of 2 interventions every 4 weeks were permitted. An intervention could occur on 2 different lesions at the same visit or on the same lesion at 2 different study visits. Within each 4-week period, the same type of intervention could not be used 2 times on the same lesion. If a subject required more than 2 interventions within a 4-week period or had 2 of the same interventions on the same lesion within that period, then that subject was to be discontinued from the study. The site was required to count any lesion that received an intervention as permanently present from the date of the intervention and must account for it in the source documentation and on the appropriate eCRF.

Safety Evaluation

The following safety procedures were conducted:

Physical examination: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Vital signs: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Chest X-Ray: At Screening

ECG: At Screening

TB screening: At Screening

Pregnancy test: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Laboratory evaluations (Chemistry; Hematology): At Screening; Baseline; Weeks 4; 12; 16; 24; 28; 32; 36.

Urinalysis: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

hsCRP: At Baseline; Week 12 and 36.

Hepatitis B Screen: At Screening

Serum HIV: At Screening

HbA1c: At Baseline; Week 12 and 36.

Lipid panel: At Baseline; Week 12 and 36.

ANA/dsDNA: At Screening

Urine Nicotine Metabolite Screening: At Screening; Week 12 and 36.

Efficacy Evaluation

The **primary efficacy endpoint** was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least 50% reduction in Abscess and inflammatory Nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12.

Ranked **secondary efficacy endpoints** were:

1. Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline.
2. Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline NRS \geq 3.

3. Change in modified Sartorius score from Baseline to Week 12.

Phase 3 trial: M11-810

Study Title: A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa- PIONEER II

Study Period: December 28, 2011 to April 28, 2014.

Study Objective: To evaluate safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS.

Study Design: This was multicenter, randomized, placebo-controlled trial.

Number of Centers: 53 centers (6 in Canada, 16 in the United States/Puerto Rico, 2 in Turkey, 5 in Switzerland, 4 in Denmark, 5 in France, 4 in Greece, 2 in Sweden, 3 in The Netherlands, and 6 in Australia).

Number of Subjects: 326

Study Population:

Key inclusion/exclusion criteria are the same as in study M11-313.

Study Visits and Procedures:

The study consisted of two periods: a 12-week double-blind treatment period (Period A) and subsequent 24-week double-blind period (Period B).

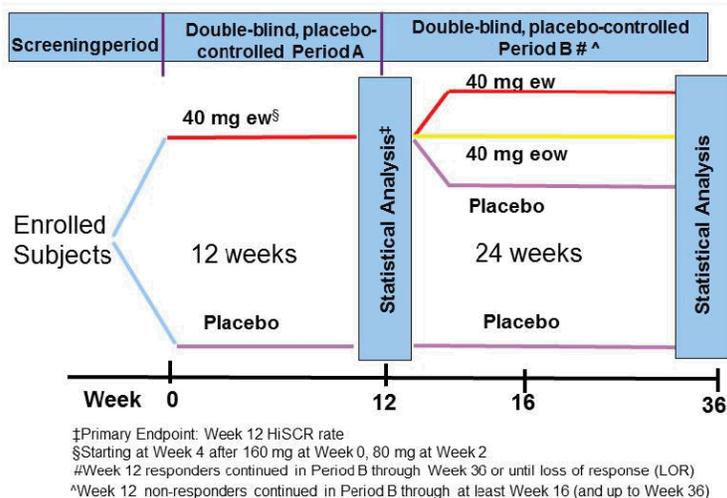
Period A

This was a 12-week, double-blind, placebo-controlled treatment period during which subjects were randomized in 1:1 ration to receive adalimumab 160mg at Week 0; 80mg at Week 2; and 40mg every week (ew) or placebo starting at Week 4. The randomization was stratified by Baseline Hurley Stage (II vs. III).

Period B

This was a 24-week, double-blind, placebo-controlled treatment period. All subjects from period A were re-randomized at Week 12. Subjects randomized to adalimumab in Period A were re-randomized in a 1:1:1 ration to receive adalimumab 40mg ew, adalimumab 40mg eow, or placebo. Subjects randomized to placebo in Period A were to be re-randomized to continue on placebo. Schematic of study design is presented in Figure 4 below.

Figure 7: Study Design Schematic (M11-810)



All subjects from Period A, who achieved Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12, were to continue in Period B through Week 36. Subjects who experienced a loss of response (LOR) in Period B (AN count greater than the average of AN counts at Baseline and Week 12) were to be discontinued from the study and had the opportunity to enter into OLE M12-555.

All subjects from Period A who did not achieve HiSCR at Week 12 were to continue in Period B through Week 36. Starting at Week 16, subjects who experienced worsening or absence of improvement (AN count greater than or equal to the AN count at Baseline or 2 consecutive visits that occurred at least 14 days apart), were to be discontinued from the study and had the opportunity to enter into OLE M12-555.

At Week 36, all subjects had the opportunity to enter the Open-Label Extension (OLE) Study M12-555 during which they were to receive adalimumab 40mg ew.

Schedule of Study Procedures is presented in Table 3 below.

Table 3: Schedule of Study Procedures

Activity	Period A						Period B						Wk 36 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call	
	Screening (Day -30 to Day -1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32				
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X ^a														
Prior and Concomitant Therapy Assessment ^b	X	X ^a	X	X	X	X	X	X	X	X	X	X	X	X		
Medical/Surgical History	X	X ^a														
Alcohol Use	X															
Nicotine Use	X					X							X			
Physical Exam	X	X	X ^c	X ^c	X ^c											
Chest X-Ray/ECG	X													X ^d		
TB Screening	X															
Vital Signs	X ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference		X				X							X			
Pregnancy Tests	X ^f	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	X ^g	
General Labs: Chemistry and Hematology	X	X ^h		X		X ^h		X		X	X	X	X ^h			

Table 3: Schedule of Study Procedures (continues)

Activity	Period A						Period B						Wk 36 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call	
	Screening (Day -30 to Day -1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32				
Urinalysis ⁱ	X	X		X		X		X		X	X	X	X			
Urine Nicotine Metabolite Screening	X					X							X			
hsCRP		X				X							X			
Hepatitis B Screen	X															
HbA1c		X				X							X			
Advanced Lipid Testing		X ^h				X ^h							X ^h			
PK Measurements ^j		X	X	X	X	X	X	X	X	X		X	X			
AAA Measurements ^j		X		X		X		X		X			X			
ANA/dsDNA ^k	X															
Pharmacogenetic Sample ^l		X														
Serum and Plasma Biomarkers		X		X		X							X			
Pharmacogenomic Sample		X				X										

Source: Applicant's submission, Module 5.3.5.1. Study report body M11-810, Section 9.5.1, page 258.

Concomitant Therapy
Antiseptic Therapy and Wound Care
 As described for Study M11-313.

Antibiotic Therapy

Concomitant use of permitted oral antibiotic therapy for treatment of HS was allowed provided the dosing regimen (dose and frequency) had been stable for at least 4 consecutive weeks (28 days) prior to Baseline. Permitted oral concomitant antibiotics included:

- Doxycycline (at a dose up to 100 mg by mouth twice-a-day)
- Minocycline (at a dose up to 100 mg by mouth twice-a-day)

Lesion Intervention: As described for Study M11-313.

Safety Evaluation

The following safety monitoring was conducted:

Physical examination: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Vital signs: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Chest X-Ray: At Screening

ECG: At Screening

TB screening: At Screening

Pregnancy test: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

Laboratory evaluations (Chemistry; Hematology): At Screening; Baseline; Weeks 4; 12; 16; 24; 28; 32; 36.

Urinalysis: At Screening; Baseline; Weeks 2; 4; 8; 12; 14; 16; 24; 28; 32; 36.

hsCRP: At Baseline; Week 12 and 36.

Hepatitis B Screen: At Screening

Serum HIV: At Screening

HbA1c: At Baseline; Week 12 and 36.

Lipid panel: At Baseline; Week 12 and 36.

ANA/dsDNA: At Screening

Urine Nicotine Metabolite Screening: At Screening; Week 12 and 36.

Efficacy Evaluation

The **primary efficacy endpoint** was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least 50% reduction in Abscess and inflammatory Nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12.

Ranked **secondary efficacy endpoints** were:

1. Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline.
2. Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline NRS \geq 3.
3. Change in modified Sartorius score from Baseline to Week 12.

Phase 3 trial: M12-555

Study Title: A Phase 3 Open-Label Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER (Open-Label Extension)

Study Period: April 12, 2012 to April 29, 2014

Study Objective: To determine the long-term safety, tolerability and efficacy of adalimumab in subjects with moderate to severe HS.

Study Design: This was an open-label trial

Number of Centers: 93

Number of Subjects: 497

Study Population:

Key Inclusion Criteria

1. Completed the study; or
2. Achieved HiSCR at the entry of Period B, then experienced a loss of response (LOR), defined as an AN count that was greater than the average of AN counts at Baseline and Week 12 of the prior Phase 3 study; or
3. Did not achieve HiSCR at the entry of Period B, then experienced Worsening or Absence of Improvement on or after Week 16 of the prior Phase 3 study, defined as an AN count \geq Baseline AN count at 2 consecutive visits (excluding Week 12) occurring \geq 14 days apart.

Study Visits and Procedures:

Study M12-555 was an open-label extension of studies M11-313 and M11-810. During study M12-555 all subjects received open-label adalimumab 40mg ew regardless of treatment assignment during prior Phase 3 study. If at any time on or after Week 24 of the open-label extension trial a subject met the following criteria, the dosing regimen could have been reduced to adalimumab 40 mg eow:

- Achieved hidradenitis suppurativa clinical response (HiSCR) during the OLE relative to the Baseline visit of the prior Phase 3 study; AND
- Achieved an abscess and inflammatory nodule (AN) count of 0 or 1 on at least 2 consecutive study visits; AND
- The physician and subject mutually decided that the risk/benefit of reducing adalimumab dosing to eow was favorable.

Subjects were allowed to decrease the dose one time. The study duration is at least 60 weeks. Schedule of Study Procedures is presented in Table 4 below.

Table 4: Schedule of Study Procedures

Activity	Baseline ^a	Wk 4	Wk 8	Wk 12	Wk 18	Wk 24	Wk 36	Wk 48	Every 12 Weeks until Study Completion	Final/Premature Discontinuation Visit	4 Wks after Last Dose of Study Drug	8 Wks after Last Dose of Study Drug	Unscheduled Study Visit	70-Day Call
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Monitor Concomitant Therapy ^b	X	X	X	X	X	X	X	X	X	X				
Physical Exam	X	X ^c	X			X ^c								
Chest X-Ray	X ^d			X ^e						X ^d				
ECG	X ^d									X ^d				
TB Screening				X ^f										
Vital Signs ^g	X	X	X	X	X	X	X	X	X	X			X	
Pregnancy Tests ^h	X	X	X	X	X	X	X	X	X	X			X	
General Labs: Chemistry and Hematology ^j	X	X		X		X	X	X	X	X				
Urinalysis ^l	X	X		X		X	X	X	X	X				
PK Measurements ^k	X			X		X	X			X	X	X		
AAA Measurements ^k	X			X		X	X			X	X	X		
Serum and Plasma Biomarkers				X				X						

Source: Applicant's submission, Module 5.3.5.1. Study report body M12-555, Section 9.5.1, page 258, page 281.

Concomitant Medication

Antiseptic Therapy: Subjects were required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes were limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.

Wound Care: Concomitant use of wound care dressings on HS wounds was allowed; however, options were limited to alginates, hydrocolloids, and hydrogels.

Antibiotic Therapy: Subjects taking rescue or permitted oral concomitant antibiotics for HS from a prior Phase 3 study (doxycycline up to 100 mg BID; minocycline up to 100 mg BID; other oral concomitant antibiotic previously approved by the study-designated physician) could be continued.

Analgesic Therapy: If a subject's **HS-related pain** worsened after Baseline, the subject was allowed to initiate analgesic therapy on PRN basis at any time as follows:

- Ibuprofen not to exceed 3.2gr/24 hours
- Acetaminophen as per labeling
- Tramadol not to exceed 400mg/24 hours

All analgesics and dose adjustments were to be captured in the source documentation and on the appropriate eCRF.

For **Non-HS-related pain** all analgesics were allowed at the recommended or prescribed dose.

Lesion Intervention: In the event that an acutely painful lesion occurred that required an immediate intervention only two types of interventions were allowed:

- Injection with intralesional triamcinolone acetonide suspension (at a concentration up to 5 mg/mL and a volume up to 1 mL) and
- Incision and drainage.

New systemic and topical therapies following incision and drainage (including antibiotics), were prohibited. Concomitant use of wound care dressings was allowed, however options were limited to alginates, hydrocolloids, and hydrogels. Subjects were to continue to use any ongoing oral and topical therapies. Concomitant medications associated with the lesion interventions were to be captured in eCRF. A total of 2 protocol-allowed interventions were permissible in any 4-week interval. An intervention could have occurred on maximally 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion could not be treated 2 times at the same visit. If a subject required more than 2 interventions in any 4-week interval, then that subject was to be discontinued from the study. The site was required to count any lesion that received an intervention as permanently present from the date of the intervention and must account for it in the source documentation and on the appropriate eCRF.

HS Surgery: In the event a subject required a surgical procedure for medically irreversible stigmata of chronic HS (i.e., non-draining fistula, sinus tract, or hypertrophic scarring) the procedure and other surgery details were to be collected on the appropriate eCRF. The site was required to count any lesion that required an HS surgical procedure as permanently present from the date of the procedure, and was to account for it in the source and on the appropriate eCRF.

Safety Evaluation

The following safety monitoring was conducted:

Physical examination: At Baseline; Weeks 4; 8; 12; 18; 24; 36; 48 and every 12 weeks until completion (at least through Week 60).

Vital signs: At Baseline; Weeks 4; 8; 12; 18; 24; 36; 48 and Final visit.

Chest X-Ray: At Baseline; Week 12 and at Final visit.

ECG: At Baseline and Final visit.

TB screening: At Week 12.

Pregnancy test: At Baseline; Weeks 4; 8; 12; 18; 24; 36; 48 and Final visit.

Laboratory evaluations (Chemistry; Hematology): At Baseline; Weeks 4; 12; 24; 36; 48 and Final visit.

Urinalysis: At Baseline; Weeks 4; 8; 12; 24; 36; 48 and Final visit.

6 Review of Efficacy

Efficacy Summary

The primary evidence of efficacy was based on two well-controlled Phase 3 trials of similar design (M11-313 and M11-810). Two Phase 3 trials were randomized, multicenter, double-blind, placebo-controlled, 36-week trials evaluating the safety and efficacy of 40mg adalimumab injection administered once weekly for the treatment of adult subjects with moderate to severe hidradenitis suppurativa.

Two trials enrolled 633 subjects, 18 years of age and older, who had a total abscess and inflammatory nodules (AN) count of greater than or equal to 3, in at least 2 distinct anatomic areas, one of which was Hurley Stage II or Hurley Stage III. Subjects administered 40mg adalimumab subcutaneous injection once weekly or placebo, for 36 consecutive weeks.

The primary endpoint was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least 50% reduction in Abscess and inflammatory Nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12. After 12 weeks of treatment, in M11-313, 41.8% of adalimumab treated subjects achieved HiSCR, compared to 26% of placebo treated subjects, a treatment effect of 15.9% ($p \leq 0.05$). In M11-810, 58.9% of adalimumab treated subjects achieved HiSCR, compared to 27.6% of placebo treated subjects, a treatment effect of 31.5% ($p \leq 0.05$). The efficacy results showed a twofold higher treatment effect in Study M11-810 compared to Study M11-313. This difference in efficacy can be explained by additional response to concomitant antibiotic use during the conduct of Study M11-810.

Ranked secondary efficacy endpoints were: Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline; Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline NRS ≥ 3 ; and Change in modified Sartorius score from Baseline to Week 12. The results of ranked secondary endpoints showed that the difference between adalimumab and placebo group were statistically significant in Study M11-811 but did not reach statistical significant in Study M11-313. Because the results of secondary endpoint were not reproduced in the second trial, these results will not be included in product labeling.

In this BLA supplement, in two Phase 3 trials, the applicant showed that adalimumab was modestly effective in the treatment of moderate to severe hidradenitis suppurativa.

6.1 Indication

The applicant's proposed indication is for the treatment of moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

6.1.1 Methods

The applicant is relying on two Phase 3 trials, M11-313 and M11-810, to provide evidence of efficacy to support approval.

The ITT population in Period A, defined as all subjects who were randomized at Week 0 in Study M11-313 and M11-810, is the population used for efficacy evaluation.

6.1.2 Demographics

Baseline characteristics of the study population are presented in the Table 5 and Table 6. Overall, baseline demographic characteristics of the study population were similar across the study arms. More subjects were female (66%), White (80%), approximately 36 years of age; overweight or obese; smokers (61%) and alcohol users (56%). The majority of subjects [414 (65.4%) were less than 40 years of age]. A total of 7 (1.1%) subjects were 65 years of age and older. These demographic characteristics are consistent with that of hidradenitis suppurativa population.

Table 5: Demographic Characteristics (ITT-A Population); Study M11-313 and Study M11-810

Demographics	M11-313		M11-810	
	Placebo (N=154)	Adalimumab (N=153)	Placebo (N=163)	Adalimumab (N=163)
Age (year)				
Mean ± SD	37.8±11.33	36.2±10.83	36.1±12.18	34.9± 9.96
Age groups (y) n (%)				
<40	89 (57.8)	102 (66.7)	108 (66.3)	115 (70.6)
40 -≤ 64	63 (40.9)	50 (32.7)	52 (31.9)	47 (28.8)
≥ 65	2 (1.3)	1 (0.7)	3 (1.8)	1 (0.6)
Gender n (%)				
Female	105(68.2)	91 (59.5)	113 (69.3)	108 (66.3)
Male	49 (31.8)	62 (40.5)	50 (30.7)	105 (32.2)
Race n (%)				
White	118 (76.6)	116 (75.8)	130 (79.8)	143 (87.7)
Black or African American	29 (18.8)	33 (21.6)	20 (12.3)	9 (5.5)
Asian	3 (1.9)	1 (0.7)	4 (2.5)	6 (3.7)
American Indian/ Alaska native	1 (0.7)	1 ((0.7)	1 (0.6)	0

Native Hawaiian or Other Pacific Islander	0	0	1 (0.6)	0
Other	2 (1.3)	2 (1.3)	6 (3.7)	3 (1.8)
Multi race	1 (0.6)	0	1 (0.6)	2 (1.2)
BMI (kg/m²)				
Mean± SD	34.5 ± 7.94	33.0 ± 7.62	32.9 ± 7.94	31.3 ± 7.41
Nicotine use n (%)				
User	92 (59.7)	81 (52.9)	109 (67.3)	105 (64.4)
Ex-user	22 (14.3)	22 (14.4)	18 (11.1)	22 (13.5)
Non-user	40 (26)	50 (32.7)	35 (21.6)	36 (22.1)
Unknown	0	0	1 (0.6)	0
Alcohol use n (%)				
User	79 (51.3)	85 (55.6)	97 (59.5)	95 (58.3)
Ex-user	8 (5.2)	3 (2.0)	4 (2.5)	5 (3.1)
Non-user	67 (43.5)	65 (42.5)	62 (38)	63 (38.7)

Source: Modified from applicant's submission; Module 5.3.5.3; Clinical Study Report M11-810; Section 11.2.1.1; Table 8, page 326; and Clinical Study Report M11-313, Section 11.2.1.1; Table 7, page 348.

Table 6: Demographic Characteristics (ITT-A Population) Pooled data

Demographics	Placebo (N=317)	Adalimumab (N=316)
Age (y) n (%)		
Mean ± SD	37±11.79	35.5±10.40
Age groups (y) n (%)		
<40	197 (62.1)	217 (68.7)
40 -≤ 64	115 (36.3)	97 (30.7)
≥ 65	5 (1.6)	2 (0.6)
Gender n (%)		
Female	218 (68.8)	199 (63.0)
Male	99 (31.2)	117 (37.0)
Race n (%)		
White	248 (78.2)	259 (82.0)
Black or African American	49 (15.5)	42 (13.3)
Asian	7 (2.2)	7 (2.2)
American Indian/ Alaska native	2 (0.6)	1 ((0.3)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0
Other	8 (2.5)	5 (1.6)
Multi race	2 (0.6)	2 (0.6)
BMI (kg/m²)		
Mean± SD	33.7 ± 7.97	32.2 ± 7.55
Nicotine use n (%)		
User	201 (64)	186 (58.9)
Ex-user	39 (12.4)	44 (13.9)
Non-user	74 (23.6)	86 (27.2)
Unknown	3 (0.9)	0
Alcohol use n (%)		
User	176 (55.9)	180 (57)
Ex-user	12 (3.8)	8 (2.5)

Non-user	127 (40.3)	128 (40.5)
Unknown	2 (0.6)	0

Source: Modified from applicant's submission, Module 5.3.5.3, ISE, section 5.3.2.1; Table 20; page 139-140.

Baseline Disease Characteristics

Baseline disease severity and characteristics were similar between treatment arms and between two studies. Baseline diseases characteristics are presented in Table below.

Table 7: Baseline Disease Characteristics (ITT-A Population) Study M11-313 and Study M11-810

Demographic Variable	M11-313		M11-810	
	Placebo (N=154)	Adalimumab (N=153)	Placebo (N=163)	Adalimumab (N=163)
Hurley Stage n (%)				
II	81 (52.6)	80 (52.3)	89 (54.6)	86 (52.8)
III	73 (47.4)	73 (47.7)	74 (45.4)	77 (47.2)
Duration of HS (years)				
<9.31 (median)	73 (47.4)	80 (52.3)	79 (48.5)	84 (51.5)
≥ 9.31 (median)	81 (52.6)	73 (47.7)	84 (51.5)	79 (48.5)
AN Count n (%)				
≤5	36 (23.4)	24 (15.7)	50 (30.7)	47 (28.8)
6-10	33 (21.4)	54 (35.3)	51 (31.3)	61 (37.4)
≥11	85 (55.2)	75 (49.0)	62 (38.0)	55 (33.7)
AN Count				
Mean ± SD	14.4 ± 14.8	14.3 ± 11.92	11.9 ± 11.02	10.7 ± 8.10
Abscess Count				
Mean ± SD	2.7 ± 3.69	2.8 ± 3.47	2.4 ± 3.34	2.0 ± 2.6
Draining fistula count n (%)				
Mean ± SD	3.8 ± 4.4	4.6 ± 5.2	3.7 ± 5.2	3.0 ± 4.11
Inflammatory Nodule Count				
Mean ± SD	11.6 ± 13.85	11.5 ± 10.92	9.4 ± 9.6	8.6 ± 6.92
Hypertrophic Scar Count				
Mean ± SD	7.5 ± 10.25	10.1 ± 33.86	7 ± 11.86	6.4 ± 14.18
Erythema (worst among all body regions) n (%)				
No redness	1 (0.6)	0	1 (0.6)	2 (1.2)
Faint, but discernable pink coloration	19 (12.3)	14 (9.2)	10 (6.1)	8 (4.9)
Moderate red coloration	70 (45.5)	74 (48.4)	77 (47.2)	67 (41.1)
Very red or bright red coloration	64 (41.6)	65 (42.5)	75 (46.0)	86 (52.8)
NRS (daily pain at worst)				
Mean ± SD	4.8 ± 2.68	5.1 ± 2.51	4.8 ± 2.73	4.3 ± 2.62
Prior Surgery for HS				
Yes	13 (8.4)	21 (13.7)	18 (11.0)	27 (16.6)
No	141 (91.6)	132 (86.2)	145 (89)	136 (83.4)

Source: Modified from applicant's submission; Module 5.3.5.3; Clinical Study Report M11-810; Section 11.2.1.2 ; Table 9, page 328; and Clinical Study Report M11-313, Section 11.2.1.2; Table 8, page 352.

Table 8: Baseline Disease Characteristics by Hurley Stage (ITT-A Population, Integrated Analyses)

Baseline Disease Characteristics	Hurley II	Hurley III	All
AN count Mean ± SD	11.6 ± 10.3	14.1 ± 13.09	12.8 ± 11.73
Abscess count Mean ± SD	1.7 ± 2.5	3.4 ± 3.85	2.5 ± 3.3
Inflammatory nodule count Mean ± SD	9.9 ± 9.53	10.7 ± 11.75	10.3 ± 10.63
Draining fistula count Mean ± SD	1.7 ± 2.87	6 ± 5.52	3.8 ± 4.77
NRS at worst Mean ± SD	4.3 ± 2.6	5.3 ± 2.61	4.8 ± 2.65

Source: Modified from applicant's submission; Module 5.3.5.3; ISS section 5.3.1.; Table 22, page 144.

Concomitant Medication

The proportion of subjects who used concomitant antibiotics (doxycycline and minocycline) differed between two trials. In the trial M11-313, 7.2% of subjects in adalimumab treatment group used concomitant antibiotics (doxycycline or minocycline) compared to 20.9% of adalimumab treatment group in trial M11-810.

Table 9: Concomitant Medications Used by ≥5% of Subjects; Study M11-313 and Study M11-810

Generic Name	M11-313		M11-810	
	Placebo (N=154)	Adalimumab (N=153)	Placebo (N=163)	Adalimumab (N=163)
Benzoyl peroxide	21 (13.6)	26 (17.0)	22 (13.5)	30 (18.4)
Chlorhexidine	61 (39.6)	55 (35.9)	88 (54.0)	68 (41.7)
Skinsan	26 (16.9)	29 (19.0)	-	-
Cyteal	14 (9.1)	16 (10.5)	-	-
Triclosan	23 (14.9)	19 (12.4)	26 (16)	39 (23.9)
Hydrogen peroxide	10 (6.5)	8 (5.2)	-	-
Biseptine	-	-	9 (5.5)	9 (5.5)
Hypochlorous acid	11 (7.1)	17 (11.1)	14 (8.6)	11 (6.7)
Corticosteroids	29 (18.8)	41 (26.8)	27 (10.4)	28 (17.2)
Doxycycline	12 (7.8)	5 (3.3)	17 (10.4)	21 (12.9)
Minocycline	1 (0.6)	6 (3.9)	14 (8.6)	13 (8.0)
Retinoids for treatment of acne	33 (21.4)	39 (25.5)	41 (25.2)	48 (29.4)
Triamcinolone	13 (8.4)	23 (15.0)	14 (8.6)	12 (7.4)
Tramadol	20 (13.0)	16 (10.5)	24 (14.7)	21 (12.9)
Paracetamol	39 (25.3)	34 (22.2)	57 (35.0)	62 (38.0)

Ibuprofen	64 (41.6)	64 (41.8)	64 (39.3)	51 (31.3)
Naproxen	12 (7.8)	4 (2.6)	-	-
Metformin	15 (9.7)	14 (9.2)	10 (6.1)	16 (9.8)
Salbutamol	15 (9.7)	14 (9.2)	-	-

Source: Modified from applicant's submission; Module 5.3.5.3; Clinical Study Report M11-313; Section 11.2.1.4; Table 11, page 358; and Clinical Study Report M11-810; Section 11.2.1.4; Table 12, page 337

Reviewer's comments: In adalimumab treatment group, three times more subjects in study M11-810 used concomitant antibiotics compared to adalimumab subjects in study M11-311. The difference in use of concomitant antibiotic therapy between these two trials may have had the effect on efficacy results. Therefore, further explorations of the effects of antibiotic use on efficacy was discussed in section 6.1.4 of this review.

6.1.3 Subject Disposition

A total of 633 subjects were randomized in Period A to receive adalimumab ew or placebo. Two subjects randomized to placebo discontinued prior to receiving the first dose therefore, and 631 subjects were dosed with the study drug. Subject disposition in Period A was balanced between two treatment arms. Subject disposition in Period A is presented in Table below.

Table 10: Subject Disposition in Period A (ITT-A Population, Integrated Analyses)

Subject Disposition in Period A	Placebo	Adalimumab
Randomized subjects	317	316
Subjects who discontinued without dose	2 (0.6)	0
Subjects randomized and dosed	315 (99.4)	316 (100)
Subjects who completed Period A	296 (93.4)	300 (94.9)
Subjects who discontinued Period A	19 (6.0)	16 (5.1)
Reason for discontinuation (all reasons)		
Adverse event	8 (2.5)	3 (0.9)
Withdrew consent	9 (2.8)	8 (2.5)
Lack of efficacy	3 (0.9)	1 (0.3)
Lost to follow-up	5 (1.6)	1 (0.3)
Protocol violation	0	1 (0.3)
Other	2 (0.6)	3 (0.9)
Number of subjects who entered Period B	296 (93.4)	300 (94.9)

Source: Modified from applicant's submission; Module 5.3.5.3; ISS section 5.3.1.; Table 19, page 137.

6.1.4 Analysis of Primary Endpoint(s)

The efficacy results of individual Phase 3 trials as well as pooled analysis results will be discussed in this section. As previously stated, the primary efficacy endpoint was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least 50% reduction in Abscess and inflammatory

Nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12.

Adalimumab was statistically superior to placebo ($p \leq 0.05$) on the primary endpoint at Week 12. Table below presents the results of the analysis of the primary endpoint for individual trials and for pooled data.

Table 11: Proportion of Subjects Achieving HiSCR at Week 12 (ITT-A Population) Study M11-313 and Study M11-810

Strata	M11-313			M11-810		
	Placebo n/N (%)	Adalimumab ew n/N (%)	Treatment Difference %	Placebo n/N (%)	Adalimumab ew n/N (%)	Treatment Difference %
All	40/154 (26.0)	64/153 (41.8)	15.9	45/163 (27.6)	96/163 (58.9)	31.5
Hurley Stage II	25 /84 (29.8)	37 /83 (44.6)	14.8	32 /87 (36.8)	53 /85 (62.4)	25.5
Hurley Stage III	15/70 (21.4)	27 /70 (38.6)	17.1	13/76 (17.0)	43/788 (55.1)	55.1

Source: Modifies from applicant's submission; Module 5.3.5.3; M11-313 Study report body; section 11.4.1.1.1; Table 21, page 384 and M11-810, Study report body, 11.4.1.1.1; Table 20, page 362. *Denotes $p \leq 0.05$

Table 12: Proportion of Subjects Achieving HiSR at Week 12 by Antibiotic Use at Baseline, Integrated Analysis (ITT_A Population)

Treatment	N	Response n (%)	Difference %
Antibiotic use at baseline: No			
Placebo	285	78 (27.4)	21.8
Adalimumab ew	285	140 (49.1)	
Antibiotic use at baseline: Yes			
Placebo	32	7 (21.9)	42.6
Adalimumab ew	31	20 (64.5)	

Source: Modified from applicant's submission; Module 5.3.5.3; ISE section 5.3.3.1.; Table 1.2_1.15.1, page 762.

Reviewer's discussion: Efficacy results for the individual trials, as well for the pooled analysis, showed that the adalimumab was statistically superior to placebo for the primary endpoint. Efficacy results of individual trials revealed higher efficacy in the trial M11-810 compared to trial M11-313. More subjects in trial M11-810 [34 (20.9%)] used concomitant baseline antibiotics (doxycycline and minocycline) compared to trial M11-313 [11(7.2%)]. In trial M11-810, there is a higher response in subjects treated with adalimumab plus antibiotics (42.6%) compared to subjects treated with adalimumab alone (28.6%)(data not presented). However, due to the low number of subjects who used concomitant antibiotics, definite conclusions could not be drawn. Concomitant antibiotic treatment did not have notable effect on efficacy in placebo treated subjects.

In regard to severity of the disease (Hurley stage), subjects with more severe disease (Hurley Stage III) had better response to adalimumab treatment compared to subjects with milder disease (Hurley Stage II).

6.1.5 Analysis of Secondary Endpoints(s)

As previously stated, the following ranked **secondary efficacy endpoints** were:

1. Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline.
2. Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline NRS \geq 3.
3. Change in modified Sartorius score from Baseline to Week 12.

The results of ranked secondary endpoints showed that the difference between adalimumab and placebo group were statistically significant in Study M11-811 but did not reach statistical significant in Study M11-313. Because the results of secondary endpoints were not reproduced in the second trial, they will not be included in the product labeling.

Table 13: Statistical Results for Ranked Secondary Endpoints Presented in Rank Order (ITT_A Population) Study M11-313 and Study M11-810

Rank	Secondary Variable	adalimumab ew vs. placebo p value	
		M11-313	M11-818
1	Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline	0.961	0.010
2	Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline NRS \geq 3	0.628	<0.001
3	Change in modified Sartorius score from Baseline to Week 12.	0.124	<0.001

Source: Modified from applicant's submission; Module 5.3.5.1; M11-810 Study report body, Section 11.4.1.1.2; Table 21, page 365; M11-313 Study report body, Section 11.4.1.1.2; Table 22, page 388.

6.1.6 Other Endpoints

The applicant evaluated 15 “Other Secondary” endpoints for Period A. The results of these evaluations will not be presented because the applicant has not prespecified statistical analysis in their Statistical Analysis Plan and, multiplicity adjustments were not employed.

6.1.7 Subpopulations

The table below presents the HiSCR rate by age, gender, race, BMI, smoking history, baseline AN count and history of prior surgery. Efficacy responses were generally similar across subgroups with exception of subgroup of Race (Black) and prior HS surgery (yes) for which sample sizes were small. Higher treatment effect was seen among subjects with lower hsCRP than those with higher hsCRP. Higher treatment effect was also seen for Hurley Stage III compared to Hurley Stage II and among subjects with concomitant use of antibiotics (presented and discussed earlier in section 6.1.4 of this review).

Table 14: Proportion of Subjects Achieving HiSCR at Week 12 Subgroup Analysis (ITT_A population)

Treatment	N	HiSCR Response: Yes n (%)	HiSCR Response: No n (%)
Age (years) <40			
Placebo	197	54 (27.4)	130 (66.0)
Adalimumab ew	217	106 (48.8)	102 (47.0)
Age (years) ≥40			
Placebo	120	31 (25.8)	83 (69.2)
Adalimumab ew	99	54 (54.5)	41 (41.4)
Gender: Female			
Placebo	218	64 (29.4)	143 (65.6)
Adalimumab ew	199	104 (52.3)	86 (43.3)
Gender: Male			
Placebo	99	21 (21.2)	70 (70.7)
Adalimumab ew	117	56 (47.9)	57 (48.7)
Race: White			
Placebo	248	70 (28.2)	164 (66.1)
Adalimumab ew	259	133 (51.4)	116 (44.8)
Race: Black			
Placebo	49	12 (24.5)	33 (67.3)
Adalimumab ew	42	18 (42.9)	22 (52.4)
Race: Other			
Placebo	20	3 (15.0)	16 (80.0)
Adalimumab ew	15	9 (60.0)	5 (33.3)
BMI: <25			
Placebo	39	16 (41.0)	22 (56.4)
Adalimumab ew	60	37 (61.7)	21 (35.0)
BMI: 25 - <30			
Placebo	74	20 (27.0)	49 (66.2)
Adalimumab ew	73	35 (47.9)	36 (49.3)
BMI: 30 - <40			
Placebo	139	33 (23.7)	96 (69.1)
Adalimumab ew	138	71 (51.4)	62 (44.9)
BMI: >40			
Placebo	63	15 (23.7)	45 (71.4)
Adalimumab ew	44	17 (38.6)	23 (52.3)

Smoking status at baseline: yes	201	56 (27.9)	136 (67.7)
Placebo	186	91 (48.9)	89 (47.8)
Adalimumab ew			
Smoking status at baseline: no	115	29 (25.2)	76 (66.1)
Placebo	130	69 (52.1)	54 (41.5)
Adalimumab ew			
hsCRP: <8.4 (median)	150	50 (33.3)	91 (60.7)
Placebo	158	98 (62.0)	54 (34.2)
Adalimumab ew			
hsCRP: >8.4 (median)	164	34 (20.7)	122 (74.4)
Placebo	157	61 (38.9)	89 (56.7)
Adalimumab ew			
Baseline AN category: ≤5	86	30 (34.9)	52 (60.5)
Placebo	71	39 (54.9)	28 (39.4)
Adalimumab ew			
Baseline AN category: 6-10	84	26 (31.0)	54 (64.3)
Placebo	115	56 (48.7)	56 (48.7)
Adalimumab ew			
Baseline AN category: ≥11	147	29 (19.7)	107 (72.8)
Placebo	130	65 (50.0)	59 (45.4)
Adalimumab ew			
Prior surgery history: no	286	74 (25.9)	193 (67.5)
Placebo	268	134 (50.0)	125 (46.6)
Adalimumab ew			
Prior surgery history: yes	31	11 (35.5)	20 (64.5)
Placebo	48	26 (54.2)	18 (37.5)
Adalimumab ew			

Source: Modified from applicant's submission; Module 5.3.5.3; ISE Table 1.2_1.2.2, page 641.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

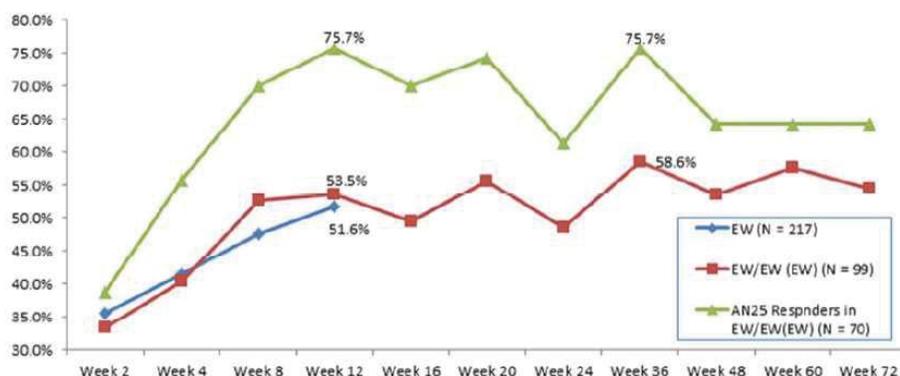
In two Phase 3 trials (M11-810 and M11-313) and one Phase 2 (M10-467) trial, the efficacy of 40mg dose of adalimumab, and two dosing frequencies, 40mg every week and 40mg every other week, were evaluated. In all three studies, the efficacy results showed that adalimumab 40mg ew was efficacious compared to placebo. However, in Phase 2 study (Study M10-467), where efficacy of adalimumab ew was evaluated, results showed that clinical response in adalimumab ew group was not statistically significant compared to placebo. Therefore, ew dosing regimen was selected by the applicant, as an efficacious regimen.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In this section, persistence of efficacy of continuous dosing with adalimumab 40mg ew (the proposed dose and dosing regimen), will be discussed. In addition, the effects of dose reduction and dose interruption will be discussed.

Continuous adalimumab 40mg ew population included subjects who entered Period A of studies M11-313 and M11-810, continued on the same regimen through Period B of their respective studies and were included into ew dosing during the open-label Study M12-555 (ew/ew/ew group). Three hundred sixteen subjects were randomized to adalimumab ew in Period A of studies M11-313 and M11-810 of whom 99 subjects continued through Period B and went on to take part in the Study M12-555. The persistence of efficacy with continuous adalimumab 40mg ew dosing, as of the data cutoff date (April 29, 2014), is presented in Figure below (in red)

Figure 8: Proportion of Subjects Achieving HiSCR by Visit (LOCF), Adalimumab ew Population (Integrated Analysis)



Note: ew = subjects randomized to adalimumab 40 mg ew in Period A who either did not enter Period B or entered Period B to receive adalimumab 40 mg ew or placebo. ew/ew (ew) = subjects randomized to adalimumab 40 mg ew in both Period A and Period B, regardless of entry into Study M12-555. As of the data cutoff date for Study M12-555 (29 April 2014), not all ongoing subjects had visits beyond Week 36ew. The number of subjects with observations at later weeks is as follows: 70 at Week 48ew, 42 at Week 60ew, and 28 at Week 72ew. Results after Week 72ew are available for fewer than 20% of subjects (Table 1.2_4.1.2).

Source: Applicant's submission; Module 5.3.5.3; ISE, section 5.5 Figure, page 237.

The applicant compared efficacy of continuous weekly dosing (ew/ew/ew) with reduced dosing frequency (ew/eow) or interruption of dosing (ew/pbo) across Period A and B of Studies M11-313 and M11-810, as well during the open-label Study M12-555 (ew). This comparison is presented in Table below. Reduction/interruption of dosing occurred from Week 12 until Week 36 (entrance into Study M12-555).

Table 15: Proportion of Subjects Achieving HiSCR Over Time from the First Dose of Adalimumab (LOCF); Studies M11-313; M11-810 and M12-555

Weeks of Adalimumab Treatment	ew/ew/ew N=84 n (%)	ew/eow/ew N=90 n (%)	ew/pbo/ew N=91 n (%)
Week 2	27 (32.1)	35 (39.8)	31 (34.4)
Week 4	31 (36.9)	37 (41.1)	36 (39.6)
Week 8	42 (50)	44 (48.9)	44 (48.4)
Week 12	42 (50)	50 (55.5)	46 (50.5)
Week 16	41 (48.8)	51 (55.6)	41 (45.1)
Week 20	47 (56)	41 (45.6)	41 (45.1)
Week 24	41 (48.8)	43 (47.8)	39 (42.9)
Week 36	53 (63.1)	49 (54.4)	48 (52.7)
Week 48	48 (57.1)	48 (53.3)	53 (58.2)
Week 60	52 (61.9)	54 (60)	52 (57.1)
Week 72	49 (58.3)	56 (62)	50 (54.9)

Source: Applicant's submission; Module 5.3.5.3; ISE, section 5.6; Table 66, page 239.

The results show that continues adalimumab ew dosing was associated with persistence of efficacy as well that dose reduction or interruption was associated with decrease of response. Re-introduction of ew dosing, in subjects who had decrease/interruption of dosing, improved the response over time. The effects of decrease/interruption of dosing on disease flare-up/rebound will be discussed in **section 7.6.4** of this review.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses were identified/performed.

7 Review of Safety

Safety Summary

The assessment of safety for the adalimumab 40mg once weekly was based on analysis of data from Phase 3 trials (M11-313; M11-810; and M12-555) and one Phase 2 trial (M10-467). In addition, data provided in the Safety Update Report was also reviewed. During the development of adalimumab for the hidradenitis suppurativa indication, a total of 727 adult (18 to years of age) subjects were exposed to repeated dosing with adalimumab, of whom 688 subjects received adalimumab 40mg once weekly. Of subjects who received adalimumab 40mg once weekly dosing, 576 subjects (79.2%) were treated for at least 6 months, 336 subjects (46.2%) were treated for at least one year and 69 subjects (9.5%) were treated over 2 years.

Safety population included 688 subjects exposed to repeated dosing of adalimumab at the proposed dose of 40mg once weekly.

During adalimumab development program for hidradenitis suppurativa indication, 3 deaths were reported (one death in M11-810; and two in M12-555). Analysis of the individual deaths, including temporal relationship to adalimumab dosing, did not suggest causal relationship (refer to section 7.3.1 of this review).

In trials comprising safety database, during the placebo controlled period (Week 0-12), a total of 10 (2.7%) subjects in the adalimumab ew treatment group and 13 (3.6%) subjects in placebo treatment group reported SAEs. During maintenance period of Study M11-313 and M11-810, (Week 13-36), 3% of subjects in the adalimumab ew/ew group, 5% of subjects in the adalimumab ew/eow group, and 2% of subjects in adalimumab ew/placebo group, experienced SAE.

Analysis of Adverse Events of Special Interest (AESIs) did not reveal new safety signals.

Evaluation of risk of disease “flare”, defined as at least 25% increase in AN counts with minimum increase of 2, relative to baseline, revealed that 12% of subjects switched to placebo experienced disease flare compared to 1% of subjects who continued on adalimumab ew.

Review of common adverse reactions (ARs) revealed that the most frequently reported ARs were headache, nasopharyngitis and diarrhea.

Vital signs (blood pressure, pulse) were monitored during conduct of Phase 2/3 trials. No clinically significant differences from baseline to the end of treatment or trends of abnormalities were identified (refer to section 7.4.3.)

Laboratory evaluations (hematology; serum chemistry) revealed that markedly abnormal laboratory results were infrequent, and did not lead to study drug discontinuation. No cases of hepatic failure or LFT elevations meeting Hy’s Law criteria were observed (refer to section 7.4.2 and 7.4.4).

In this reviewer’s opinion, the applicant provided adequate evidence of safety for adalimumab 40mg once weekly and, no safety signals were identified that would preclude an approval.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consists of data from two placebo-controlled Phase 3 trials, M11-313 and M11-810, one Phase 3 open-label trial and one Phase 2 trial. These trials were

chosen as the focus of the safety review due to their similarity of study design; enrolled subjects were the targeted patient population for the proposed indication; and the treatment was at doses that reflect anticipated use (40mg ew).

7.1.2 Categorization of Adverse Events

All adverse events were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system, Version 16.1. The coding of adverse events in this BLA supplement appeared adequate and allowed for accurate estimation of adverse event risks.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary focus of this safety review was data from Phase 3 trials M11-313 and M11-810, and Phase 2 trial M10-467. Pooled data from these three trials was used to compare incidences of adverse events (AEs). These trials were chosen as the focus of the safety review because of the similarity of design and enrolled subjects, similar duration of placebo-controlled period, and adalimumab dosing regimen that reflects anticipated use. Data obtained during the placebo-controlled portion of these trials allowed the direct comparison of AE rates in adalimumab treated subjects to rates of AEs in placebo treated subjects. The shortcoming of this analysis is that allows for an evaluation of only short-term safety.

Data from the non-controlled periods of these trials and open label trial M12-555 were used to assess potential safety signals that may occur at later time points following longer exposure to adalimumab. However, data from non-controlled periods is difficult to interpret due to lack of a concurrent comparison arm. Exposure-adjusted incidence rates will be used to account for the difference in duration of exposure between treatment arms.

The applicant conducted pooled data analysis using the following strategy:

- **Placebo-Controlled Analysis Set:** All subjects who received at least one dose of study drug in Period A of studies M10-467; M11-313 and M11-810. Treatment groups include:
 - Adalimumab ew
 - Adalimumab eow
 - Adalimumab total (ew and eow dosing groups)
 - Placebo
- **Maintenance Analysis Set:** All subjects who received adalimumab ew during Period A and received at least one dose of adalimumab ew; eow or placebo during Period B of studies M11-810 or M11-313. Treatment groups include:
 - Adalimumab ew in Period B (adalimumab ew/ew)
 - Adalimumab eow in Period B (adalimumab ew/eow)

- Placebo in Period B (adalimumab ew/placebo)
 Subgroups include:
 - HiSCR responders at the entry of Period B
 - HiSCR nonresponders at the entry of Period B
 - Subjects who achieved AN25 at entry of Period B
- **All Adalimumab ew Analysis Set:** All subjects who received at least 1 dose of adalimumab ew in studies M10-467, M11-810, M11-313 and M12-555.
- **All Adalimumab Analysis Set:** All subjects who received a least one dose of adalimumab (ew or eow) in studies M10-467, M11-810, M11-313 and M12-555.

The shortcoming of **Maintenance Analysis Set** is that the data from subjects who were on placebo in Period A and continued on placebo during Period B (pbo/pbo) of study M11-810, were not included in the analysis. Instead, subjects treated with adalimumab in Period A and then re-randomized to placebo in Period B, were used as comparator placebo population. This reviewer will present analyses that includes pbo/pbo subjects from study M11-810. Subjects treated with placebo during period A of study M11-313 were switched to adalimumab ew during Period B and could not be used as comparator group.

The shortcoming of **All Adalimumab ew Analysis Set** and **All Adalimumab Analysis Set** is that it includes the same data used in **Placebo-Controlled Analysis Set** and **Maintenance Analysis Set** in addition to data from study M12-555. Therefore, this data will be presented without detailed discussion.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During the development of adalimumab for HS indication, a total of 727 subjects with HS received at least one dose of adalimumab 40mg, of whom 688 subjects received 40mg once weekly dosing. Duration of exposure of subjects who received at least 1 dose of adalimumab ew in studies M10-467, M11-810, M11-313 and M12-555 is presented in Table below.

Table 16: Exposure to Adalimumab ew for Studies M10-467, M11-810, M11-313 and M12-555

Duration of Exposure (Days)	Adalimumab ew N=688 n (%)
1-15	688 (100)
170-197 (6 months)	491 (71.4)
338-365 (1 year)	242 (35.2)

548 -729 (2 years)	56 (26.3)
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Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Section 4.2, Table 7, page 191.

Overall Exposure to adalimumab in terms of dose, frequency and duration of dosing, and the target population (see below), was adequate for evaluation of safety.

Demographics of the target population

Baseline demographic characteristics of the study population were similar across treatment arms for the three placebo-controlled trials. The majority of subjects were female, white, less than 65 years of age; overweight or obese; smokers and alcohol users. These demographic characteristics are consistent with that of the population with HS. Summary of baseline demographic characteristics for studies M10-467, M11-810, M11-313 and M12-555, is presented in Table below.

Table 17: Baseline Demographic Characteristics for Studies M10-467, M11-810, and M11-313 (Pooled data)

Demographics	Adalimumab			
	Placebo (N= 366)	eow (N=52)	ew (N=367)	Total (N=419)
Age (year)				
Mean ± SD	37.1±11.83	36.1±12.5	35.5±10.69	36.3± 11.25
Age groups (y) n (%)				
<40	229 (62.6)	31 (59.6)	114 (31.1)	134 (32.0)
40 -≤ 64	129 (35.2)	20 (38.5)	114 (32.0)	263 (33.5)
≥ 65	8 (2.2)	1 (1.9)	3 (1.0)	4 (1.0)
Gender n (%)				
Female	252 (68.9)	38 (73.1)	235 (64.0)	525 (66.9)
Male	114 (31.1)	14 (26.9)	132 (36.0)	260 (33.1)
Race n (%)				
White	285 (77.9)	36 (69.2)	296 (80.7)	332 (79.2)
Black or African American	55 (15.0)	12 (23.1)	51 (13.9)	118 (15.0)
Asian	7 (1.9)	0	9 (2.5)	9 (2.1)
American Indian/ Alaska native	2 (0.5)	0	2 (0.5)	2 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	0	0
Other	13 (3.6)	2 (3.8)	7 (1.9)	9 (2.1)
Multi race	3 (0.8)	2 (3.8)	2 (0.5)	4 (1.0)
BMI (kg/m²)				
Mean± SD	33.68 ± 7.96	35.23 ± 9.40	32.29 ± 7.65	32.66 ± 7.94
Nicotine use n (%)				
User	230 (62.8)	26 (50.0)	216 (58.9)	242 (57.8)
Ex-user	51 (13.9)	5 (9.6)	50 (13.6)	55 (13.1)
Non-user	84 (23.0)	21 (40.4)	101 (27.5)	122 (29.1)
Unknown	0	0	1 (0.6)	0
Alcohol use n (%)				
User	204(55.7)	30 (57.7)	215 (58.6)	245 (58.5)
Ex-user	15 (4.1)	0	10 (2.7)	10 (2.4)

Non-user	147 (40.2)	22 (42.3)	142 (38.7)	164 (39.6)
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Source: Applicant's submission, Module 5.3.5.3, ISS, section 4.4.1.1, Table 11, page 202.

7.2.2 Explorations for Dose Response

The adalimumab dose response evaluation was conducted in Phase 2 trial M10-467. In two Phase 3 trials, M11-313 and M11-810, only adalimumab ew dosing was evaluated.

The applicant selected the adalimumab ew dosing based on the results of trial M10-467 during which 2 different dosing regimens of adalimumab were evaluated. A total 154 subjects with HS (baseline Hurly Stage I; II or II; $PGA \geq 3$; and with ≥ 2 distinct anatomical area involvement) were randomized into 3 groups: adalimumab 40mg ew; adalimumab 40mg eow or placebo. The primary endpoint was the proportion of subjects achieving clinical response at Week 16, defined as a PGA score of clear (0), minimal (1), or mild (2), with a reduction from Baseline of ≥ 2 grades. After 16 weeks of treatment, primary endpoint was achieved by 18% of subjects in the adalimumab ew group compared to placebo group (3.9%). The proportion of subjects in adalimumab eow group was not statistically significantly different from placebo (8% and 10%, respectively). In the second portion of the study (Week 16-52), a decline in response rate was observed following the decrease from adalimumab ew to eow dosing. Safety evaluation did not reveal safety signals for either 40mg eow or 40mg ew dosing.

Based on these data, the applicant selected adalimumab ew dosing to conduct Phase 3 trials.

104 weeks of exposure (with weekly dosing) is the maximal duration of 40mg ew dose studied, at the time of BLA supplement submission. This duration of treatment is acceptable for the evaluation of safety of adalimumab in the indication of HS.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was conducted by the applicant.

7.2.4 Routine Clinical Testing

Routine safety monitoring included clinical evaluation and laboratory testing at specified time points:

- Physical examination
- A chest radiograph
- 12-lead ECG.
- Vital signs, including temperature, pulse, and blood pressure
- Laboratory evaluations: cholesterol panel; clinical chemistry; complete blood count; urinalysis; and high-sensitivity C-reactive protein, hemoglobin A1c,

pregnancy test for female subjects of childbearing potential, ANA, dsDNA, Hepatitis B surface antigen

7.2.5 Metabolic, Clearance, and Interaction Workup

No new studies to evaluate metabolism, clearance and interactions, were conducted.

No formal studies were conducted in subjects with renal or hepatic impairment.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adalimumab belongs to a class on TNF- α inhibitor biologic products. The labeling for adalimumab includes boxed warning for the risk of serious infections, opportunistic infections, lymphomas and other malignancies. Similar boxed warnings have been included in labeling of other approved TNF inhibitor biologic products, including infliximab (REMICADE); etanercept (Enbrel); golimumab (SIPMPONI); certolizumab (CIMZIA).

The applicant defined a set of adverse events of special interest (AESI) based on the mechanism of action of adalimumab and its possible class effects. The applicant evaluated the following AESI:

Infections

- All infections
- Serious infection
- Legionella infection
- Diverticulitis
- Opportunistic infection, excluding oral candidiasis and TB
- Oral candidiasis
- TB
 - Active TB
 - Latent TB
- Parasitic infection
- Reactivation of hepatitis B
- Progressive multifocal leukoencephalopathy (PML)

Malignancies

- Malignancies
- Lymphomas
- Hepatosplenic T-cell lymphoma (HSTCL)
- Nonmelanoma skin cancer (NMSC)
- Melanoma
- Leukemia
- Other malignancies, except lymphoma, HSTCL, leukemia, NMSC, and melanoma

Immune Reactions

- Allergic reactions (including angioedema/anaphylaxis)
- Lupus-like reactions and systemic lupus erythematosus (SLE)
- Vasculitis
 - Cutaneous vasculitis
 - Noncutaneous vasculitis
- Sarcoidosis
- Autoimmune hepatitis

Cardiovascular/Vascular

- Myocardial infarction (MI)
- Cerebrovascular accident (CVA)
- Congestive heart failure (CHF)
- Pulmonary embolism

Respiratory

- Interstitial lung disease (ILD)

Gastrointestinal Events

- Intestinal perforation
- Pancreatitis

Skin and Subcutaneous Tissue Disorders

- Stevens-Johnson syndrome
- Erythema multiforme
- Worsening and new onset of psoriasis

Nervous System Disorder

- Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis and others)
- Amyotrophic lateral sclerosis (ALS)
- Reversible posterior leukoencephalopathy syndrome (RPLS)

Hematologic Events

- Hematologic disorders (including pancytopenia)

Hepatic Events

- Liver failure and other liver events (except gall bladder-related events)

Other

- Humira administration-related medication errors
- Injection site reactions

The AESI rate per 100 patient years (PY) of exposure was calculated for each treatment group.

In addition to above listed AESIs, the applicant performed post-hoc analysis of serious infections to identify skin and soft tissue infections (SSTI). SSTIs were defined as microbial invasion of the epidermis, dermis, and/or subcutaneous tissues accompanied by signs and symptoms of inflammation. Adjudication was performed by infectious disease specialists not associated with the applicant.

7.3 Major Safety Results

7.3.1 Deaths

During adalimumab development program for HS indication, 3 deaths were reported, one in study M11-810 (subject # (b) (6)) and two in study M12-555 (subject # (b) (6) and subject # (b) (6)).

Subject # (b) (6) was a 35 year old male with past medical history of diabetes mellitus, smoker for 16 years and family history of early coronary artery disease (coronary artery bypass surgery in mother at age 41 and in father at age 45). Subject was in the adalimumab ew/eow group. On Day 196 (Post-Treatment Day 4), the subject presented to Emergency Room (ER) with non-ST elevation myocardial infarction (NSTEMI). His hospitalization was complicated with congestive heart failure. The event was considered resolved on Day 208 (Post-Treatment Day 16).

On Day 198, the subject experienced an event of worsening HS. Subject was treated with antibiotics and the event resolved on Day 211.

On Day 226 (Post-Treatment Day 34) the subject presented to ER with chest pain. Subject was treated in ER and released home.

On Day 234, (Post-Treatment Day 42) the subject presented to ER with chest pain and shortness of breath. He had creatinine phosphokinase of 55.6 U/L (reference range <24.00U/L). The subject went into cardio-respiratory arrest and died on the same day. This death was considered by the investigator as probably not related to the adalimumab.

Subject # (b) (6) was a 62 year old female with past medical history of Hashimoto's thyroiditis, obesity, secondary hyperparathyroidism. Subject was in placebo/placebo/ew group (received placebo in study M11-810 and adalimumab ew in OLE study). On Day 93 (Post-Treatment Day 3) of study M12-555, the subject experienced AE of autoimmune pancreatitis, cholangitis and severe sepsis. Autoimmune pancreatitis was treated with prednisolone and sepsis was treated with antibiotics.

On Day 119 the subject experienced septic shock, cardiac arrest and respiratory failure. After cardiopulmonary resuscitation the subject was placed on mechanical ventilation but remained hemodynamically unstable and died on Day 120 (Post-Treatment Day 30). This case of death was considered by the investigator as not related to the treatment with adalimumab.

Subject # (b) (6) was that of a 49 year old white male with pertinent medical history of hypertension, hypercholesterolemia, and smoking who experienced acute pulmonary

edema that led to death. On Day 423 (9 days post adalimumab dose) the subject experienced dyspnea and reduced physical condition for which he was hospitalized. On Day 424 the subject was admitted to Intensive Care Unit due to respiratory insufficiency. The subject was intubated and ventilated, however the subject died of cardiopulmonary failure. The primary cause of death noted on death certificate was fulminant pulmonary edema. The investigator considered this event of acute pulmonary edema to be probably not related to study drug.

Discussion: This reviewer performed analysis of events of death, including temporal relationship to adalimumab dosing. This reviewer found that two cases (subject # (b) (6) and subject # (b) (6)) were confounded and causality could not be definitely attributed to the treatment. For the case of death in subject # (b) (6), the information was not sufficient to assess causality.

- *Subject # (b) (6) 35 year old male, who died due myocardial infarction and cardio-respiratory arrest, had a strong family history of early coronary artery disease, comorbid condition of diabetes mellitus and smoking that are all associated with increased risk of cardiovascular events.*
- *Subject # (b) (6), a 62 year old female who died of complications of autoimmune pancreatitis, cholangitis and sepsis. Association of Hashimoto's thyroiditis and other autoimmune diseases, including autoimmune pancreatitis, has been documented in literature¹. Autoimmune pancreatitis was complicated with development of cholangitis that progressed into sepsis and septic shock.*
- *Subject # (b) (6), a 49 year old male who died of acute pulmonary edema. The information was not sufficient to assess causality.*

It is in this reviewer's opinion that the reported cases of deaths do not appear to represent a treatment related safety signal in patient population with hidradenitis suppurativa.

7.3.2 Nonfatal Serious Adverse Events

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During placebo-controlled period of three studies, 13 (3.1%) subjects treated with adalimumab (ew and eow) and 13 (3.6%) of subjects treated with placebo, reported treatment emergent Serious Adverse Events (SAEs). In both adalimumab treatment groups, all SAEs were reported by a one subject each. The number and percentage of subjects who reported SAEs and are also higher in adalimumab treated subjects are presented in the Table below.

Table 18: SAEs Reported during Placebo-Controlled Period of Studies M10-467; M11-313 and M11-810 and Higher in Adalimumab Group

MedDRA Proffered Term	n (%) Placebo (N=366)	Adalimumab n (%)	
		ew (N=367)	eow (N=52)
Any TESAE	13 (3.6)	10 (2.7)	3 (5.8)
Hidradenitis	5 (1.4)	1 (0.3)	1 (1.9)
Anemia	1 (0.3)	1 (0.3)	0
Chronic obstructive pulmonary disease	0	1 (0.3)	0
Escherichia infection	0	1 (0.3)	0
Genital infection bacterial	0	1 (0.3)	0
Infection	0	1 (0.3)	0
Interstitial lung disease	0	0	1 (1.9)
Non-cardiac chest pain	0	1 (0.3)	0
Pilonidal cyst	0	0	1 (1.9)
Pyelonephritis	0	1 (0.3)	0
Renal failure acute	0	1 (0.3)	0
Sexual abuse	0	1 (0.3)	0
Tendon rupture	0	1 (0.3)	0
Vocal cord neoplasm	0	1 (0.3)	0

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.4.1.1 Table 33, page 272. TESAE was defined as any SAE with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier.

Serious Adverse Reactions

During placebo-controlled period, 3 (0.8%) subjects in adalimumab ew group; 1 (1.9) subject in adalimumab eow group and 2 (0.5%) subjects in placebo group reported SAEs that were at least possibly related to the study drug. The number and percentage of subjects who reported SAEs at least possibly related to the study drug are presented by treatment group in Table below.

Table 19: SAEs at Least Possibly Related to Study Drug during Placebo-Controlled Period of Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	n (%) Placebo (N=366)	Adalimumab n (%)	
		ew (N=367)	eow (N=52)
Any TESAE at least possibly related to study drug (per investigator)	2 (0.5)	3 (0.8)	1 (1.9)
Effusion	1 (0.3)	0	0
Hidradenitis	1 (0.3)	1 (0.3)	0
Infection	0	1 (0.3)	0
Interstitial lung disease ^a	0	0	1 (1.9)
Intervertebral disc calcification	1 (0.3)	0	0
Pyelonephritis	0	1 (0.3)	0
Tendonitis	1 (0.3)	0	0

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.4.1.2, Table 34, page 275. a: Lower term is interstitial pneumonia.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During Period B of studies M11-313 and M11-810, 3 (3%) subjects in adalimumab ew group reported 3 SAEs; and 5 (5%) subjects in adalimumab eow group reported 7 SAEs (presented in Table below).

Table 20: SAEs Reported during Period B of Studies M11-313 and M11-810

MedDRA Proffered Term	Adalimumab			
	placebo/placebo (N=151) n (%)	ew/placebo (N=100) n (%)	ew/ew (N=99) n (%)	ew/eow (N=101) n (%)
Any TESAE	0	2 (2.0)	3 (3.0)	5 (5.0.)
Lymphadenitis	0	0	0	1 (1.0)
Acute myocardial infarction	0	0	0	1 (1.0)
Cardiorespiratory arrest	0	0	0	1 (1.0)
Pneumonia	0	0	1 (1.0)	0
Rash	0	0	1 (1.0)	0
Ectopic pregnancy	0	0	1 (1.0)	0
Abortion induced	0	0	0	1 (1.0)
Hidradenitis	0	2 (2.0)	0	3 (3.0)

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.4.1., Table 2.4_2.2.1, link on page 273 and Module 5.3.5.1, Study Report Body M11-810, section 12.3.1.2, Table 14.3_2.2.2, link on page 453.

SAEs considered by the investigator to be possibly related to the study drug were reported by 2 subjects in adalimumab ew group (rash and pneumonia) and, by 2 subjects in adalimumab eow group (lymphadenitis and acute myocardial infarction). Discussion about events of acute myocardial infarction and cardiorespiratory arrest are presented in section **7.3.1 Deaths**, of this review.

All Adalimumab ew Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

During the exposure to adalimumab ew, a total of 66 (9.6%) of subjects reported 98 (18.3 E/100PY) SAEs. Most SAEs were only reported by one subject. The following SAEs were reported by ≥2 subjects each: hidradenitis, palpitations, non-cardiac chest pain, pneumonia, postoperative wound infection, sepsis, septic shock, anemia and ectopic pregnancy.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

During the exposure to adalimumab (ew or eow) a total of 78 (10.7%) subjects reported treatment emergent SAEs. Most SAEs were only reported by one subject. SAEs reported by two or more subjects who received at least one dose of adalimumab (ew or eow) are presented in Table below. The most frequently reported SAE was hidradenitis, reported by 22 (3%) of subjects.

Table 21: SAEs Reported in Two or More Adalimumab Treated Subjects; All Adalimumab Analysis Set; Study M10-467; M11-313; M11-810 and M12-555

Preferred Term	Adalimumab (N=727) n (%)
Hidradenitis	22 (3.0)
Cellulitis	3 (0.4)
Anemia	2 (0.3)
Ectopic pregnancy	2 (0.3)
Non-cardiac chest pain	2 (0.3)
Palpitations	2 (0.3)
Pilonidal cyst	2 (0.3)
Pneumonia	2 (0.3)
Postoperative wound infection	2 (0.3)
Sepsis	2 (0.3)
Septic shock	2 (0.3)

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.4.2.1, Table 36, page 281.

Discussion regarding SAEs: Review of SAEs did not reveal increased incidence of treatment emergent SAEs in adalimumab treated subjects compared to placebo treated subjects (placebo-controlled period). The incidence of treatment related SAEs was not increased in adalimumab treated subjects compared to placebo treated subjects (placebo-controlled period). For all subjects treated with at least one dose of adalimumab (ew or eow), the most frequently reported SAE was hidradenitis (3%). Most of SAEs were reported by a single subject each. No new safety signals for SAEs were identified by this reviewer.

7.3.3 Dropouts and/or Discontinuations

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During the placebo-controlled period, treatment emergent AEs leading to discontinuation were reported in 9 (2.1%) subjects treated with the adalimumab and 10 (2.7%) subjects treated with the placebo. All AEs leading to discontinuation of the study drug were reported in ≤ 1 subjects except for hidradenitis (3 subjects in the adalimumab group and 2 subjects in the placebo group). AEs leading to discontinuation of the study drug are presented in Table below.

Table 22: AEs Leading to Discontinuation of Study Drug during Placebo-Controlled Period; Studies M10-467; M11-810; and M11-313

Preferred Term	n (%)	Adalimumab n (%)	
	Placebo (N=366)	ew (N=367)	eow (N=52)
Any TEAE leading to discontinuation of stud drug	10 (2.7)	7 (1.9)	2 (3.8)
Arthralgia	1 (0.3)	0	0
Atrial fibrillation	0	1 (0.3)	0
Diabetes mellitus inadequate control	1 (0.3)	0	0
Dizziness	1 (0.3)	0	0
Fatigue	1 (0.3)	0	0
Headache	1 (0.3)	0	0
Hidradenitis	2 (0.5)	2 (0.5)	1 (1.9)
Interstitial lung disease	0	0	1 (1.9)
Invasive ductal breast carcinoma	1 (0.3)	0	0
Parapsoriasis ^a	0	1 (0.3)	0
Pneumonia	1 (0.3)	0	0
Polymyalgia rheumatica	1 (0.3)	0	0
Presyncope	1 (0.3)	0	0
Rash pustular	0	1 (0.3)	0
Drug eruption	0	1 (0.3)	0
Viral infection	1 (0.3)	0	0
Vocal cord neoplasm ^b	0	1 (0.3)	0

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.5.1, Table 39, page 290.

a: verbatim term for "parapsoriasis" was "pityriasis lichenoides"; b: determined to be benign.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During Period B of studies M11-313 and M11-810, most frequently reported AEs that led to discontinuation of study drug were hidradenitis and psoriasis. Overall number of AEs leading to discontinuation of study drug was low.

Table 23: AEs Leading to Discontinuation of Study Drug during Maintenance Period; Studies M11-313 and M11-810

System organ class/PT	placebo/placebo N=151 n (%)	placebo/ew N=145 n (%)	Ew/placebo N=100 n (%)	Ew/eow N=101 n (%)	Ew/ew N=99 n (%)
Any AE	3 (1.9%)	7 (4.8)	2 (2.0)	1 (1.0)	2 (2.0)
Blood and Lymphatic system disorders					
Leukopenia	1	0	0	0	0
Cardiac disorders					
Acute MI	0	0	0	1	0
Infections and Infestations					
Appendicitis	1 (0.7)	0	0	0	0
Clostridium difficile colitis	1 (0.7)	0	0	0	0
Pharyngitis streptococcal	0	1 (0.7)	0	0	0
Post procedural infection	0	1 (0.7)	0	0	0
Sinusitis	0	1 (0.7)	0	0	0
Skin and subcutaneous tissue disorders					

Dermatitis psoriasiform	0	0	1 (1.0)	0	0
Hidradentis	0	0	1 (1.0)	1 (1.0)	1 (1.0)
Lichenoid keratosis	0	1 (0.7)	0	0	0
Psoriasis	0	1 (0.7)	0	0	0
Pustular psoriasis	0	2 (1.4)	0	0	0
Rash	0	0	0	0	1 (1.0)
Vascular disorders					
Intra-abdominal hematoma	1 (0.7)	0	0	0	0

Source: Modified from applicant's submission; Module 5.3.5.3; ISS, Section 5.5.1., link page 295; Module 5.3.5.1, Study Report Body M11-313, Section 12.2.2.3 Table 14.3_2.3.2, link on page 467; Module 5.3.5.1, Study Report Body M11-810, Section 12.2.2.3, Table 14.3_2.3.2, link on page 446;

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

A total of 70 (9.6%) of subjects treated with adalimumab (ew or eow) were discontinued due to adverse events. The most AEs that led to discontinuation of study drug were reported in ≤1 subject with exception for AEs listed in Table below. The most frequently reported AEs leading to discontinuation were hidradenitis 23 (3.2%); pustular psoriasis 6 (0.8%); and psoriasis 3 (0.4%).

Table 24: AEs Leading to Discontinuation of Study Drug in Two or More Adalimumab Treated Subjects; All Adalimumab Analysis Set; Study M10-467; M11-313; M11-810 and M12-555

MedDRA Proffered Term	Adalimumab (N=727) n (%)
Hidradentis	23 (3.2)
Pustular psoriasis	6 (0.8)
Psoriasis	3 (0.4)
Drug eruption	2 (0.3)
Paresthesia	2 (0.3)
Rash pustular	2 (0.3)
Weight increased	2 (0.3)

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.5.2, Table 41, page 296.

Discussion: The most frequently reported adverse events leading to discontinuation of the study drug were hidradenitis and psoriasis. Worsening of hidradenitis due to decrease of dosing frequency (eow) or during randomized withdrawal from adalimumab is not unexpected.

*New or worsening of psoriasis during treatment with adalimumab has been reported in trials for other indications; during postmarketing experience and; in literature^{2,3}. This adverse event is included in **Section 6.2 Postmarketing Experience** of current adalimumab labeling. This reviewer does not recommend additional labeling changes regarding psoriasis.*

7.3.4 Significant Adverse Events

No additional significant adverse events were reported during the conduct of studies that support this application.

7.3.5 Submission Specific Primary Safety Concerns

The applicant evaluated AESI as discussed in Section 7.2.6 of this review. During the development of adalimumab for HS indication, no subject treated with adalimumab reported the following AESIs:

- Legionella infection
- Active TB
- Reactivation of hepatitis B
- Progressive multifocal leukoencephalopathy (PML)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Melanoma
- Leukemia
- Vasculitis
- Sarcoidosis
- Intestinal perforation
- Stevens-Johnson syndrome
- Demyelinating disorder
- Amyotrophic lateral sclerosis (ALS),
- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Humira administration-related medication errors
- Liver failure

AESI reported during the development of adalimumab for HS will be presented below.

A. All Infections

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

The most frequently reported infections in adalimumab treated subjects were: nasopharyngitis 31 (7.4%), upper respiratory tract infection 21 (5.0%), influenza 8 (1.9%), urinary tract infection 7 (1.7%) and gastroenteritis 6 (1.4%). Infections reported in any subjects treated with adalimumab during placebo-controlled period of studies M10-467; M11-313 and M11-810 are presented in Table below.

Table 25: Infections Reported in Any Subject Treated with Adalimumab during Placebo-Controlled Period for Studies M10-467; M11-313; and M11-810

MedDRA Proffered Term	Placebo (N=366) n (%)	Adalimumab		Total (N=419) n (%)
		ew (N=367) n (%)	eow (N=52) n (%)	
Any infection	114 (31.1)	96 (26.2)	22 (42.3)	118 (28.2)
Nasopharyngitis	32 (8.7)	24 (6.5)	7 (13.5)	31 (7.4)
Upper respiratory tract infection	15 (4.1)	17 (4.6)	4 (7.7)	21 (5.0)
Influenza	6 (1.6)	7 (1.9)	1 (1.9)	8 (1.9)
Urinary tract infection	8 (2.2)	6 (1.6)	1 (1.9)	7 (1.7)
Gastroenteritis	4 (1.1)	5 (1.4)	1 (1.9)	6 (1.4)
Sinusitis	5 (1.4)	5 (1.4)	0	5 (1.2)
Vulvovaginal mycotic infection	3 (0.8)	4 (1.1)	0	4 (1.0)
Bronchitis	8 (2.2)	3 (0.8)	0	3 (0.7)
Cellulitis	5 (1.4)	3 (0.8)	0	3 (0.7)
Pharyngitis	0	3 (0.8)	0	3 (0.7)
Tonsillitis	5 (1.4)	3 (0.8)	0	3 (0.7)
Rhinitis	4 (1.1)	1 (0.3)	1 (1.9)	2 (0.5)
Ear infection	3 (0.8)	2 (0.5)	0	2 (0.5)
Wound infection	0	2 (0.5)	0	2 (0.5)
Herpes simplex	1 (0.3)	0	2 (3.8)	2 (0.5)
Herpes zoster	2 (0.5)	1 (0.3)	1 (1.9)	2 (0.5)
Lower respiratory tract infection	2 (0.5)	1 (0.3)	1 (1.9)	2 (0.5)
Pilonidal cyst	1 (0.3)	0	2 (3.8)	2 (0.5)
Localized infection	0	1 (0.3)	1 (1.9)	2 (0.5)
Laryngitis	0	1 (0.3)	1 (1.9)	2 (0.5)
Paronychia	1 (0.3)	2 (0.5)	0	2 (0.5)
Fungal skin infection	0	2 (0.5)	0	2 (0.5)
Escherichia infection	0	2 (0.5)	0	2 (0.5)
Skin bacterial infection	0	0	1 (1.9)	1 (0.2)
Subcutaneous abscess	1 (0.3)	0	1 (1.9)	1 (0.2)
Tinea pedis	4 (1.1)	1 (0.3)	0	1 (0.2)
Vaginal infection	1 (0.3)	0	1 (1.9)	1 (0.2)
Tooth abscess	1 (0.3)	0	1 (1.9)	1 (0.2)
Pneumonia	3 (0.8)	0	1 (1.9)	1 (0.2)
Pharyngitis streptococcal	2 (0.5)	1 (0.3)	0	1 (0.2)
Hordeolum	3 (0.8)	1 (0.3)	0	1 (0.2)

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.6.2.1, Table 46, page 319.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During Maintenance Period of studies M11-313 and M11-810, 32 (32.3%) subjects in the adalimumab ew/ew group, 31(30.7%) subjects in the adalimumab ew/eow group, 29 (29%) subjects in the adalimumab ew/placebo group, and 35 (23.2%) subjects in the placebo/placebo group, reported infections.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Three hundred seventy seven subjects (51.9%) reported treatment emergent infections. The most frequently reported infections were nasopharyngitis, upper respiratory tract infection, and urinary tract infection. Of subjects who reported infections, 27 (7.2%)

were severe events and 158 (42.9%) were considered by the investigator to be possibly related to the study drug.

B. Serious Infections

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During placebo-controlled period, all serious infections were reported by a single subject each in all treatment groups. Serious infections that were considered by the investigator to be possibly related to the study drug were reported in 2 adalimumab treated subjects (infection and pyelonephritis). Serious infections reported during Placebo-Controlled Period are presented below.

Table 26: Serious Infections Reported during Placebo-Controlled Period for Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	Placebo (N=366) n (%)	Adalimumab	
		ew (N=367) n (%)	eow (N=52) n (%)
Any serious infection	2 (0.5)	3 (0.8)	1 (1.9)
Escherichia infection	0	1 (0.3)	0
Gastroenteritis	1 (0.3)	0	0
Genital infection bacterial	0	1 (0.3)	0
Infection	0	1 (0.3)	0
Pilonidal cyst	0	0	1 (1.9)
Pyelonephritis	0	1 (0.3)	0
Viral infection	1 (0.3)	0	0

Source: Modified from applicant's submission; Module 5.3.5.3, ISS, section 5.6.3.1, Table 48, page 325.

Maintenance Analysis Set (Studies M11-313 and M11-810)

In the Maintenance Analysis Set, one subjects in the adalimumab ew/ew group reported serious infection (severe pneumonia) which was considered by the investigator to be probably related to the study drug. No subjects in adalimumab ew/eow and adalimumab ew/placebo groups reported serious infections.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

A total of 21 (2.9%) subjects reported 25 serious infections. The incidence rate was 3.9 E/100PYs. Of 21 subjects who reported serious infections, 7(33.3%) subjects reported infections that were considered by the investigator as possibly related and 3 (14.3%) subjects reported infections (purulent discharge, pustular rash and viral pneumonia) that were considered probably related to study drug.

C. Skin and Soft Tissues Serious Infections (SSTIs)

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During placebo-controlled period, 6 subjects reported a total of 8 events adjudicated as SSTIs. The following events were reported:

- Five AEs of hidradenitis were reported by 4 subjects. Of 5 hidradenitis events, 3 events were reported by 2 subjects on placebo and 2 events reported by 2 subjects on adalimumab.
- Two SSTIs (Escherichia infection and genital bacterial infection) were reported by one subject.
- One AE of pilonidal cyst was reported by one subject.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

In All Adalimumab Analysis Set, 30 SAEs were adjudicated as SSTIs. Six SSTIs (Escherichia infection, genital bacterial infection, penile swelling, scrotal swelling, purulent discharge, pustular rash) occurred in the same subject. Thirteen SSTIs were events of hidradenitis, 2 of which were reported in subjects on placebo and 11 in subjects on adalimumab.

D. Opportunistic Infections (Excluding Oral Candidiasis and TB)

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject reported an opportunistic infection of cutaneous coccidioidomycosis. This AE was reported on Day 157 (23 days after the last dose of adalimumab ew in Study M10-467). The event was not serious, moderate in severity, resolved in 2 days and considered by the investigator to be related to study drug.

E. Oral Candidiasis

All Adalimumab Analysis Set (studies M10-467; M11-313; M11-810 and M12-555)

Three subjects reported oral candidiasis while receiving adalimumab ew during Study M12-555. Of three subjects, two received concomitant treatment with inhaled corticosteroids and one subject received antibiotic and oral corticosteroids for treatment of bronchitis.

F. Latent TB

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

No subject reported active TB during conduct of all four studies.

Three subjects reported latent TB while receiving adalimumab ew during Study M12-555. Two of these subjects had negative PPD tests at the screening of Study M11-810 and positive test during Study M12-555. Both subjects were placed on prophylaxis therapy. The third subject had negative Quantiferon –TB test at Screening of the initial study and positive result during Study M12-555. This subject was discontinued from study due to this AE.

G. Parasitic Infections

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

In All Adalimumab Analysis Set, 3 subjects reported parasitic infections: trichomoniasis; bed bug infestation and acarodermatitis. These AEs were considered to be unrelated to the study drug as these infections are common in the general population.

H. Diverticulitis

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Two subjects reported diverticulitis while receiving adalimumab ew (one subject during Period A of Study M11-313 and one subjects during Study M11-555). Both events were considered by the investigators as not related to study drug.

I. All Malignancies

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Five subjects reported malignancies. AE of Hodgkin’s lymphoma was considered by the applicant as possibly related to study drug and the AE or seminoma was consider by the investigator as possibly related to the study drug. AEs of skin cancer, vocal cord neoplasm (benign) and breast cancer were considered by the investigator as not related to study drug (for details see section 7.6.1. **Human Carcinogenicity** of this review).

Table 27: Treatment–Emergent Malignancies; All Adalimumab Analysis Set; Studies M10-467; M11-313; M11-810 and M12-555

MedDRA Proffered Term	Adalimumab N=727 n (%)
Any treatment-emergent malignancy	5 (0.7)
Breast cancer stage III	1 (0.1)
Hodgkin’s lymphoma	1 (0.1)
Seminoma	1 (0.1)
Squamous cell carcinoma of the skin	1 (0.1)
Vocal cord neoplasm	1 (0.1)

Source: Applicant’s submission, Module 5.3.5.3; ISS, section 5.6.10, Table 58, page 353.

J. Lymphoma

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject reported Hodgkin’s lymphoma while receiving adalimumab ew in Study M12-555. This event occurred 148 days after the first dose of adalimumab ew. The applicant considered the event to be possibly related to study drug (for details see section 7.6.1. **Human Carcinogenicity** of this review).

K. Nonmelanoma Skin Cancer

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject reported squamous carcinoma of skin 85 days after initiation of adalimumab treatment (adalimumab ew/eow group, Study M11-810). This AE was considered by the investigator as probably not related to study drug (for details see section 7.6.1. **Human Carcinogenicity** of this review).

L. Other malignancies, except lymphoma, HSTCL, leukemia, NMSC, and melanoma.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Three subjects reported malignancies: vocal cord neoplasm (benign), breast cancer stage III and seminoma. These AEs were discussed in section **7.6.1. Human Carcinogenicity** of this review.

M. Allergic Reactions

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo-Controlled Period a total of 7 (1.7%) subjects in adalimumab groups and 3 (0.8%) subjects in placebo group reported AEs of allergic reaction. No subject reported serious or severe allergic reactions. Three subjects in adalimumab ew group reported asthma that were all exacerbation or worsening of a pre-existing condition. Two events of pruritus and three events of urticaria in adalimumab treated subjects were considered by the investigator as at least possibly related to study drug.

Table 28: Allergic Reactions during Placebo-Controlled Period for Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	Placebo	Adalimumab	
	(N=366) n (%)	ew (N=367) n (%)	eow (N=52) n (%)
Any allergic reaction	3 (0.8)	6 (1.6)	1 (1.9)
Asthma	0	3 (0.8)	0
Drug hypersensitivity	1 (0.3)	0	0
Pruritus generalized	0	1 (0.3)	1 (1.9)
Urticaria	2 (0.5)	3 (0.8)	0

Source: Modified from the applicant's submission. Module 5.3.5.3. ISS, Section 5.6.17.1, Table 62, page 363.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During maintenance period 3 subjects treated with adalimumab (ew/eow) and 2 subjects treated with placebo (ew/placebo), reported allergic reactions. Allergic reactions in adalimumab treated subjects were considered by the investigator as not related to study drug. No subject reported serious or severe allergic reactions.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Twenty seven (3.7%) of subjects reported allergic reactions. All allergic reaction were non serious and mild to moderate in severity. Only one subject discontinued study drug due to allergic reaction (rash).

Table 29: Allergic Reactions; All Adalimumab Analysis Set; Studies M10-467; M11-313; M11-810 and M12-555

MedDRA Proffered Term	Adalimumab N=727 n (%)
Any allergic reaction	27 (3.7)
Urticaria	8 (1.1)
Asthma	7 (1.0)
Pruritus generalized	5 (0.7)
Eye pruritus	2 (0.3)
Hypersensitivity	2 (0.3)
Injection site urticaria	2 (0.3)
Drug hypersensitivity	1 (0.1)
Rash	1 (0.1)

Source: Applicant's submission. Module 5.3.5.3. ISS, Section 5.6.17.1, Table 63, page 364.

N. Lupus-Like Reactions and Systemic Lupus Erythematosus

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject in ew/pbo/ew population, reported severe event of cutaneous lupus erythematosus after the last dose of placebo in Period B of Study M11-810 and prior to first dose of adalimumab ew in Study M12-555. The subject underwent skin biopsy and began treatment with hydroxychloroquine. Subsequently, the subject started treatment with adalimumab ew in Study M12-555. The event was ongoing as of cutoff date of April 29, 2014. The subject did not have history of systemic lupus erythematosus prior to entry into the study.

O. Autoimmune Hepatitis

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject experienced autoimmune hepatitis of moderate severity while on adalimumab ew during Study M12-555. Subject was on placebo during study M11-810. This event was considered possibly related to study drug. Treatment with study drug was interrupted.

P. Myocardial Infarction

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject experienced myocardial infarction while on adalimumab eow in study M11-810. The subject subsequently had cardio-respiratory arrest 38 days later that led to death. Discussion regarding this AE is presented in section 7.3.1 Deaths, of this review.

Q. Congestive Heart Failure

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Three subjects experienced CHF while on adalimumab ew or eow therapy. One event of CHF was a SAE. All three events were considered by the investigator as not related to study drug.

R. Cerebrovascular Accident (CVA)

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Two subjects experienced transient ischemic attack while on adalimumab ew. These events were considered by the investigator as not related to study drug.

S. Pulmonary Embolism

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject experienced pulmonary embolism which occurred 11 days after the last dose of adalimumab ew in study M12-555. This AE was considered by the investigator as not related to study drug.

T. Interstitial Lung Disease

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject experienced non serious AE of restrictive pulmonary disease during Period B of study M11-313. This event was considered by the investigator as not related to study drug.

U. Pancreatitis

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject experienced AE of autoimmune pancreatitis during stud M12-555. This subject subsequently developed cholangitis, sepsis, septic shock that led to death. Discussion regarding this AE is presented in section **7.3.1 Deaths**, of this review.

V. Erythema Multiforme

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

One subject reported erythema multiforme while on adalimumab ew in study M12-555. This event was considered by the investigator as related to study drug.

W. Worsening/New Onset Psoriasis

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo-Controlled period, 2 subjects in placebo group reported worsening of psoriasis. No subject in adalimumab group reported worsening/new onset psoriasis.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During Maintenance Period, 3 subjects in adalimumab ew/ew group and 1 each in adalimumab ew/eow and ew/pbo reported worsening/new onset psoriasis. Except for 1 subject in adalimumab ew/eow, all other AEs of worsening/new onset psoriasis were considered by the investigator at least possibly related to study drug.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

Twenty three subjects (3.2%) reported worsening/new onset psoriasis. Six subjects had prior history of psoriasis. With the exception of 1 subject, all AEs of worsening/new onset psoriasis were considered by the investigator as possibly/probably related to study drug.

Table 30: Worsening/New Onset Psoriasis; All Adalimumab Analysis Set; Studies M10-467; M11-313; M11-810 and M12-555

MedDRA Proffered Term	Adalimumab N=727 n (%)
Any worsening/new onset psoriasis	23 (3.2)
Psoriasis	10 (1.4)
Pustular psoriasis	6 (0.8)
Dermatitis psoriasiform	5 (0.7)
Guttate psoriasis	2 (0.3)

Source: Applicant's submission. Module 5.3.5.3., ISS, Section 5.6.31.2, Table 73, page 390.

X. Hematologic Disorders

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo-Controlled Period, three subjects in adalimumab group experienced anemia and 5 in placebo group experienced anemia and neutropenia.

Table 31: Hematologic Disorders during Placebo-Controlled Period for Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	Placebo (N=366) n (%)	Adalimumab	
		ew (N=367) n (%)	eow (N=52) n (%)
Any hematologic disorder	5 (1.4)	3 (0.8)	0
Anemia	3 (0.8)	3 (0.8)	0
Neutropenia	2 (0.5)	0	0

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 5.6.35, Table 75, page 400.

Maintenance Analysis Set (Studies M11-313 and M11-810)

Five subjects experienced hematologic disorder of anemia during Maintenance Period. Four subjects were on adalimumab ew or eow, and one subject was on placebo. None of AEs were serious or severe and no subject discontinued study drug.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

In All Adalimumab Analysis Set, a total of 22 (3.0%) subjects reported hematologic disorders.

Table 32: Hematologic Disorders; All Adalimumab Analysis Set; Studies M10-467; M11-313; M11-810 and M12-555

MedDRA Proffered Term	Adalimumab N=727 n (%)
Any hematologic disorder	22 (3.2)
Anemia	19 (2.6)
Lymphopenia	2 (0.3)
Neutropenia	2 (0.3)

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 5.6.35.1 Table 76, page 401.

Y. Liver Failure and Other Liver Events (Except Gall Bladder-Related Events) All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

No subject experienced liver failure. A total of 3 subjects (hepatic steatosis; autoimmune hepatitis; and drug-induced liver injury). Events of hepatic steatosis and autoimmune hepatitis were considered by investigator as possibly and probably related to study drug, respectfully.

Adverse event of drug-induced liver injury, with associated elevation of liver function tests, was attributed to use of concomitant isoniazid (INH). INH was initiated for treatment of positive TB test at Screening. This AE resolved upon discontinuation of INH and was considered by investigator as not related to study drug.

Z. Injection Site Reactions

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

A total of 19 (4.5%) subjects in adalimumab treatment group and 10 (2.7%) subject in placebo group reported injection site reactions. Most frequently reported injection site reactions in adalimumab treated subjects were: injection site erythema 5 (1.2%) and injection site bruising 3 (0.7%).

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

For Adalimumab Analysis Set, a total of 54 (7.4%) subjects reported injection site reactions. Most frequently reported injection site reactions were: injection site erythema 18 (2.5%); injection site reaction 14 (1.9%) and 13 (1.85) injection site pruritus.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

Common Treatment Emergent Adverse Events (TEAEs)

During Placebo-Controlled Period, TEAEs most frequently reported in $\geq 1\%$ of adalimumab ew subjects and higher by $\geq 1\%$ than in placebo subjects were headache and nausea.

Table 33: Common TEAEs in $\geq 1\%$ of Adalimumab ew Subjects and Higher by $\geq 1\%$ than Placebo Subjects; Placebo Controlled Period; Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	Placebo (N=366) n (%)	Adalimumab	
		ew (N=367) n (%)	eow (N=52) n (%)
Any TEAE	233 (63)	211 (58)	33 (63)
Headache	38 (10)	43 (12)	7 (14)
Nausea	10 (3)	14 (4)	2 (4)
Diarrhea	8 (2)	12 (3)	2 (4)
Dizziness	6 (2)	11 (3)	1 (2)
Arthralgia	3 (1)	9 (3)	0
Gastroesophageal reflux disease	2 (1)	6 (2)	0
Abdominal pain	0	4 (1)	1 (2)
Injection site erythema	0	5 (1)	0
Injection site pruritus	0	5 (1)	0
Lymphadenopathy	0	4 (1)	0

Source: Modified from applicant's submission. Module 5.2.5.3., ISS, Section 5.2.1.1.; Table 24; page 239.

Adverse Reactions

Adverse Reactions were defined as TEAEs that were considered by the investigator as at least possibly related to study drug. This reviewer presented adverse reactions reported in $\geq 1\%$ of subjects in adalimumab ew subjects and higher than in placebo subjects and adverse reactions that might be associated with the mode of action of the drug or clinically relevant (Table).

Table 34: Adverse Reactions in ≥1% of Adalimumab Subjects and Higher than Placebo Subjects; Placebo Controlled Period; Studies M10-467; M11-313 and M11-810

MedDRA Proffered Term	Adalimumab		
	Placebo (N=366) n (%)	ew (N=367) n (%)	eow (N=52) n (%)
Any Adverse Event	99 (27)	106 (29)	16 (31)
Headache	11 (3)	17 (5)	4 (8)
Nasopharyngitis	9 (2)	11 (3)	3 (6)
Diarrhea	3 (1)	8 (2)	1 (2)
Dizziness	1 (0)	6 (2)	1 (2)
Injection site erythema	0	5 (1)	0
Injection site pruritus	0	5 (1)	0
Arthralgia	0	5 (1)	0

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 5.2.1.2, Table 2.4_1.1.6, Cross reference link on page 246.

Maintenance Analysis Set (Studies M11-313 and M11-810)

During Period B studies M11-311 and M11-810, the most frequently reported treatment emergent adverse events in adalimumab ew subjects were: headache, nasopharyngitis, folliculitis and influenza.

Table 35: TEAE Reported in ≥2% of Subjects in ew/ew Subjects during Maintenance Period for Study M11-313 and M11-810

System organ class/PT	placebo /placebo N=151 n (%)	PYs=36.5 Events (E/100PY)	placebo/ ew N=145 n (%)	PYs=54.5 Events (E/100PY)	ew/ placebo N=100 n (%)	PYs=31.8 Events (E/100PY)	ew/eow N=101 n (%)	PYs=33.1 Events (E/100PY)	ew/ew N=99 n (%)	PYs=35.4 Events (E/100PY)
Any AE										
Headache	4 (2.6)	5 (14)	9 (6)	14 (26)	8 (8)	13 (41)	6 (6)	8 (24)	7 (7)	12 (34)
Nasopharyngitis	5 (3)	6 (16)	11 (8)	12 (22)	10 (10)	16 (50)	4 (4)	8 (24)	6 (6)	7 (20)
Hidradenitis	14 (9)	16 (44)	16 (11)	16 (29)	20 (20)	23 (72)	18 (18)	19 (57)	5 (5)	7 (20)
Upper respiratory tract infection	13 (9)	17 (47)	5 (3)	6 (11)	7 (7)	9 (28)	7 (7)	8 (24)	5 (5)	5 (14)
Folliculitis	0	0	2 (1)	2 (4)	1 (1)	1 (3)	1 (1)	2 (6)	4 (4)	4 (11)
Influenza	3 (2)	3 (8)	0	0	2 (2)	3 (9)	0	0	4 (4)	4 (11)
Back pain	4 (3)	4 (11)	1 (1)	1 (2)	1 (1)	1 (3)	1 (1)	1 (3)	3 (3)	3 (9)
Cough	2 (1)	2 (6)	2 (1)	3 (6)	1 (1)	1 (3)	2 (2)	2 (6)	3 (3)	3 (9)
Gastritis	1 (1)	1 (3)	0	0	0	0	0	0	3 (3)	3 (9)
Gastroenteritis viral	0	0	0	0	0	0	2 (2)	2 (6)	3 (3)	3 (9)
Intertrigo		2 (6)	1 (1)	1 (2)	1 (1)	2 (6)	1 (1)	3 (3)	3 (3)	3 (9)
Nausea	0	0	6 (4)	6 (11)	1 (1)	3 (3)	1 (1)	1 (3)	3 (3)	3 (9)
Pyrexia	2 (1)	3 (8)	2 (1)	2 (4)	1 (1)	1 (3)	5 (5)	5 (15)	3 (3)	3 (9)
Anemia	0	0	1 (1)	1 (2)	2 (2)	2 (6)	1 (1)	2 (6)	2 (2)	2 (6)
Arthralgia	2 (1)	2 (6)	1 (1)	1 (2)	3 (3)	3 (9)	1 (1)	1 (3)	2 (2)	2 (6)
Dermatitis psoriasiform	0	0	1 (1)	1 (2)	1 (1)	1 (3)	0	0	2 (2)	2 (6)

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Diarrhea	2 (1)	2 (6)	3 (2)	3 (6)	2 (2)	2 (6)	4 (4)	4 (12)	2 (2)	2 (6)
Hypertension		1 (3)	2 (1)		3 (3)	3 (9)	0	0	2 (2)	2 (6)
Insomnia	2 (1)	2 (6)	1 (1)	1 (2)	0	0	1 (1)	1 (3)	2 (2)	2 (6)
Pneumonia	1 (1)	1 (3)	2 (1)	2 (4)	1 (1)	1 (3)	2 (2)	2 (6)	2 (2)	2 (6)
Sinusitis	1 (1)	1 (3)	4 (3)	4 (7)	1 (1)	1 (3)	0	0	2 (2)	2 (6)
Urinary tract infection	3 (2)	3 (8)	4 (3)	4 (7)	2 (2)	2 (6)	3 (3)	4 (12)	2 (2)	3 (9)
Viral upper respiratory tract infection	0	0	0	0	0	0	0	0	2 (2)	2 (6)
Weight decreased	0	0	0	0	0	0	0	0	2 (2)	2 (6)

Source: Modified from applicant's submission. Module 5.2.5.3., ISS, Section 5.2.2.1, Table 27, page 249; cross reference for Table 2.4_2.1.2.2 on page 2111 and Table 2.4_2.1.8 on page 2202. Study Report Body M11-313, Section 12.2.2.2. cross reference on page 475 for Table 14.3_1.2.1.2 on page 4977 and Table 14.3_1.2.2.2, on page 5107. Study Report Body M11-810, Section 12.2.2.2., cross reference on page 445 for Table 14.3_1.2.1.2 on page and Table 14.3_1.2.2.2 on page

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

In All Adalimumab Analysis Set, the most frequently reported TEAEs were: hidradenitis, nasopharyngitis and headache.

Table 36: TEAEs in All Adalimumab Analysis Set; Studies M10-467; M11-810; M11-313 and M12-555

MedDRA Proffered Term	Adalimumab	
	N=727 n (%)	PY-635.7 Events (E/100 PYs)
Any Adverse Event	572 (79)	2975 (468)
Hidradenitis	153 (21)	215 (33.8)
Nasopharyngitis	104 (14)	151 (24)
Headache	97 (13)	175 (28)
Upper respiratory tract infection	77 (11)	103 (16)
Nausea	38 (5)	42 (7)
Urinary tract infection	37 (5)	43 (7)
Arthralgia	36 (5)	40 (6)

Source: Modified from applicant's submission. Module 5.2.5.3., ISS, Section 5.2.3.1, Table 30; page 263.

Discussion: To adjudicate AEs as being reasonably and plausibly related to the drug treatment, this reviewer took into consideration the totality of the data. Data from all three study population sets, that encompass short-term as well long term use, were evaluated to see if there is a pattern of events that occurred with short/long term use. The overall number, type and pattern of adverse events did not reveal new safety signals. The common adverse event data demonstrated a similar safety profile for adalimumab with that included in labeling for other indications. This reviewer concurs with the applicant's proposed labeling of adverse reactions.

7.4.2 Laboratory Findings

Criteria for clinically notable laboratory abnormalities were based on Common Toxicity Criteria (CTC) version 3 [Common Terminology Criteria for Adverse Events (CTCAE) version 3.0]

Hematology

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During the Placebo-Controlled Period, there were no clinically significant shifts in hematology values from Baseline to the Final visit with exception of:

- Shift of lymphocyte values from Low or Normal at Baseline to High at Final visit, observed in 18 (5%) of subjects in adalimumab ew group and in 3 (0.9%) subjects in placebo group.
- Shift of platelet count from Low or Normal at Baseline to High at Final visit observed in 17% of subjects in the adalimumab eow group and 4% of subjects in placebo group. Due to difference in sample size between two treatment groups (325 in placebo group and 40 in adalimumab group), the conclusion regarding the significance of changes in platelet values, cannot be drawn.

For subjects who met criteria for potentially clinically significant hematology values, there was no increase in incidence of clinically significant values of CTCAE Grade ≥ 2 or Grade ≥ 3 in adalimumab ew or eow treatment groups compared to placebo or between two adalimumab treatment groups. Hematology values of CTCAE Grade ≥ 3 were observed for hemoglobin in 1 (0.3%) subject in adalimumab ew group and 2 (0.6%) subjects in placebo group.

Table 37: Number and Percentage of Subjects Who Met Criteria for Potentially Clinically Significant Hematology Values for Placebo-Controlled Period (Studies M10-467; M11-313 and M11-810)

Laboratory Parameters	Placebo N=366 n/Total (%)	Adalimumab	
		ew N=367 n/Total (%)	eow N=52 n/Total (%)
CTC Grade ≥ 2			
Hemoglobin	6/345 (1.7)	6/352 (1.7)	1/48 (2.1)
WBC count	1/359 (0.3)	0/361	0/49
Neutrophils	3/356 (0.8)	2/361 (0.6)	0/49
Lymphocytes	2/357 (0.6)	0/361	0/49
Platelet count	0/355	0/360	0/49
CTC Grade ≥ 3			
Hemoglobin	2/357 (0.6)	1/359 (0.3)	0/49
WBC count	0/359	0/361	0/49
Neutrophils	2/356 (0.6)	0/361	0/49
Lymphocytes	0/357	0/361	0/49
Platelet count	0/355	0/360	0/49

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.1.1, Table 85; page 427.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)
 For subjects meeting criteria for potentially clinically significant hematology values of CTCAE Grade ≥ 3 were observed in less than 1% of all adalimumab treated subjects.

Table 38: Number and Percentage of Subjects Who Met Criteria for Potentially Clinically Significant Hematology Values for Studies M10-467; M11-313; M11-810 and M12-555 through April 29, 2014 (All Adalimumab Analysis Set)

Laboratory Parameters	Adalimumab (N-727) n/N (%)	
	CTC Grade ≥ 2	CTC Grade ≥ 3
Hemoglobin	27/687 (3.9)	6/709 (0.8)
WBC count	2/710 (0.3)	1/711 (0.1)
Neutrophils	8/710 (1.1)	3/710 (0.4)
Lymphocytes	5/710 (0.7)	2/711 (0.3)
Platelet count	1/710 (0.1)	1/710 (0.1)

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.1.2, Table 86; page 428.

Clinical Chemistry

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo Controlled Period, During the Placebo-Controlled Period, there were no clinically significant shifts in chemistry values from Baseline to the Final visit with exception of:

- Shift of in cholesterol levels from Low or Normal at Baseline to High at Final visit, observed in 35 (14.2%) of subjects in adalimumab ew group and in 20 (8.2%) subjects in placebo group.
- Shift of in triglyceride levels from Low or Normal at Baseline to High at Final visit, observed in 31 (10.7%) of subjects in adalimumab ew group and in 19 (6.7%) subjects in placebo group.
- Shift of in phosphate levels from High or Normal at Baseline to Low at Final visit, observed in 12 (3.4%) of subjects in adalimumab ew group and in 2 (0.6%) subjects in placebo group.

For subjects who met criterial for potentially clinically significant chemistry values, there clinically significant values of CTCAE Grade ≥ 3 occurred in ≤ 1 % of subjects in adalimumab ew and placebo groups with exception of glucose-hyperglycemia observed in 4 (1.1%) subject in adalimumab ew group compared to placebo observed in 1 (0.3%) subjects in placebo group.

Table 39: Number and Percentage of Subjects Who Met Criteria for Potentially Cynically Significant Chemistry Values for Studies M10-467; M11-313; M11-810 and M12-555 (Placebo Controlled Analysis Set)

Laboratory Parameters	Placebo N=366 n/Total (%)	Adalimumab	
		ew N=367 n/Total (%)	eow N=52 n/Total (%)
CTC Grade ≥2			
ALT	2/357 (0.6)	2/356 (0.6)	2/50 (4.0)
AST	2/357 (0.6)	3/359 (0.8)	0/50
Alkaline phosphatase	0/356	0/359	0/50
Total bilirubin	0/357	0/361	0/50
Creatinine	0/354	1/361 (0.3)	1/50 (2.0)
Uric acid	1/352 (0.3)	2/359 (0.6)	0/50
Phosphate	9/347 (2.6)	16/348 (4.6)	2/49 (4.1)
Calcium -hypercalcemia	1/357 (0.3)	0/361	0/50
Calcium-hypocalcemia	1/356 (0.3)	2/361 (0.6)	0/50
Sodium-hyponatremia	0/357	1/361 (0.3)	0/50
Sodium- hyponatremia	0/357	2/262 (0.6)	0/50
Potassium-hyperkalemia	0/357	0/361	0/50
Potassium-hypokalemia	0/357	0/361	0/50
Glucose- hyperglycemia	10/343 (2.9)	8/351 (2.3)	1/48 (2.1)
Glucose- hypoglycemia	0/356	0/359	0/49
Albumen	4/357 (1.1)	2/359 (0.6)	0/50
Cholesterol- hypercholesterolemia	1/338 (0.3)	3/351 (0.9)	0/50
Triglycerides- hypertriglyceridemia	0/335	8/351 (2.3)	1/49 (2.0)
CTC Grade ≥3			
ALT	2/357 (0.6)	0/359	0/50
AST	2/357 (0.6)	0/360	0/50
Alkaline phosphatase	0/357	0/361	0/50
Total bilirubin	0/357	0/361	0/50
Creatinine	1/357 (0.3)	0/361	0/50
Uric acid	1/352 (0.3)	2/359 (0.6)	0/50
Phosphate	1/357 (0.3)	0/361	0/50
Calcium -hypercalcemia	1 /357 (0.3)	0/361	0/50
Calcium-hypocalcemia	0/356	0/361	0/50
Sodium-hyponatremia	0/356	0/361	0/50
Sodium- hyponatremia	0/357	2/361 (0.6)	0/50
Potassium-hyperkalemia	0/355	0/361	0/50
Potassium-hyponatremia	0/356	0/361	0/50
Glucose- hyperglycemia	1/350 (0.3)	4/360 (1.1)	0/50
Glucose- hypoglycemia	0/358	0/360	0/50
Albumen	0/357	1/361 (0.3)	0/50
Cholesterol- hypercholesterolemia	0/359	2/353 (0.6)	0/50
Triglycerides- hypertriglyceridemia	0/359	1/353 (0.3)	0/50

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.2.1, Table 87; page 432.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

In subjects meeting criteria for potentially clinically significant abnormality in chemistry values, the most frequently occurring chemistry values of CTCAE Grade ≥ 3 , were hyperglycemia and hyperuricemia.

Table 40: Number and Percentage of Subjects Who Met Criteria for Potentially Clinically Significant Chemistry Values for Studies M10-467; M11-313; M11-810; and M12-555 through April 29, 2014 (All Adalimumab Analysis Set)

Laboratory Parameters	Adalimumab N=727 n /Total (%)	
	CTCAE Grade ≥ 2	CTCAE Grade ≥ 3
ALT	13/708 (1.8)	1/711 (0.1)
AST	9/711 (1.3)	0/712
Alkaline phosphatase	1/711 (0.1)	1/713 (0.1)
Total bilirubin	1/713 (0.1)	1/713 (0.1)
Creatinine	3/711 (0.4)	1/713 (0.1)
Uric acid	12/711 (1.7)	12/711 (1.7)
Phosphate	76/695 (10.9)	5/713 (0.7)
Calcium -hypercalcemia	1/713 (0.1)	0/713
Calcium-hypocalcemia	7/712 (1.0)	1/713 (0.1)
Sodium-hypernatremia	1/713 (0.1)	0/713
Sodium- hyponatremia	8/713 (1.1)	8/713 (1.1)
Potassium-hyperkalemia	7/713 (1.0)	1/713 (0.1)
Potassium-hypokalemia	0/713	0/713
Glucose- hyperglycemia	42/690 (6.1)	17/707 (2.4)
Glucose- hypoglycemia	8/710 (1.1)	2/711 (0.3)
Albumen	13/708 (1.8)	2/713 (0.3)
Cholesterol- hypercholesterolemia	7/699 (1.0)	2/702 (0.3)
Triglycerides- hypertriglyceridemia	22/698 (3.2)	3/702 (0.4)

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.2.2, Table 89; page 435.

Liver Function Values

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During the Placebo-Controlled Period, the incidence of potentially significant liver function values in adalimumab treated subjects were similar compared to placebo.

Table 41: Incidence of Potentially Clinically Significant Liver Function Laboratory Values for Studies M10-467; M11-313; and M11-810 (Placebo-Controlled Analysis Set)

Criterion	Placebo N=366 n/Total (%)	Adalimumab	
		ew N=367 n/Total (%)	eow N=52 n/Total (%)
ALT ≥3 x ULN	2/357 (0.6)	1/361 (0.3)	2/50 (4.0)
ALT ≥5 x ULN	2/357 (0.6)	0/361	1/50 (2.0)
ALT ≥10 x ULN	1/357 (0.3)	0/361	0/50
ALT ≥20 x ULN	0/357	0/361	0/50
AST ≥3 x ULN	2/357 (0.6)	1/361 (0.3)	0/50
AST ≥5 x ULN	2/357 (0.6)	0/361	0/50
AST ≥10 x ULN	1/357 (0.3)	0/361	0/50
AST ≥20 x ULN	0/357	0/361	0/50
Total bilirubin ≥ 2 x ULN	0/357	0/361	0/50
Alkaline phosphatase ≥1.5 x ULN	3/357 (0.8)	2/361 (0.6)	1/50 (2.0)
ALT and/or AST ≥x3 ULN and concurrent total bilirubin ≥ 1.5 x ULN	0/357	0/361	0/50
ALT and/or AST ≥x3 ULN and concurrent total bilirubin ≥ 2 x ULN	0/357	0/361	0/50

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.2.1, Table 88; page 434.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

The incidence of potentially significant liver function values for subjects treated with adalimumab are presented below.

Table 42: Incidence of Potentially Clinically Significant Liver Function Laboratory Values for Studies M10-467; M11-313; M11-810 and M12-555 through April 29, 2014 (All Adalimumab Analysis Set)

Criterion	Adalimumab N=727 n/Total (%)
ALT ≥3 x ULN	10/713 (1.4)
ALT ≥5 x ULN	2/713 (0.3)
ALT ≥10 x ULN	1/713 (0.1)
ALT ≥20 x ULN	0/713
AST ≥3 x ULN	6/713 (0.8)
AST ≥5 x ULN	0/713
AST ≥10 x ULN	0/713
AST ≥20 x ULN	0/713
Total bilirubin ≥ 2 x ULN	1/713 (0.1)
Alkaline phosphatase ≥1.5 x ULN	13/713 (1.8)
ALT and/or AST ≥ 3 x ULN and concurrent total bilirubin ≥ 1.5 x ULN	1/713 (0.1)
ALT and/or AST ≥3 x ULN and concurrent total bilirubin ≥ 2 x ULN	1/713 (0.1)

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 6.3.2.2, Table 90; page 437.

During Study M12-555, two subjects were reported with severe elevation of liver enzymes. These events are discussed below.

Subject # (b) (6) experienced a non-serious event of severe hepatic steatosis on Day 85 of Study M12-555. The subject had elevation of ALT of 505 U/L. The subject underwent hepatic echography. Study drug was interrupted and restarted on Day 99. The event was considered resolved on Day 105. Subsequently, on day 169, the subject had ALT value of 28 U/L.

Subject # (b) (6) experienced multiple SAEs, including cholangitis, autoimmune pancreatitis, septic shock, respiratory failure, cardiac arrest and death during Study M12-555. On treatment day 105, this subject experienced AST of 118, ALT of 17 and total bilirubin of 11.8. This subject was discussed in more detail in **Section 7.3.1 Deaths** of this review. This SAE was not considered by the investigator to be not related to study drug. The applicant considered the event of cholangitis, sepsis, and septic shock to be possibly related to study drug with an alternative etiology of comorbid medical conditions.

Discussion: Review of cases of severe elevation of liver function tests did not reveal a signal for severe hepatotoxicity. Section 6 ADVERSE REACTION, subsection 6.1 Clinical Trials Experience of adalimumab labeling, contains information regarding liver enzyme elevations reported in placebo-controlled trials for other indications. Incidence of severe elevation of liver enzymes reported in placebo-controlled trials for HS indication is similar to placebo and to those reported in trials for other indications.

Urinalysis

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo-Controlled Period, reports of abnormal urinalysis were infrequent and considered not clinically meaningful (data not presented).

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

For all subjects treated with adalimumab, reports of abnormal urinalysis were infrequent and considered not clinically meaningful (data not presented).

7.4.3 Vital Signs

Placebo-Controlled Analysis Set (Studies M10-467; M11-313 and M11-810)

During Placebo-Controlled Period, mean change in vital sign values from Baseline to the final visit and the incidence of potentially clinically significant vital sign values, were not considered by the investigator as clinically meaningful. The number of subjects with potentially clinically significant vital sign values was similar in adalimumab and placebo subjects.

Table 43: Number and Percentage of Subjects Who Met Criteria for Potentially Clinically Significant Vital Signs Values for Studies M10-467; M11-313; M11-810; and M12-555 (Placebo-Controlled Analysis Set)

Laboratory Parameter	Placebo (N=366)	Adalimumab n/N (%)	
		Ew (N=367)	Eow (N=52)
Systolic blood pressure-sitting (mmHg)			
≤90 mmHg or ≥20 mmHg decrease from Baseline	61/363 (16.8)	55/367 (15.0)	9/52 (17.3)
≥180 mmHg or ≥20 mmHg increase from Baseline	66/363 (18.2)	66/367 (18.0)	10/52 (19.2)
Diastolic blood pressure-sitting (mmHg)			
≤50 mmHg or ≥15 mmHg decrease from Baseline	55/363 (15.3)	46/367 (12.5)	5/52 (9.6)
≥105 mmHg or ≥15 mmHg or increase from Baseline	56/363 (15.4)	59/367 (16.1)	10/52 (19.2)
Pulse- sitting (BPM)			
≤50 BPM or ≥15 BPM decrease from Baseline	61/363 (16.8)	66/367 (18.0)	13/52 (25.0)
≥120 BPM or ≥15 BPM increase from Baseline	83/363 (22.9)	74/367 (20.2)	16/52 (30.8)

Source: Modified from applicant's submission. Module 5.3.5.3., ISS, Section 7.1.1, Table 91; page 439.

All Adalimumab Analysis Set (Studies M10-467; M11-313; M11-810 and M12-555)

The number of subjects with potentially clinically significant vital sign values were not considered by the investigator to be clinically meaningful. Number of subjects with potentially clinically significant vital sign values is presented below.

Table 44: Number and Percentage of Subjects with Potentially Clinically Significant Vital Sign Values for Studies M10-467; M11-313; M11-810; and M12-555 (All Adalimumab Analysis Set)

Value	Adalimumab (N=727) n/N (%)
Systolic blood pressure-sitting (mmHg)	
≤90 mmHg or ≥20 mmHg decrease from Baseline	172/719 (23.9)
≥180 mmHg or ≥20 mmHg increase from Baseline	203/719 (28.2)
Diastolic blood pressure-sitting (mmHg)	
≤50 mmHg or ≥15 mmHg decrease from Baseline	166/719 (23.1)
≥105 mmHg or ≥15 mmHg or increase from Baseline	175/719 (24.3)
Pulse- sitting (BPM)	
≤50 BPM or ≥15 BPM decrease from Baseline	207/719 (28.8)
≥120 BPM or ≥15 BPM increase from Baseline	258/719 (35.9)

Source: Applicant's submission. Module 5.3.5.3.; ISS Section 7.1.2; Table 92; page 440.

7.4.4 Electrocardiograms (ECGs)

No systematic ECG monitoring was conducted during the development of adalimumab for HS indication. A resting 12-lead ECG was to be obtained during Screening period of all 4 studies. Repeat ECG was to be obtained only if, in the opinion of the investigator, clinically significant AEs developed during the study that warranted a repeat examination. The applicant has not provided data on ECG monitoring.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

The immunogenicity of adalimumab was evaluated in studies M10-467; M11-313 and M11-810 using validated double antigen sandwich enzyme-linked immunosorbent assay (ELISA) method. This method detects only free (unbound) antibodies in serum. The limitation of this assay is that AAA antibodies can be detected only when serum adalimumab level is <2 mcg/mL. The applicant is currently developing an improved immunogenicity assay (to fulfill PMR #3 listed in the FDA approval letter of MLA 125057/232 for ulcerative colitis indication dated September 28, 2012). Due to timing of the assay validation, immunogenicity results using new assay were not included at the time of submission of this supplement.

Review of immunogenicity results using ELISA method are presented below. The applicant classified a sample as anti-adalimumab antibody positive (AAA+) if the AAA concentration in serum was >20ng/mL and the serum sample was collected within 30 days after an adalimumab dose.

In Study M10-467, a total of 16 (10.4%) subjects were AAA+. Five subjects (4.9%) were AAA+ during Period A [2/51 (3.9%) subjects were in adalimumab ew group and 3/52 (5.8%) subjects were in adalimumab eow group] and 11 (7.1%) subjects were AAA+ during Period B (adalimumab eow subjects).

In studies M11-313 and M11-810 a total of 10/316 (3.2%) subjects were AAA+ during Period A. During Period B, 10/99 (10.1%) subjects in adalimumab ew/ew group were AAA+. The percent of subjects who were AAA+ during two Phase 3 studies, are presented below.

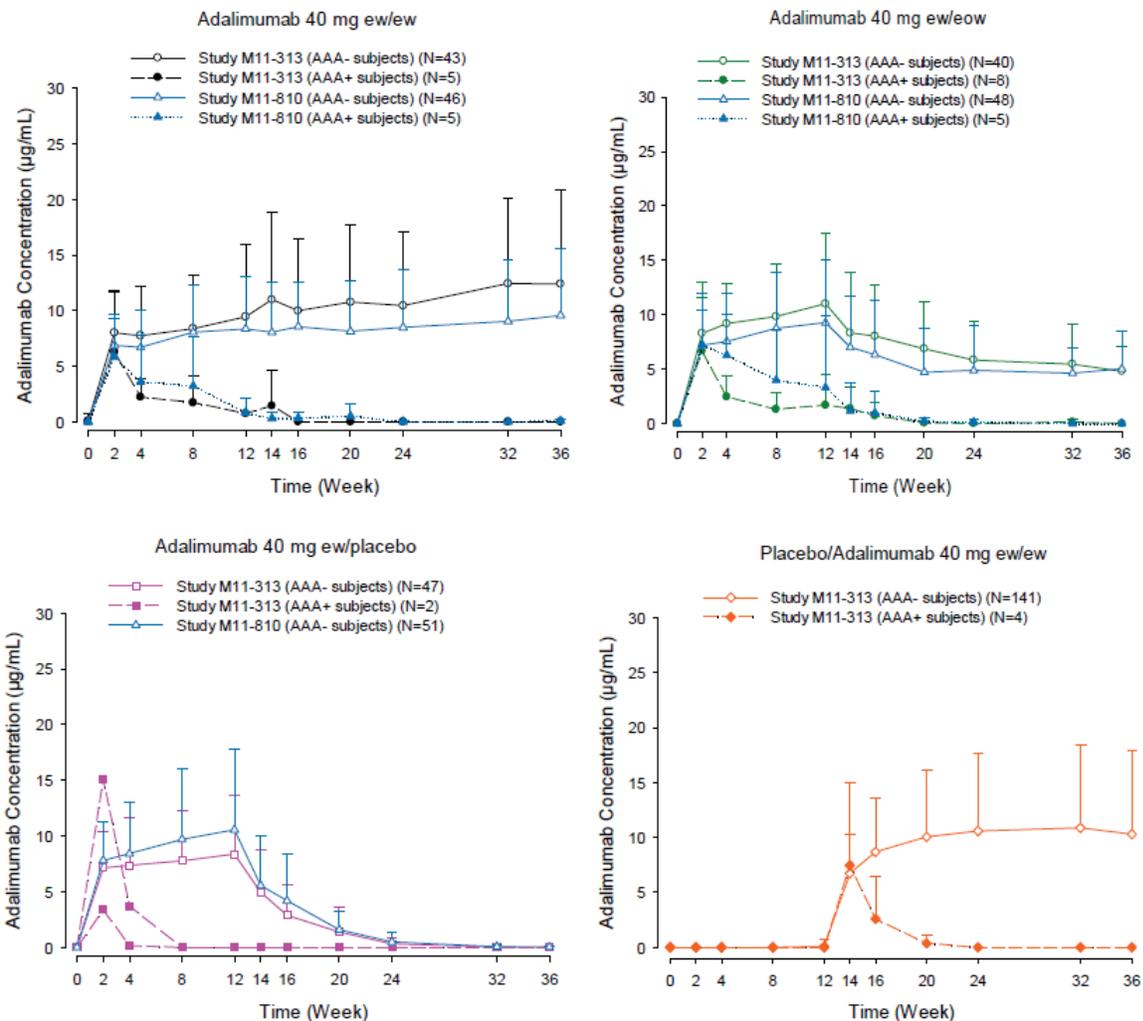
Table 45: AAA Positive Rates (Studies M11-313 and M11- 810)

Treatment Group	Study M11-313	Study M11-810
Period A (Weeks 0-12)		
Adalimumab 40mg ew	8/153 (5.2%)	2/163 (1.2%)
Period B (Weeks 12-36)		
Adalimumab 40mg ew/ew	5/48 (10.4%)	5/51 (9.8%)
Adalimumab 40mg ew/eow	8/48 (16.7%)	5/53 (9.4%)
Adalimumab 40mg ew/pbo	2/49 (4.1%)	0/51 (0%)
pbo/Adalimumab 40mg ew	4/145 (2.8%)	-

Source: Modified from applicant's submission: Summary of Clinical Pharmacology Studies; Section 2.7.2.4.1, Table 8; page 23.

The applicant evaluated serum concentration of adalimumab vs. time, for all treatment groups, during conduct of study M11-313 and M11-810. The results are presented in figures below. The mean serum concentrations were lower in AAA+ subjects compared to that of AAA- subjects, and remained low through the studies.

Figure 9: Mean (+SD) Serum Adalimumab Concentrations Versus time by Treatment Group and AAA Status (Studies M11-313 and M11-810)



Source: Applicant's submission; Summary of Clinical Pharmacology Studies 2.7.2.4.1; Figure 8; page 24.

The applicant evaluated the impact of antibody status on efficacy. None of subjects who were AAA+ achieved primary efficacy endpoint (HiSCR) at Week 12. However, the total number of AAA+ subjects was low and definite conclusion regarding the impact on efficacy cannot be drawn.

Evaluation of impact of antibody status on safety did not reveal a pattern of increased incidence of AEs in subjects with positive AAAs. However, due to low number of AAA+ subjects, definite conclusions cannot be drawn.

Table 46: Number and Percentage of Subjects with TEAEs Stratified by AAA Status (Studies M11-313 and M11-810)

Subjects With	Study M11-313		Study M11-810	
	AAA-	AAA+	AAA-	AAA+
	(N = 278) n (%)	(N = 20) n (%)	(N = 153) n (%)	(N = 10) n (%)
Any AE	190 (68.3)	12 (60.0)	111 (72.5)	7 (70.0)
Any serious AE	11 (4.0)	2 (10.0)	7 (4.6)	0
Any AE leading to discontinuation of study drug	9 (3.2)	1 (5.0)	6 (3.9)	0
Any severe AE	27 (9.7)	2 (10.0)	14 (9.2)	0
Any AE at least possibly drug related ^a	87 (31.3)	6 (30.0)	62 (40.5)	4 (40.0)
Any SAE at least possibly drug related ^a	3 (1.1)	1 (5.0)	5 (3.3)	0
Any infectious AE	97 (34.9)	6 (30.0)	64 (41.8)	4 (40.0)
Any serious infectious AE	2 (0.7)	0	2 (1.3)	0
Any diverticulitis	1 (0.4)	0	0	0
Any non-melanoma skin cancer	0	0	1 (0.7)	0
Any AE leading to death	0	0	1 (0.7)	0
Any parasitic infection	0	0	1 (0.7)	0
Any allergic reaction including angioedema/anaphylaxis	6 (2.2)	0	4 (2.6)	1 (10.0)
Any malignancy	0	0	1 (0.7)	0
Any lupus-like reactions and systemic lupus erythematosus	0	0	1 (0.7)	0
Any myocardial infarction	0	0	1 (0.7)	0
Any congestive heart failure	0	0	1 (0.7)	0
Any worsening/new onset of psoriasis	7 (2.5)	0	3 (2.0)	0
Any hematologic disorders including pancytopenia	5 (1.8)	0	2 (1.3)	0
Any liver failure and other liver event	0	0	1 (0.7)	0
Any injection site reaction related AE	15 (5.4)	1 (5.0)	13 (8.5)	0

Source: Applicant's submission, Module 2; Section 2.7.2; subsection 2.7.2.4.1, Table 9, page 26.

On March 26, 2015 the applicant submitted a response to Agency's Clinical Pharmacology Information Request of March 13, 2015. In their submission, the applicant provided information on safety and efficacy in subjects who had anti-adalimumab antibody positive serum samples that were collected more than 30 days after an adalimumab dose. The applicant conducted sensitivity analysis using reclassified subjects with AAA concentrations >20ng/mL measured > 30 days after last adalimumab dose as AAA positive. Proportion of AAA+ subjects did not change in Period A of both studies because all subjects treated with adalimumab ew and therefore did not have AAA concentrations measured more than 30 days after a given dose.

Table 47: AAA Positive Rates Upon Inclusion of Re-Classified Subjects (Studies M11-313 and M11-810)

Treatment Group	Study M11-313	Study M11-810	Total
Period A (Weeks 0-12)			
Adalimumab 40mg ew	8/153 (5.2%)	2/163 (1.2%)	10/316 (3.2%)
Period B (Weeks 12-36)			
Adalimumab 40mg ew/ew	5/48 (10.4%)	5/51 (9.8%)	10/99 (10.1%)
Adalimumab 40mg ew/eow	8/48 (16.7%)	6/53 (11.3%)	14/101 (13.9%)
Adalimumab 40mg ew/pbo	17/49 (34.7%)	12/51 (23.5%)	28/100 (28%)
pbo/Adalimumab 40mg ew	5/145 (3.4%)	-	5/145 (3.4)
Period A+B (Weeks 0-36)	36/298 (12.1%)	23/163 (14.1%)	59/461 (12.8%)

Source: Applicant's submission; Response to Information Request; Table 1, page 6.

As presented in Table above, re-classified subjects were all in Period B of Phase 3 studies and, except for one subject, were all on placebo. Therefore, these additional subjects did not have any impact on efficacy.

The applicant evaluated impact of immunogenicity on safety by comparing incidence of AEs between AAA+, including re-classified subjects, and AAA- subjects. There were no notable changes in AE rates when compared to the original analysis (presented in Table above). There were no new association between AAA+ status and incidence of AEs upon inclusion of re-classified subjects into the analysis.

Table 48: Number and Percent of Subjects with TEAEs Stratified by AAA Status (Studies M11-313 and M11-810)

Category	Study M11-313		Study M11-810	
	AAA- N=262 n (%)	AAA+ N=36 n (%)	AAA- N=140 n (%)	AAA+ N=23 n (%)
Any AE	179 (68.3)	23 (63.9)	101 (72.1)	17 (73.9)
Any SAE	10 (3.8)	3 (8.3)	7 (5.0)	0
Any AE leading to discontinuation	9 (3.4)	1 (2.8)	6 (4.3)	0
Any severe AE	26 (9.9)	3 (8.3)	12 (8.6)	2 (8.7)
Any AE at least possibly related to study drug	81 (30.9)	12 (33.2)	57 (40.7)	9 (39.1)
Any SAE at least possibly related to study drug	2 (0.8)	2 (5.6)	5 (3.6)	0
Any infection	90 (34.4)	13 (36.1)	57 (40.7)	11 (47.8)
Any serious infection	1 (0.4)	1 (2.8)	2 (1.4)	0
Any diverticulitis	1 (0.4)	0	0	0
Any NMSC	0	0	1 (0.7)	0

Any AE leading to death	0	0	1 (0.7)	0
Any parasitic infections			1 (0.7)	0
Any allergic reaction including angioedema/anaphylaxis	6 (2.3)	0	3 (2.1)	2 (8.7)
Any malignancy	0	0	1 (0.7)	0
Any lupus-like reactions and SLE	0	0	1 (0.7)	0
Any myocardial infarction	0	0	1 (0.7)	0
Any congestive heart failure	0	0	1 (0.7)	0
Any worsening/new onset of psoriasis	7 (2.7)	0	3 (2.1)	0
Any hematologic disorder including pancytopenia	5 (1.9)	0	2 (1.4)	0
Any liver failure and other liver event	0	0	1 (0.7)	0
Any injection site reaction related AE	14 (5.3)	2 (5.6)	13 (9.3)	0

Source: Applicant's submission; Response to Information Request, Tables 2 and 3, pages 8 and 9. .

Discussion:

During the pre-sBLA meeting (July 30, 2014), the Agency agreed that the applicant may submit immunogenicity data using a new improved immunogenicity assay that will be able to detect AAA antibodies when serum adalimumab levels are above 2 mcg/mL by the fourth quarter of 2015 and, that a postmarketing requirement may be issued for the data submission. This reviewer agrees that PMR for data submission should be issued.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

During two Phase 3 trials (M11-810 and M11-313) and one Phase 2 (M10-467) trial, only 40mg dose of adalimumab, and two dosing frequencies, 40mg every week and 40mg every other week, were evaluated. During open-label extension trial M12-555, subjects were treated only with adalimumab ew. Safety data comparing two dosing regimens was available for approximately 420 subjects for the duration of dosing of 12 weeks during Placebo Controlled Period of studies M11-810 and M11-313 and M10-467. Additional data was also available for comparison between dosing regimens for 300 subjects for the duration of 14 weeks of Maintenance Period (Period B) of studies M11-810 and M11-313.

During Placebo Controlled Period of these 3 trials there was no pattern of increased incidence of adverse events with the increased frequency of adalimumab dosing. The results showed that there was an increase incidence of AEs in eow treatment group compared to ew treatment group, for all AE categories. These results can be explained by the difference in sample size of two treatment groups (52 subjects in eow group and 367 in ew treatment group). There was no increased incidence of AEs in adalimumab ew group compared to placebo.

During Period B of two Phase 3 trials, when adjusted for the duration of exposure, there was no pattern of increase incidence of adverse events with increased frequency of dosing. Of SAE at least possibly related to study drug, 2 (2%) of subjects in adalimumab ew/ew group reported 2 SAEs (pneumonia and rash) and 2 (2%) of subjects in ew/eow group reported 2 SAEs (lymphadenitis and acute myocardial infarction).

7.5.2 Time Dependency for Adverse Events

AEs over the entire treatment period of all HS studies are summarized in table below. Data obtained during the placebo-controlled part of trials evaluated short-term safety. Data from the non-controlled periods of trials and open label trial M12-555 were used to assess potential safety signals that may occur following prolonged exposure to adalimumab. Data for subjects treated with adalimumab at the proposed dosing frequency of ew (no switch to placebo or decrease to eow), are included in the table below. There was increase of frequency of SAEs at least possibly related to study drug in subjects treated with adalimumab ew for up to 24 weeks compared to adalimumab ew subjects treated up to 16 weeks. However, there was no increase in frequency of SAEs at least possibly related to study drug in adalimumab ew subjects with the longest duration of exposure (up to 2 years).

For all categories of AEs, there was no increase of frequency of any type of adverse events in subjects with the longest exposure to adalimumab ew, compared to subjects with a shorter adalimumab exposures.

Table 49: Number and Percentage of Subjects with AEs Treated with Uninterrupted Adalimumab ew, by Duration of Exposure

Category	Placebo-Controlled Period Up to 16 weeks				Maintenance Period Up to 24 weeks		Up to 2 years	
	Placebo		Adalimumab ew		Adalimumab ew/ew		Adalimumab ew/ew/ew/ew	
	N=366 n (%)	PY=85.8 Events (E/100 PY)	N=367 n (%)	PY=87.1 Events (E/100 PY)	N=99 n (%)	PY=35.4 Events (E/100 PY)	N=84 n (%)	PY=102.2 Events (E/100 PY)
Any AE	233 (63.7)	639 (744.8)	211 (57.5)	538 (669.3)	59 (59.6)	167 (471.8)	68 (81)	463 (453)
Any SAE	13 (3.6)	22 (25.6)	10 (2.7)	12 (13.8)	3 (3)	5 (14.1)	5 (6)	6 (5.9)
Any AE leading to discontinuation	10 (2.7)	12 (14)	7 (1.9)	7 (8)	2 (2)	2 (5.6)	8 (9.5)	10 (9.8)
Any severe AE	24 (6.6)	39 (45.5)	20 (5.4)	28 (32.1)	4 (4)	13 (36.7)	15 (17.9)	23 (22.5)
Any AE at least possibly related to study drug	99 (27)	191 (222.6)	106 (28.9)	224 (257.2)	25 (25.3)	47 (132.8)	39 (46.4)	139 (136)
Any SAE at least possibly related to study drug	2 (0.5)	4 (4.7)	3 (0.8)	3 (3.4)	2 (2)	4 (11.3)	1 (1.2)	1 (1)
Any infection	114 (31.1)	159 (185.3)	96 (26.2)	134 (153.8)	32 (32.3)	45 (127.1)	55 (65.5)	118 (115.5)
Any serious infection	2 (0.5)	2 (2.3)	3 (0.8)	4 (4.6)	1 (1.0)	1 (2.8)	1 (1.2)	1 (1.0)
Any opportunistic infection	0	0	0	0	0	0	0	0
Any TB	0	0	0	0	0	0	0	0
Any Lymphoma	0	0	0	0	0	0	0	0
Any NMSC	0	0	0	0	0	0	0	0
Any malignancy	1 (0.3)	1 (1.2)	1 (0.3)	1 (1.1)	0	0	0	0
Any demyelinating disorder	0	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0

Source: Modified from applicant's submission. Module 5.3.5.3.; ISS Table 21; page 230; Table 22; page 232; Clinical study report- interim M12-555, Table 39, page 399.

7.5.3 Drug-Demographic Interactions

Age

During Placebo Controlled Period, in subjects treated with adalimumab ew or eow, there was no difference in incidence by age [<40 years of age (younger) vs. ≥40 years (older)] of overall TEAEs, including SAEs, AEs leading to study drug discontinuation, AEs leading to death, and severe AEs.

Among subjects experiencing AESI, there was greater proportion of younger subjects (6%) who experienced injection site reaction compared to older subjects (1.4%). Similar results were observed in the placebo treated subjects.

Greater number of older subjects experienced the following common AEs compared to younger subjects:

- Pruritus: 4.3% in older subjects vs. 0.7% in younger.
- Lower respiratory tract infection: 1.4% in older subjects vs. 0% in younger
- Bronchitis: 1.4% in older subjects vs. 0.4% in younger
- Pyrexia: 1.4% in older subjects vs. 0.7% in younger
- Hordeolum: 0.7% in older subjects vs. 0% in younger

Discussion: Safety analysis of effects of drug treatment by age has not revealed consistent pattern of higher incidence of AEs in subjects in <40 years of age vs. subjects ≥40 years of age. For the AEs where there was a difference, number of events was small and definitive conclusions could not be drawn.

Sex

During Placebo Controlled Period, in subjects treated with adalimumab ew or eow, there was no difference in incidence by sex of overall TEAEs, including SAEs, AEs leading to study drug discontinuation, AEs leading to death, AESI and severe AEs.

There was higher incidence of female subjects who experienced the following common AEs compared to male subjects:

- Oropharyngeal pain: 3% in female subjects vs. 0% in male subjects.
- Gastroesophageal reflux disease: 2.2% in female subjects vs. 0% in male subjects.
- Muscle spasms: 1.5% in female subjects vs. 0% in males subjects.
- Nervous system disorders: 20% in female subjects vs. 11% in male subjects. The most frequently reported AE was headache: 15% in female subjects and 7% in male subjects.

In subjects treated with adalimumab ew, there was higher incidence of female subjects who experienced AESI of:

- Allergic reactions: 3% in female subjects vs. 0% of male subjects and

- Injection site reactions: 6% of female subjects vs. 3% of male subjects.

Discussion: Analysis of effects of drug treatment by sex did not reveal consistent pattern of higher incidence of AEs in subjects of either sex. For the AEs where there was a difference, number of events was small and definitive conclusions could not be drawn.

Race

During Placebo Controlled Period, in subjects treated with adalimumab ew or eow, there was no treatment by race difference (non-white vs white) in incidence of overall TEAEs (56.3% vs. 58.7%).

There was higher incidence the following AEs reported in non-white subjects compared to white subjects:

- AEs at least possibly related to study drug: 34.5% in non-white subjects vs. 27.7% in white subjects.
- SAEs: 6.9% in non-white subjects vs. 2.1% in white subjects. Similar results were observed in the placebo group.
- SAEs at least possibly related to study drug: 3.4% in non-white subjects vs. 0.3% in white subjects.
- Infections: 31% in non-white subjects vs. 27.4% in white subjects.
- Serious infections: 4.6% in non-white subjects vs. 0% in white subjects.

Discussion: Safety analysis of effects of drug treatment by race has revealed higher incidence of SAEs; SAEs possibly related to study drug and any AE possibly related to study drug. In addition, in non-white subjects there was increased incidence of infections including serious infections, compared to white subjects. These results may suggest racial differences in risk to developing significant AEs. However, there was a difference in sample size between non-white subjects (87) and white subjects (332), and definite conclusion could not be drawn.

BMI

During the Placebo Controlled Period, in subjects treated with adalimumab ew or eow, there was higher incidence of overall AEs in subjects with BMI ≥ 40 (67.1%) compared to subjects with BMI < 40 as well as the following AEs:

- Serious AEs: 4.1% in subjects with BMI ≥ 40 compared to 2.9% in subjects with BMI < 40 .
- AEs leading to discontinuation: 4.1% in subjects with BMI ≥ 40 compared to 2.9% in subjects with BMI < 40 .
- Severe AEs: 6.8% in subjects with BMI ≥ 40 compared to 5.5% in subjects with BMI < 40 .
- AE at least possibly related to study drug: 35.6% in subjects with BMI ≥ 40 compared to 27.8% in subjects with BMI < 40 .

- Infections: 41.1% in subjects with BMI \geq 40 compared to 25.5% in subjects with BMI $<$ 40.
- Upper respiratory tract infection: 9.6% in subjects with BMI \geq 40 compared to 4.1% in subjects with BMI $<$ 40.

Discussion: These results may suggest that subjects with higher BMI may have increased risk of developing adverse events. However, there was a difference in sample size between the two demographic groups, subjects with BMI $<$ 40 (73) and subjects with BMI \geq 40 (288), that prevented drawing definite conclusion.

Baseline Hurley Stage

During Placebo Controlled Period, the subgroup of subjects with Hurley Stage I were allowed only in study M10-467, and the number of subjects was $<$ 25 across treatment subgroups. Therefore, meaningful comparison between subgroups that included subjects with Hurley Stage I, could not be made. Comparison of incidence of AEs in subjects with Hurley Stage II vs. subjects with Hurley Stage III, did not reveal pattern or trend of difference between two subgroups.

7.5.4 Drug-Disease Interactions

During period B studies M11-313 and M11-810 a disease flare was reported in 21% of subjects who received adalimumab ew dosing in period A and switched to placebo during period B. Refer to section 7.6.4 for detailed information.

7.5.5 Drug-Drug Interactions

Specific *in vitro* or *in vivo* studies to evaluate the drug-drug interactions were not conducted during the hidradenitis development program.

Adalimumab is a cytokine modulator and as such may modify the formation and activity of CYP enzymes. Consequently, adalimumab may affect the metabolism or pharmacokinetics of small molecule drugs that are substrates for P450 enzyme. Section 7 DRUG INTERACTIONS, subsection 7.4 Cytochrome P450 Substrates of the adalimumab labeling contains the following general language: "The formation of CYP 450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α , IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP 450 enzymes. Upon initiation of discontinuation of HUMIRA in patients being treated with CYP 450 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."

In addition, adalimumab labeling contains recommendation against use of adalimumab in combination with anakinra, abatacept and other TNF inhibitors due to increased risk

of serious infections. Concomitant use of additional biologic products was not allowed during the conduct of hidradenitis studies.

The pharmacology reviewer, Dr. Jie Wang, recommended that the applicant evaluate whether adalimumab alters the PK or metabolism of CYP substrates in HS patients treated with adalimumab. It was recommended that evaluation includes but not limited to CYP3A4, CYP2C19, CYP2C9, CYP2D6 and CYP1A2. Dr. Wang recommended that this study be a part of postmarketing commitment.

Discussion: This reviewer agrees with the recommendation of Dr. Wang for additional drug-drug interaction study discussed above.

7.6 Additional Safety Evaluations

No additional safety evaluations were conducted.

7.6.1 Human Carcinogenicity

The risk of malignancy is a safety concern in patients treated with immunosuppressive products like adalimumab. **Section 5 WARNINGS AND PRECAUTIONS**, subsection **5.2 Malignancies** of adalimumab labeling contains information of increased risk of developing lymphomas and non-melanoma skin cancer.

During the development of adalimumab for hidradenitis indication, a total of 4 malignancies were reported: breast cancer; Hodgkin's lymphoma; seminoma; and squamous cell carcinoma of skin. No malignancies were reported in placebo only treated subjects. Additionally, one case of benign vocal cord neoplasm was reported.

Subject # (b) (6): Subject was a 36 year old white male who reported SAE of **Hodgkin's lymphoma** 148 days after the first dose of adalimumab ew in Study M12-555. The subject was on adalimumab ew/placebo during preceding Study M11-313. This SAE was considered by the investigator to be probably not related to study drug. The applicant assessed this case as possibly related to the study drug. Taking into consideration the duration of exposure and the known increased risk for developing lymphoma in patients treated with adalimumab, one case of Hodgkin's lymphoma, in this reviewer's opinion, is probably related to the treatment with adalimumab.

Subject # (b) (6): Subject was a 43 year old white female with pertinent history of smoking, alcohol use, and family history of breast cancer, reported **breast cancer** stage III, Day 297 (last dose of study drug on Day 162) in study M12-555. Subject was in placebo/adalimumab ew treatment group in the preceding Study M11-810. This adverse event was considered by investigator as not related to study drug. The applicant considered this malignancy as probably not related to study drug. Taking into consideration the high incidence of breast cancer among women in the US (124.6 per

100,000, age-adjusted, based on 2007-2011 SEER), the subject's positive family history of breast cancer and the duration of exposure, it is in this reviewer's opinion that causal relationship to study drug cannot be completely excluded.

Subject # (b) (6): Subject was 37 year old male with past history of smoking, reported testicular **seminoma**, on Day 421 in Study M12-555. Subject was in adalimumab ew/eow group during preceding Study M11-313. This malignancy was considered by the investigator as possibly related to study drug. The applicant considered this adverse event as probably not related to study drug. Taking into consideration the incidence of testicular cancer in the US (5.6 per 100,000 men per year, age adjusted, based on 2007-2011 SEER); subject's duration of exposure to adalimumab and generally long latency period for development of malignancies, it is in this reviewer's opinion that the relationship between the AE and the study drug, cannot be established with certainty.

Subject # (b) (6): Subject was a 36 year old white female with prior history of smoking, who reported **squamous cell carcinoma of skin**, 85 days after the first dose of adalimumab. Subject was treated with adalimumab ew/eow in study M11-810. This adverse event was considered probably not related to the study drug. Although treatment with adalimumab is associated with increased risk of developing skin cancer, it is in this reviewer's opinion that this adverse event is unlikely related to study drug given the short period of exposure.

Subject # (b) (6): Subject was a 26 year old white female with pertinent history of smoking who reported **benign vocal cord neoplasm** on Day 81 while on adalimumab ew in study M10-467. Given the timepoint at which this benign neoplasm was reported, it is in this reviewer's opinion that it is unlikely that the study drug was causative agent.

7.6.2 Human Reproduction and Pregnancy Data

During the development of adalimumab in hidradenitis indication, female subjects of childbearing potential were required to use effective methods of contraception during the participation in the trial and for additional 150 days after the last dose of study drug. A subject who became pregnant during the study was to be discontinued from study drug.

In hidradenitis trials, a total of 13 pregnancies were reported. Four subjects gave birth to live infants of whom 2 were reported as healthy and 2 did not have additional information.

One additional subject gave birth to a live premature infant. This subject developed pre-eclampsia 202 days after the last dose of study drug. The subject underwent emergency cesarean section and gave birth to premature 34-week infant. The investigator considered the event probably not related to the study drug.

Two subjects had ectopic pregnancies. One subject reported spontaneous abortion (subject # (b) (6) discussed below), two subjects underwent elective abortion and one subject gave birth to stillborn fetus (subject # (b) (6) discussed below).

At the time of study report, additional two subjects were still pregnant with no additional information was available.

Subject # (b) (6), a 35 year old female with prior history of gestational hypertension, delivered stillborn fetus 146 days after the last dose of the study drug. This subject developed gestational hypertension during pregnancy for which she underwent induced labor and delivery. Examination of placenta tissue showed features consistent with marked pregnancy-induced hypertension. The investigator considered this AE as not related to study drug.

Subject # (b) (6), a 29 year old female, had spontaneous abortion during the first trimester of pregnancy and 9 days after the last dose of the study drug. No additional information was available. The investigator assessed this AE as probably not related to study drug.

Adalimumab is labeled as Pregnancy Category B. Reports from hidradenitis studies do not suggest new safety signals. This reviewer recommends no changes of section **8.1 Pregnancy** of adalimumab labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

All trials supporting this application were conducted in adult subjects (18 years of age and older), for the population for whom the applicant seeks approval.

The applicant submitted their Initial Pediatric Study Plan (iPSP) on January 23, 2014. In their iPSP the applicant requested a full waiver of the requirement to conduct pediatric studies for the indication of treatment of moderate to severe hidradenitis suppurativa for the following reason: Necessary studies are impossible or highly impractical [21CFR 314.55 (c)(2)(ii)]. Applicant's submission was review by DDDP and presented to Pediatric Review Committee (PeRC) on March 19, 2014. Following PeRC meeting, the following comments were communicated to the sponsor:

- "Patients less than 12 years of age: we agree with a partial waiver
- For patients 12 to <16 and 11 months of age: we recommend deferral until you can collect and submit information on the natural history of the hidradenitis suppurativa in adolescents the treatment of HS in adolescents, and the incidence and prevalence of HS in adolescents, after which the decision to defer studies for pediatric patients 12 to less than 17 years can be reevaluated. Specify the protocol submission date, study initiation date, and final report submission date in your iPSP.

We are aware that you are planning to study natural history of HS through an observational disease registry in adult patients with HS. Consider inclusion of pediatric subjects 12 to <16 and 11 months of age into your observational study.”

The applicant agreed with the Agency’s recommendations and submitted their amended iPSP on June 4, 2014. In their submission, the applicant requested partial deferral of studies in adolescents age 12 to less than 17 in order to collect information on natural history of the hidradenitis suppurativa in adolescents, and the incidence and prevalence of HS in adolescents. In order to achieve this goal, the applicant planned the following:

1. Amending the current HS Disease Registry (Protocol H13-147) to permit adolescent subjects to participate in order to obtain information on the natural history of the disease and inform on the prevalence of patients with HS of severity that would require biologic therapy.
2. Survey of US dermatologists to confirm the number of potential adolescent patients ages 12 to 17 with moderate to severe HS available to participate in a clinical study
3. Review of the Phase 2 to 3 studies and registry to further elucidate onset of moderate to severe HS in the patients participating in the adult clinical studies
4. Confirmation of the claims database prevalence approach:
 - A diagnosis/chart review, and
 - Conducting a sensitivity analysis for HS prevalence by using a different US claims database
5. Review of US and international data from other sources (i.e., collaboration with other registries, etc.) including a comprehensive literature review

The applicant proposed the following timeline for the submission of their data:

- Protocol submission: 1 year after FDA approval of the adult indication for HS
- Study initiation date: 18 months after FDA approval of the adult indication for HS
- Final report submission: September 2021

The division agreed with the applicant’s plan to collect the information on adolescent population with HS and with the proposed timeline for conduct of study and submission of data. Applicant’s amended iPSP and division’s concurrence was presented to PeRC on 6/25/2014. The PeRC agreed with applicant’s iPSP. This agreement was communicated to the sponsor on June 30, 2014.

In this efficacy supplement, the applicant submitted PSP with a request of partial waiver of the requirement to conduct studies in pediatric patients up to 12 years of age, due to extremely low prevalence of the disease. In addition, the applicant is requesting a partial deferral of studies for adolescent patients from 12 to younger than 17 years of age to gather additional information on the natural history, treatment, and incidence and prevalence of hidradenitis suppurativa (HS) in adolescents. Additionally, the applicant proposed the timeline for the submission of their data. Current PSP is the same as iPSP upon which the Agency and the applicant agreed.

On May 13, 2015, the applicant's request for orphan-drug designation of adalimumab for the treatment of moderate to severe hidradenitis suppurativa was granted by the Office of Orphan Products Development. Therefore, this application for the new indication for the treatment of hidradenitis suppurativa is no longer subject to the Pediatric Research Equity Act of 2007, and the applicant will not be required to conduct studies in pediatric patients. No PMR or PMC will be issued for conduct of studies in children for adalimumab in the treatment of moderate to severe hidradenitis suppurativa.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant did not identify reports of adalimumab overdose in clinical studies for hidradenitis indication.

Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency for adalimumab.

The applicant stated that no withdrawal effects are anticipated with stopping adalimumab. In addition, the applicant stated that no rebound effect was found with discontinuation or decreased frequency of adalimumab administration and only deterioration in control of hidradenitis symptoms were noted.

Evaluation of reported AEs of hidradenitis revealed the highest incidence of AE of hidradenitis was reported in subjects who were switched from adalimumab ew to placebo at Week 12 of studies M11-313 and M11-810. The incidence of AE of hidradenitis in these subjects was higher when compared to subjects originally treated with placebo and continued on placebo after Week 12. In addition, incidence of AE of hidradenitis in subjects treated originally with adalimumab ew and switched to adalimumab eow, was higher when compared to placebo/placebo treated subject. These results suggest possible rebound of HS upon decrease of adalimumab dosing frequency or discontinuation of dosing.

Table 50: Incidence of Hidradenitis in Period B; Study M11-313 and Study M11-810

System organ class/PT	placebo/ placebo N=151 n (%)	PYs=36.5 Events (E/100PY)	placebo/ ew N=145 n (%)	PYs=54.5 Events (E/100PY)	ew/ placebo N=100 n (%)	PYs=31.8 Events (E/100PY)	ew/eow N=101 n (%)	PYs=33. 1 Events (E/100P Y)	ew/ew N=99 n (%)	PYs=35.4 Events (E/100PY)
Hidradenitis	14 (9)	16 (44)	16 (11)	16 (29)	20 (20)	23 (72)	18 (18)	19 (57)	5 (5)	7 (20)

Source: Modified from applicant's submission. Module 5.2.5.3., ISS, Section 5.2.2.1, Table 27, page 249; cross reference for Table 2.4_2.1.2.2 on page 2111 and Table 2.4_2.1.8 on page 2202.

Study Report Body M11-313, Section 12.2.2.2. cross reference on page 475 for Table 14.3_1.2.1.2 on page 4977 and Table 14.3_1.2.2.2, on page 5107. Study Report Body M11-810, Section 12.2.2.2., cross reference on page 445 for Table 14.3_1.2.1.2 on page and Table 14.3_1.2.2.2 on page

The applicant evaluated a “risk of flare” defined as at least 25% increase in AN counts with minimum increase of 2, relative to baseline. The proportion of subjects who experienced flare was higher in subjects switched from adalimumab ew to adalimumab eow or placebo (presented in Table below). These results indicate that decrease of dosing frequency or discontinuation of adalimumab may result in increase of disease severity beyond that present at the baseline.

Table 51: Proportion of Subjects Experiences a “Flare” in Abscess, Inflammatory Nodules, and Draining Fistulas; Study M11-313 and Study M11-810 (Period B)

Trial	Flare in Period B	Adalimumab ew/eow	Adalimumab ew/ew	Adalimumab ew/Placebo	Placebo/ew ¹ or Placebo/Placebo ²
M11-313	Abscess	6/48 (13%)	4/48 (8%)	12/49 (25%)	15/145 (10%)
	Inflammatory nodules	12/48 (25%)	9/48 (19%)	13/49 (27%)	35/145 (24%)
	Draining Fistulas	9/48 (19%)	12/48 (25%)	13/49 (27%)	26/145 (18%)
M11-810	Abscess	10/53 (19%)	10/51 (20%)	11/51 (22%)	41/151 (27%)
	Inflammatory nodules	13/53 (25%)	6/51 (12%)	13/51 (25%)	48/151 (32%)
	Draining Fistulas	12/53 (23%)	7/51 (14%)	10/51 (20%)	53/151 (35%)

Source: Statistical review. Flare is defined as 25% or more increase from baseline + minimum of 2 additional lesions. (1) for Study 313; (2) for Study 810

When analysis of flare in AN counts only was performed, flare occurred in approximately 22% of adalimumab treated subjects who switched to placebo during Period B of studies M11-313 and M11-810. Refer to statistical review by Carin Kim, Ph.D.

Table 52: Flare in Abscess and Inflammatory Nodules (AN) in Study M11-313 and M11-818 (Period B)

Trial	Flare in Period B	Adalimumab ew/eow	Adalimumab ew/ew	Adalimumab ew/Placebo	Placebo/ew ¹ or Placebo/Placebo ²
M11-313	AN	11/48 (23%)	8/48 (17%)	9/49 (18%)	25/145 (17%)
M11-810	AN	11/53 (21%)	6/51 (12%)	13/51 (25%)	56/151 (37%)

Source: Statistical review. Flare is defined as 25% or more increase from baseline + minimum of 2 additional lesions. (1) for Study 313; (2) for Study 810

The applicant assessed the worsening of disease by the proportion of subjects who experienced worsening by at least one Hurley Stage in at least 1 involved anatomic region, among subjects who had Hurley Stage <3 in at least one anatomical region, at baseline. The number of subjects who experienced worsening in Hurley Stage was

higher in subjects who switched from adalimumab ew to adalimumab eow or to placebo (presented in Table below). Again, these results are consistent with data discussed above.

Table 53: Proportion of Subjects who Experienced Worsening in Hurley Stage in at Least One Affected Anatomic Region (NRI) Among Subjects Who Have Hurley Stage <3 in at Least One Anatomic Region at Baseline (ITT_B_PRR Population)

Treatment	Total N	Responder n (%)	Non-Responder n (%)
ew/pbo	73	51 (69.9)	22 (30.1)
ew/eow	70	48 (68.6)	22 (31.4)
ew/ew	70	38 (54.3)	31 (44.3)

Source: Modified from applicant's submission. Module 5.3.5.3., ISE, Table 1.2_6.24.1, page 1843.

Discussion: Above discussed results show that worsening of hidradenitis occurred upon decrease in adalimumab dosing frequency or discontinuation of dosing. It is expected that worsening of the disease would occur with the withdrawal of treatment. However, upon discontinuation of adalimumab dosing, higher number of subjects in adalimumab ew/pbo group (21%) experienced worsening of the disease (a disease "flare") beyond baseline severity, (HS lesion count worsening or Hurley Stage) compared to adalimumab ew/eow or ew/ew. Additionally, worsening of Hurley Stage was more pronounced in subjects who were responders at Week 12 compared to nonresponders. This reviewer recommends that the risk of "flare" upon discontinuation of adalimumab or upon decrease of dosing frequency be included in product labeling.

7.7 Additional Submissions / Safety Issues

The cut-off date for safety data included in the original submission was April 29, 2014. The applicant submitted a 120-Day safety update HS on March 10, 2015 summarizing new safety information available from ongoing trial M12-555, as well as relevant information on previously reported SAEs. The 120-Day safety update includes additional safety information for subjects in the All Adalimumab Analysis Set through the cut-off date of November 10, 2014.

Overall, the exposure adjusted rate of TEAEs was similar to that in All Adalimumab Analysis Set reported in the ISS with the exception of one new death; increased rate of latent TB (four additional subjects with latent TB were detected during routine TB screening); and NMSC (three additional subjects reported NMSC).

The overview of number and percentage of subjects with TEAEs for All Adalimumab Analysis Set (reported in ISS) and safety update is presented in table below.

Table 54: Overview of Number and Percentage of Subjects with TEAEs for Studies M11-810, M11-313, M10-467, and M12-555 (All Adalimumab Analysis Set)-ISS and Safety Update

Category	ISS Adalimumab		Safety Update Adalimumab	
	N=727 n (%)	PY=635.7 Events E/100 PY	N=733 n (%)	PY=808.1 Events E/100 PY
Any AE	572 (78.7)	2975 (468)	591 (80.6)	3444 (426.2)
Any SAE	78 (10.7)	115 (18.1)	96 (13.1)	137 (17)
Any AE leading to discontinuation	70 (9.6)	84 (13.2)	86 (11.7)	1042 (12.9)
Any severe AE	107 (14.7)	169 (26.6)	120 (16.4)	197 (24.4)
Any AE at least possibly related to study drug	322 (44.3)	958 (150.7)	342 (46.7)	1076 (133.2)
Any SAE at least possibly related to study drug	20 (2.8)	26 (4.1)	23 (3.1)	30 (3.7)
Any infection	377 (51.9)	789 (124.1)	402 (54.8)	919 (113.7)
Any serious infection	21 (2.9)	25 (3.9)	24 (3.3)	28 (3.5)
Any opportunistic infection	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any TB	3 (0.4)	3 (0.5)	7 (1.0)	7 (0.9)
Any Lymphoma	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any NMSC	1 (0.1)	1 (0.2)	3 (0.4)	3 (0.4)
Any malignancy other than lymphoma, HSTCL, leukemia, NMSC of melanoma	3 (0.4)	3 (0.5)	4 (0.5)	4 (0.4)
Any demyelinating disorder	0	0	0	0
Any TEAE leading to death	2 (0.3)	2 (0.3)	3 (0.4)	3 (0.4)
Deaths	2 (0.3)	2 (0.3)	3 (0.4)	3 (0.4)

Source: Applicant's submission, 4-Mant Safety Update, Table 11, page 129.

One new **death** (Subject # (b)(6)) was discussed in section 7.3.1 of this review.

Twenty two additional TESAEs were reported by 18 subjects during 120-Day update. With the exception of SAEs of hidradenitis (6 additional cases), all other reported SAEs were reported in one additional subject each.

The incidence rate of AEs that led to discontinuation during 120-Day update was similar to that reported in the All Adalimumab Analysis Set in ISS. Sixteen additional subjects discontinued due to AEs during 120-Day update. With the exception of hidradenitis

(discontinued by 6 subjects), all other AEs that led to discontinuation were reported by one additional subject each.

The incidence rate of AESI during 120-Day update was similar to that reported in the All Adalimumab Analysis Set in ISS, with exception of increase incidence of latent TB and malignancy. The overview of number and percentage of subjects with AESIs for All Adalimumab Analysis Set (reported in ISS) and safety update is presented in table below.

Table 55: Overview of Number and Percentage of Subjects with AESI for Studies M11-313, M11-810, M10-467 and M12-555 (all Adalimumab Analysis Set)-ISS and Safety Update

Category	ISS Adalimumab		Safety Update Adalimumab	
	N=727 n (%)	PY=635.7 Events E/100 PY	N=733 n (%)	PY=808.1 Events E/100 PY
Any diverticulitis	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.2)
Any oral candidiasis	3 (0.4)	3 (0.5)	4 (0.5)	4 (0.5)
Any latent TB	3 (0.4)	3 (0.5)	7 (1.0)	7 (0.9)
Any parasitic infection	3 (0.4)	3 (0.5)	4 (0.5)	4 (0.5)
Any malignancy	5 (0.7)	5 (0.8)	8 (1.1)	8 (1.0)
Any allergic reaction including angioedema /anaphylaxis	27 (3.7)	35 (5.5)	32 (4.4)	44 (5.4)
Any lupus-like reactions and SLE	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any MI	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any CVA	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.2)
Any CHF	3 (0.4)	3 (0.5)	3 (0.4)	3 (0.4)
Any pulmonary embolism	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any ILD	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any erythema multiforme	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Any worsening /new onset of psoriasis	23 (3.2)	27 (4.2)	31 (4.2)	35 (4.3)
Any hematologic disorders including pancytopenia	22 (3.0)	26 (4.1)	22 (3.0)	26 (3.2)
Any liver failure and other liver event	3 (0.4)	3 (0.5)	5 (0.7)	6 (0.7)
Any injection site reaction	54 (7.4)	107 (16.8)	58 (7.9)	113 (14.0)

Source: Applicant's submission, 4-Mant Safety Update, Table 20, page 177.

Malignancies

During 120-Day update period, 3 new malignancies were reported: 2 squamous cell carcinoma of skin and one basal cell carcinoma of skin.

Serious infections

During 120-Day update there were 3 additional serious infections reported: one new case of peritonsillar abscess and one additional case each of pilonidal cyst and pneumonia.

Discussion: During 120-Day update, no increase of rates of AEs or new safety signals, were recognized.

8 Postmarket Experience

The international birth date (IBD) for adalimumab is December 31, 2002. Adalimumab was originally approved for the treatment of rheumatoid arthritis. Since then, adalimumab was approved in the US for the following indications: juvenile idiopathic arthritis, psoriatic arthritis, adult Crohn's disease, pediatric Crohn's disease, plaque psoriasis, ankylosing spondylitis, ulcerative colitis. The estimated cumulative postmarketing exposure since the IBD through 31 December 2013 is 2.9 million PYs. The applicant is monitoring for potential new safety signals through postmarketing surveillance. The surveillance includes reports of serious adverse events from clinical studies, all spontaneous reports, the literature, regulatory agencies, postmarketing studies, and registries. The applicant sponsored adalimumab safety registries that are currently ongoing with more than 32,000 adult and pediatric patients. The applicant states that new safety risks identified from the postmarketing experience are reflected in the current labeling for the product. The type and severity of AEs reported in clinical trials for HS are consistent with postmarketing safety experience with adalimumab in the approved adult indications.

9 Appendices

9.1 Literature Review/References

1. Terzin V, Földesi I, Kovács L, Pokorny G, Wittmann T, Czakó L. Association between autoimmune pancreatitis and systemic autoimmune diseases. *World J Gastroenterol*. 2012 Jun 7;18 (21):2649-53
2. Sauder MG, Gassman SJ. Clinical management of paradoxical psoriasiform reaction during TNF- α therapy. *Actas Dermosifiliogr*. 2014 Oct. 105 (8): 752-61.
3. Shmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor- α inhibitors: the Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol*. 2012 Nov; 67 (5): e179-85.

9.2 Labeling Recommendations

For Section **14CLINICAL STUDIES, subsection 14.9** Hidradenitis Suppurativa this reviewer recommends the following wording regarding rebound effect:
During Period B of Studies HS-I and HS-II, flare of HS, defined as $\geq 25\%$ increase from baseline in abscess and inflammatory nodule counts and with minimum of 2 additional lesions, was documented in 22 of the 100 Humira treated subjects who were re-randomized to placebo.

9.3 Advisory Committee Meeting

BLA 125057/S393 was not presented to the Dermatology Drug Advisory Committee because no safety or efficacy issues were identified that would warrant advisory committee input.

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/s/

SNEZANA TRAJKOVIC
07/20/2015

JILL A LINDSTROM
07/30/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

CHEMISTRY 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: July 06, 2015
To: File for STN: sBLA 125057/393
RPM: Cristina Attinelle, CDER/ODEIII/DDDP
From: Jun Park, Ph.D., Product Reviewer, CDER/OBP/DBRR II
Through: Juhong Liu, Ph.D., Acting Review Chief, CDER/OBP/DBRR II
Applicant: AbbVie, Inc.
Product: Humira® (adalimumab)
Supplement Receipt Date: November 10, 2014
PDUFA Date: September 10, 2015

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 active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

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 requests a categorical exclusion from the requirement for environmental assessment for this sBLA.

This BLA efficacy supplement is approvable from a CMC perspective. There are no CMC-related PMRs 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
07/08/2015

JUHONG LIU
07/08/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

PHARMACOLOGY 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: 125057
Supporting document/s: 4877, 4970 [Supplement 393 (Efficacy)]
Applicant's letter date: November 10, 2014, January 3, 2015
CDER stamp date: November 10, 2014, January 3, 2015
Product: Humira (adalimumab) injection
Indication: Hidradenitis suppurativa
Applicant: AbbVie Inc.
Review Division: DDDP
Reviewer: Barbara Hill, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Kendall Marcus, MD
Project Manager: Cristina Attinello

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125057 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 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.

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1 Executive Summary

1.1 Introduction

This efficacy supplement provides clinical data from four clinical studies intended to support an indication for use in adult patients with moderate to severe hidradenitis suppurativa.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were included in this efficacy supplement. Humira was originally approved for the treatment of rheumatoid arthritis on December 31, 2002. Humira subsequently received approval for the treatment polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis and ulcerative colitis.

1.3 Recommendations

1.3.1 Approvability

BLA 125057/393 is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The nonclinical sections of the Humira label included in this efficacy supplement are provided below. The only change made to the nonclinical sections of the label is the addition of one sentence in Section 12.1. The acceptability of this additional sentence will be determined by the Clinical and Clinical Pharmacology review team.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

Reviewer's comments: The pharmacologic class for Humira is correct.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy

and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (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 blood, and 0-16.1 µg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had 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

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab.

Reviewer's comments: No changes were made to Section 8.1 of the Humira label.

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. *Increased levels of TNF are also found in hidradenitis suppurativa lesions. 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 IC50 of 1-2 X 10⁻¹⁰M).

Reviewer's comments: One sentence was added (annotated in italics font) near the end of the first paragraph in Section 12.1. Pharmacology/Toxicology recommends that this sentence be deleted from the label because it does not provide any useful information concerning mechanism of action. However, the acceptability of this sentence will be determined by the Clinical and Clinical Pharmacology review team.

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. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

Reviewer's comments: No changes were made to Section 13.1 of the Humira label.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

331731-18-1

Generic Name

Adalimumab

Code Name

N/A

Chemical Name

Adalimumab

Molecular Formula/Molecular Weight

C₆₄₂₈H₉₉₁₂N₁₈₉₄O₁₉₈₇S₄₆/144190.3 g/mol

Structure or Biochemical Description

Human IgG1 anti-TNF monoclonal antibody

Pharmacologic Class

Tumor necrosis factor (TNF) blocker; Human IgG1 anti-TNF monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 102320 (adalimumab, hidradenitis suppurativa)

2.3 Drug Formulation

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/0.8 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.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The proposed dosing regimen for the treatment of hidradenitis suppurativa is provided below.

- 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 week

2.7 Regulatory Background

The original IND for this indication was submitted on August 18, 2008. An End of Phase 2 meeting was conducted on January 19, 2011. A Pre-Phase 3 meeting was conducted on April 13, 2011. A Pre-sBLA meeting was conducted on July 30, 2014.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted in this efficacy supplement.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Adalimumab is a fully human antibody that binds specifically to TNF- α and neutralizes the biological function of TNF- α by blocking its interaction with the p55 and p75 cell surface TNF- α receptors.

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new nonclinical pharmacokinetic studies were included in this efficacy supplement. Refer to the Humira label for a summary of clinical pharmacokinetic data available for Humira.

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

No new nonclinical repeat dose toxicity studies were included in this efficacy supplement. The nonclinical toxicity profile has been previously well established in the

original BLA submission. The primary clinical adverse events for Humira that are contained in a boxed warning in the Humira label include serious infections and malignancy.

7 Genetic Toxicology

The following information concerning adalimumab genotoxicity is included in the Humira label.

“No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.”

8 Carcinogenicity

The following information concerning adalimumab carcinogenicity is included in the Humira label.

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

9 Reproductive and Developmental Toxicology

The following information concerning adalimumab effects on fertility is included in the Humira label.

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

The following information concerning adalimumab effects on reproductive and developmental toxicology is included in the Humira label.

“Pregnancy Category B

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (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 blood, and 0-16.1 µg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had 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

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab.”

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

This efficacy supplement did not contain any new nonclinical studies. No new nonclinical studies are needed for this efficacy supplement. A review of the nonclinical sections of the Humira label is provided in Section 1.3.3 of this review.

12 Appendix/Attachments

None

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/s/

BARBARA A HILL
07/08/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

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 #: sBLA 125057/393

Drug Name: Humira (adalimumab)

Indication(s): Treatment of adult patients with moderate to severe hidradenitis suppurativa

Applicant: AbbVie Inc.

Date(s): Stamp date: 11/10/2014;
PDUFA: 9/10/2015

Review Priority: Standard

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Carin Kim, Ph.D.

Concurring Reviewers: Mohamed Alosh, Ph.D.

Medical Division: Division of Dermatology and Dental Products (DDDP)

Clinical Team: Snezana Trajkovic, M.D.
Jill Lindstrom, M.D.

Project Manager: Cristina Attinello

Keywords:
Hidradenitis Suppurativa, Superiority

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1. EXECUTIVE SUMMARY

The applicant, AbbVie, submitted results of two Phase 3 trials (Trials 313 and 810) to support the safety and efficacy of Humira (adalimumab) for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).

The SPA-agreed upon primary endpoint was the “proportion of subjects achieving HS clinical response (HiSCR) at Week 12” where HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess and no increase of draining fistula count. Efficacy results for the primary endpoint were statistically significant ($p=0.003$ and <0.001 for Trials 313 and 810, respectively). Although the two trials showed statistically significant findings for the primary endpoint, the treatment effect in Trial 810 was almost twice as that of Trial 313 (31% vs. 16%). This differential treatment effect was also shown for the secondary endpoint of the proportion of subjects with abscess and inflammatory nodules (AN) count of 0, 1, 2 at Week 12 among those with baseline Hurley Stage II. For the analysis of this secondary endpoint, Trial 313 did not achieve statistical significance ($p=0.961$) whereas Trial 810 did ($p=0.006$).

Table 1 presents the efficacy results for the primary endpoint, the proportion of subjects achieving HS clinical response (HiSCR) at Week 12 where HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess and no increase of draining fistula count, for the intent to treat (ITT) population with missing data imputed as non-responders (NRI).

Table 1. Proportion of subjects achieving HiSCR at Week 12 (ITT; NRI)

	Trial 313		Trial 810	
	Humira N=153	Placebo N=154	Humira N=163	Placebo N=163
Primary endpoint	64 (42%)	40 (26%)	96 (59%)	45 (28%)
p-value ⁽¹⁾	0.003		<0.001	

Source: Reviewer’s results. (1) CMH by Hurley Stage at baseline (Study 313), and CMH by Hurley Stage at baseline and concomitant use (Study 810).

In an attempt to explain the differential treatment effects across the two trials, the background factors including the disease severity for subjects in the two trials were compared. This comparison showed that subjects enrolled in Trial 810 had lower baseline disease severity, as reflected in the baseline AN counts, compared to those in Trial 313. In addition, about 19% of the subjects in Trial 810 were allowed to continue their baseline concomitant antibiotic use.

While this observation about the differences in the baseline AN counts across the two trials may explain the difference in the findings for the secondary endpoint of the proportion of subjects with AN counts of 0, 1, 2 at Week 12 among those with baseline Hurley Stage II, it appeared such difference in the baseline disease severity did not explain the difference in the primary endpoint. With that, we considered investigating the

treatment effect by study centers, and findings from such investigation showed that Trial 313 had more variability in response rates compared to those of Trial 810.

As the first secondary endpoint of the proportion of subjects with AN counts of 0, 1, 2 among those with baseline Hurley Stage II for Trial 313 was not statistically significant, this prevented further analyses of the other secondary endpoints as the Type I error rate would not be controlled for.

2. INTRODUCTION

2.1 Overview

The applicant submitted results from two Phase 3 trials (Trials 313 and 810) to support the efficacy and safety of Humira for the treatment of moderate to severe hidradenitis suppurativa (HS). The two trials differed in that (i) Trial 810 had approximately 20% of subjects that continued baseline oral antibiotic therapy during the study, and (ii) in the maintenance period (noted as Period B, Weeks 12-36) while placebo subjects were treated with Humira 40 mg every week (EW) in Trial 313, the placebo subjects in Trial 810 continued to receive placebo.

The following table is a clinical study overview for the two pivotal trials.

Table 2. Clinical Study Overview for the Pivotal Trials (313 and 810)

Study	Study Sites	Study Population	Treatment Arms	N	Dates
313 (N=307)	54 international centers	<ul style="list-style-type: none"> • Age \geq18, • A diagnosis of HS for at least 1 year, HS lesions present in at least 2 distinct anatomic areas, one of which was Hurley Stage II or III, 	Humira	153	11/29/2011 -
			Placebo	154	1/28/2014
810 (N=326)	65 international centers	<ul style="list-style-type: none"> • inadequate response to at least 3-month oral antibiotics for treatment of HS, • AN count \geq 3 at baseline. 	Humira	163	12/28/2011 -
			Placebo	163	4/28/2014

Source: Reviewer table.

2.2 Regulatory History

The clinical development program for Humira for the treatment of moderate to severe HS was conducted under IND 102320.

There was an End of Phase 2 meeting on 1/19/2011, a Pre Phase 3 teleconference with the sponsor on 4/27/2011. Following the Pre-Phase 3 teleconference, the two pivotal Phase 3 trials were the subject of a Special Protocol Assessment (SPA) and the SPA

Agreement Letter was sent to the sponsor on 8/4/2011. Per the SPA Agreement Letter, the Agency and the sponsor agreed to the general designs of Trials 313 and 810, the primary endpoint, the primary analysis method, the definition of Intent to Treat (ITT) population, the primary imputation method along with the proposed sensitivity analyses, and the sequential approach for analyzing the secondary endpoints to control multiplicity. Further, the Agency agreed to the sponsor's proposal to analyze the efficacy results from Period B (Weeks 12-36) as exploratory; however, the Agency stated that safety data from Period B would be part of overall safety evaluation of the sponsor's product for this indication.

Specifically, on the SPA Agreement Letter, the Agency stated that the sponsor should "adequately propose a plan to evaluate and measure inflammatory lesions for size, erythema, and tenderness, and evaluate worsening of lesions that do not progress into next stage:

- Increase in size, erythema, or tenderness of nodule that does not progress into abscess
- Increase in size, erythema, or tenderness of abscess that does not progress into fistula
- Increase in length of fistulas and tracks, or progression of non-draining to draining fistula and tracks".

For non-agreements, while the Agency noted that while the sponsor's approach to identifying the appropriate subject population was generally acceptable, the clinical meaningfulness of the sponsor's proposed inclusion criterion of baseline lesion count of only 3 or 4 was not clear, and that such inclusion criterion might make it difficult to interpret efficacy results if too large of a proportion of subjects had such low baseline lesion counts.

On 7/2/2014, there was a Guidance Meeting was held between the Agency and the sponsor to discuss the format of the Case Report Tabulation datasets (CRTs), Analysis-Ready Datasets (ARDs), and Analysis-Ready Programs (ARPs), and there was a Pre-BLA meeting between the Agency and the sponsor to discuss the planned sBLA submission on 7/30/2014.

On 11/10/2014, the applicant submitted a sBLA submission, and on 5/13/2015, Humira was granted orphan designation for the proposed HS indication.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: \\cdsesub1\evsprod\bla125057\0340\m5\datasets\.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary objective of the trials was to determine the clinical safety and efficacy of Humira compared to placebo in subjects with moderate to severe HS after 12 weeks of treatment.

A secondary objective of the trials was to evaluate safety and efficacy for continuous weekly dosing versus dose reduction versus maintenance of response off therapy from Week 12 to Week 36.

For enrollment, subjects ≥ 18 years of age and older, with a diagnosis of HS for at least 1 year prior to baseline, HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which was Hurley Stage II or III, had inadequate response to at least 3-month trial of oral antibiotics for treatment of HS, stable HS for at least 2 months prior to screening and also at the baseline visit, and had a total of abscess and inflammatory nodules (AN) count ≥ 3 at baseline were enrolled.

The applicant provided the following Hurley Stage descriptions:

Hurley Staging	Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
	Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars). A subject with at least 1 anatomic region with Hurley Stage II disease and with no anatomic regions with Hurley Stage III disease was classified as Hurley Stage II.
	Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement. A subject with at least 1 anatomic region with Hurley Stage III disease was classified as Hurley Stage III.

Source: applicant's study report

In both Trials 313 and 810, there were two periods:

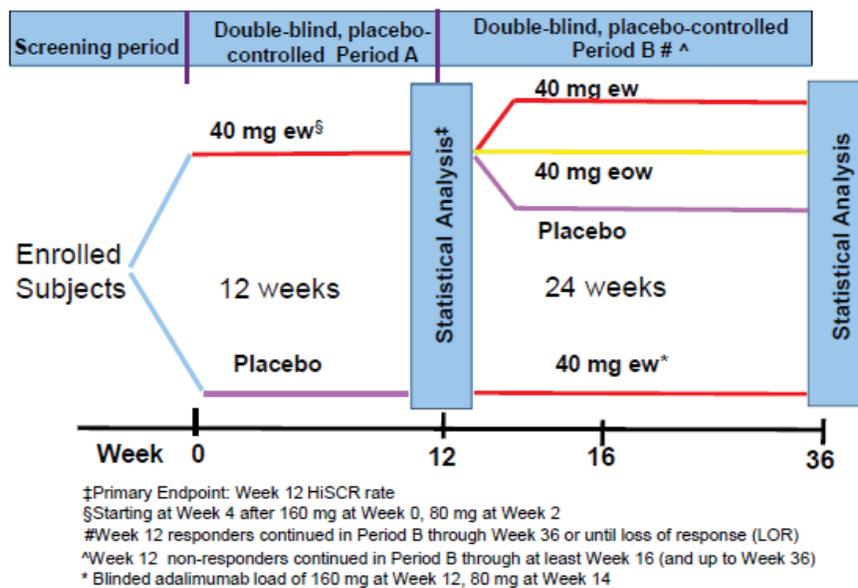
- **Period A** (12 weeks): randomized subjects stratified by baseline Hurley Stage (II or III) in a 1:1 ratio:
 - Adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week (EW)
 - Placebo

- **Period B** (24 weeks): re-randomized all subjects that completed Period A in a 1:1:1 ratio. Re-randomization was stratified by Week 12 Hidradenitis Suppurativa Clinical Response (HiSCR) [response vs. non-response], and by baseline Hurley Stage (II or III):
 - Adalimumab 40 mg EW
 - Adalimumab 40 mg every other week (EOW)
 - Placebo.

The protocol specified that for Trial 313, subjects randomized to placebo in Period A received adalimumab 40 mg EW, and for Trial 810, placebo subjects in Period A received placebo in Period B.

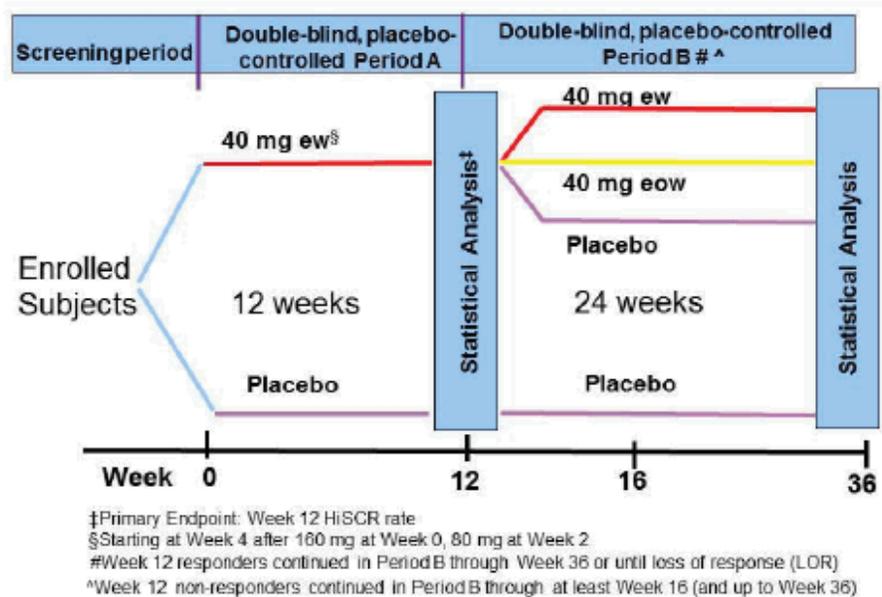
The following is a study design schematic for the pivotal trials.

Figure 1. Applicant’s study design schematic (Trial 313)



Source: applicant’s submission.

Figure 2. Applicant’s study design schematic (Trial 810)



Randomization was done using the Interactive Voice Response System/Interactive Web Response System (IXRS). The protocol called for randomization stratified by baseline Hurley Stage (II vs. III) for Trial 313 and by baseline Hurley Stage (II vs. III) and concomitant antibiotics use (yes vs. no) for Trial 810. According to the protocols for both trials, the number of subjects in Hurley Stage III was not to exceed 150 (50% of the total planned number of subjects), and the number of subjects with an AN count of 3 or 4 was not to exceed 60 (20% of the total planned number of subjects). For Trial 810 which allowed concomitant use of permitted oral antibiotic therapy for treatment of HS, provided that the dosing regimen had been stable for at least 4 consecutive weeks (28 days) prior to baseline, the number of subjects who were on baseline concomitant antibiotics was not to exceed 90 (30% of the total planned number of subjects (page 248). The protocol specified that the permitted oral concomitant antibiotics included:

- Doxycycline (dose up to 100 mg by mouth BID)
- Minocycline (dose up to 100 mg by mouth BID)

The protocol defined the Loss of Response (LOR) and “Worsening or Absence of Improvement as below”:

- “loss of response” (LOR) in Period B was defined as those with an abscess and inflammatory nodule (AN) count that was greater than the average of AN counts at baseline and Week 12. Subjects who experience LOR discontinued from the study, and had the opportunity to enter an open-label extension study (M122-555) to receive adalimumab 40 mg EW.
- Worsening or Absence of Improvement was defined as an AN count that was greater than or equal to the AN count at baseline on 2 consecutive visits

The applicant's calculation of the Sartorius Scale was provided in Appendix A of the protocol.

1. Collect lesion counts in 12 anatomic regions: left axilla, right axilla, left sub/inframammary area, right sub/inframammary area, intermammary area, left buttock, right buttock, left inguinal (crural) fold, right inguinal (crural) fold, perianal, perineum, other.
2. For each anatomic region, calculate the regional Sartorius score as follows.

Regional Sartorius Score = Region

- +2* number of inflammatory nodules
- +2* number of non-inflammatory nodules
- +4*number of abscesses
- +4*number of draining fistulas
- +4*number of non-draining fistulas
- +1*number of hypertrophic scars
- + distance
- + separate

where

Region = 3, if any lesion count in this anatomic region > 0,
= 0, otherwise,

Distance = 0 if no active lesion,
2, if longest distance between two relevant lesions or size < 50 mm
4, if longest distance between two relevant lesions or size ≥ 50 mm and < 100 mm
6, if longest distance between two relevant lesions or size ≥ 100 mm.

3. The total Sartorius score would be the sum of 12 regional Sartorius scores.

For the analysis of the secondary endpoints, the protocol specified that the categorical variables were analyzed using the CMH test adjusted for baseline Hurley Stage (and concomitant use of oral antibiotics for Trial 810), and the continuous variables analyzed using ANCOVA with baseline value, and baseline Hurley Stage (and concomitant use of oral antibiotics for Trial 810).

To control the Type I error rate, secondary endpoints were adjusted for multiplicity using a sequential approach, and this was agreed upon per the SPA letter (dated: 8/4/2011).

For handling missing data, the primary imputation method was to impute missing as non-responders. If a subject used a rescue medication, then the subject was considered as non-responder. As sensitivity analyses, the applicant also used the last observation carried forward (LOCF) as well as multiple imputation.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

In both trials, for Period A (first 12 weeks), about 6% of the subjects discontinued the trial. The most common reason for discontinuation was withdrawal of consent, followed by adverse events.

Table 3. Subject Disposition (Period A – First 12 weeks)

	Trial 313		Trial 810	
	Humira	Placebo	Humira	Placebo
Randomized	153	154	163	163
Discontinued	8 (5%)	7 (5%)	8 (5%)	12 (7%)
<i>Adverse Events</i>	0	1	3	5
<i>Withdrew consent</i>	4	4	4	3
<i>Lack of efficacy</i>	1	2	-	-
<i>Loss to Followup</i>	-	-	0	3
<i>Exceeded protocol-specified number of interventions</i>	1	0	-	-
<i>Protocol violation</i>	1	0	-	-
<i>Other</i>	2	0	1	1

Source: Applicant's table

For Period B (weeks 12-36), in both trials, the discontinuation rate was high (above 40%) and Humira-treated subjects that were re-randomized to placebo in Period B had higher discontinuation rates (55%). According to the study report, the most common reason for discontinuation was “per IXRS instruction” where subjects meeting the criterion of loss of response (LOR) or worsening or absence of improvement (WOAI) were requested by the IXRS system to discontinue from the study and enter the open-label extension study, Study M12-555.

Per the SPA agreement letter, the data in Period B were explored as part of the overall safety evaluation, and these are discussed in Section 3.4 of this review.

Table 4. Subject Disposition for Trial 313 (Period B: Weeks 12-36)

	Trial 313			
	Humira EW/EW	Humira EW/EOW	Humira EW/placebo	Placebo/EW
Randomized	48	48	49	145
Discontinued	20 (42%)	21 (44%)	27 (55%)	52 (36%)
<i>Adverse Events</i>	1	2	2	6
<i>Withdrew consent</i>	2	1	-	6
<i>Lack of efficacy</i>	2	2	3	1
<i>Loss to Followup</i>	-	1	1	6
<i>Per IXRS instruction⁽¹⁾</i>	14	18	24	31
<i>Exceeded protocol-specified number of interventions</i>	-	-	-	-
<i>Protocol violation</i>	-	-	-	-
<i>Other</i>	3	1	1	7

Source: Applicant's table

- (1) According to the study report, subjects meeting the criterion of loss of response (LOR) or worsening or absence of improvement (WOAI) were requested by the IXRS system to discontinue from the study and enter the open-label extension study, Study M12-555.

Table 5. Subject Disposition for Trial 810 (Period B: Weeks 12-36)

	Trial 810			
	Humira EW/EW	Humira EW/EOW	Humira EW/placebo	Placebo/Placebo
Randomized	51	53	51	151
Discontinued	23 (45%)	28 (53%)	28 (55%)	111 (74%)
<i>Adverse Events</i>	1	2	-	4
<i>Withdrew consent</i>	1	1	2	11
<i>Lack of efficacy</i>	3	1	2	17
<i>Loss to Followup</i>	-	2	-	3
<i>Per IXRS instruction⁽¹⁾</i>	21	22	26	88
<i>Exceeded protocol-specified number of interventions</i>	-	-	-	-
<i>Protocol violation</i>	-	-	-	-
<i>Other</i>	-	1	-	4

Source: Applicant's table

- (1) According to the study report, subjects meeting the criterion of loss of response (LOR) or worsening or absence of improvement (WOAI) were requested by the IXRS system to discontinue from the study and enter the open-label extension study, Study M12-555.

Table 6 presents the baseline demographics for the two Phase 3 trials (313 and 810). The baseline demographics were generally balanced across the treatment arms for the two trials. Approximately 67% of the subjects were female and 33% were male, and approximately 80% were Caucasians. Only 7 subjects were of the age ≥ 65 years, and the rest of the enrolled subjects were <65 years of age.

Table 6. Baseline demographic characteristics

	Trial 313		Trial 810	
	Adalimumab N=153	Placebo N=154	Adalimumab N=163	Placebo N=163
Sex				
<i>Female</i>	91 (60%)	105 (68%)	108 (66%)	113 (69%)
<i>Male</i>	62 (41%)	49 (32%)	55 (34%)	50 (31%)
Race				
<i>White</i>	116 (76%)	118 (77%)	143 (88%)	130 (80%)
<i>Black</i>	33 (22%)	29 (19%)	9 (6%)	20 (12%)
<i>Asian</i>	1 (1%)	3 (2%)	6 (4%)	4 (3%)
<i>Other</i>	3 (2%)	3 (2%)	5 (3%)	9 (6%)
Age				
< 65	152 (99%)	152 (99%)	162 (99%)	160 (98%)
≥ 65	1 (1%)	2 (1%)	1 (1%)	3 (2%)

Source: Applicant's table.

Table 7 presents the baseline disease severity for the two Phase 3 trials (313 and 810). Approximately 53% of the subjects were of Hurley Stage II at baseline. Within each trial, there were no noticeable imbalance in the mean, median values for the AN, abscess, draining fistula, and the inflammatory nodule counts across the treatment arms. However, subjects enrolled in Trial 313 generally had higher baseline disease severity than those in Trial 810 as reflected by the mean, median AN, abscess, draining fistula, inflammatory

nodule counts. Further, a larger proportion of subjects in Trial 313 (53%) had a baseline AN counts ≥ 11 compared to those in Trial 810 (36%). The impact of such difference in the baseline AN counts across the two trials were further investigated in Section 3.2.3 of this review.

Table 7. Baseline Disease Severity

	Trial 313		Trial 810	
	Adalimumab N=153	Placebo N=154	Adalimumab N=163	Placebo N=163
Hurley Stage				
II	80 (52%)	81 (53%)	86 (53%)	89 (55%)
III	73 (48%)	73 (47%)	77 (47%)	74 (45%)
Baseline AN ⁽¹⁾ count				
≤ 5	24 (16%)	36 (23%)	47 (29%)	50 (31%)
6-10	54 (35%)	33 (21%)	61 (37%)	51 (31%)
≥ 11	75 (49%)	85 (55%)	55 (34%)	62 (38%)
AN ⁽¹⁾ Count				
Mean \pm SD	14.3 \pm 11.9	14.4 \pm 14.8	10.7 \pm 8.1	11.9 \pm 11
Median	10	11	8	8
Range	3-78	3-141	3-50	3-66
Abscess count				
Mean \pm SD	2.8 \pm 3.5	2.7 \pm 3.7	2.0 \pm 2.6	2.4 \pm 3.3
Median	2.0	2	1	1
Range	0-17	0-24	0-13	0-16
Draining Fistula count				
Mean \pm SD	4.6 \pm 5.2	3.8 \pm 4.4	3.0 \pm 4.1	3.7 \pm 5.2
Median	3	2	1	1
Range	0-20	0-20	0-20	0-20
Inflammatory Nodule Count				
Mean \pm SD	11.5 \pm 10.9	11.6 \pm 13.9	8.6 \pm 6.9	9.4 \pm 9.6
Median	8	7	6	6
Range	0-76	0-138	0-42	0-62

(1) AN: Abscess and inflammatory nodule
Source: Applicant's table.

3.2.3 Results and Conclusions

3.2.3.1 Week 12 Efficacy Results

In both Trials 313 and 810, Humira was superior to placebo at Week 12 ($p=0.003$ and $p<0.001$, respectively) for the primary endpoint of the proportion of subjects achieving HiSCR (Hidradenitis Suppurativa Clinical Response) at Week 12.

Table 8 presents the efficacy results for the primary endpoint, the proportion of subjects achieving HS clinical response (HiSCR) at Week 12 where HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess and no increase of draining fistula count, for the intent to treat (ITT) population with missing data imputed as non-responders (NRI). It should be noted that as the proportion of missing data was relatively small across the treatment arms (i.e., 6%), and the use of an alternative method

for imputation such as the last observation carried forward (LOCF) gave similar results to those reported in Table 8.

Table 8. Proportion of subjects achieving HiSCR at Week 12 (ITT; NRI)

Trial 313			Trial 810		
	Humira N=153	Placebo N=154		Humira N=163	Placebo N=163
Primary endpoint	64 (42%)	40 (26%)	Primary endpoint	96 (59%)	45 (28%)
p-value ⁽¹⁾	0.003		p-value ⁽¹⁾	<0.001	
by Hurley Stage ⁽²⁾			by Hurley Stage and by concomitant antibiotics use		
II	35/80 (44%)	23/81 (28%)	No	47/75 (63%)	30/76 (39%)
			Yes	7/11 (64%)	3/13 (23%)
III	29/73 (40%)	17/73 (23%)	No	29/57 (51%)	8/56 (14%)
			Yes	13/20 (65%)	4/18 (22%)

Source: Reviewer table.

(1) CMH by Hurley Stage at baseline (Study 313), and CMH by Hurley Stage at baseline and concomitant use (Study 810);

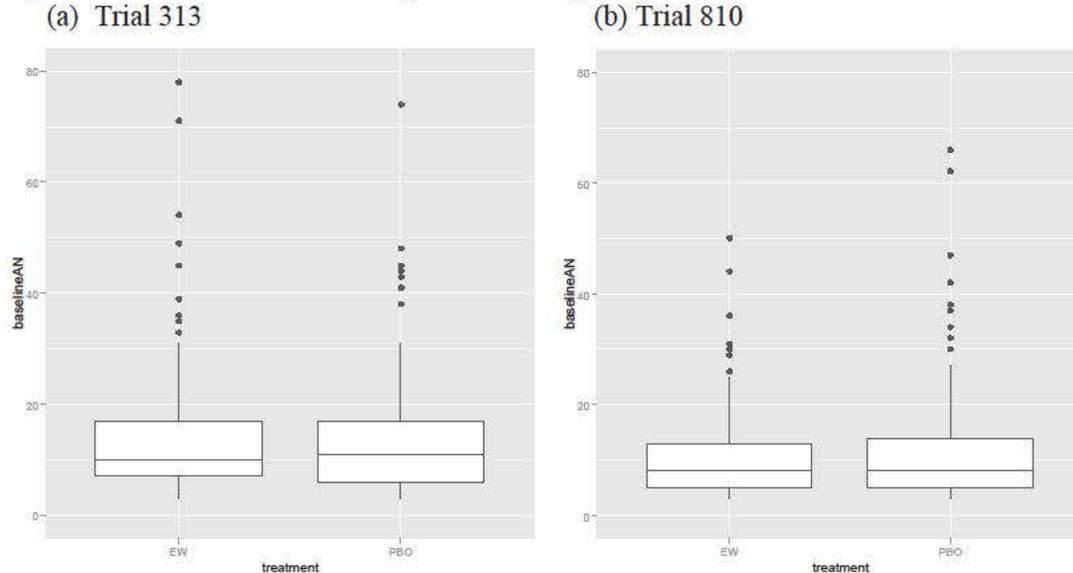
(2) the applicant stated that they used the Hurley Stage at randomization instead of the baseline Hurley Stage value. As a result, in Trial 313, 3 subjects in each treatment arm were allocated from Hurley Stage III to II, and in Trial 810, 1 and 2 subjects in Humira and placebo arms, respectively, were allocated from Hurley Stage III to II.

Considering the efficacy results by the baseline Hurley Stage, Table 8 showed that the treatment effect for Hurley Stage II and III were similar in Trial 313 (16% and 17% for Hurley Stage II and III, respectively). However, this was not the case for Trial 810 as the corresponding results for subject in Hurley Stage II and III without the antibiotic use were 24% and 37%, respectively.

As for the effect of antibiotic use on the efficacy results in Trial 810, although the number of subjects with those that used concomitant antibiotics was relatively small, the results in Table 8 showed that the treatment effect for the subjects with concomitant antibiotic use was generally higher than those without the antibiotic use for both Hurley Stages II and III. However, this differential treatment effect by the baseline concomitant antibiotic use was not consistent when the response rates among the placebo subjects were investigated. In Table 8, for those placebo subjects with baseline Hurley Stage II, the response rates for those without the antibiotic use was 39% compared to 23% for those with antibiotic use. However, this was reversed for those with Hurley Stage III as the response rates for the placebo subjects without the antibiotic use was 14% compared to 22% for subjects with the antibiotic use.

As the treatment effect was larger in Trial 810 compared to that of Trial 313, to investigate whether such difference in the treatment effect across trials might be due to the baseline AN counts, this reviewer plotted the baseline AN counts by treatment group for each trial in Figure 3. The interquartile (IQR) box sizes showed that the spread of baseline AN counts was larger for Trial 313 compared to those of Trial 810, and that subjects enrolled in Trial 313 also had higher mean baseline AN counts compared to those enrolled in Trial 810.

Figure 3. Baseline AN count by treatment group



Source: reviewer figure. The Y-axis of baseline AN count was cut at 80 in order to make better comparisons across the trials. As a result, an outlier of baseline AN count of 141 in the placebo arm in Trial 313 is not shown in the boxplot above.

A sensitivity analysis that excluded subjects with baseline AN counts >40 showed that the treatment effects were not impacted by these outliers as the proportion of subjects that achieved HiSCR in Trial 313 were 42% (58/139) and 27% (38/143) for the Humira and the placebo arms, respectively, and the corresponding HiSCR rates for Trial 810 were 59% (94/158) and 29% (43/150), respectively.

As the mean and median baseline AN counts for Trial 810 were relatively lower than those of Trial 313 (see Table 7), we investigated the impact of the baseline AN counts on the efficacy results.

Table 9 presents the efficacy results by the baseline AN counts. Findings from Table 9 showed that in Trial 313, while there were efficacy in the lowest baseline AN category (i.e., 3-5), and the highest baseline AN count category (i.e., ≥ 11), there was no efficacy in the baseline AN counts of 6-10 category. In contrast, for Trial 810, there appeared to be a trend in efficacy as the treatment effects were 13%, 34%, and 44% for the baseline AN count categories of 3-5, 6-10, and ≥ 11 , respectively.

Further investigation of efficacy results by baseline AN counts and by baseline Hurley Stages are presented in Table 9. It should be noted that with further classification by both baseline Hurley Stage and baseline AN counts, the number of subjects become small to draw a meaningful conclusion. However, the results are presented in the table below for completeness.

Table 9. Proportion of subjects achieving HiSCR at Week 12 by Hurley Stage and by baseline AN counts

		Trial 313		Trial 810	
		Humira N=153	Placebo N=154	Humira N=163	Placebo N=163
Primary endpoint		64 (42%)	40 (26%)	96 (59%)	45 (28%)
Baseline AN counts					
	3-5	13/24 (54%)	9/36 (25%)	27/47 (55%)	21/50 (42%)
	6-10	19/54 (35%)	12/33 (36%)	37/61 (61%)	14/51 (27%)
	≥11	32/75 (43%)	19/85 (22%)	33/55 (60%)	10/62 (16%)
Hurley Stage	Baseline AN counts				
II	3-5	8/17 (47%)	8/27 (30%)	17/27 (63%)	17/34 (50%)
	6-10	9/28 (32%)	6/14 (43%)	22/34 (65%)	11/29 (38%)
	≥11	18/35 (51%)	9/40 (23%)	15/25 (60%)	5/26 (19%)
III	3-5	5/7 (71%)	1/9 (11%)	9/20 (45%)	4/16 (25%)
	6-10	10/26 (38%)	6/19 (32%)	15/27 (56%)	3/22 (14%)
	≥11	14/40 (35%)	10/45 (22%)	18/30 (60%)	5/36 (14%)

Source: reviewer table

The applicant proposed to sequentially test the following secondary endpoints:

1. Proportion of subjects who achieved AN count of 0, 1, 2 at Week 12, among subjects with Hurley Stage II at baseline.
2. Proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient’s Global Assessment of Skin Pain (NRS30) – at its worst at Week 12 among subjects with baseline NRS ≥3.
3. Change in modified Sartorius score from baseline to Week 12.

The results of the secondary endpoint of the proportion of subjects with AN count of 0, 1, 2 at week 12 among those with baseline Hurley Stage II are presented in Table 10 below. Although not prespecified as a secondary endpoint, for reference and for comparison, the results for those with baseline Hurley Stage III are also presented in the table below.

As seen in Table 10, for Trial 313, the secondary endpoint of the proportion of subjects with AN count of 0, 1, 2 at Week 12 among those with baseline Hurley Stage II did not achieve statistical significance (p=0.961). As such, based on the prespecified sequential approach for analyzing the secondary endpoints, further analyses of the secondary endpoints should not be made for Trial 313. For Trial 810, Humira was superior to placebo at Week 12 (p=0.006) for the secondary endpoint of the proportion of subjects with AN count of 0, 1, 2 at Week 12. However, with only one trial that showed statistical significance, there is no replication of study findings for the secondary endpoints.

In contrast to the findings from the primary endpoint of HiSCR, for the endpoint of AN count ≤2 at Week 12, results in Table 10 showed that subjects with higher baseline AN counts generally had lower response rates at Week 12. It should be noted that subjects in Trial 313 generally had higher baseline disease severity compared to those in Trial 810, and 19% of the subjects in Trial 810 used concomitant antibiotics.

Table 10. Secondary endpoint of the proportion of subjects with AN count of 0, 1, 2 at Week 12 among those with baseline Hurley Stage II for Trials 313 and 810

		Trial 313		Trial 810	
		Humira N=153	Placebo N=154	Humira N=163	Placebo N=163
Hurley Stage II	AN ≤2 at Week 12	22/80 (28%)	22/81 (27%)	46/86 (53%)	29/89 (33%)
	p-value ⁽¹⁾	0.961		0.006	
	Baseline AN count				
	3-5	9/17 (53%)	11/27 (41%)	19/27 (70%)	18/34 (53%)
	6-10	8/28 (29%)	4/14 (29%)	20/34 (59%)	10/29 (34%)
	≥11	5/35 (14%)	7/40 (18%)	7/25 (28%)	1/26 (4%)
III	AN ≤ 2 at Week 12	21/73 (29%)	10/73 (14%)	24/77 (31%)	8/74 (11%)
	Baseline AN count				
	3-5	5/7 (71%)	2/9 (22%)	10/20 (50%)	5/16 (31%)
	6-10	9/26 (35%)	3/19 (16%)	10/27 (37%)	2/22 (9%)
	≥11	7/40 (18%)	5/45 (11%)	4/30 (13%)	1/36 (3%)

Source: reviewer's table. Results for Hurley Stage III are shown only as a reference.

(1) CMH by Hurley Stage at baseline (Study 313), and CMH by Hurley Stage at baseline and concomitant use (Study 810)

For the second secondary endpoint of the proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at its worst at Week 12 among subjects with baseline NRS ≥3, as with the first secondary endpoint of AN count of 0, 1, 2 among those with baseline Hurley Stage II, for Trial 313, Humira was not statistically superior to placebo (p=0.63) whereas it was for Trial 810 (p<0.001). It should be noted that for Trial 313, as the first secondary endpoint of the AN count of 0, 1, 2 among those with baseline Hurley Stage II was not statistically significant, further testing should not be allowed to control the Type I error rate; however, for completeness, the numerical results are presented below.

For Trial 313, while the treatment effect for the NRS30 endpoint was about 2% for both Hurley Stages II and III, among those subjects that did not receive the antibiotics for Trial 810, the treatment effects were 20% and 33% for those with baseline Hurley Stage II and III, respectively. As the number of subjects were small with those that received the antibiotics, it would be difficult to draw any meaningful conclusion. It should be noted that while the applicant used the Hurley Stage stratum at randomization for the analysis, this reviewer used the protocol-specified analysis method that used the baseline Hurley Stage stratum for the analyses.

Table 12. Analysis results of the secondary endpoint of the proportion of subjects who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient’s Global Assessment of Skin Pain (NRS30) – at its worst at Week 12 among subjects with baseline NRS \geq 3 for Trials 313 and 810

Trial 313			Trial 810		
	Humira	Placebo		Humira	Placebo
NRS30	34/122 (28%)	27/109 (25%)	NRS30	48/105 (46%)	23/111 (21%)
p-value ⁽¹⁾	0.63			<0.001	
by baseline Hurley Stage			by baseline Hurley Stage and by concomitant antibiotics use		
II	20/66 (30%)	15/54 (28%)	No	18/42 (43%)	10/44 (23%)
			Yes	2/5 (40%)	3/8 (38%)
III	14/56 (25%)	12/55 (22%)	No	20/47 (43%)	5/48(10%)
			Yes	8/11 (73%)	5/11 (45%)

Source: Reviewer table.

(1) CMH by Hurley Stage at baseline (Study 313), and CMH by Hurley Stage at baseline and concomitant use (Study 810).

3.4 Evaluation of Safety

During Period A of the Phase 3 trials, the most frequently reported treatment-emergent adverse events were hidradenitis in Trial 313, and headache in Trial 810. For an in-depth evaluation of safety signals, refer to the medical officer’s review.

Table 14. Most frequently ($\geq 2\%$) reported treatment-emergent adverse events (Period A)

	Trial 313		Trial 810	
	Humira N=153	Placebo N=152	Humira N=163	Placebo N=163
Any AE	81 (53%)	94 (62%)	94 (58%)	109 (67%)
Hidradenitis	14 (9%)	20 (13%)	7 (4%)	21 (13%)
Nasopharyngitis	9 (6%)	16 (11%)	9 (6%)	10 (6%)
Headache	14 (9%)	15 (10%)	21 (13%)	21 (13%)
Nausea	3 (2%)	4 (3%)	7 (4%)	5 (3%)
Fatigue	3 (2%)	4 (3%)	5 (3%)	3 (2%)
Upper respiratory tract infection	5 (3%)	4 (3%)	8 (5%)	9 (6%)
Back pain	3 (2%)	4 (3%)	-	-
Oropharyngeal pain	2 (1%)	4 (3%)	-	-
Abdominal pain upper	1 (1%)	3 (2%)	-	-
Pyrexia	1 (1%)	3 (2%)	-	-
Influenza	2 (1%)	3 (2%)	-	-
UTI	5 (3%)	3 (2%)	1 (1%)	5 (3%)
C-reactive protein increased	3 (2%)	3 (2%)	-	-
Weight increased	3 (2%)	3 (2%)	-	-
Cough	2 (1%)	3 (2%)	-	-
Dyspnocea	0	3 (2%)	-	-
Hypertension	1 (1%)	3 (2%)	-	-
Dizziness	4 (3%)	2 (1%)	7 (4%)	2 (1%)
Sinusitis	3 (2%)	1 (1%)	-	-
Arthralgia	3 (2%)	0	-	-
Depression	3 (2%)	0	-	-
Diarrhea	-	-	9 (6%)	4 (3%)
Injection site pain	-	-	6 (4%)	5 (3%)
Gastroenteritis	-	-	5 (3%)	4 (3%)
Asthenia	-	-	0	6 (4%)
Bronchitis	-	-	2 (1%)	4 (3%)
Vomiting	-	-	4 (3%)	2 (1%)
Insomnia	-	-	1 (1%)	4 (3%)
Folliculitis	-	-	4 (3%)	-

Source: sponsor's table 61

Per the clinical team's request, a safety signal of "flare" in abscess, inflammatory nodules, and draining fistula by switching from Humira to placebo in Period B was evaluated and analyzed. Per the protocol, "flare" was defined as having 25% or more increase from baseline and a minimum of 2 additional lesions.

In both trials, approximately 25% of the Humira-treated subjects that switched to placebo arm in Period B experienced flare in abscess, inflammatory nodules, and draining fistula.

Table 15. “Flare” in Abscess, Inflammatory Nodules, and Draining Fistula in Trial 313 (Period B)

Trial	Flare in Period B	Humira EW/EOW	Humira EW/EW	Humira EW /Placebo	Placebo/EW ⁽¹⁾ or Placebo/Placebo ⁽²⁾
313	Abscess	6/48 (13%)	4/48 (8%)	12/49 (25%)	15/145 (10%)
	Inflammatory Nodules	12/48 (25%)	9/48 (19%)	13/49 (27%)	35/145 (24%)
	Draining Fistula	9/48 (19%)	12/48 (25%)	13/49 (27%)	26/145 (18%)
810	Abscess	10/53 (19%)	10/51 (20%)	11/51 (22%)	41/151 (27%)
	Inflammatory Nodules	13/53 (25%)	6/51 (12%)	13/51 (25%)	48/151 (32%)
	Draining Fistula	12/53 (23%)	7/51 (14%)	10/51 (20%)	53/151 (35%)

Source: Reviewer Table. Flare is defined as 25% or more increase from baseline + minimum of 2 additional lesions. (1) for Trial 313; (2) for Trial 810

Because the protocol-specified enrollment criterion called for abscess and inflammatory nodules jointly as AN counts, an analysis of flare in AN counts were considered. Flare in AN counts occurred in approximately 22% of the Humira-treated subjects that switched to placebo arm in Period B. The reduction in flare rates by considering the AN counts as opposed to the individual abscess and inflammatory nodules is due to how the flare is defined (i.e., while a subject might be classified as flare on the individual abscess or inflammatory nodules, such subject might not necessarily meet the flare definition based on an AN count).

Table 16. “Flare” in Abscess and Inflammatory Nodules (AN) in Trials 313 and 810 (Period B)

Trial	Flare in Period B	Humira EW/EOW	Humira EW/EW	Humira EW /Placebo	Placebo/EW ⁽¹⁾ or Placebo/Placebo ⁽²⁾
313	AN	11/48 (23%)	8/48 (17%)	9/49 (18%)	25/145 (17%)
810	AN	22/53 (21%)	6/51 (12%)	13/51 (25%)	56/151 (37%)

Source: Reviewer Table. Flare is defined as 25% or more increase from baseline + minimum of 2 additional lesions. (1) for Trial 313; (2) for Trial 810

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the efficacy by gender, age, race, weight as well as by center for the Phase 3 trials was considered.

4.1 Efficacy by Gender, Race, and Age

Table 17 presents the proportion of subjects achieving HiSCR at Week 12 by gender, race, and age strata at baseline for Trials 313 and 810. Approximately 65% of the subjects were female, and the treatment effects were slightly higher for male subjects than those of the female subjects. Majority of the subjects enrolled in the trials were

Caucasians (approximately 75%), and of <65 of age (approximately 99%). Therefore, any differences in efficacy for the non-Caucasians and the older age (≥ 65) subgroups would be difficult to detect.

Table 17. Proportion of subjects achieving HiSCR at Week 12 (ITT; NRI) by gender, race, and age groups

	Trial 313		Trial 810	
	Humira N=153	Placebo N=154	Humira N=163	Placebo N=163
Gender				
<i>Female</i>	40/91 (44%)	30/105 (29%)	64/108 (59%)	34/113 (30%)
<i>Male</i>	24/62 (39%)	10/49 (20%)	32/55 (58%)	11/50 (22%)
Race				
<i>White</i>	48/116 (41%)	30/118 (25%)	85/143 (59%)	40/130 (31%)
<i>Black</i>	14/33 (42%)	7/29 (24%)	4/9 (44%)	5/20 (25%)
<i>Others</i>	2/4 (50%)	3/7 (43%)	7/11 (64%)	0/13 (0%)
Age				
<65	63/152 (41%)	40/152 (26%)	95/162 (59%)	45/160 (28%)
≥ 65	1/1 (100%)	0/2 (0%)	1/1 (100%)	0/3 (0%)

Source: reviewer table.

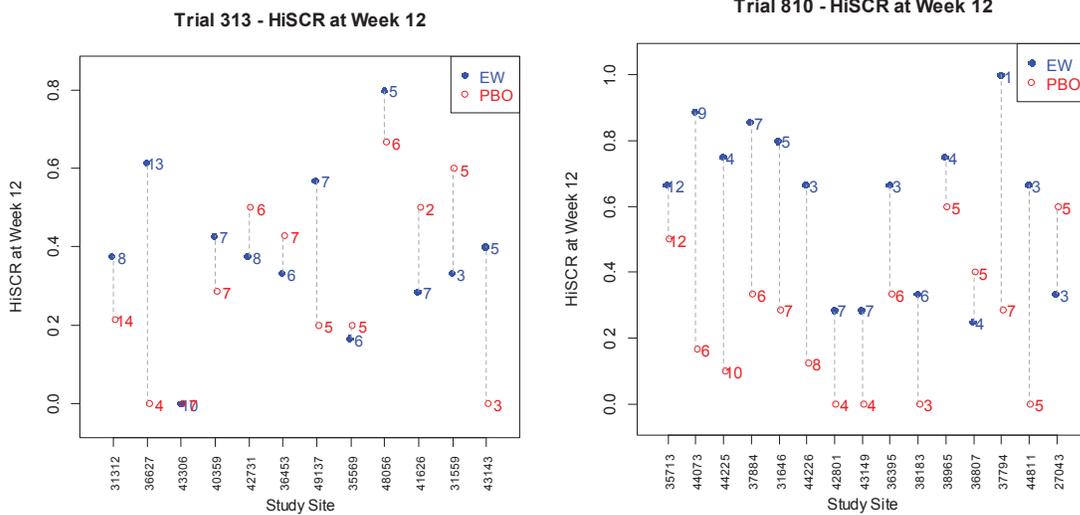
4.2 Efficacy by Center

Figure 4 shows the efficacy by center plots for Trials 313 and 810. For the purpose of investigating the site to site variability in efficacy, only those sites that enrolled more than 8 subjects are plotted below as there were many centers that enrolled a small number of subjects (note: randomization was not stratified by center). The x-axis of the plots is in the descending order of:

- (i) The sites with the most number of enrolled subjects, then
- (ii) The sites with the larger treatment effect if there are more than one site with the same number of enrolled subjects.

With the sites that had a reasonable number of subjects that were included in the plots below, it should be noted that in Trial 313, 5 of the 12 centers showed that the placebo outperformed Humira for achieving HiSCR response at Week 12 whereas in Trial 810, only 2 of the 15 centers showed that the placebo outperformed Humira. Such findings in Figure 4 showed that there was more site-to-site variability in efficacy in Trial 313 compared to that in Trial 810. It should be noted that randomization was not stratified by center, but by baseline Hurley Stage (for both Trials 313 and 810), and also by baseline concomitant antibiotic use (for Trial 810 only).

Figure 4. Efficacy by Center plots



Source: reviewer plots

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Although the two trials showed statistically significant findings, the treatment effect in Trial 810 was almost twice as that of Trial 313 (31% vs. 16%). This differential treatment effect was also shown for the secondary endpoint of the proportion of subjects with abscess and inflammatory nodules (AN) count of 0, 1, 2 at Week 12 among those with baseline Hurley Stage II. For the analysis of this secondary endpoint, Trial 313 did not achieve statistical significance ($p=0.961$) whereas Trial 810 did ($p=0.006$).

In an attempt to explain the differential treatment effects across the two trials, the background factors including the disease severity for subjects in the two trials were compared. This comparison showed that subjects enrolled in Trial 810 had lower baseline disease severity, as reflected in the baseline AN counts, compared to those in Trial 313. In addition, about 19% of the subjects in Trial 810 were allowed to continue their baseline concomitant antibiotic use.

While this observation about the differences in the baseline disease severity between the two trials may explain the difference in the findings for the secondary endpoint of the proportion of subjects with AN counts of 0, 1, 2 at Week 12 among those with baseline HS II; however, it appeared that the difference in the baseline disease severity did not explain the difference in the primary endpoint. With that, we considered investigating the treatment effect by study centers, and findings from such investigation showed that Trial 313 had more variability in response rates compared to those of Trial 810.

As the first secondary endpoint of the proportion of subjects with AN counts of 0, 1, 2 among those with baseline HS II for Trial 313 was not statistically significant, this prevented further analyses of the other secondary endpoints as the Type I error rate would not be controlled for.

5.2 Conclusions and Recommendations

For establishing an efficacy claim, the applicant conducted two pivotal trials (Trials 313 and 810) to support the safety and efficacy of Humira (adalimumab) for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).

The trials enrolled subjects ≥ 18 years of age and older, with a diagnosis of HS for at least 1 year prior to baseline, HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which was Hurley Stage II or III, had inadequate response to at least 3-month trial of oral antibiotics for treatment of HS, stable HS for at least 2 months prior to screening and also at the baseline visit, and had a total of abscess and inflammatory nodules (AN) count ≥ 3 at baseline.

The SPA-agreed upon primary endpoint was the “proportion of subjects achieving HS clinical response (HiSCR) at Week 12” where HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess and no increase of draining fistula count. Efficacy results for the primary endpoint were statistically significant ($p=0.003$ and <0.001 for Trials 313 and 810, respectively).

Table 1 presents the efficacy results for the primary endpoint, the proportion of subjects achieving HS clinical response (HiSCR) at Week 12 where HiSCR was defined as at least 50% reduction in inflammatory lesion count and no increase in abscess and no increase of draining fistula count, for the intent to treat (ITT) population with missing data imputed as non-responders (NRI).

Table 1. Proportion of subjects achieving HiSCR at Week 12 (ITT; NRI)

	Trial 313		Trial 810	
	Humira N=153	Placebo N=154	Humira N=163	Placebo N=163
Primary endpoint	64 (42%)	40 (26%)	96 (59%)	45 (28%)
p-value ⁽¹⁾	0.003		<0.001	

Source: Reviewer’s results. (1) CMH by Hurley Stage at baseline (Study 313), and CMH by Hurley Stage at baseline and concomitant use (Study 810).

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/s/

CARIN J KIM
07/09/2015

MOHAMED A ALOSH
07/09/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

sBLA:	STN 125,057/393
Submission Type:	Efficacy supplement
Brand Name:	HUMIRA®
Drug Name:	Adalimumab
Submission Date:	11/10/2014
PDUFA Goal Date:	09/10/2015
Priority:	Standard
Proposed Indication:	Treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.
Proposed Dosing Regimen:	160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29.
Dosage Forms and Strength:	Solution (50 mg/mL) for injection presented in prefilled syringe or autoinjector (currently marketed formulation/presentations).
Applicant:	AbbVie Inc.
Clinical Pharmacology & Pharmacometric Reviewer:	Jie Wang, Ph.D.
Pharmacometrics Team Leader:	Jeffrey Florian, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	CDER/ODEIII/DDDP

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1. EXECUTIVE SUMMARY

HUMIRA[®] (adalimumab) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNF α). HUMIRA was initially approved for the treatment of rheumatoid arthritis (RA) in December 2002 and subsequently approved for multiple indications, including psoriatic arthritis (October 2005), ankylosing spondylitis (August 2006), Crohn's disease (February 2007), psoriasis (January 2008), juvenile idiopathic arthritis (February 2008), ulcerative colitis (September 2012), and pediatric Crohn's disease (September 2014).

The current efficacy supplement application is to include a new indication for HUMIRA for the treatment of active moderate to severe hidradenitis suppurativa (HS or acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

The proposed dosing regimen is 160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29. HUMIRA is administered by subcutaneous injection.

The sBLA contains four clinical trials, i.e., Studies M10-467, M11-810, M11-313 and M12-555. Study M10-467 was a Phase 2, placebo-controlled, dose-ranging study. Studies M11-810 and M11-313 had similar study design and both were randomized, double-blind, placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of adalimumab at Week 12 (Period A) and Week 36 (Period B). Study M12-555 was an open-label extension study evaluating the efficacy and safety of adalimumab for the subjects rolled over from Studies M11-810 and M11-313 through additional 60 weeks. Study M12-555 is currently ongoing.

1.1. Recommendations

The Clinical Pharmacology information provided in the sBLA is sufficient to support a recommendation for approval of HUMIRA for the treatment of active moderate to severe HS in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

1.2. Post-Marketing Commitments/Requirements

- PMC/PMR #1: Utilize the validated anti-adalimumab antibody (AAA) assay (as described in the FDA Fulfillment of Postmarketing Requirement Letter dated on April 1, 2015) to analyze the immunogenicity profile of adalimumab using banked patient samples from Phase 3 trials M11-810 and M11-313. The Applicant should evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety based on the AAA data generated with the newly validated assay.
- PMC/PMR #2: To conduct a clinical drug-drug interaction (DDI) study to evaluate whether adalimumab alters the PK or metabolism of CYP substrates in HS patients treated with adalimumab. The DDI study should use a “cocktail” approach to simultaneously evaluate the effect of adalimumab on the PK of probe substrates metabolized by CYP enzymes including but not limited to CYP3A4, CYP2C19, CYP2C9, CYP2D6 and CYP1A2.

1.3. Summary of Clinical Pharmacology Findings

1.3.1. Dose-/Exposure-response relationships and the recommended dosing regimen

The overall efficacy and safety data as well as the dose-/exposure-response relationships for efficacy and safety supported the recommended dosing regimen of 40 mg every week (ew) starting from Day 29 with 160 mg initially on Day 1 and 80 mg on Day 15 as proposed by the Applicant.

At Week 12, a greater proportion of subjects treated with adalimumab 40 mg ew achieved HiSCR when compared to the placebo treated subjects (50.6% vs. 26.8%) in two phase 3 trials combined, and at the individual study level (58.9% vs. 27.6% in Study M11-810 and 41.8% vs. 26.0% in Study M11-313.)

A demographic factor (body weight) and a baseline disease condition (CRP level) were found to correlate with the Week 12 HiSCR response rate in adalimumab treated subjects: a higher baseline CRP level and a higher body weight were associated with a lower response rate. The HiSCR response rates were 64.6%, 59.5%, 43.4% and 37.2% across the four quartiles by increasing baseline CRP level, and 57.0%, 53.2%, 46.2% and 48.7% across the four quartiles by increasing body weight. However, neither the body weight nor the baseline CRP level was a significant covariate for explaining differences in the observed HiSCR response rate based on an exposure-response analysis. On the other hand, the CRP levels at baseline and at Week 12 were among several covariates found to significantly influence the placebo response (e.g., higher CRP levels associated with a lower likelihood of response). Therefore, no dose adjustment would be recommended based on either the body weight or the baseline CRP level.

Furthermore, there is evidence of efficacy with the proposed dosing regimen even in patients with both higher baseline CRP level and higher body weight. A subgroup analysis showed that adalimumab treated subjects with both high baseline CRP level (>21 mcg/mL) and high body weight (>107 kg) achieved a HiSCR response numerically higher than the overall response rate in subjects who received placebo (35% vs. 26.8%).

Exposure-response for HiSCR at Week 12 (the primary efficacy endpoint) in Phase 3 trials

Phase 3 study results demonstrated an exposure-response relationship between HiSCR response rate and serum adalimumab concentrations at Week 12; higher serum adalimumab concentrations were associated with greater HiSCR response rates. The HiSCR response rates were 28.2%, 46.2%, 70.5% and 60.3% across four quartiles of increasing Week 12 serum adalimumab concentration compared to a 26.8% response rate in the placebo group (Table 1.3.1.a.). The response rate appeared to have achieved a plateau at the third quartile of adalimumab concentrations.

The demographic factor (body weight) and disease factor (baseline CRP level) could have contributed to the overall E-R relationship because both body weight and baseline CRP level were covariates that could impact adalimumab exposure. For example, subjects with adalimumab concentration in the lowest quartile “Q1” were found to be associated with relatively higher baseline CRP level and higher body weight. However, neither the body weight nor the baseline CRP level was a significant covariate to the observed exposure-response relationship, whereas the CRP levels at baseline and at Week 12 were among several covariates found to significantly influence the placebo response.

The data showed that the median CRP levels decreased from baseline to Week 12 in general.

Table 1.3.1.a. HiSCR response at Week 12. Q1, Q2, Q3 and Q4 represent four quartiles by increasing Week 12 serum adalimumab concentrations. (*Data source: Reviewer’s analysis using the dataset ‘ada-logreg.xpt’ provided by the Applicant in response to Clinical Pharmacology Information Request letter dated on March 13, 2015.*)

	Placebo (N=317)	Subgroups by Week 12 serum adalimumab concentration quartiles				
		Q1 (N=78)	Q2 (N=78)	Q3 (N=78)	Q4 (N=78)	Combined (N=312)
Adalimumab (mcg/mL) median [range]	0	1.31 [0 to <=4.01]	6.13 [>4.01 to <=8.27]	10.4 [>8.27 to <=12.6]	16.3 [>12.6 to <=29.4]	8.32 [0 to 29.4]
HiSCR responders% (n)	26.8% (85)	28.2% (22)	46.2% (36)	70.5% (55)	60.3% (47)	51.3% (160)
Baseline BW (kg) median [range]	94.0 [41.0-221]	99.0 [60.0-165]	93.0 [52.0-179]	93.5 [60.0-142]	80.7 [43.0-150]	91 [43-179]
Baseline CRP (mcg/mL) median [range]	9.2 [0.2-246]	16.9 [0.3-189]	11.1 [0.2-75.1]	5.9 [0.2-103]	5.1 [0.1-49.5]	8.3 [0.1-189]
Week 12 CRP (mcg/mL) median [range]	8.2 [0.2-154]	12.7 [0.2-151]	6.1 [0.2-42.7]	2.75 [0.3-23.5]	2.7 [0.2-39.3]	4.9 [0.1-151]

Dose-response for HiSCR at Week 36 in Phase 3 trials

The dose-response for HiSCR in the Period B of the Phase 3 trials supported that adalimumab 40 mg ew was more effective in achieving or sustaining HiSCR compared to 40 mg every other week (eow). The proportions of subjects achieving HiSCR at Week 36 in the two Phase 3 trials were shown in Table 1.3.1.b.

Table 1.3.1.b. HiSCR response at Week 36. At Week 12, subjects who had received adalimumab 40 mg every week (ew) in Period A were re-randomized in Period B to 1 of 3 treatment groups: adalimumab 40 mg ew (ew/ew), adalimumab 40 mg every other week (ew/eow), or placebo (ew/placebo) from Week 12 to Week 35. (*Data source: Tables 32-34, Summary of Clinical Efficacy, R&D/13/7395.*)

	HiSCR response rate at Week 36 (Group size)		
	40 mg ew/placebo	40 mg ew/eow	40 mg ew/ew
Overall	28.0% (N=100)	30.7% (N=101)	43.4% (N=99)
Week 12 HiSCR Responders	32.1% (N=53)	46.2% (N=52)	48.1% (N=52)
Week 12 HiSCR Non-responders	23.4% (N=47)	14.3% (N=49)	38.3% (N=47)

Dose-Response for safety

Overall, there was no apparent dose-response relationship for safety in HS Phase 3 trials.

1.3.2. Pharmacokinetics

In subjects with HS, following a dose of 160 mg on Week 0 and a dose of 80 mg on Week 2, the mean±SD serum adalimumab trough concentrations were 7.45±4.52 mcg/mL and 7.45±4.18 mcg/mL at Week 4 in Studies M11-313 and M11-810, respectively. Following the adalimumab 40 mg ew treatment starting on Week 4, serum adalimumab trough concentrations were 8.66±6.39 mcg/mL and 8.95±6.27 mcg/mL at Week 12 in Studies M11-313 and M11-810, respectively. At Week 12, subjects who achieved HiSCR (i.e., responders) had higher adalimumab concentrations compared to non-responders; Week 12 adalimumab concentrations were 10.6±6.3 mcg/mL vs. 7.2±6.04 mcg/mL in Study M11-313 and 10.3±6.0 mcg/mL vs. 6.9±6.12 mcg/mL in Study M11-810.

The mean±SD clearance (CL) of adalimumab in subjects with HS was 0.77±0.58 L/day (median=0.59 L/day) based on population PK analyses. Additionally, adalimumab CL increased with increasing body weight and increasing baseline CRP level based on the *post-hoc* estimates of individual CL values.

The serum concentrations of adalimumab in subjects with HS were lower than in other disease populations including UC, CD, and Psoriasis given the same dosing regimen.

1.3.3. Immunogenicity and its impact on PK and efficacy

In HS Phase 3 trials, the overall incidence of anti-adalimumab antibody (AAA) development in patients treated with HUMIRA was 12.6% (58/461). However, due to the limitation of the assay, AAA could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment and in whom adalimumab serum levels subsequently declined to <2 mcg/mL, the immunogenicity incidence was 28%.

The formation of AAA was associated with reduced serum adalimumab concentrations and a lower HiSCR response.

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2. QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What are the highlights of the drug substance and the formulation of the drug product?

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNF α). HUMIRA is currently registered and marketed as solution for injection presented as single-use prefilled syringe (PFS) and prefilled pen for subcutaneous injection.

The HS clinical trials used the currently marketed PFS presentation containing the solution of 40 mg adalimumab in 0.8 mL liquid (50 mg/mL). There were no drug substance (DS) or drug product (DP) manufacturing changes during the clinical development of adalimumab for the HS indication; therefore, no new biopharmaceutics studies were submitted as part of the sBLA application.

2.1.2. What are the proposed indication and mechanism of action?

The proposed indication is for the treatment of active moderate to severe HS (or acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

HS is a chronic inflammatory skin disease characterized by recurrent inflamed nodules and abscesses. Increased levels of TNF- α may have a pathogenic role in HS lesions. Adalimumab binds to TNF- α and blocks its interaction with the cell surface TNF- α receptors.

2.1.3. What is the proposed dosing regimen and route of administration?

The proposed dosing regimen is 160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29. HUMIRA is administered by subcutaneous injection.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support efficacy, safety and dosing claims?

The sBLA contains four clinical studies: Studies M10-467, M11-810, M11-313 and M12-555.

Study M10-467 – Phase 2 dose-ranging study

At Week 0, subjects with HS were randomized in a 1:1:1 ratio to receive placebo, adalimumab 40 mg eow (starting at Week 1 with loading dose of 80 mg at Week 0), or adalimumab 40 mg ew (starting at Week 4 with loading dose of 160 mg at Week 0 and 80 mg at Week 2).

At Week 16, subjects who continued the study in the open-label period received adalimumab 40 mg eow starting at Week 17 through Week 28.

At Week 28 or 31, if a subject had a PGA of moderate disease or worse (score of ≥ 3), the subject had the option of dose escalation to adalimumab 40 mg ew.

Studies M11-810 and M11-313 – Phase 3 studies

As agreed upon with the Agency via Special Protocol Assessment, Studies M11-810 and M11-313 were both randomized, double-blind, placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of adalimumab at Week 12 (Period A) and Week 36 (Period B); and the two studies had similar study design (Figure 2.2.1).

In Period A, patients received placebo or adalimumab with initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg ew starting at Week 4.

At Week 12, patients who had received adalimumab in Period A were re-randomized in Period B to 1 of 3 treatment groups: adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo from Week 12 to Week 35. Re-randomization was stratified by Week 12 clinical response (responder versus non-responder) and by Baseline Hurley Stage (II versus III). In Study M11-313, subjects who had been randomized to placebo in Period A were assigned to receive adalimumab 40 mg ew in Period B whereas in Study M11-810, subjects who had been randomized to placebo in Period A were assigned to receive placebo in Period B.

At Week 36, subjects were eligible to enroll into Study M12-555 to receive adalimumab 40 mg ew.

In both Phase 3 studies, serum adalimumab concentrations were measured at Baseline, Weeks 2, 4, 8, 12, 14, 16, 20, 24, 32, and 36. Anti-drug antibodies were assessed at Baseline, Weeks 4, 12, 16, 24, and 36.

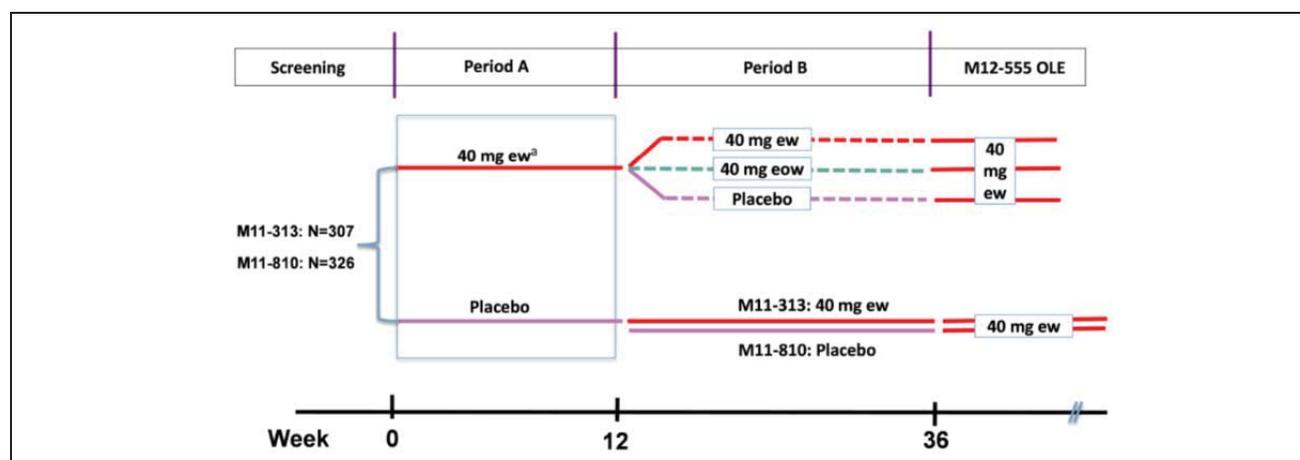


Figure 2.2.1. Study design for Phase 3 studies M11-810 and M11-313. ^a Starting at Week 4 after 160 mg at Week 0 and 80 mg at Week 2. Study M11-313 evaluated 307 patients. A total of 290 patients were re-randomized in Period B and 170 subjects completed the study. Study M11-810 evaluated 326 patients. A total of 306 patients were re-randomized in Period B and 116 subjects completed the study. At Week 36 in both studies, subjects were eligible to enroll into Study M12-555 to receive adalimumab 40 mg ew. (Data source: Clinical Overview, Figure 1, Page 9).

Study M12-555

Study M12-555 was an open-label extension study evaluating efficacy and safety of adalimumab 40 mg ew for the subjects rolled over from Studies M11-810 and M11-313 through additional 60 weeks. Study M12-555 is currently ongoing.

2.2.2. What are the clinical endpoints for efficacy evaluation and how are they measured?

The primary efficacy variable in the Phase 3 studies was the proportion of subjects achieving *Hidradenitis Suppurativa Clinical Response (HiSCR)*, which was defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count at Week 12 relative to baseline.

The primary efficacy variable in the Phase 2 study was the proportion of subjects achieving clinical response, defined as achieving a PGA of clear, minimal, or mild, with a minimum of 2 grades improvement (reduction) from baseline at Week 16. The PGA of disease severity was on a 6-point scale (0 to 5) with 0 being clear and 5 being very severe.

2.2.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, adalimumab concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) method that was submitted and reviewed in the original BLA application for the RA indication.

2.3. Dose-/Exposure-Response

The overall efficacy and safety data as well as the dose-/exposure-relationships for efficacy and safety supported the recommended dosing regimen of 40 mg every week starting from Day 29 with 160 mg initially on Day 1 and 80 mg on Day 15 as proposed by the Applicant.

2.3.1. What are the characteristics of the dose-/exposure-response relationship for efficacy?

Phase 2 dose-response for PGA response - supporting Phase 3 dose selection

The proportion of subjects who achieved a clinical response was 3.9%, 9.6% and 17.6% in placebo, adalimumab 40 mg ew, and adalimumab 40 mg ew treatment groups, respectively (Table 2.3.1.a).

Table 2.3.1.a. Proportion of subjects achieving clinical response at Week 16 in Study M10-467. [#] $p < 0.05$, compared to placebo. ^a With an initial dose of 80 mg at Week 0; ^b With an initial dose of 160 mg at Week 0 and 80 mg at Week 2. (Data source: Table 17, M10-467, CSR R&D/10/1424)

	Placebo	Adalimumab 40 mg ew ^a	Adalimumab 40 mg ew ^b
Clinical Responders n/N (%)	2/51 (3.9%)	5/52 (9.6%)	9/51 (17.6%) [#]

Phase 3 primary efficacy results - HiSCR as the primary endpoint

In both Phase 3 Studies M11-810 and M11-313, the adalimumab 40 mg ew group had a statistically significantly higher proportion of subjects achieved HiSCR at Week 12 compared to the placebo group (Figure 2.3.1.a). The higher response rate in the adalimumab 40 mg ew group compared with the placebo groups was observed starting at Week 2 (Figure 2.3.1.b).

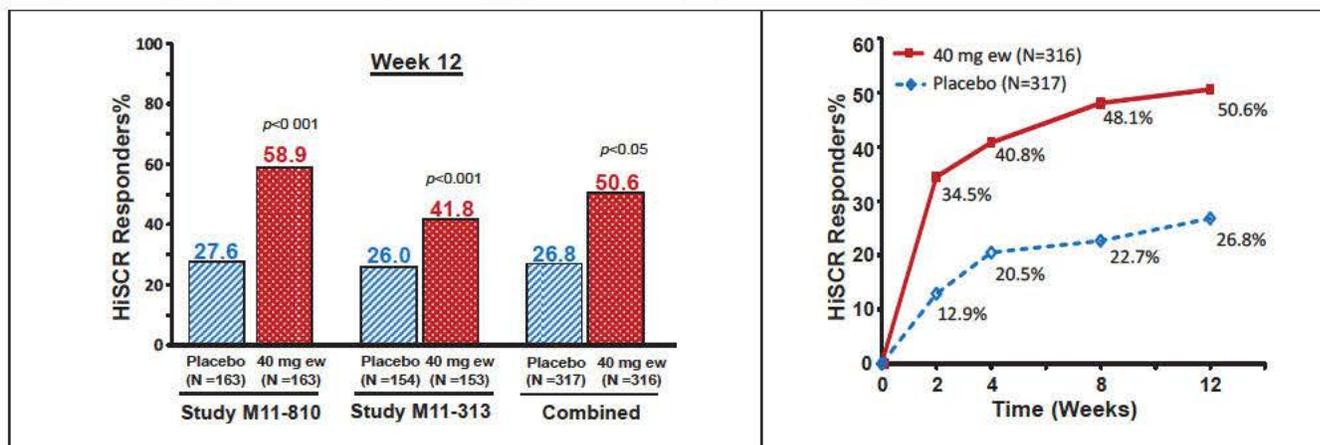


Figure 2.3.1.a. Proportion of subjects achieving HiSCR at Week 12 in Phase 3 Studies M11-810 and M11-313. ITT_A population: Intent-to-treat population that included all subjects who were randomized in Period A of each Phase 3 Study. (Data source: Table 2 and Table 26, Summary of Clinical Efficacy, R&D/13/739.)

Figure 2.3.1.b. Proportion of subjects achieving HiSCR by visit in Period A in Phase 3 Studies M11-810 and M11-313 combined. ITT_A population. (Data source: Figure 4, Summary of Clinical Efficacy, R&D/13/739.)

Phase 3 exposure-response for the primary efficacy endpoint HiSCR at Week 12

An exposure-response relationship was observed for the primary efficacy variable, with higher serum adalimumab concentrations in general associated with greater HiSCR response rates at Week 12. The HiSCR response rates were 28.2%, 46.2%, 70.5% and 60.3% across the four quartiles of Week 12 serum adalimumab concentration compared to a 26.8% response rate in the placebo group (Table 2.3.1.b.). Univariate logistic regression analysis showed that adalimumab concentration at Week 12 was a significant predictor of increasing HiSCR response at Week 12 (p -value <0.0001).

Table 2.3.1.b. HiSCR response rates at Week 12 by Week 12 serum adalimumab concentration quartiles.

(Data source: Reviewer’s analysis using the dataset ‘ada-logreg.xpt’ that was provided by the Applicant in response to Clinical Pharmacology Information Request letter dated on March 13, 2015.)

	Subgroups by Week 12 serum adalimumab concentration quartiles					
	Placebo (N=317)	Q1 (N=78)	Q2 (N=78)	Q3 (N=78)	Q4 (N=78)	Combined (N=312)
Adalimumab (mcg/mL), median [range]	0	1.31 [0 to <=4.01]	6.13 [>4.01 to <=8.27]	10.4 [>8.27 to <=12.6]	16.3 [>12.6 to <=29.4]	8.32 [0 to 29.4]
HiSCR responders% (n)	26.8% (85)	28.2% (22)	46.2% (36)	70.5% (55)	60.3% (47)	51.3% (160)
Baseline BW (kg), median [range]	94.0 [41.0-221.0]	99.0 [60.0-165.0]	93.0 [52.0-179.0]	93.5 [60.0-142.0]	80.7 [43.0-150.0]	91 [43-179]
Baseline CRP (mcg/mL) median [range]	9.2 [0.2-246]	16.9 [0.3-189]	11.1 [0.2-75.10]	5.9 [0.2-103]	5.1 [0.1-49.5]	8.3 [0.1-189]
Week 12 CRP (mcg/mL) Median [range]	8.2 [0.2-154]	12.7 [0.2-151]	6.1 [0.2-42.70]	2.75 [0.3-23.5]	2.7 [0.2-39.3]	4.9 [0.1-151]

A multivariate logistic regression analysis was conducted by the Applicant in response to an information request from the FDA dated March 13, 2014, in which the final logistic regression model included an Emax relationship for drug effect on HiSCR (Figure 2.3.1). Similar to the analysis results presented in Table 2.3.1.b by the reviewer, the HiSCR response rate appeared to have achieved a plateau at the third quartile of adalimumab concentrations.

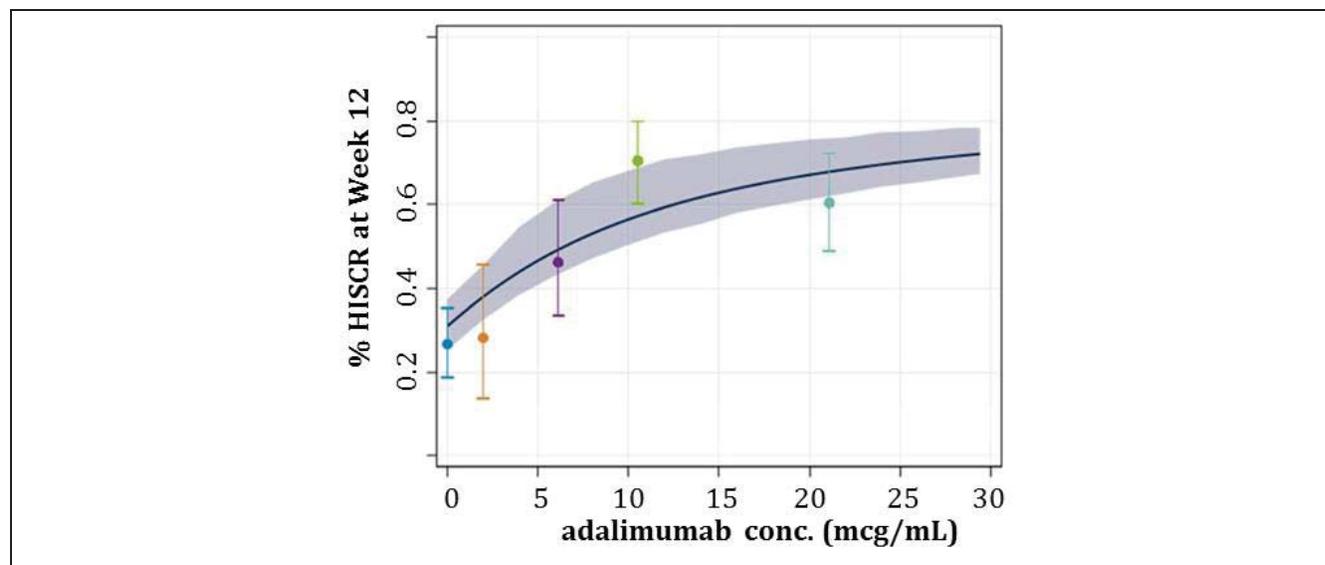


Figure 2.3.1. Logistic regression of HiSCR response by serum adalimumab concentrations at Week 12. An Emax logistic regression model fit was conducted by the Applicant. The shaded area represents 90% prediction interval. From left to right, the four legends represent the placebo group and quartiles by adalimumab concentration. (Data source: Figure 5, Response to March 13, 2015 Clinical Pharmacology IR)

The base E_{max} model with serum adalimumab concentrations as a predictor for HiSCR response was further used to test for effects of patient or disease covariates on placebo response or drug effect. Multiple covariates were tested including body weight and baseline CRP; neither body weight nor baseline CRP level was a significant covariate on the EC50 of the observed exposure-response relationship. On the other hand, the CRP levels at baseline and at Week 12 were among several covariates found to significantly influence the placebo response. Therefore, no dose adjustment would be recommended based on either the body weight or the baseline CRP level.

The data showed that the median CRP levels decreased from baseline to Week 12 following adalimumab treatment. The decrease in CRP levels was greater in the responder subgroups than in the non-responder subgroups, and the adalimumab treatment responders had a greater decrease in CRP than the placebo responders. The clinical implication of this observation is not certain at this time.

2.3.2. What are the characteristics of dose-/exposure-response relationship for efficacy following “long-term” treatment?

The currently available efficacy results for up to 72 weeks treatment overall supported continuous dosing of adalimumab 40 mg ew over dose reduction to 40 mg eow after the initial 12-week treatment.

Phase 2 PGA response after up to 52 weeks treatment (open-label period in trial M10-467)

The Phase 2 efficacy results showed that (1) majority of subjects who achieved PGA < 3 at Week 16 did not maintain this level of response with the adalimumab 40 mg eow dosing regimen through Week 52, and (2) at Week 52 the highest proportion of clinical responders was observed in subjects who received adalimumab 40 mg ew in the placebo-controlled period and had dose escalated back to 40 mg ew during the maintenance period after a period of treatment with 40 mg eow.

- Loss of response while on 40 mg eow regimen in the open-label period

Among subjects who achieved PGA < 3 at Week 16 and began treatment with adalimumab eow in the open-label period, 63.6% (7/11) and 62.5% (15/24), respectively, of those previously treated with adalimumab eow and ew in double-blind period were unable to maintain this level of response. (*Data source: Table 37, M10-467 Clinical Study Report, R&D/10/1424.*)

- Dose escalation from eow regimen to ew regimen in the open-label period

The proportion of subjects achieving clinical response, at Weeks 16 and 52 was presented in [Table 2.3.2.a](#) and shown separately for all responders and responders without dose escalation in open-label period. Discounting the contribution of dose escalation, the proportion of clinical responders at Week 52 was 5.8% and 9.8% for subjects who initially received adalimumab 40 mg eow and 40 mg ew, respectively. When responders due to dose escalation to 40 mg ew during open-label period were included, the proportion of clinical responders at Week 52 was 11.5% and 19.6% for subjects who initially received adalimumab 40 mg eow and 40 mg ew, respectively.

Table 2.3.2.a. Number and proportion of subjects achieving clinical response at Weeks 16 and 52. (<i>Data source: Table 39, M10-467 Clinical Study Report, R&D/10/1424.</i>)				
	Responders without dose escalation		All responders (with and without dose escalation)	
	40 mg eow/eow (N=52)	40 mg ew/eow (N=51)	40 mg eow/eow (N=52)	40 mg ew/eow (N=51)
Week 16	5 (9.6%)	9 (17.6%)	5 (9.6%)	9 (17.6%)
Week 52	3 (5.8%)	5 (9.8%)	6 (11.5%)	10 (19.6%)

Phase 3 dose-response for HiSCR at Week 36 - maintenance phase

The dose-response for HiSCR based on two Phase 3 trials combined supported that adalimumab 40 mg ew was more effective in achieving HiSCR compared to 40 mg eow (Figure 2.3.2.a).

Among all subjects randomized into Period B (both responders and non-responders at Week 12), the overall proportion of subjects who achieved HiSCR at Week 36 was greater for 40 mg ew regimen than for 40 mg eow regimen (43.4% vs. 30.7%), but the 40 mg ew regimen and placebo had relatively similar response rate (30.7% vs. 28.0%). Subgroup analysis showed that at Week 36 the 40 mg ew regimen achieved a higher response rate (38.3% vs. 14.3%) than 40 mg eow regimen in Week 12 non-responder subgroup; whereas ew and eow regimens had a similar response rate (48.1% vs. 46.2%) in the Week 12 responder subgroup. Of note, the Week 36 HiSCR response rate for placebo subjects was 23.4% in the Week 12 non-responders and 32.1% in Week 12 responders. Therefore, the unfavorable overall response rate for 40 mg eow regimen was largely due to a lower response rate in the Week 12 non-responder subgroup.

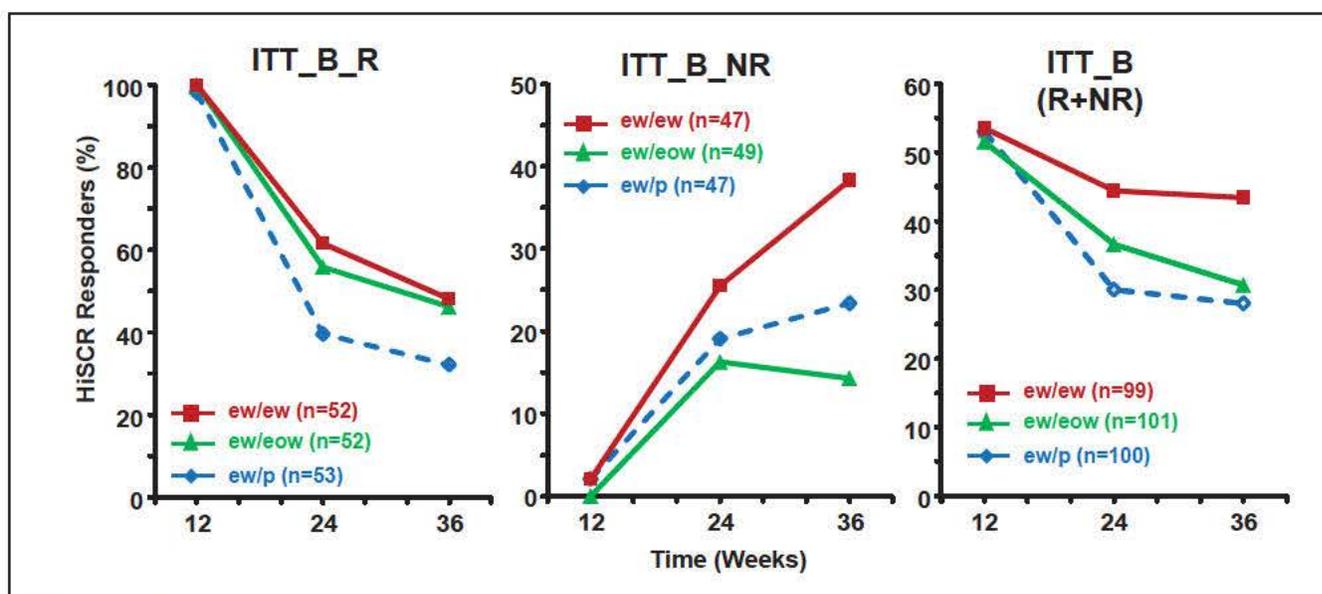


Figure 2.3.2.a. Proportion of subjects achieving HiSCR by visit in Period B of the Phase 3 studies M11-313 and M11-810 combined. ITT_B (R+NR) is the intent-to-treat population in period B that included all the subjects who were randomized in Period A and were re-randomized to enter Period B of the Phase 3 trials. ITT_B_R were the subpopulation who were HiSCR responders at the entry to Period B. ITT_B_NR were the subpopulation who were HiSCR non-responders at the entry to Period B. ew, every week; eow, every other week; p, placebo. (Data source: Tables 32-34, Summary of Clinical Efficacy, R&D/13/739)

HiSCR response in long-term treatment in Study M12-555

Integrated efficacy results across Studies M11-810, M11-313 and Study M12-555 supported that adalimumab 40 mg ew dosing would achieve and maintain the HiSCR responses. All subjects enrolled in Study M12-555 and received 40 mg ew dosing achieved similar HiSCR rates at Week 72 regardless of the treatment assignments in the first 36 weeks during Studies M11-810 and M11-313.

Specifically, the response rates were 58.3%, 62.2%, and 54.9% in the adalimumab 40 mg ew/ew/ew, ew/eow/ew, and ew/placebo/ew treatment groups, respectively (Figure 2.3.2.b). These data suggested that efficacy could be regained by retreatment after withdrawal of treatment because the response rates at Week 72 were higher than that for ew/p group at Week 36 (28%) and also higher than the overall response rate of 50.6% at Week 12 in two phase 3 trials combined.

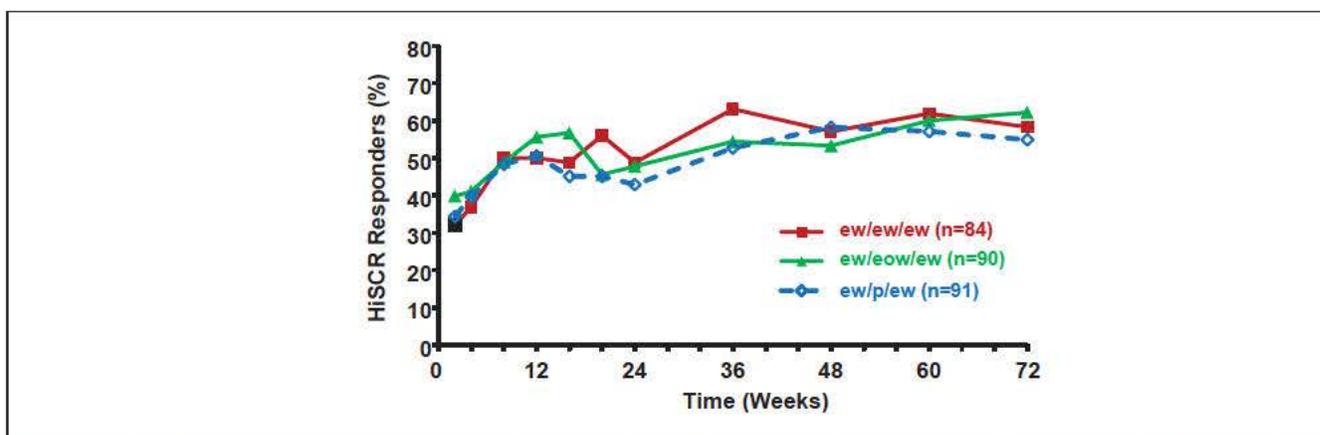


Figure 2.3.2.b. Proportion of subjects achieving HiSCR by visit in the combined Phase 3 studies M11-313 and M11-810 and open-label Study M12-555. ew/ew/ew population included the subjects who continuously received 40 mg ew through the studies. ew/eow/ew population included the subjects who received 40 mg ew in Period A of the Phase 3 trials, reduced dose frequency to eow at Week 12 and returned to ew in the event of loss of response (LOR), worsening or absence of improvement (WOAI), or at Week 36. ew/p/ew population included the subjects who received 40 mg ew in Period A of the Phase 3 trials, received placebo at Week 12 and re-initiation in the event of LOR, WOAI, or at Week 36. ew, every week; eow, every other week; p, placebo. (Data source: Tables 42, Summary of Clinical Efficacy, R&D/13/739)

2.3.3. What are the characteristics of the dose-response relationships for safety?

Overall, the safety profiles did not suggest evidence of a dose-response relationship for safety between adalimumab 40 mg ew and adalimumab 40 mg eow dosing regimens.

Table 2.3.3.a summarized the safety data in treatment groups of placebo, adalimumab 40 mg eow, adalimumab 40 mg ew in placebo-controlled period of the Phase 2 and Phase 3 Studies M10-467, M11-810 and M11-313 combined. The incidences for any AE were 64%, 64% and 58%, and the incidences for any infection were 31%, 42% and 22%, for the placebo, 40 mg eow, and 40 mg ew treatment groups, respectively.

Table 2.3.3.a. Adverse events by treatment groups at Week 12 in Period A (or placebo-controlled period) of the Studies M10-467, M11-810 and M11-313. (Data source: Table 7, Clinical Overview)

	AE incidence by treatment groups		
	Placebo (n=366)	40 mg eow (n=52)	40 mg ew (n=367)
Any AE	233 (64%)	33 (64%)	211 (58%)
Any infection	114 (31%)	22 (42%)	96 (22%)

Table 2.3.3.b summarized the safety data in treatment groups of 40 mg ew/placebo, 40 mg ew/eow, and 40 mg ew/ew through the end of Period B (Week 36) of the Phase 3 Studies M11-810 and M11-313 combined. The incidences for any AE were 65%, 57% and 60%, and the incidences for any infection were 29%, 31% and 32%, for the 40 mg ew/placebo, 40 mg ew/eow, and 40 mg ew/ew treatment groups, respectively.

Table 2.3.3.b. Adverse events by treatment groups at Week 36 in Period B of the Phase 3 Studies M11-810 and M11-313. (Data source: Table 8, Clinical Overview)

	AE incidences by adalimumab treatment groups		
	40 mg ew→placebo (n=100)	40 mg ew→eow (n=101)	40 mg ew→ew (n=99)
Any AE	65 (65%)	58 (57%)	59 (60%)
Any infection	29 (29%)	31 (31%)	32 (32%)

2.4. Pharmacokinetics

In the HS trials, only trough adalimumab concentrations were available to characterize temporal PK profiles from various dosing regimens. The initial adalimumab doses of 160 mg at Week 0 and 80 mg at Week 2 allowed the adalimumab concentration to rise rapidly toward the steady state. A population PK model was used to estimate the clearance (CL) and volume of distribution (V). Based on the population pharmacokinetic analyses, the mean±SD for CL and V of adalimumab were 0.77±0.58 L/day (median=0.59 L/day) and 13.9±3.4 L (median=13.7 L), respectively.

2.4.1. What are the PK characteristics of adalimumab in subjects with HS?

Figure 2.4.1 presents the mean (+SD) adalimumab trough concentrations over time in Phase 3 Studies M11-313 and M11-810.

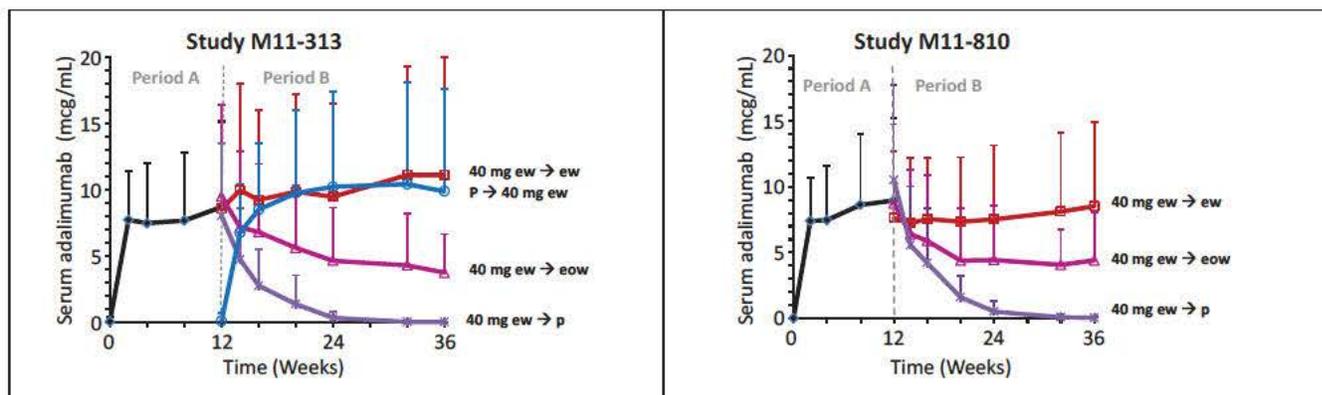


Figure 2.4.1. Mean trough serum (+SD) adalimumab concentrations in subjects with HS in Phase 3 studies M11-313 (left) and M11-810 (right). (Data source: Reviewer's plot of the data in Table 2.4.1.a and Table 2.4.1.b below)

Period A

Subjects in both studies received a dose of 160 mg on Week 0 and a dose of 80 mg on Week 2, and they achieved the mean adalimumab trough concentrations of about 7 to 8 mcg/mL at Week 2 and Week 4. Following the adalimumab 40 mg ew treatment starting on Week 4, the mean adalimumab trough concentrations were about 8 to 9 mcg/mL at Week 8 and Week 12 (Table 2.4.1.a).

Subjects who achieved HiSCR response (responders) at Week 12 had relatively higher mean adalimumab concentrations compared to non-responders (approximately 10 mcg/mL vs. 7 mcg/mL at Week 12) in both Studies M11-313 and M11-810 (Table 2.4.1.b). In the HiSCR responders, the adalimumab concentration increased slightly from approximately 8 mcg/mL at Week 2 to approximately 10 mcg/mL at Week 12; whereas the adalimumab concentrations at Week 2 and Week 12 were relatively similar in HiSCR non-responders.

Table 2.4.1.a. Mean±SD serum adalimumab concentrations in subjects with HS in Period A of the Phase 3 studies. Adalimumab was administered at Week 0 (160 mg) and Week 2 (80 mg) followed by 40 mg ew treatment starting at Week 4. (Data source: Summary of Clinical Pharmacology, Table 3, Page 12)

Studies	Adalimumab concentrations (mcg/mL, Mean±SD, n)				
	Week 0	Week 2	Week 4	Week 8	Week 12
Study M11-313	0.026±0.327 (n=153)	7.69±3.69 (n=149)	7.45±4.52 (n=148)	7.64±5.12 (n=146)	8.66±6.39 (n=145)
Study M11-810	0±0 (n=163)	7.38±3.29 (n=161)	7.45±4.18 (n=161)	8.61±5.41 (n=158)	8.95±6.27 (n=153)

Table 2.4.1.b. Serum adalimumab concentrations by HiSCR response at Week 12 for subjects randomized to adalimumab 40 mg ew in Period A of the Phase 3 studies. (Data source: Table 6, page 40, M11-313 Pharmacokinetic Report, R&D/13/1066; and Table 6, page 40, M11-810 Pharmacokinetic Report, R&D/14/0335)

Studies	HiSCR response	Adalimumab concentrations, mcg/mL (mean±SD, n)				
		Week 0	Week 2	Week 4	Week 8	Week 12
M11-313	responders	0.063±0.506 (n=64)	8.03±3.69 (n=62)	8.27±4.09 (n=62)	8.74±5.01 (n=63)	10.6±6.34 (n=63)
	non-responders	0±0 (n=81)	7.40±3.74 (n=81)	6.79±4.49 (n=81)	6.95±5.01 (n=78)	7.20±6.04 (n=79)
M11-810	responders	0±0 (n=96)	7.75±3.11 (n=96)	8.36±4.08 (n=95)	9.82±5.32 (n=96)	10.3±6.04 (n=93)
	non-responders	0±0 (n=62)	6.62±3.40 (n=60)	6.10±4.00 (n=62)	6.81±5.05 (n=61)	6.92±6.12 (n=59)

Period B

The PK data in Period B (Week 12-Week 36) were summarized in Table 2.4.1.c.

- In subjects who continued on adalimumab 40 mg ew regimen in Period B (40 mg ew→ew), the mean serum adalimumab concentrations were in general maintained at the steady state with mean values ranging from 7 to 11 mcg/mL.
- In subjects who transitioned from adalimumab 40 mg ew in Period A to 40 mg eow in Period B (40 mg ew→eow), the mean adalimumab serum concentrations declined starting from Week 14 and achieved steady state at approximately at Week 20 to Week 24. At Week 36, their mean concentrations were about 4 mcg/mL.
- In subjects who transitioned from adalimumab 40 mg ew in Period A to placebo in Period B (40 mg ew→p), adalimumab serum concentrations declined with time and became undetectable after Week 24.
- For subjects who transitioned from placebo in Period A to adalimumab 40 mg ew in Period B (p→40 mg ew), the steady state serum adalimumab concentrations were achieved approximately by Week 20, with a mean concentration of about 10 mcg/mL.

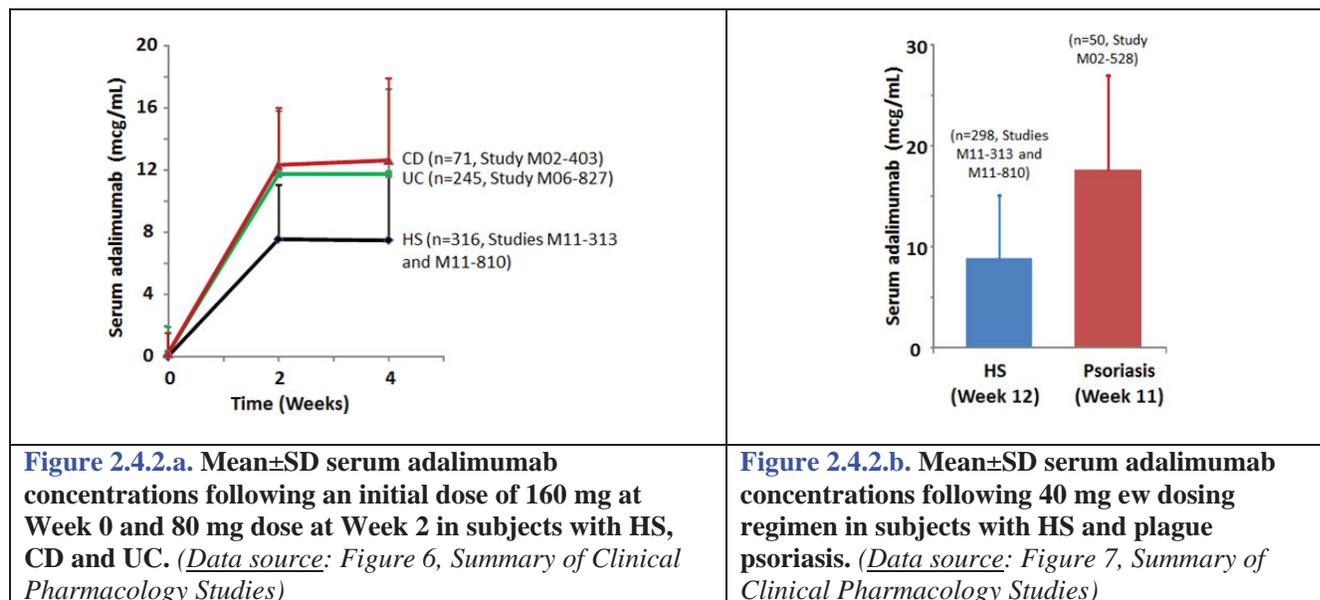
Table 2.4.1.c. Mean±SD serum adalimumab concentrations in subjects with HS in Period B of the Phase 3 studies by treatment groups. p, placebo; (Data source: Table 5, M11-313 Pharmacokinetic Report, R&D/13/1066)

Studies	Treatment groups	Adalimumab concentrations (mcg/mL, Mean±SD, n)						
		Week 12	Week 14	Week 16	Week 20	Week 24	Week 32	Week 36
M11-313	40 mg ew→ew	8.53±6.70 (n=48)	9.93±8.06 (n=45)	9.21±6.80 (n=39)	9.83±7.33 (n=35)	9.45±7.06 (n=32)	11.1±8.19 (n=28)	11.1±8.90 (n=28)
	40 mg ew→eow	9.46±6.96 (n=48)	7.14±5.74 (n=41)	6.78±5.15 (n=35)	5.60±4.70 (n=32)	4.63±4.01 (n=29)	4.28±3.91 (n=27)	3.73±2.89 (n=27)
	40 mg ew→p	8.02±5.48 (n=49)	4.73±3.85 (n=45)	2.74±2.74 (n=41)	1.35±2.18 (n=34)	0.318±0.5 39 (n=31)	0.021±0.0 79 (n=23)	0.010±0.0 47 (n=22)
	p→40 mg ew	0.069±0.6 37 (n=141)	6.74±3.67 (n=138)	8.48±4.99 (n=122)	9.72±6.24 (n=116)	10.2±7.18 (n=111)	10.4±7.70 (n=95)	9.86±7.72 (n=92)
M11-810	40 mg ew→ew	7.60±5.11 (n=50)	7.22±4.95 (n=47)	7.55±4.65 (n=41)	7.33±4.92 (n=38)	7.51±5.64 (n=35)	8.10±5.99 (n=29)	8.51±6.40 (n=27)
	40 mg ew→eow	8.71±6.05 (n=53)	6.39±4.88 (n=48)	5.87±5.01 (n=45)	4.37±4.01 (n=39)	4.42±4.11 (n=31)	4.06±2.68 (n=24)	4.39±3.71 (n=24)
	40 mg ew→p	10.5±7.26 (n=50)	5.55±4.47 (n=47)	4.19±4.18 (n=37)	1.58±1.66 (n=34)	0.486±0.8 07 (n=29)	0.071±0.1 87 (n=23)	0.020±0.0 81 (n=22)

2.4.2. What are the differences of adalimumab PK in HS compared to other indications?

Serum adalimumab concentrations in subjects with HS appeared to be lower (~ 50-60%) compared to those observed in other disease populations, including UC, CD, and Psoriasis, when adalimumab was administered following the same dosing regimen.

Following the initial doses of 160 mg at Week 0 and 80 mg at Week 2, the mean±SD serum adalimumab trough concentrations were 7.53±3.49 mcg/mL and 7.45±7.34 mcg/mL in subjects with HS, 11.7±4.07 mcg/mL and 11.7±5.5 mcg/mL in subjects with UC, and 12.3±3.68 mcg/mL and 12.6±5.25 mcg/mL in subjects with CD at Week 2 and Week 4, respectively (Figure 2.4.2.a). Following the 40 mg ew treatment to steady state, the mean±SD adalimumab concentrations in subjects with HS were 8.81±6.32 mcg/mL at Week 12 compared to 17.6±9.31 mcg/mL in subjects with plaque psoriasis at Week 11 (Figure 2.4.2.b).



2.5. Intrinsic Factors

2.5.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure in HS patients?

The Applicant used a population PK analysis approach to assess the inter-subject exposure variability and intrinsic factors contributing to the variability in subjects with HS. The analyses were performed based on combined data from Studies M10-467, M11-313 and M11-810 (n=600) using a structural model established in previous development programs for other indications.

Baseline C-reactive protein (CRP) level and body weight were the most significant covariates for CL; CL increased with increasing CRP and body weight. Body weight was also a significant covariate for V; V increased with increasing body weight. Additionally, formation of anti-adalimumab antibodies was also found to be associated with lower serum adalimumab concentrations and higher CL (see section 2.7 and pharmacometrics review for details).

Body weight

The adalimumab clearance and apparent volume of distribution increased with increasing body weight (Figure 2.5.1.a, left panel). The *post-hoc* estimates of individual CL values by body weight quartiles

are summarized in Figure 2.5.1.a (right panel). The mean±SD CL values were 0.56±0.47 L/day, 0.63±0.43 L/day, 0.85±0.57 L/day, and 1.03±0.69 L/day across the baseline body weight quartiles. Similarly, V values increased with increasing body weight. Of note, a fraction of data points scattered substantially above the regression line in the CL vs. BW plot, indicating other factors contributed to the variability of CL in addition to BW.

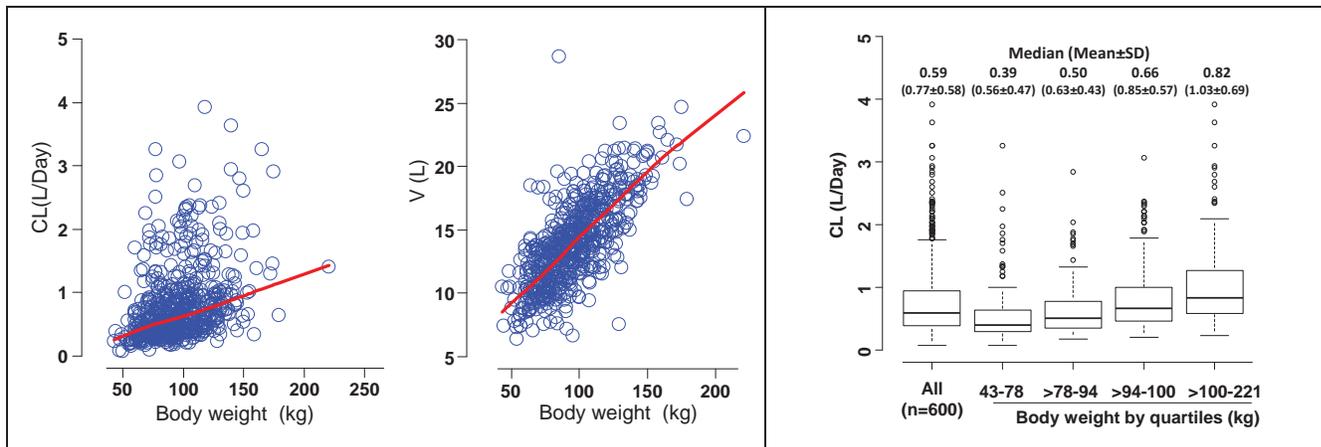


Figure 2.5.1.a. The influences of body weight on adalimumab clearance and apparent volume of distribution based on *post-hoc* population PK analysis. (Data source: reviewer’s analysis using dataset “ada-pksim-revaava.xpt” and NONMEM code “poppk-newada.ctl” provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

Baseline CRP

The mean±SD value of baseline CRP levels for all 600 subjects in the population PK database was 16.4±21.6 (ranging from 0.1 to 189 mcg/mL, median value of 7.9 mcg/mL). Based on the *post-hoc* estimate of individual CL value from the population PK analysis, the adalimumab clearance increased with increasing baseline CRP level (Figure 2.5.1.b). The mean clearance values were 0.54±0.38 L/day, 0.61±0.39 L/day, 0.79±0.55 L/day, and 1.14±0.73 L/day across the baseline CRP level quartiles. Of note, a fraction of data points scattered substantially above the regression line for the CL vs. CRP plot, indicating other factors, e.g., BW, contributed to the variability of CL in addition to CRP.

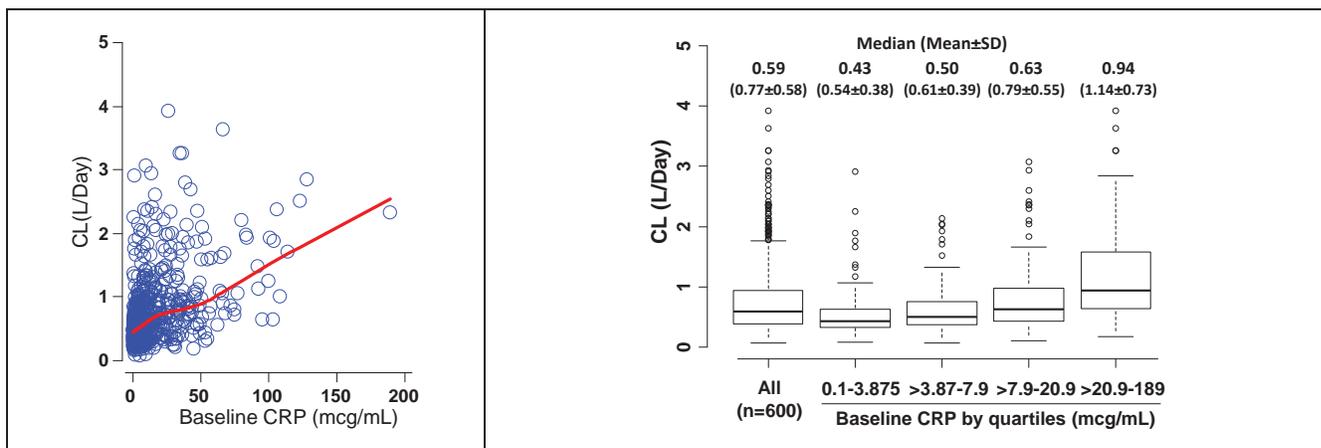


Figure 2.5.1.b. The influence of baseline CRP level on adalimumab clearance based on *post-hoc* population PK analysis. (Data source: reviewer’s analysis using dataset “ada-pksim-revaava.xpt” and NONMEM code “poppk-newada.ctl” provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

Age

The subjects in the population PK database had age ranging from 18 to 67 years (median=35). The adalimumab clearance increases slightly with increasing age. The median CL value by subjects age quartiles were 0.49 L/day, 0.56 L/day, 0.67 L/day, and 0.65 L/day, respectively.

There were only 6 subjects with age >65 years and the median CL value among the six subjects was 0.74 L/day.

Race

A total of 472 of 600 subjects (79%) were white in the population PK database. Based on the limited number of non-white subjects, the *post-hoc* population PK analysis did not indicate significant influences of race on adalimumab clearance (Figure 2.5.1.c).

Sex

PK data from 204 men and 396 women were included in the population PK database. The *post-hoc* population PK analysis did not show significant influences of sex on adalimumab clearance (Figure 2.5.1.c).

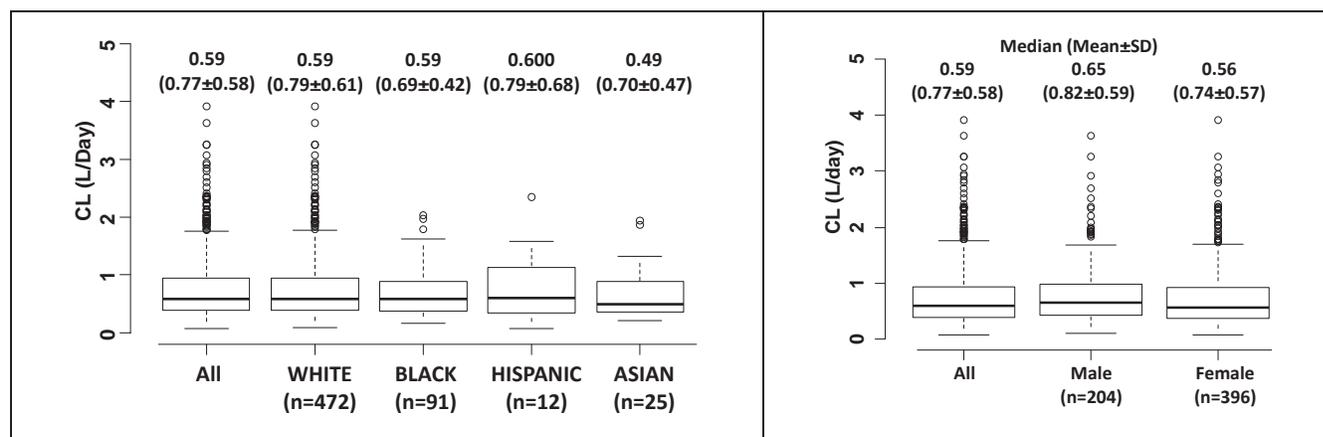


Figure 2.5.1.c. The influences of race and sex on adalimumab clearance based on *post-hoc* PopPK analysis. (Data source: reviewer's analysis using dataset "ada-pksim-revaaa.xpt" and NONMEM code "poppk-newada.ctl" provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

2.5.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended?

Based on the identified covariates that impact adalimumab exposure in subjects with HS and the identified exposure-response relationship for efficacy, subjects with high baseline CRP level and/or high body weight were associated with lower adalimumab exposure and lower HiSCR response rate at Week 12; however, dose adjustment based on body weight or CRP level is not recommended for the following reasons:

- Subjects with high baseline CRP level and/or high body weight did not preclude a HiSCR response because subgroup analysis showed that they still achieved an HiSCR response rate numerically higher than the overall response rate observed in placebo group.
- Subjects with high baseline CRP level could represent a disease condition with a more severe inflammatory process; therefore, it is not clear whether increasing exposure in these subjects could achieve additional therapeutic benefit.

- The proposed maintenance dosing regimen 40 mg ew for the HS indication is already the highest among all approved indications for HUMIRA. The safety for an even higher dose is unknown.

Because of the observed E-R relationship for HiSCR at Week 12 and the decreasing adalimumab exposure with increasing CRP level and increasing body weight, we conducted subgroup analyses for HiSCR by baseline CRP level and by body weight. Compared to the placebo response of 26.8%, the results below showed higher response rates in all subgroups at Week 12:

- The HiSCR response rate decreased with increasing baseline CRP levels: 65%, 60%, 43% and 37% across the four quartiles of baseline CRP levels (Table 2.5.2.a).
- The HiSCR response rate decreased with increasing baseline body weight: 57%, 53%, 46% and 49% across the four quartiles of baseline bodyweight (Table 2.5.2.b).
- The HiSCR response rate was 35% (9/26) in subjects whose CRP and body weight were both in the highest quartile, i.e., CRP level >21 mcg/mL and body weight >107 kg (Figure 2.5.2.a).
- There was a correlation between body weight and baseline CRP level where subjects with higher body weight were also associated with higher baseline CRP level (Figure 2.5.2.b).

Table 2.5.2.a. The HiSCR response rates by baseline CRP level quartiles. (Data source: Reviewer’s analysis. Dataset: ‘ada-logreg.xpt’ [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: ‘poppkpd data analysis.R’)

	Placebo (N=317)	Subgroups by baseline CRP level quartiles				
		Q1 (N=79)	Q2 (N=79)	Q3 (N=76)	Q4 (N=78)	Combined (N=312)
Baseline CRP, mcg/mL, median [range]	9.2 [0.2-246]	1.4 [0.1 to <=3.3]	5.2 [>3.3 to <=8.3]	12.5 [>8.3 to <=21.2]	37.8 [>21.2 to 189]	8.3 [0.1-189]
HiSCR responders% (n)	26.8% (85)	64.6% (51)	59.5% (47)	43.4% (33)	37.2% (29)	51.3% (160)
Week 12 CRP, mcg/mL, median [range]	8.2 [0.2-154]	1.1 [0.1-69.1]	2.9 [0.4-30.0]	7.0 [1.8-42.8]	21.1 [1.5-151]	4.9 [0.1-151]
Adalimumab (mcg/mL), median [range]	0	11.3 [0-29.4]	8.7 [0-25.2]	8.2 [0-29.0]	4.8 [0-21.1]	8.32 [0 to 29.4]

Table 2.5.2.b. The HiSCR response rates by baseline bodyweight quartiles. (Data source: Reviewer’s analysis. Dataset: ‘ada-logreg.xpt’ [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: ‘poppkpd data analysis.R’)

	Placebo (N=317)	Subgroups by baseline bodyweight quartiles				
		Q1 (N=79)	Q2 (N=79)	Q3 (N=78)	Q4 (N=76)	Combined (N=312)
Baseline bodyweight, kg, median [range]	94 [41-221]	67 [43 to <=76]	84 [>76 to <=91]	98 [>1 to <=107]	121 [>107 to 179]	91 [43-179]
HiSCR responders% (n)	26.8% (85)	57.0% (45)	53.2% (42)	46.2% (36)	48.7% (37)	51.3% (160)
Baseline CRP, mcg/mL, median [range]	9.2 [0.2-246]	3.3 [0.1 -103]	6.5 [0.2-104]	9.6 [0.1-189]	13.9 [0.8-83.8]	8.3 [0.1-189]
Week 12 CRP, mcg/mL, median [range]	8.2 [0.2-154]	2.3 [0.1-75.7]	4.9 [0.4-102]	6.3 [0.2-151]	7.1 [0.4-97.1]	4.9 [0.1-151]
Adalimumab(mcg/mL), median [range]	0	11.8 [0-29.4]	8.9 [0-23.8]	7.8 [0-21.1]	6.8 [0-19.1]	8.32 [0 to 29.4]

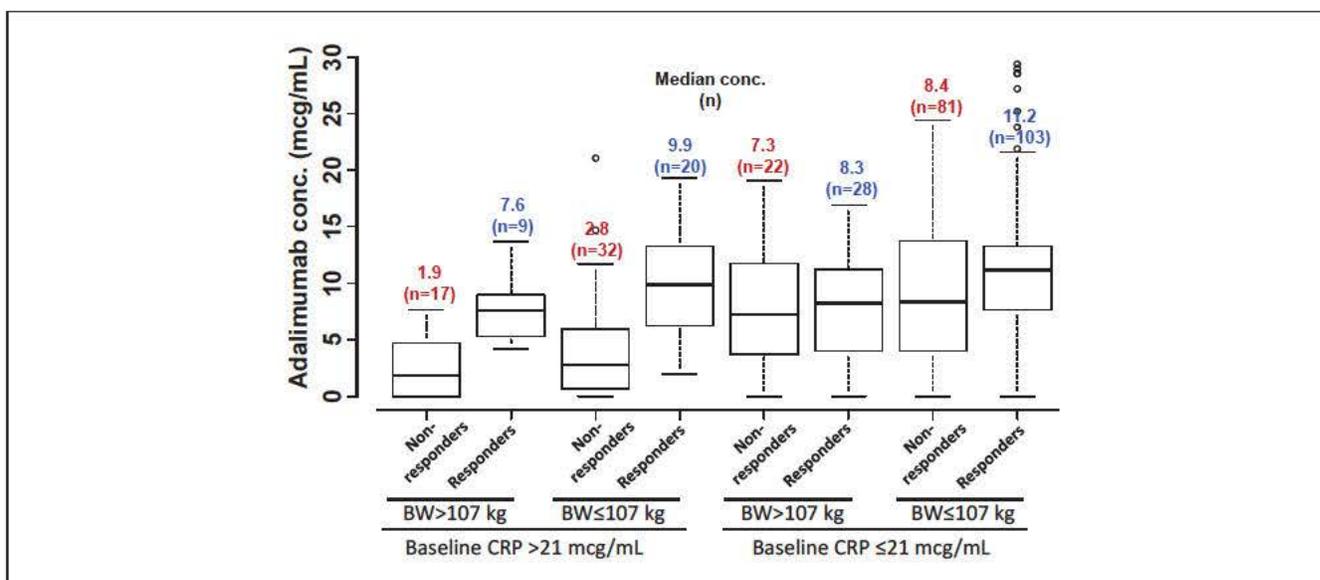


Figure 2.5.2.a. The HiSCR response rates by baseline bodyweight (>107 kg or ≤107 kg) and baseline CRP level (>21 mcg/mL or ≤21 mcg/mL). (Data source: Reviewer's analysis. Dataset: 'ada-logreg.xpt' [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: 'popkpd data analysis.R')

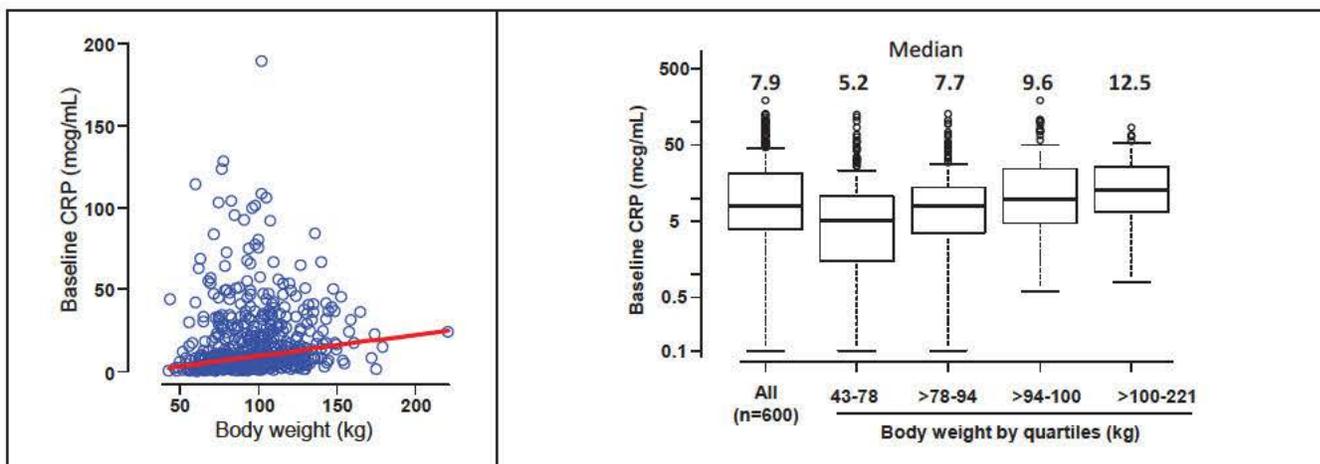


Figure 2.5.2.b. Subjects with higher body weight were associated with higher baseline CRP level. (Data source: reviewer's analysis using dataset "ada-pksim-revaaa.xpt" and NONMEM code "popk-newada.ctl" provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

2.6. Extrinsic Factors

2.6.1. What are the extrinsic factors that influence exposure and/or response?

Extrinsic factors that could significantly affect adalimumab exposure and/or response have not been studied or identified.

2.6.2. What are the drug-drug interactions?

Drug-drug interaction (DDI) studies have not been conducted for adalimumab.

2.6.3. Does the label specify co-administration of another drug?

No.

2.6.4. What other co-medications are likely to be administered to the target population(s)?

Currently there are no approved therapies for HS. In Phase 3 Studies M11-313 and M11-810, almost all subjects reported prior antibiotic use and all subjects received some concomitant medications during the study period (*Date source: section 11.2, CSR M11-313, R&D/13/1011; section 11.2, CSR M11-810, R&D/14/0252*). The major co-medications include antibiotics (e.g., minocycline and doxycycline) and pain relievers (e.g., acetaminophen and ibuprofen).

2.6.5. Is there a known mechanistic basis for pharmacodynamic- or disease-drug-drug interactions?

Yes, there is a potential for HS disease-drug-drug interaction (disease-DDI). We recommend that the Applicant conducts a clinical trial as a PMC study to assess whether adalimumab alters the metabolism or PK of CYP substrates in HS patients treated with adalimumab.

HS is a disease condition that involves altered expression of proinflammatory cytokines. Cytokines or cytokine modulators could modify the formation and activity of CYP enzymes and consequently affect the metabolism or PK of small molecule drugs that are substrates for P450 enzymes. HS disease improvement following biological treatment may normalize the CYP enzyme expression and activity. Because multiple CYP enzymes may be affected, we recommend that the disease-DDI study uses a “cocktail” approach to simultaneously evaluate the effect of adalimumab on the PK of probe substrates metabolized by CYP enzymes including but not limited to CYP3A4, CYP2C19, CYP2C9, CYP2D6 and CYP1A2.

The section 7.4 Cytochrome P450 Substrates of the current HUMIRA product labeling contains the following general language “*The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α , 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.*”

The current product labeling may not be adequate to inform HUMIRA disease-DDI potential in HS patients for the following considerations: (1) a higher maintenance dose (40 mg ew) of HUMIRA is recommended for the HS indication compared to the maintenance dose (40 mg eow) currently approved for other indications; therefore, the disease-DDI potential could be higher in HS patients than in other disease populations, (2) the serum concentrations of adalimumab in subjects with HS were lower than those in other disease populations (e.g., UC, CD, and Psoriasis) at the same dosing regimen, which indicates that HS may represent a different inflammatory disease condition compared to others, and (3) there are currently no other approved biological product for the treatment of HS; therefore, the disease-DDI potential for HUMIRA in HS patients could not be assessed based on other available therapies.

2.7. Immunogenicity

The following terminologies were used in describing the subject immunogenicity status:

- AAA+ subjects: Subjects who received at least one dose of adalimumab and had at least one immunogenicity sample tested positive for AAA.

- “on-treatment” AAA+ subjects: AAA+ subjects who had at least one immunogenicity sample tested positive for AAA and the sample was collected within 30 days after an adalimumab dose.
- “re-classified” AAA+ subjects: AAA+ subjects who were not “on-treatment” AAA+ subjects, i.e., AAA+ subjects whose AAA+ samples were all collected after at least 30 days post an adalimumab dose.

The immunogenicity data in the original sBLA application used the “on-treatment” AAA+ classification for immunogenicity data reporting and analysis. The Applicant provided additional immunogenicity data in the “*Response to March 13, 2015-Clinical Pharmacology Information Request*” submission in which the “re-classified” AAA+ subjects were additionally included into the immunogenicity data reporting and analysis.

2.7.1. What was the incidence of the formation of the anti-adalimumab antibodies (AAA)?

Over the 36-week treatment duration in the Phase 3 Studies M11-810 and M11-313, 12.6% (58/461) of subjects developed AAA, i.e., subjects who received at least one dose of adalimumab and had at least one immunogenicity sample tested positive for AAA. Among the 58 AAA+ subjects, 30 were “on-treatment” AAA+ subjects and 28 were “re-classified” AAA+ subjects. The overall immunogenicity incidence increased from Week 12 to Week 36. Following adalimumab 40 mg ew treatment through Week 12 in Period A, 3.2% (10/316) subjects developed AAA. For subjects continued through Week 36 in Period B, the subject AAA+ incidence ranged from 10.1% to 28.0% across different treatment groups (Table 2.7.1).

Table 2.7.1. The incidence of AAA formation in HS subjects treated with adalimumab in Studies M11-313 and M11-810 combined. The values in black text reflected subject who were “on-treatment” AAA+, i.e., subjects with AAA positive samples collected > 30 days after the last adalimumab dose were not counted. The values in *red italic text* reflected subjects who were either “on-treatment” AAA+ or “reclassified” AAA+, i.e., all subjects with AAA positive samples were counted regardless the immunogenicity sampling time. (*Data source: Reviewer’s analysis. Note: The data are consistent with the Applicant’s analysis results presented in Table 8, Summary of Clinical Pharmacology Studies and Table 1, Response to March 13, 2015 Clinical Pharmacology IR.*)

Treatment groups		AAA incidence (%)		
		Study M11-313	Study M11-810	Total
Through Week 12 (Period A)	adalimumab 40 mg ew	5.2% (8/153)	1.2% (2/163)	3.2% (10/316)
Through Week 36 (for subjects continued Period B)	adalimumab 40 mg ew→ew	10.4% (5/48) ^a	9.8% (5/51) ^b	10.1% (10/99)
	adalimumab 40 mg ew→eow	16.7% (8/48) ^c	9.4% (5/53)	12.9% (13/101)
			<i>11.3% (6/53)^d</i>	<i>13.9% (14/101)</i>
	adalimumab 40 mg ew→p	4.1% (2/49)	0% (0/51)	2% (2/100)
	p→adalimumab 40 mg ew	<i>32.7% (16/49)^e</i>	<i>23.5% (12/51)^f</i>	<i>28% (28/100)</i>
		2.8% (4/145) ^g	--	2.8% (4/145)
		<i>3.4% (5/145)</i>		<i>3.4% (5/145)</i>
All subjects combined through Periods A and B (Weeks 0-36)		6.7% (20/298)	6.1% (10/163)	6.5% (30/461)
		<i>11.7% (35/298)</i>	<i>14.1% (23/163)</i>	<i>12.6% (58/461)</i>
^a Two subjects became AAA+ in Period A. ^b Two subjects became AAA+ in Period A. ^c Three subjects became AAA+ in Period A. ^d One additional subject's AAA+ sample was taken > 30 days from the last adalimumab dose. ^e Two subjects became AAA+ in Period A. Fourteen additional subjects had AAA+ samples taken > 30 days after the last adalimumab dose. ^f Twelve additional subjects had AAA+ samples taken > 30 days after the last adalimumab dose. ^g One additional subject's AAA+ sample was taken > 30 days from the last adalimumab dose, according to the response to IR.				

Reviewer’s comments: Most (26 out of 28) “re-classified” AAA+ subjects were observed in the “adalimumab 40 mg → placebo” treatment group in Period B of the Phase 3 studies. Due to a decline in adalimumab concentrations in these subjects during the placebo treatment period the presence of AAA was detected. Because of the historical drug interference issue with the ELISA assay, AAA could be detected only when serum adalimumab levels were <2 mcg/mL (see section 2.8 for more details). Therefore, it should be noted that the AAA in these subjects was most likely formed during the active adalimumab treatment period not in the placebo treatment period although it is not feasible to determine the exact time of AAA formation based on the current data.

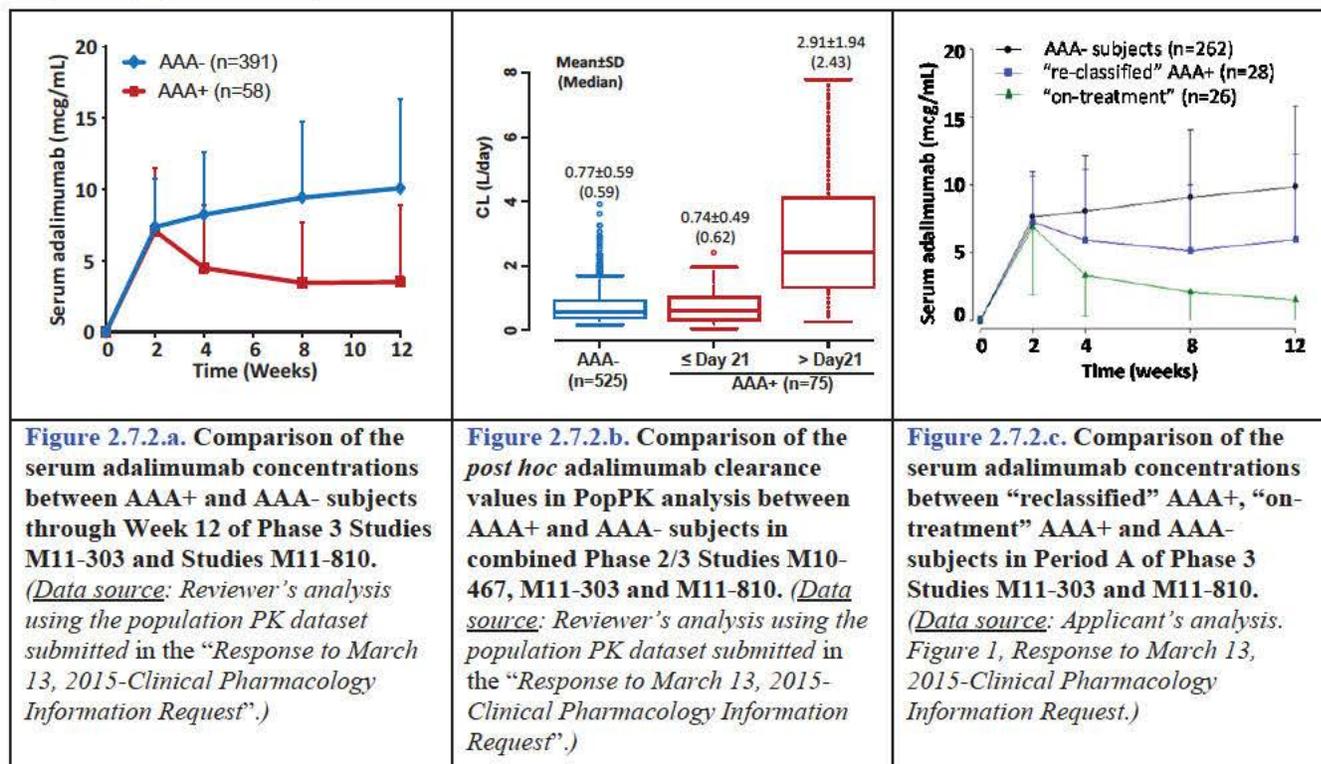
2.7.2. What were the impacts of immunogenicity on adalimumab PK in subjects with HS?

The formation of AAA was associated with reduced serum adalimumab concentrations.

In the Phase 3 studies, the mean±SD serum adalimumab concentrations were similar between the AAA+ subjects (7.1±4.4 mcg/mL) and AAA- subjects (7.3±3.4 mcg/mL) at Week 2. Starting at Week 4 through Week 12, the mean±SD serum adalimumab concentrations were lower in AAA+ subjects (range: 3.4±4.2 mcg/mL to 4.5±4.4 mcg/mL) compared to AAA- subjects (range: 8.2±4.4 mcg/mL to 10.1±6.3 mcg/mL); see Figure 2.7.2.a.

The population PK analysis also showed higher clearance values in AAA+ subjects compared to AAA- subjects. The mean±SD clearance value in AAA+ subjects after Day 21 was 2.91±1.94 L/day compared to 0.77±0.59 L/day in AAA- subjects (Figure 2.7.2.b); whereas the estimated clearance values before Day 21 in AAA+ subjects were similar to the clearance values in AAA- subjects. See *Pharmacometrics Review* for more details.

The Applicant’s analysis also showed that both “on-treatment” AAA+ and “re-classified” AAA+ subjects had lower serum adalimumab concentrations compared to AAA- subjects and that “on-treatment” AAA+ subjects had lower adalimumab concentrations compared to “re-classified” AAA+ subjects (Figure 2.7.2.c).



2.7.3. What was the impact of immunogenicity on efficacy?

The formation of AAA was associated with reduced clinical response rate for HiSCR at Week 12 for the subjects who received the 40 mg adalimumab ew treatment in Period A of the Phase 3 studies. None of the subjects who were “on-treatment” AAA+ in Period A from Study M11-313 (0%, 0/8 subjects) or Study M11-810 (0%, 0/2 subjects) achieved HiSCR at Week 12.

When all AAA+ subjects (both “on-treatment” and “reclassified” AAA+) were included in the efficacy impact analysis, 26.7% (8 out of 30) AAA+ subjects in study M11-313 and 47.8% (11 out of 23) AAA+ subjects in Study M11-810 achieved HiSCR at Week 12, compared to the overall response rates of 42% and 59% in the two Phase 3 studies, respectively.

2.7.4. What was the impact of immunogenicity on safety?

Overall, the formation of AAA did not appear to have a significant impact on the safety of adalimumab in HS subjects. For the safety analysis of all subjects in the Phase 3 studies, the rates of any AE, any infectious AE, and any injection site reaction related AE were comparable between AAA+ and AAA- subjects (Table 2.7.4.a) and were comparable between “on-treatment” AAA+ and AAA- subjects (Table 2.7.4.b).

Table 2.7.4.a. The number and percentage of subjects with treatment-emergent AEs stratified by AAA status in Studies M11-313 and M11-810. ISR, injection site reaction; (*Data source: Table 2 and Table 3, Response to March 13, 2015-Clinical Pharmacology Information Request*)

	AE incidence, n (%)					
	Study M11-313		Study M11-810		Combined	
	AAA- (n=262)	AAA+ (n=36)	AAA- (n=140)	AAA+ (n=23)	AAA- (n=402)	AAA+ (n=59)
Any AE	179 (68%)	23 (64%)	101 (72%)	17 (74%)	280 (70%)	40 (68%)
Any infections AE	90 (34%)	13 (36%)	57 (41%)	11 (48%)	147 (37%)	24 (41%)
Any ISR related AE	14 (5%)	2 (6%)	13 (9%)	0 (0%)	27 (7%)	2 (3%)

Table 2.7.4.b. The number and percentage of subjects with treatment-emergent AEs stratified by “on-treatment” AAA+ Status in Studies M11-313 and M11-810. ISR, injection site reaction; (*Data source: Table 9, Summary of Clinical Pharmacology Studies*)

	AE incidence, n (%)					
	Study M11-313		Study M11-810		Combined	
	AAA- (n=278)	AAA+ (n=20)	AAA- (n=153)	AAA+ (n=10)	AAA- (n=431)	AAA+ (n=30)
Any AE	190 (68%)	12 (60%)	111 (73%)	7 (70%)	301 (70%)	19 (63%)
Any infections AE	97 (35%)	6 (30%)	64 (42%)	4 (40%)	161 (37%)	10 (33%)
Any ISR related AE	15 (5%)	1 (5%)	13 (8%)	0 (0%)	28 (6%)	1 (3%)

2.8. Bioanalytical methods

2.8.1. What bioanalytical methods are used for immunogenicity assessment? Briefly describe the performance of the assays.

Serum AAA was assayed by an ELISA based on a double-antigen technique developed and used since the original BLA application. The assay detects free (unbound) AAA. Due to the historical drug interference issue of the ELISA assay, AAA could be detected only when serum adalimumab levels were <2 mcg/mL. In the characterization of immunogenicity sample AAA status, the sponsor first

measured the adalimumab concentration in the sample, and AAA assessment was conducted only on samples with serum adalimumab concentrations less than 2 mcg/mL whereas serum samples with adalimumab concentrations ≥ 2 mcg/mL were not analyzed for AAA.

Reviewer’s comments: *The applicant is currently developing an improved immunogenicity assay to fulfill PMR #3 listed in the FDA approval letter of BLA 125057/232 (UC indication) dated September 28, 2012. Due to the timing of the completion of the new assay validation, immunogenicity results using the improved assay were not available for the current sBLA. We recommend that the Applicant conducts a PMC/PMR study to reanalyze the banked immunogenicity samples from the HS phase 3 trials using the improved assay and submit the new immunogenicity data for review.*

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The ~~text in red~~ text indicates recommended deletion by the reviewer. The **texts in blue** are recommended labeling changes by the reviewer.

Proposed labeling by the Applicant and Reviewer’s recommendations	Comments
<p>(b) (4) Immunogenicity</p> <p>In (b) (4) with moderate to severe HS, the rate of anti-adalimumab antibody development in patients treated with HUMIRA was (b) (4). However, (b) (4) 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 (b) (4) (b) (4)</p>	<p>See section 2.7 of this review.</p>
<p>12.3 Pharmacokinetics</p> <p>In (b) (4) 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 (b) (4) 7 to 11 µg/mL during HUMIRA 40 mg every week treatment.</p>	<p>See section 2.4 of this review.</p>

4. PHARMACOMETRICS REVIEW

sBLA:	STN 125,057/393
Submission Type:	Efficacy supplement
Product name:	HUMIRA® (adalimumab)
Applicant:	AbbVie Inc.
Pharmacometrics Reviewer:	Jie Wang, Ph.D.
Pharmacometrics Team Leader:	Jeffrey Florian, Ph.D.

4.1. Recommendations and summary of findings

- The submitted pharmacometric information are acceptable to support a recommendation of approval of HUMIRA (adalimumab) for the treatment of active moderate to severe HS in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.
- The dose-/exposure-response relationships for efficacy and safety of adalimumab in HS patients support a recommendation of 160 mg initially on Day 1, 80 mg on Day 15, and 40 mg every week starting from Day 29 as proposed by the Applicant.
- Phase 3 study results demonstrated an exposure-response relationship between HiSCR response rate and serum adalimumab concentrations at Week 12; higher serum adalimumab concentrations were associated with greater HiSCR response rates. The HiSCR response rates were 28.2%, 46.2%, 70.5% and 60.3% across the four quartiles of increasing Week 12 serum adalimumab concentration compared to a 26.8% response rate in the placebo group (Table 1.3.1.a.). The response rate appeared to have achieved a plateau at the third quartile of adalimumab concentrations.
- Based on the identified covariates that impact adalimumab exposure in subjects with HS and the identified exposure-response relationship for efficacy, subjects with higher baseline C-reactive protein (CRP) level and/or higher body weight were associated with lower adalimumab exposure and lower HiSCR response rate at Week 12; however, neither body weight nor the baseline CRP level was a significant covariate to the observed exposure-response relationship. On the other hand, the CRP levels at baseline and at Week 12 were among several covariates found to significantly influence the placebo response. HS subjects with both high baseline CRP level (e.g., >21 mcg/mL) and high body weight (e.g., >107 kg) did not preclude a HiSCR response because subgroup analysis showed that they still achieved HiSCR response rates numerically higher than the overall response rate observed in placebo group. Therefore, no dose adjustment would be recommended based on either the body weight or the baseline CRP level.

4.2. Pertinent background information

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNF α). HUMIRA was initially approved for the treatment of rheumatoid arthritis (RA) in December 2002 and subsequently approved for multiple indications, including psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, juvenile idiopathic arthritis, ulcerative colitis, and pediatric Crohn's disease.

Proposed indication

The current efficacy supplement application is to include a new indication for HUMIRA for the treatment of active moderate to severe hidradenitis suppurativa (HS or acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

Proposed dosing regimen

The proposed dosing regimen is 160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29.

HUMIRA is administered by subcutaneous injection.

Clinical studies to support efficacy, safety and dosing claims

The sBLA is based on four clinical studies: Studies M10-467, M11-810, M11-313 and M12-555.

Study M10-467 was a Phase 2, placebo-controlled, dose-ranging study. Studies M11-810 and M11-313 had similar study design and were two randomized, double-blind, placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of adalimumab at Week 12 (Period A) and Week 36 (Period B). Study M12-555 was an open-label extension study evaluating the efficacy and safety of adalimumab for the subjects rolled over from Studies M11-810 and M11-313 through additional 60 weeks. Study M12-555 is currently ongoing (See *section 2.2* of the *Clinical Pharmacology Review* for details).

Clinical endpoints for efficacy evaluation

The primary efficacy variable in the Phase 3 studies was the proportion of subjects achieving *Hidradenitis Suppurativa Clinical Response (HiSCR)*, which was defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count at Week 12 relative to baseline.

4.3. Question-based review findings

4.3.1. What are the major factors responsible for the inter-subjects variability in adalimumab exposure in subjects with HS?

The Applicant's population PK model analysis identified three major factors contributing to the inter-subjects variability in adalimumab exposure in HS patients: body weight, baseline CRP level, and formation of anti-adalimumab antibodies (AAA). Adalimumab clearance (CL) increased with increasing baseline CRP level, increasing body weight, or after formation of AAA. Body weight was also a significant covariate for apparent volume of distribution (V).

4.3.1.1. Body weight

The adalimumab clearance and apparent volume of distribution increased with increasing body weight ([Figure 4.3.1.1](#), left panel). The *post-hoc* estimates of individual CL values by body weight quartiles are summarized in [Figure 4.3.1.1](#) (right panel). The mean±SD CL values were 0.56±0.47 L/day, 0.63±0.43 L/day, 0.85±0.57 L/day and 1.03±0.69 L/day across the baseline body weight quartiles. Similarly, V values increased with increasing body weight. Of note, a fraction of data points scattered substantially above the regression line in the CL vs. BW plot, indicating other factors contributed to the variability of CL in addition to BW.

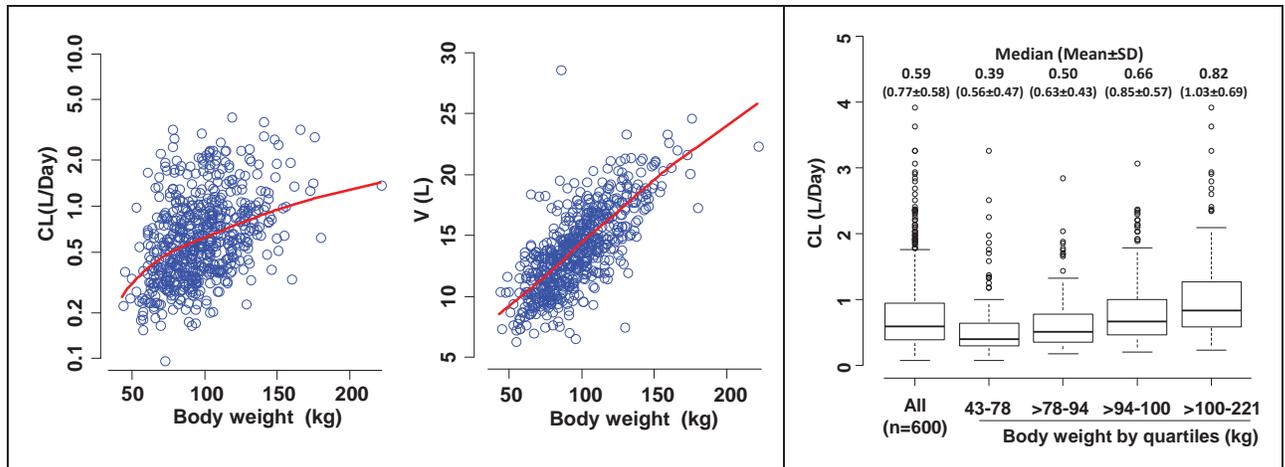


Figure 4.3.1.1. The influences of body weight on adalimumab clearance (CL) and apparent volume of distribution (V) based on *post-hoc* population PK analysis (Note: clearance is plotted as log-transformed scale on the left plot). (Data source: reviewer’s analysis using dataset “ada-pksim-revaaa.xpt” and NONMEM code “poppk-newada.ctf” provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

4.3.1.2. Baseline CRP

The adalimumab CL increased with increasing baseline CRP level (Figure 4.3.1.2). Based on the *post-hoc* estimate of individual CL value from the population PK analysis, the mean±SD clearance values were 0.54±0.38 L/day, 0.61±0.39 L/day, 0.79±0.55 L/day and 1.14±0.73 L/day across the baseline CRP level quartiles.

The mean±SD value of baseline CRP levels for all 600 subjects in the population PK database was 16.4±21.6 (ranging from 0.1 to 189 mcg/mL with a median value of 7.9 mcg/mL).

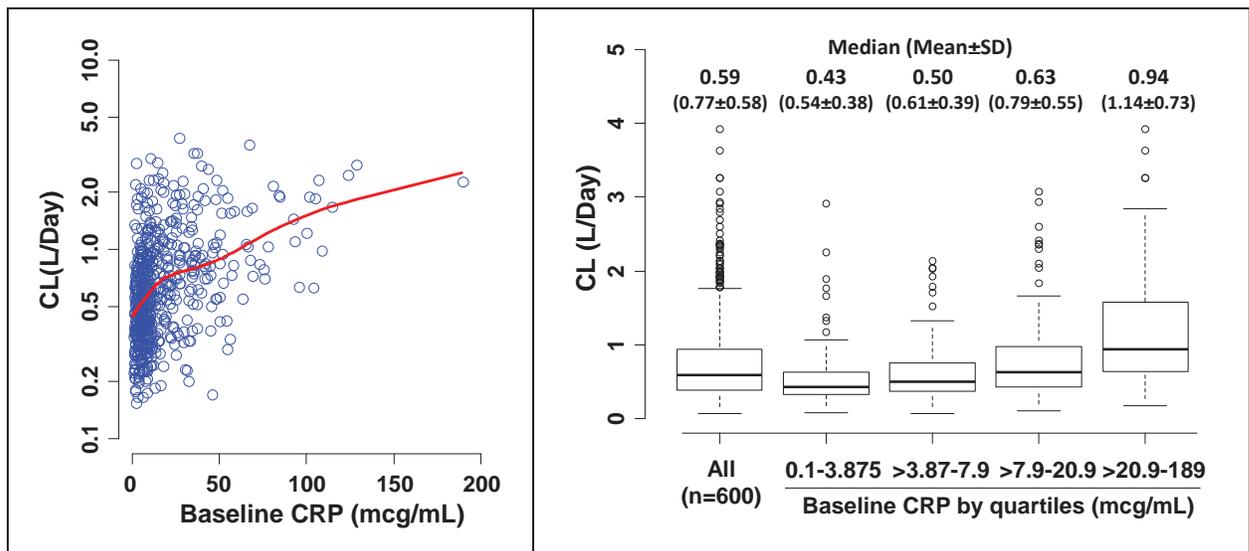


Figure 4.3.1.2. The influences of baseline CRP level on adalimumab clearance (CL) based on *post-hoc* population PK analysis (Note: clearance is plotted as log-transformed scale on the plot). (Data source: reviewer’s analysis using dataset “ada-pksim-revaaa.xpt” and NONMEM code “poppk-newada.ctf” provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

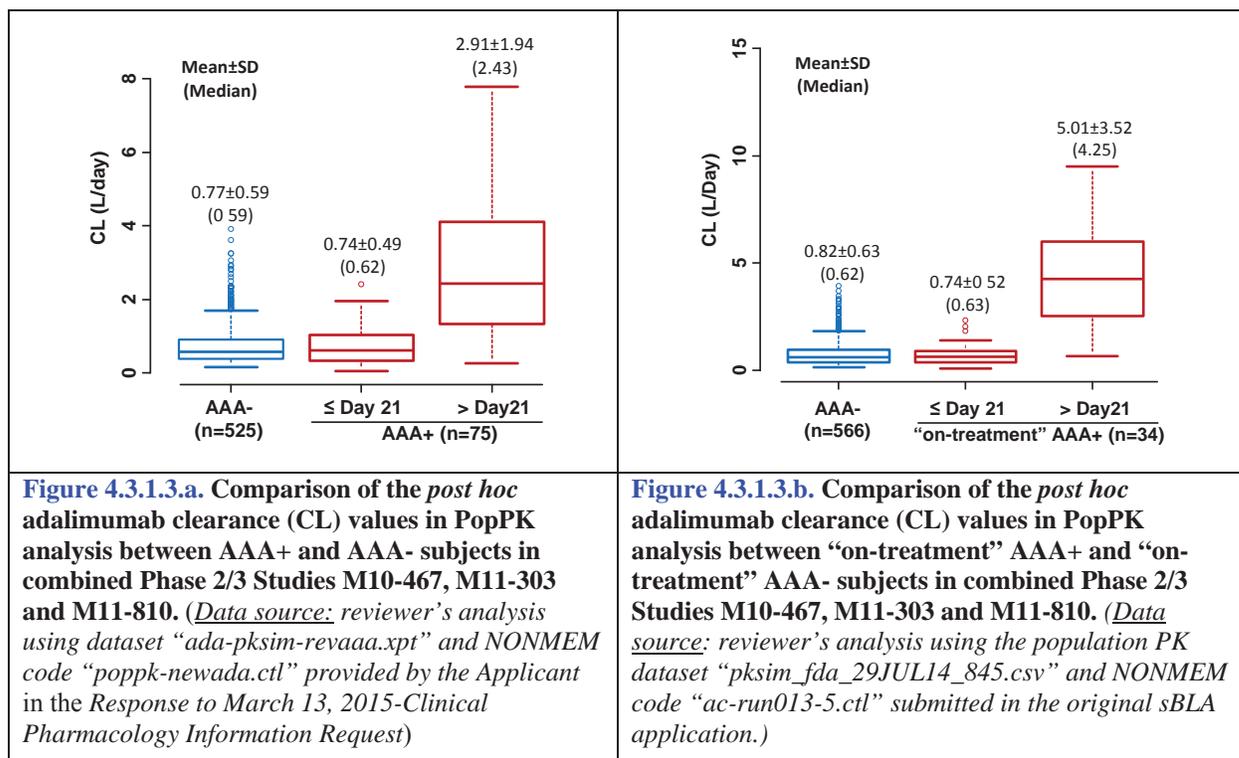
4.3.1.3. Immunogenicity: formation of AAA

The population PK analysis and observed adalimumab concentration data supported that the formation of AAA was associated with increased CL value of adalimumab in subjects with HS.

Based on the *post-hoc* estimate of individual CL value from the population PK analysis, the CL values (after Day 21 following the first dose administration) in AAA+ subjects were 3.8-fold higher than AAA- subjects. The Mean±SD CL value in AAA+ subjects was 2.91±1.94 L/day compared to 0.77±0.59 L/day in AAA- subjects (Figure 4.3.1.3.a).

The formation of “on-treatment” AAA appeared to have an even greater impact on adalimumab CL than the general AAA+ subjects. Based on the *post-hoc* estimate of individual CL value from the population PK analysis, the CL values (after Day 21 following the first dose administration) in “on-treatment” AAA+ subjects were 6.1-fold higher than “on-treatment” AAA- subjects. The Mean±SD clearance value in “on-treatment” AAA+ subjects was 5.01±3.52 L/day compared to 0.82±0.63 L/day in “on-treatment” AAA- subjects (Figure 4.3.1.3b).

See Section 2.7 of *Clinical Pharmacology Review* for subject immunogenicity status definitions and the evaluation of the impact of immunogenicity on efficacy and safety.



4.3.2. Is there evidence of an exposure-response relationship for efficacy between serum adalimumab concentration and HiSCR response rate at Week 12 in the HS Phase 3 trials?

Yes, there was an exposure-response relationship for HiSCR response rate and serum adalimumab concentrations at Week 12; higher serum adalimumab concentrations were associated with greater HiSCR response rates. In HS Phase 3 trials, a statistically significantly higher proportion of subjects treated with the adalimumab 40 mg ew versus placebo achieved HiSCR response at Week 12. The HiSCR response rates were 28.2%, 46.2%, 70.5% and 60.3% across the four quartiles of Week 12 serum adalimumab concentration compared to a 26.8% response rate in the placebo group (Table 4.3.2.1.).

Table 4.3.2.1. The HiSCR response rates by Week 12 serum adalimumab concentration quartiles. (*Data source: Reviewer's analysis using Applicant's dataset 'ada-logreg.xpt'*.)

	Placebo (N=317)	Subgroups by Week 12 serum adalimumab concentration quartiles				
		Q1 (N=78)	Q2 (N=78)	Q3 (N=78)	Q4 (N=78)	Combined (N=312)
Adalimumab (mcg/mL), median [range]	0	1.31 [0 to <=4.01]	6.13 [>4.01 to <=8.27]	10.4 [>8.27 to <=12.6]	16.3 [>12.6 to <=29.4]	8.32 [0 to 29.4]
HiSCR responders% (n)	26.8% (85)	28.2% (22)	46.2% (36)	70.5% (55)	60.3% (47)	51.3% (160)
Baseline BW (kg), median [range]	94.0 [41.0-221.0]	99.0 [60.0-165.0]	93.0 [52.0-179.0]	93.5 [60.0-142.0]	80.7 [43.0-150.0]	91 [43-179]
Baseline CRP (mcg/mL), median [range]	9.2 [0.2-246]	16.9 [0.3-189]	11.1 [0.2-75.10]	5.9 [0.2-103]	5.1 [0.1-49.5]	8.3 [0.1-189]
Week12 CRP (mcg/mL), median [range]	8.2 [0.2-154]	12.7 [0.2-151]	6.1 [0.2-42.70]	2.75 [0.3-23.5]	2.7 [0.2-39.3]	4.9 [0.1-151]

The E-R analysis also showed that the serum adalimumab concentration quartiles at Week 12 had an inverse correlation with CRP levels measured at both the baseline and at Week 12 with higher CRP levels being associated with lower serum adaimumb concentrations. The fourth quartile of the serum adalimumab concentrations was also associated with lower median bodyweight. These results were consistent with the populaiton PK analysis results which showed that baseline CRP level and body weight were the significant covariates for CL.

Univariate logistic regression showed that adalimumab concentration at Week 12 was a significant predictor of increasing HiSCR response at Week 12 (p -value<0.0001) (Figure 4.3.2.1).

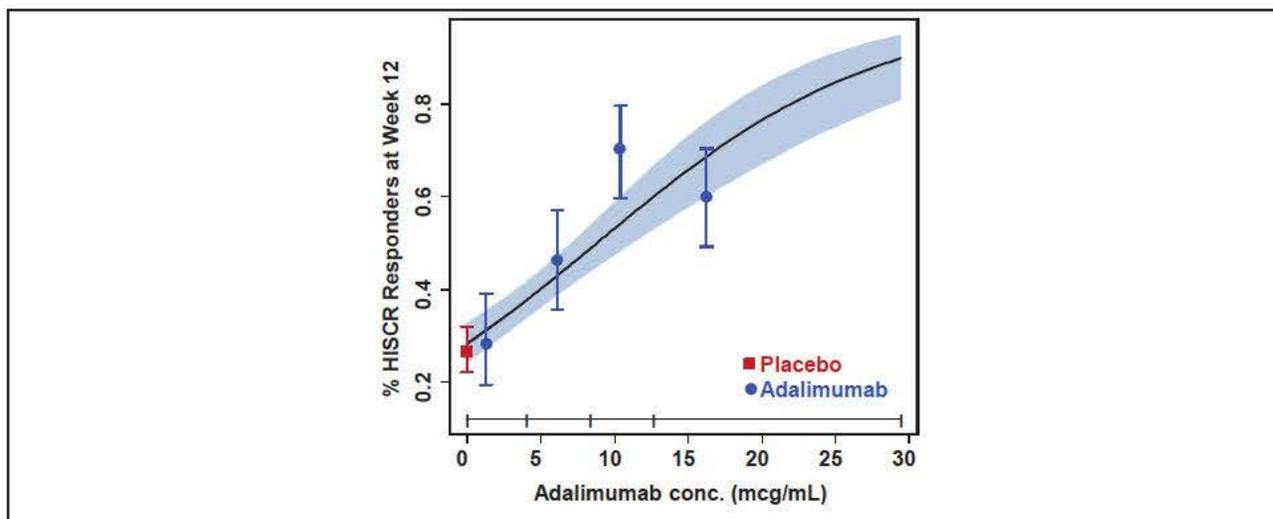


Figure 4.3.2.1. Logistic regression of HiSCR response by serum adalimumab concentrations at Week 12. The shaded area represents 90% prediction interval. From left to right, the legends represent the placebo group and adalimumab concentration quartiles. The HiSCR response rates were 28.2%, 46.2%, 70.5% and 60.3% across the four quartiles of Week 12 serum adalimumab concentration. (*Data source: Reviewer's analysis using Applicant's dataset 'ada-logreg.xpt'*)

The Applicant conducted a multivariate logistic regression analysis in response to an information request from the FDA dated March 13, 2014, in which the final logistic regression model include an Emax relationship for drug effect on HiSCR. See section 4.4.2 for detailed information.

4.3.3. Can the dose be optimized in subgroup of patients with lower efficacy, i.e., patients with high body weight and/or high baseline CRP level?

Based on the identified covariates that impact adalimumab exposure in subjects with HS and the identified exposure-response relationship for efficacy, subjects with high baseline CRP level and/or high body weight were associated with lower adalimumab exposure and lower HiSCR response rate at Week 12; however, dose adjustment based on body weight or CRP level is not recommended for the following reasons:

- Subjects with high baseline CRP level and high body weight did not preclude a HiSCR response because subgroup analysis showed that they still achieved HiSCR response rates numerically higher than the overall response rate observed in placebo group.
- Subjects with high baseline CRP level could represent a disease condition with a more severe inflammatory process; therefore, it is not clear whether increasing exposure in these subjects could achieve additional therapeutic benefit.
- The proposed maintenance dosing regimen 40 mg ew for the HS indication is already the highest among all approved indications for HUMIRA. The safety for an even higher dose is unknown.

Because of the observed E-R relationship for HiSCR at Week 12 and the decreasing adalimumab exposure with increasing CRP level and increasing body weight, we conducted subgroup analyses for HiSCR by baseline CRP level and by body weight. The results are presented below.

Subgroup analysis by baseline CRP level

The HiSCR response rate decreased with increasing baseline CRP levels (Table 4.3.3.1). The HiSCR response rates were 65%, 60%, 43% and 37% across the four quartiles of baseline CRP levels, all numerically higher than the overall placebo response rate of 26.8%.

Table 4.3.3.1. The HiSCR response rates by baseline CRP level quartiles. (Data source: Reviewer's analysis. Dataset: 'ada-logreg.xpt' [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: 'popkpd data analysis.R')

	Subgroups by baseline CRP level quartiles					
	Placebo (N=317)	Q1 (N=79)	Q2 (N=79)	Q3 (N=76)	Q4 (N=78)	Combined (N=312)
Baseline CRP, mcg/mL, median [range]	9.2 [0.2-246]	1.4 [0.1 to <=3.3]	5.2 [>3.3 to <=8.3]	12.5 [>8.3 to <=21.2]	37.8 [>21.2 to 189]	8.3 [0.1-189]
HiSCR responders % (n)	26.8% (85)	64.6% (51)	59.5% (47)	43.4% (33)	37.2% (29)	51.3% (160)
Week 12 CRP, mcg/mL, median [range]	8.2 [0.2-154]	1.1 [0.1-69.1]	2.9 [0.4-30.0]	7.0 [1.8-42.8]	21.1 [1.5-151]	4.9 [0.1-151]
Adalimumab (mcg/mL), median [range]	0	11.3 [0-29.4]	8.7 [0-25.2]	8.2 [0-29.0]	4.8 [0-21.1]	8.32 [0 to 29.4]

Subgroup analysis by body weight

The HiSCR response rate decreased with increasing baseline body weight (Table 4.3.3.2). The HiSCR response rates were 57%, 53%, 46% and 37% across the four quartiles of baseline bodyweight, all numerically higher than the overall placebo response rate of 26.8%.

Table 4.3.3.2. The HiSCR response rates by baseline body weight quartiles. (Data source: Reviewer's analysis. Dataset: 'ada-logreg.xpt' [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: 'popkpdp data analysis.R')

	Subgroups by baseline body weight quartiles					
	Placebo (N=317)	Q1 (N=79)	Q2 (N=79)	Q3 (N=78)	Q4 (N=76)	Combined (N=312)
Baseline bodyweight, kg, median [range]	94 [41-221]	67 [43 to <=76]	84 [>76 to <=91]	98 [>1 to <=107]	121 [>107 to 179]	91 [43-179]
HiSCR responders% (n)	26.8% (85)	57.0% (45)	53.2% (42)	46.2% (36)	48.7% (37)	51.3% (160)
Baseline CRP, mcg/mL, median [range]	9.2 [0.2-246]	3.3 [0.1 -103]	6.5 [0.2-104]	9.6 [0.1-189]	13.9 [0.8-83.8]	8.3 [0.1-189]
Week 12 CRP, mcg/mL, median [range]	8.2 [0.2-154]	2.3 [0.1-75.7]	4.9 [0.4-102]	6.3 [0.2-151]	7.1 [0.4-97.1]	4.9 [0.1-151]
Adalimumab(mcg/mL), median [range]	0	11.8 [0-29.4]	8.9 [0-23.8]	7.8 [0-21.1]	6.8 [0-19.1]	8.32 [0 to 29.4]

Subgroup analysis by both baseline CRP level and body weight

The purpose of this analysis is to evaluate whether subjects with both high baseline CRP level and high body weight would still be able to achieve HiSCR response. In subjects whose CRP and body weight were both in the highest quartile, i.e., CRP level >21 mcg/mL and body weight >107 kg, the HiSCR response rate was 35% (9/26) which was numerically higher than the overall placebo response rate of 26.8% (Figure 4.3.3.1). Of note, there was a correlation between body weight and baseline CRP level where subjects with higher body weight were also associated with higher baseline CRP level (Figure 2.5.2.b).

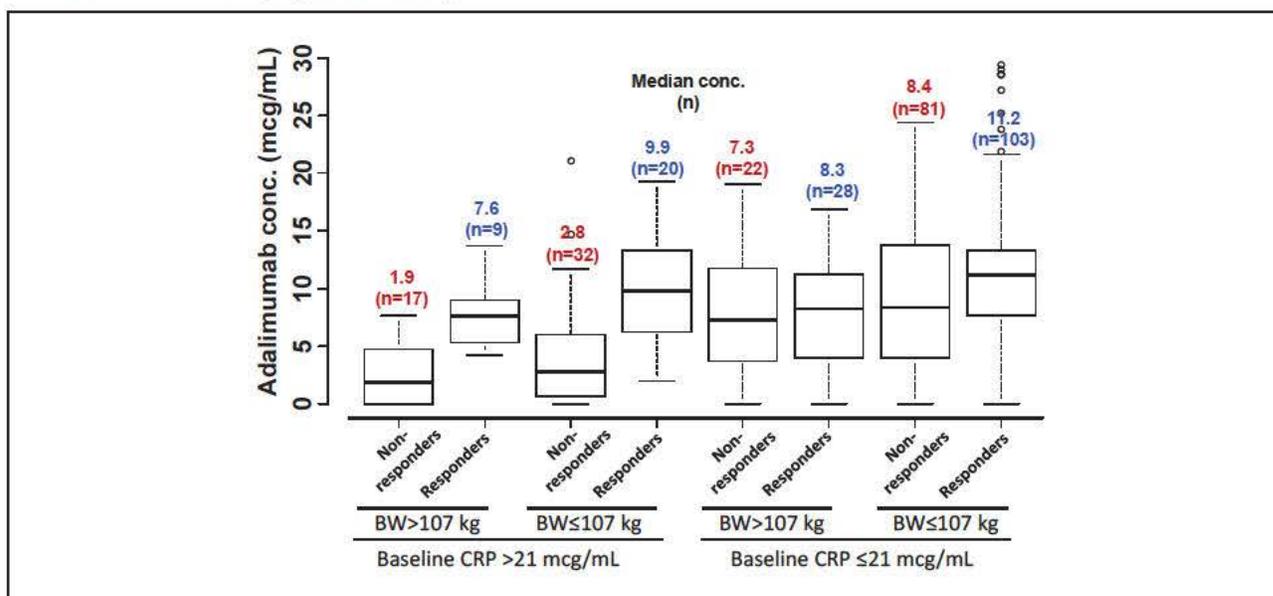


Figure 4.3.3.1. The HiSCR response rates by baseline body weight (>107 kg or ≤107 kg) and baseline CRP level (>21 mcg/mL or ≤21 mcg/mL). (Data source: Reviewer's analysis. Dataset: 'ada-logreg.xpt' [submitted on 03/26/2015 in response to Clinical Pharmacology IR letter]. Analysis R code: 'popkpdp data analysis.R')

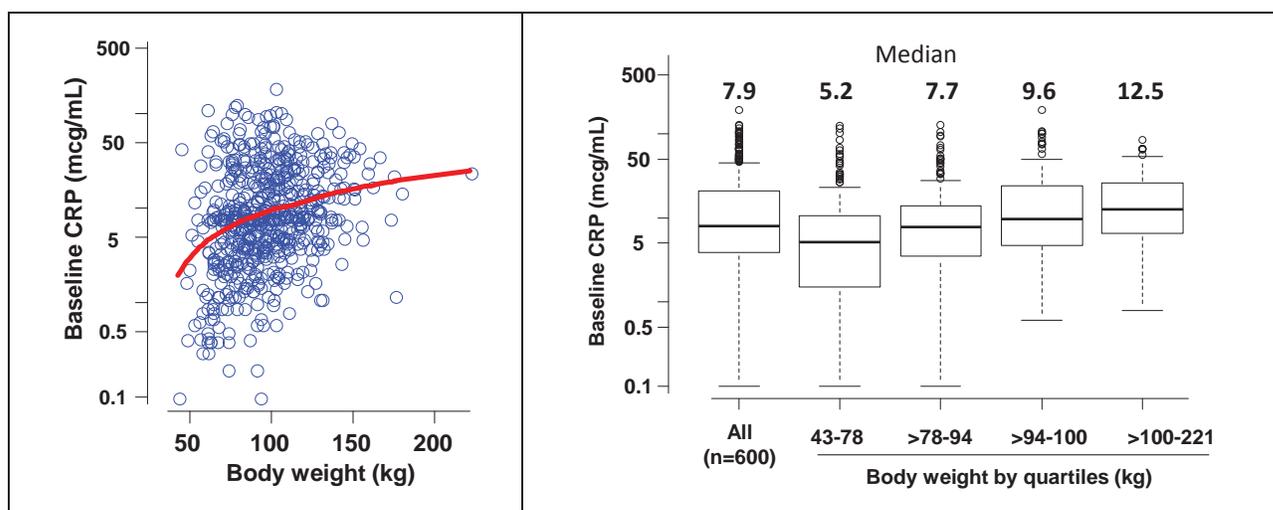


Figure 2.5.2.b. Subjects with higher body weight were associated with higher baseline CRP level (Note: the y-axis of both figures are plotted as log-transformed scale). (Data source: reviewer's analysis using dataset "ada-pksim-revaaa.xpt" and NONMEM code "poppk-newada.ctf" provided by the Applicant in the Response to March 13, 2015-Clinical Pharmacology Information Request)

4.4. Pharmacometric models and analysis results by the Applicant

4.4.1. Population PK model of adalimumab in subjects HS

4.4.1.1. Data source and NONMEM dataset

The Applicant developed a population PK model for adalimumab in HS subjects using a NONMEM dataset with sparse PK data from Phase 2 study M10-467 and Phase 3 studies M11-313 and M11-810. In Study M10-467, pre-dose serum adalimumab concentrations were measured at Baseline and at Weeks 4, 8, 16, 28, 31, 39, 45 and Week 52. In Studies M11-313 and M11-810, pre-dose serum adalimumab concentrations were measured at Baseline and at Weeks 2, 4, 8, 12, 14, 16, 20, 24, 32, and 36.

Among 787 subjects enrolled in the Phase 2/3 studies (154 subjects in Study M10-467, 307 subjects in Study M11-313, and 326 subjects in Study M11-810), a total of 187 subjects were excluded from the population PK analysis because they did not receive active adalimumab treatment at the time of PK analysis (5 subjects in Study M10-467, 7 subjects in Study M11-313, and 163 subjects in Study M11-810) or because they did not have a PK sample with a measurable adalimumab concentration (12 subjects across the three studies). For the population PK analysis, adalimumab concentration values below LLOQ during active treatment were set to LLOQ/2. Overall, a total of 600 subjects and 3,806 PK samples were included in the population PK analyses.

Among the 600 subjects, 396 (66%) were female, 472 (79%) were white, the age range was 18 to 67 years (mean±SD, 37±11 years), the body weight range was 43 to 221 kg (mean±SD, 96±24 kg) (Data source: Table 1, population pharmacokinetic exposure-response report, R&D/14/1054).

4.4.1.2. PopPK model

The population PK model included a first order absorption one-compartment model with correlated exponential terms for inter-individual variability on CL/F and V2/F, a combined residual error model, and a shift factor on CL/F for AAA+ subjects (which led to an increase of CL/F after 3 weeks of adalimumab treatment). The applicant also tested a two compartment model but the data from the current studies was too sparse to fit a two-compartment model ($\Delta\text{OFV} = 0.038$). The final PopPK model is described below:

$$CL/F = \theta_1 \cdot COV1 \cdot COV2 \cdot COV3 \cdot EXP(\eta_1)$$

$$COV1 = AAA_{eff} \quad \begin{array}{l} AAA_{eff} = 1, \text{ for AAA- subjects} \\ AAA_{eff} = 1, \text{ for AAA+ subjects and PK sampling Time} \leq 21 \text{ days} \\ AAA_{eff} = \theta_4, \text{ for AAA+ subjects and PK sampling Time} > 21 \text{ days} \end{array}$$

$$COV2 = (CRP/CRP_{median})^{\theta_5}, \quad CRP_{median} = 7.9 \text{ mcg/mL}$$

$$COV3 = (WTKG/WTKG_{median})^{\theta_6}, \quad WTKG_{median} = 94 \text{ kg}$$

$$V2/F = \theta_3 \cdot COV4 \cdot exp(\eta_2)$$

The impact of AAA on CL/F was estimated by a shift factor in AAA+ subjects, which indicates the onset time when CL/F was increased following AAA formation. The OFV was the lowest when the onset time for AAA shift factor on CL/F was at 3 weeks following the initial adalimumab treatment compared to when the onset time was defined at 1, 2, 4 weeks. Therefore, two values of CL/F were estimated for AAA+ subjects: a basal CL/F for the first 21 days and a shifted CL/F after 21 days due to AAA formation.

Baseline CRP on CL/F was the most significant covariate found in the univariate inclusion. In addition, baseline body weight on CL/F, baseline body weight on V₂/F, age on CL/F and baseline albumin on CL/F were identified as significant covariates in the subsequent forward inclusion procedures.

The covariate of albumin on CL/F was eliminated during the backward elimination procedure.

4.4.1.3. Estimated PK parameters

Based on the population PK analysis, the population means of adalimumab CL/F and V2/F in HS subjects were estimated to be 0.667 L/day and 13.5 L, respectively. Significant covariates for CL/F included the presence of AAA, baseline CRP and baseline body weight. Baseline body weight was also a significant covariate for V2/F. Inter-individual variability for adalimumab CL/F and V2/F was 58.8% and 30.2%, respectively. [Table 4.3.1.3](#) provides the summary PK parameters and their variability of adalimumab in subjects with HS based on the PopPK analysis.

Table 4.3.1.3. Parameter estimates and variability for adalimumab population PK: Final Model. (<i>Data source: Table 6, Population pharmacokinetic exposure-response report, R&D/14/1054</i>)			
Parameter	Population estimates (SEE)	%RSE	95% CI
CL/F (L/day)	0.667 (0.018)	2.65	0.632 – 0.702
V2/F (L)	13.5 (0.459)	3.40	12.6 – 14.4
ka (1/day)	0.195 (0.019)	9.90	0.157 – 0.233
AAA on CL/F	6.76 (0.751)	11.1	5.29 – 8.23
CRP on CL/F	0.173 (0.021)	12.0	0.132 – 0.214
WTKG on CL/F	0.888 (0.107)	12.1	0.678 – 1.10

WTKG on V2/F	0.707 (0.097)	13.7	0.516 – 0.898
Inter-Individual Variability on CL/F (%CV)	0.346 (58.8)	NA	NA
Inter-Individual Variability on V2/F (%CV)	0.091 (30.2)	NA	NA
Residual Error Term – Proportional	0.052 (0.004)	NA	NA
Residual Error Term – Additive	2.06 (0.139)	NA	NA

NA = not applicable
SEE = Standard Error of Estimate
%RSE was estimated as the SEE divided by the population estimate multiplied by 100.
95% CI = 95% Confidence Interval = Estimate \pm 1.96•SEE
%CV = SQRT(ETA) multiplied by 100

4.4.1.4. Goodness-of-fit plots and visual predictive check

The goodness-of-fit for the final population PK model was evaluated graphically as presented in Figure 4.3.1.4.1. For visual predictive checks of the final population PK model, the Applicant generated 1000 simulated replicates of the PK dataset using the \$SIMULATION option in NONMEM. The observed data were plotted against the 90% prediction (5th to 95th percentile) interval for the simulated concentrations versus time (Figure 4.3.1.4.2). The goodness-of-fit plots and visual predictive check in general showed that the population PK model described the central tendency of the observed data.

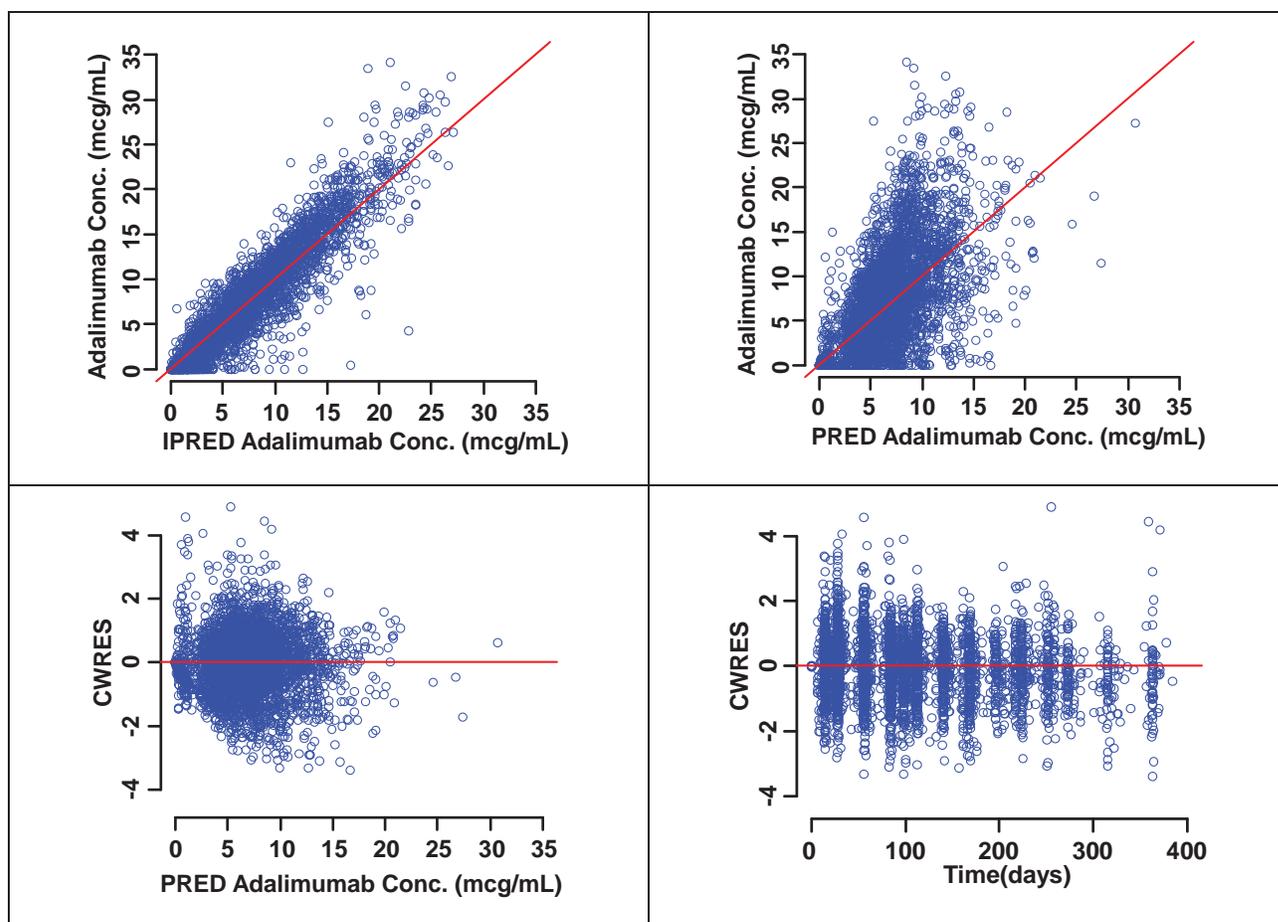


Figure 4.3.1.4.1. Individual (upper left) and population predicted (upper right) versus observed concentrations and conditional weighted residuals versus predicted concentrations (lower left) and versus time (lower right) for final population PK model. (Data source: Reviewer’s plots. These plots are the same as the plots provided by the Applicant in Figure 7, R&D/14/1054)

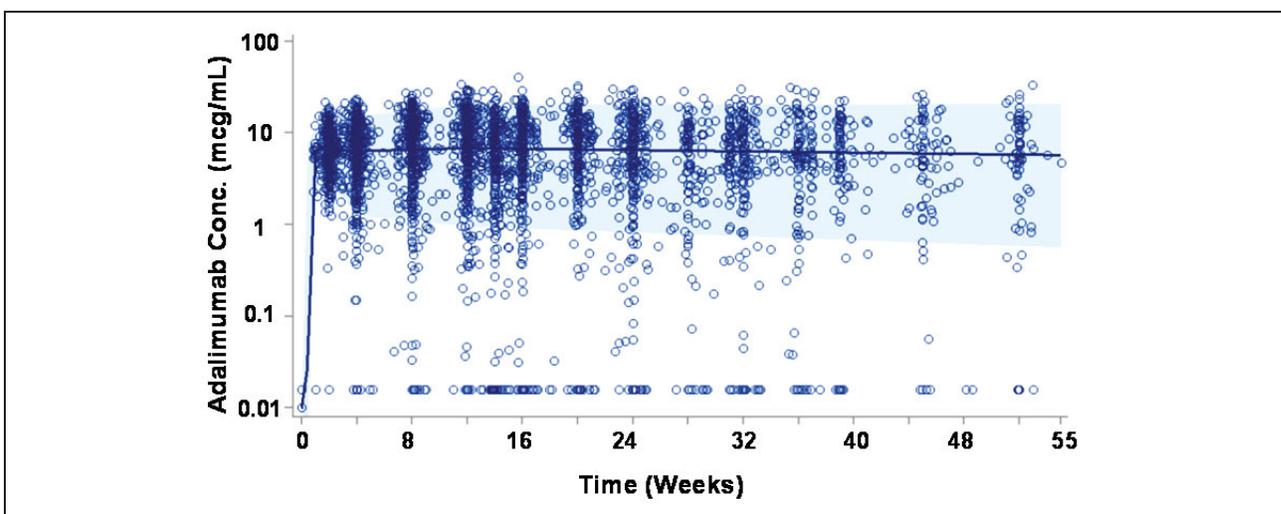


Figure 4.3.1.4.2. Visual predictive checks for final population PK model. The plot shows the observed data with 5th to 95th percentile interval of the simulated/predicted concentrations versus time. Note that majority (~70%) of the observed data points at 0.016 mcg/mL (LLOQ/2) were from AAA+ subjects. (*Data source: Applicant's plots. Figure 8, R&D/14/1054*)

4.4.2. E-R and subgroup analysis for HiSCR response rates at Week 12

In response to Clinical Pharmacology Information Request dated March 13, 2015, the Applicant conducted subgroup analysis of Week 12 HiSCR response rates by subjects body weight, baseline and Week 12 CRP levels, and baseline Hurley Stage and logistic regression analysis of the Week 12 HiSCR response rates by adalimumab concentrations. The Applicant's analysis results are summarized below.

4.4.2.1. Subgroup analysis of Week 12 HiSCR rates by body weight, baseline CRP level, Week 12 CRP and baseline Hurley Stage

Summary tables for the univariate relationships between adalimumab exposure or HiSCR response and patient or disease covariates are provided below in Table 4.3.2.1.1 through Table 4.3.2.1.7. The subgroup analysis results indicated the following:

- An E-R relationship was observed for the Week 12 HiSCR response rate and Week 12 adalimumab concentrations. Subjects with higher serum adalimumab concentrations were associated with greater HiSCR response rates (Table 4.3.2.1.1).
- Body weight showed inverse correlations with both Week 12 adalimumab concentrations and Week 12 HiSCR response rates. Subjects with higher body weight were associated with lower adalimumab concentrations and lower HiSCR response rates (Table 4.3.2.1.2).
- Baseline and Week 12 CRP levels both showed inverse correlations with Week 12 adalimumab concentrations and Week 12 HiSCR response rates. Subjects with either higher baseline or Week 12 CRP levels are associated with lower adalimumab concentrations and lower HiSCR response rates (Table 4.3.2.1.3 and Table 4.3.2.1.4).

- Compared to baseline Hurley State 2, subjects with baseline Hurley Stage 3 were associated with higher CRP levels and lower adalimumab concentrations (Table 4.3.2.1.5 and Table 4.3.2.1.6). Baseline Hurley Stage did not show a correlation with subjects body weight (Table 4.3.2.1.7).

Table 4.3.2.1.1. Week 12 HiSCR response rates by adalimumab concentration quartiles. (*Data source: Table 5, Response to Clinical Pharmacology Information Request March 13, 2015*)

Adalimumab concentration quartiles (mcg/mL)	HiSCR at Week 12 (%)
Placebo	26.8
[0-3.96]	28.2
[4.02-8.27]	46.2
[8.37-12.6]	70.5
[12.7-29.4]	60.3

Table 4.3.2.1.2. Week 12 HiSCR response rates by body weight quartiles for subjects received adalimumab 40 mg ew. (*Data source: Table 6 and Table 9, Response to Clinical Pharmacology Information Request March 13, 2015*)

Body weight quartiles (kg)	Median Week 12 adalimumab concentrations (mcg/mL)	HiSCR at Week 12 (%)
[43-76]	12.3	57.0
[77-91]	9.03	52.5
[92-107]	8.57	46.2
[108-179]	7.60	46.8

Table 4.3.2.1.3. Week 12 HiSCR response rate by baseline CRP level quartiles for subjects received adalimumab 40 mg ew. (*Data source: Table 7, Table 10 and Table 15, Response to Clinical Pharmacology Information Request March 13, 2015*)

Baseline CRP level quartiles (mcg/mL)	Median Week 12 adalimumab concentrations (mcg/mL)	HiSCR at Week 12 (%)
[0.1-3.3]	11.8	64.6
[3.4-8.3]	8.93	59.5
[8.4-21.6]	9.65	43.0
[22-189]	5.76	35.4

Table 4.3.2.1.4. Week 12 HiSCR response rate by Week 12 CRP level quartiles for subjects received adalimumab 40 mg ew. (*Data source: Table 8 and Table 11, Response to Clinical Pharmacology Information Request March 13, 2015*)

Week 12 CRP level quartiles (mcg/mL)	Median Week 12 adalimumab concentrations (mcg/mL)	HiSCR at Week 12 (%)
[0.1-1.9]	12.3	65.4
[2-4.9]	9.56	58.0
[5-10.5]	7.90	50.0
[10.7-151]	5.37	29.1

Table 4.3.2.1.5. Adalimumab concentrations at Week 12 by baseline Hurley Stage for subjects received adalimumab 40 mg ew. (*Data source: Table 12, Response to Clinical Pharmacology Information Request March 13, 2015*)

Baseline Hurley Stage	Week 12 adalimumab concentrations (mcg/mL)		
	Median	Min	Max
2	9.49	0.16	29.4
3	7.96	0.05	29.0

Table 4.3.2.1.6. Baseline CRP level by baseline Hurley Stage. (*Data source: Table 13, Response to Clinical Pharmacology Information Request March 13, 2015*)

Baseline Hurley Stage	Baseline CRP level (mcg/mL)		
	Median	Min	Max
2	5.50	0.10	159
3	13.5	0.10	246

Table 4.3.2.1.7. Baseline body weight by baseline Hurley Stage. (*Data source: Table 14, Response to Clinical Pharmacology Information Request March 13, 2015*)

Baseline Hurley Stage	Baseline body weight (kg)		
	Median	Min	Max
2	91.0	43.0	221
3	94.0	41.0	184

4.4.2.2. Logistic regression of HiSCR rates by adalimumab concentrations at Week 12

The Applicant conducted logistic regression analysis to evaluate the effects patient demographics and disease severity measures on E-R relationship between HiSCR response rate and Week 12 adalimumab concentrations. The Applicant tested linear, E_{max} , and sigmoid E_{max} models and selected the E_{max} model because the comparison of the three models revealed a significant drop in OFV ($p < 0.05$) with the E_{max} model compared to the linear and sigmoid E_{max} models. The Applicant then used the E_{max} model with serum adalimumab concentrations as a predictor for HiSCR response to test for effects of patient or disease covariates on placebo response or drug effect. The results showed the following:

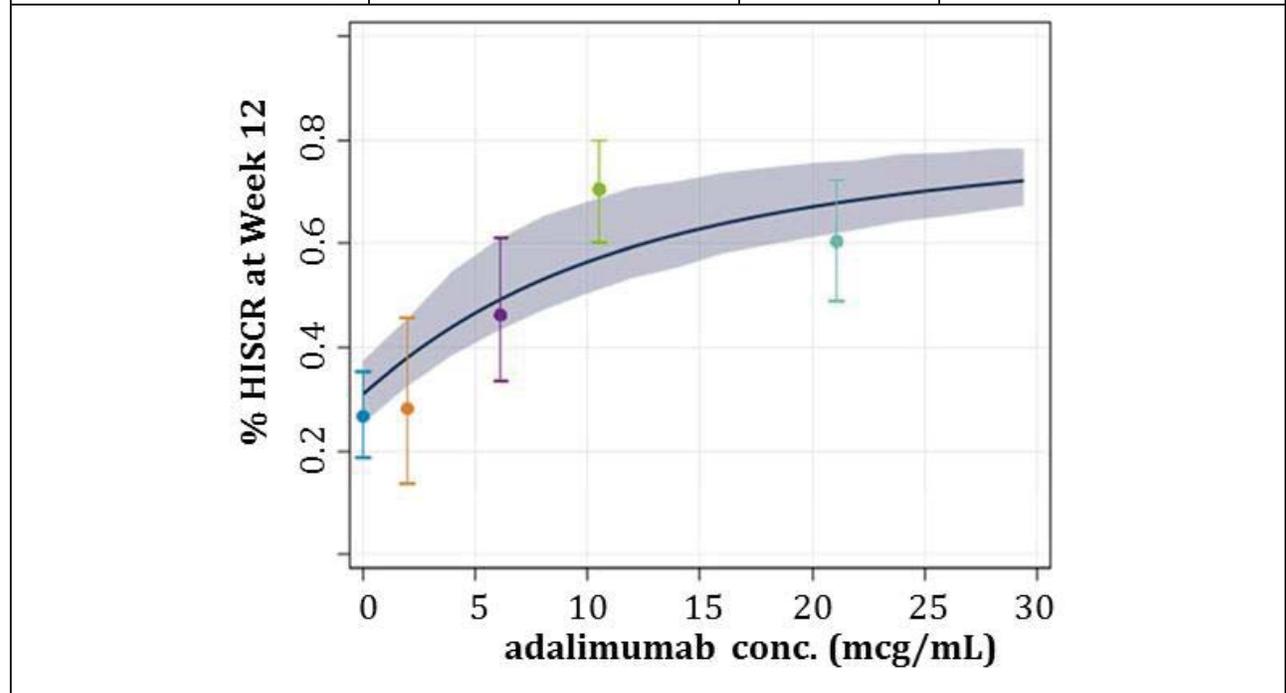
- Among covariates including age, body weight, sex, race, smoking status, AAA status, baseline AN count, baseline NRS score, baseline Sartorius score, baseline draining fistula count, baseline Hurley Stage, duration of HS, co-administration of antibiotics, baseline albumin, baseline CRP, CRP at Week 12, and change in CRP from baseline at Week 12, none was significant on the drug effect on HiSCR response (EC_{50}). This indicates that patient demographics or disease severity measures did not significantly affect the E-R relationship between serum adalimumab concentrations and HiSCR response.
- Covariates including baseline Sartorius score, baseline NRS score, baseline albumin, baseline CRP, CRP at Week 12 were statistically significant on placebo response (model intercept). CRP at Week 12 was the most significant covariate and was added to the model. No more covariates remained significant in the multivariate analysis after addition of Week 12 CRP.

- The final logistic regression model include an E_{max} relationship for drug effect on HiSCR and Week 12 CRP level as a significant predictor of HiSCR response in patients on placebo (Table 4.3.2.2.1).

Reviewer’s comment: The Applicant’s E_{max} model included CRP level at Week 12 as a covariate on placebo response (E₀ or intercept). Because Week 12 CRP level reflects the inflammatory disease condition at the primary efficacy HiSCR assessment time, it is not unexpected that it had an effect on the placebo response rate. However, Week 12 CRP level is an observation available only after treatment is completed and the fallback should be to the covariate of baseline CRP level. As this approach only impacts E₀ of the E_{max} model, it does not alter the reviewer’s conclusions that the available information does not support a need for dose adjustments based on body weight or baseline CRP level.

Table 4.3.2.2.1. Final parameter estimates for the logistic-regression E_{max} model. Figure shows model fit of 90% prediction interval by serum adalimumab concentration quartiles. (Data source: Table 13 and Figure 5, Response to Clinical Pharmacology Information Request March 13, 2015)

Parameter	Population Estimate (SEE)	%RSE	95% Confidence Interval
Intercept	-0.80 (0.14)	-17.93	-1.09 - -0.52
E _{max}	2.63 (fix)	NA	NA
EC50 (mcg/mL)	14.70 (4.93)	33.54	5.04-24.36
CRP at Week 12 on intercept	0.42 (0.10)	24.47	0.22-0.62



CLINICAL PHARMACOLOGY INDIVIDUAL STUDY SUMMARY

sBLA:	STN 125,057/393
Submission Type:	Efficacy supplement
Brand Name:	HUMIRA®
Drug Name:	Adalimumab
Submission Date:	11/10/2014
PDUFA Goal Date:	09/10/2015
Priority:	Standard
Proposed Indication:	Treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.
Proposed Dosing Regimen:	The proposed dosing regimen is 160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29.
Dosage Forms and Strength:	Solution for injection presented in prefilled syringe or autoinjector (currently marketed formulation/presentation).
Applicant:	AbbVie Inc.
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	CDER/ODEIII/DDDP

5. CLINICAL PHAMACOLOGY INDIVIDULE STUDY SUMMARY

This section provides the Individual Study Summary (ISS) for Studies M10-467, M11-810, and M11-313. There are no regulatory recommendations made based on ISS. Refer to the Clinical Pharmacology Question-Based Review (QBR) regarding the Clinical Pharmacology recommendations on the sBLA.

5.1. Study M10-467

5.1.1. Study Title:

- A Phase 2 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Chronic Hidradenitis Suppurativa (HS)

5.1.1. Study Period:

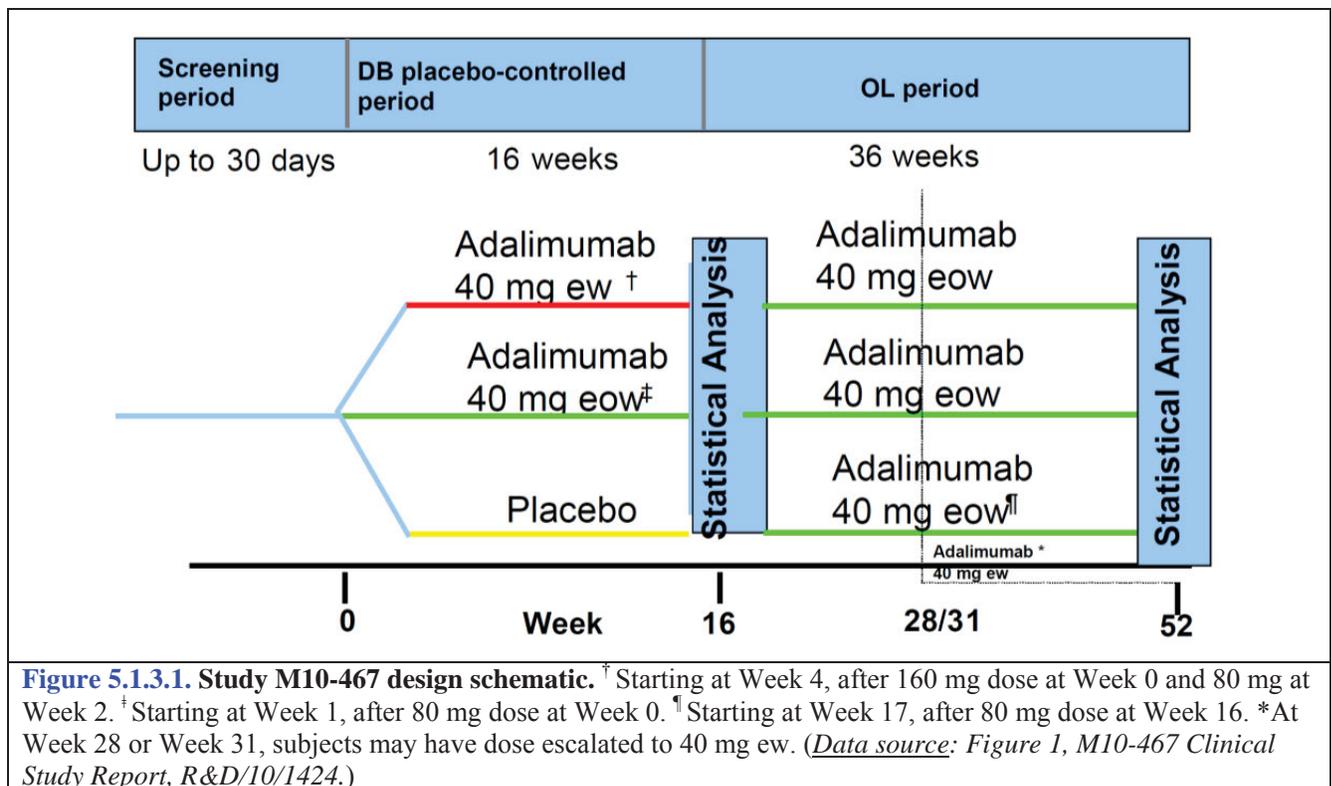
- April 22, 2009 (First subject first visit) to November 09, 2010 (Last subject last visit)

5.1.2. Test Product:

- Adalimumab 40 mg/0.8 mL, pre-filled syringes (Bulk Product Lot Numbers: 07-012406, 08-019941, 09-025414)

5.1.3. Study Design:

Study M10-467 was a Phase 2, double-blind (DB), placebo-controlled, randomized study with an open-label (OL) phase in subjects with moderate to severe chronic HS. The study included a 30-day screening period, a 16-week placebo-controlled period, a 36-week OL period, and a 70-day follow-up period (Figure 5.1.3.1).



Dosing regimens

In the DB period, subjects were randomized in a 1:1:1 ratio at Week 0 to receive adalimumab 40 mg every week (ew), 40 mg every other week (eow), or placebo:

- Subjects randomized to adalimumab 40 mg ew received a loading dose of adalimumab 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg ew starting at Week 4 through Week 15.

- Subjects randomized to adalimumab 40 mg eow received a loading dose of adalimumab 80 mg at Week 0, followed by 40 mg eow starting at Week 1 through Week 15.
- Subjects randomized to placebo received matching placebo, administered ew, starting at Week 0 through Week 15.

All subjects enrolled in the study who completed the DB period were eligible to participate in the OL period. In the OL period, subjects received OL adalimumab 40 mg eow with the option to escalate to 40 mg ew dosing.

- Subjects from the placebo arm in the DB treatment period received a blinded dose of 80 mg adalimumab at Week 16 in the OL treatment period.
- All subjects were treated with 40 mg eow starting at Week 17 through Week 28.
- At Week 28 or 31, if a subject had a Physician's Global Assessment (PGA) of moderate disease or worse (score of ≥ 3), the principal investigator, and the subject were to evaluate the risk/benefit of having the subject dose escalate to 40 mg ew adalimumab.
- If the subject dose escalated to 40 mg ew adalimumab, the subject remained on 40 mg ew adalimumab for the remainder of the study.
- Subjects who did not dose escalate at Week 28 or Week 31 remained on adalimumab 40 mg eow through Week 51.

Primary efficacy endpoint:

The primary efficacy variable was the proportion of subjects achieving clinical response, defined as achieving a PGA of clear, minimal, or mild, with a minimum of 2 grades improvement (reduction) from baseline on the PGA at Week 16.

The PGA of disease severity was on a 6-point scale (0 to 5) with 0 being clear (no abscesses, no draining fistulas, and no nodules) and 5 being very severe (more than 5 abscesses or draining fistulas).

Pharmacokinetics

Blood samples were obtained for the measurement of serum adalimumab concentrations at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45, and Week 52, and at the early termination (ET) visit if the subject discontinued prior to Week 52.

Immunogenicity

Serum for measurement of anti-adalimumab antibody (AAA) were obtained at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45, and Week 52/ET.

5.1.5. Efficacy results

A total of 154 subjects were randomized: 51 to placebo, 52 to adalimumab 40 mg eow, and 51 to adalimumab 40 mg ew. A total of 11 subjects discontinued from the DB period of the study. One hundred and three (103) subjects completed the study.

Primary Efficacy at Week 16

The proportions of subjects that achieved clinical response at Week 16 were 3.9%, 9.6% and 17.6%, in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew treatment groups, respectively. In each treatment group, subjects with baseline Hurley stages of I/II appeared to have numerically higher proportions of clinical response compared to subjects with baseline Hurley stage of III (Table 5.1.5.1).

Table 5.1.5.1. Proportion of subjects who achieved clinical response at Week 16. (Analysis was based on on-responder imputation (NRI) in which subjects with missing PGA scores were counted as non-responders; *, $p < 0.05$; *Data source: Table 17, M10-467 Clinical Study Report, R&D/10/1424.*)

Baseline Hurley Stage	Clinical Response at Week 16, n/N (%)		
	Placebo	Adalimumab 40 mg eow	Adalimumab 40 mg ew
All Stages	2/51 (3.9%)	5/52 (9.6%)	9/51 (17.6%)*
Stage I/II	2/36 (5.6%)	5/37 (13.5%)	8/36 (22.2%)
Stage III	0/15 (0%)	0/15 (0%)	1/15 (6.7%)

Loss of response in the OL period

Loss of response during the OL period was evaluated in subjects who had $PGA < 3$ at entry into OL regardless of whether they achieved ≥ 2 grade improvement in the DB period. Among those subjects, 63.6% (7/11) of treated with adalimumab eow in DB and 62.5% (15/24) of those treated with adalimumab ew in DB were unable to maintain the $PGA < 3$ response throughout Period 2 while receiving adalimumab 40 mg eow (*Data source: Table 37, M10-467 Clinical Study Report, R&D/10/1424.*)

Efficacy after dose escalation in the OL period

Overall, 89 subjects dose escalated from adalimumab 40 mg eow to ew in the OL period. Among these subjects, 68 provided Week 52 PGA assessments and 13 of them achieved clinical response (NRI: 13/89, 14.6%; as observed: 13/68, 19.1%) at Week 52 (*Data source: Table 38, M10-467 Clinical Study Report, R&D/10/1424.*)

The proportion of subjects achieving clinical response at Weeks 16 and 52 is presented in [Table 5.1.5.2](#) and is shown separately for all responders and responders without dose escalation in Period 2. Discounting the contribution of dose escalation, the proportion of subjects achieving clinical response was low ($< 10\%$) at Week 52, regardless of whether subjects had initiated therapy with eow dosing or ew dosing. After dose escalated to ew dosing frequency at Week 28 or Week 31, 8 additional subjects became responders (3 received eow and 5 received ew dosing in DB Period 1). At Week 52, the highest proportion of clinical responders was observed among those subjects who had been randomized to the adalimumab ew group during the DB period and had dose escalated back to ew dosing during the OL period.

Table 5.1.5.2. Proportion of subjects achieving clinical response at Week 16 and Week 52 (NRI, ITT-INT Population). (*Data source: Table 39, M10-467 Clinical Study Report, R&D/10/1424.*)

	n (%) of subjects			
	Responders without dose escalation in Period 2		All responders (including those dose escalated in Period 2)	
Treatment in DB/OL/ dose escalation (N total)	eow/eow (N=52)	ew/eow (N=51)	eow/eow/ew (N=52)	ew/eow/ew (N=51)
Period 1 (DB), Week 16	5 (9.6%)	9 (17.6%)	5 (9.6%)	9 (17.6%)
Period 2 (OL), Week 52	3 (5.8%)	5 (9.8%)	6 (11.5%)	10 (19.6%)

5.1.6. PK results

The mean adalimumab concentrations across the DB period were about 10-12 mcg/mL and 6-7 mcg/mL, respectively, for subjects who received adalimumab 40 mg ew and 40 mg eow treatments. The serum adalimumab concentrations through Week 16 by treatment groups in the DB period are presented in [Table 5.1.6.1.](#)

Table 5.1.6.1. Summary of mean±SD serum adalimumab concentrations in DB period 1 of Study M10-476.
(Data source: Table 1, Summary of Clinical Pharmacology)

Time	Mean±SD serum adalimumab concentrations (mcg/mL)			
	Week 0	Week 4	Week 8	Week 16
ew (N=51)	0	10.0±5.32	11.3±6.93	12.4±9.16
eow (N=52)	0	7.00±3.62	6.46±4.57	5.89±5.16

5.1.7. Immunogenicity results

In the Phase 2 Study M10-467, a total of 16 subjects among 154 subjects (10.4%) developed anti-adalimumab antibody (AAA) during the entire study period (Week 0 to Week 52). Five subjects (4.9%, 5/103) were determined as AAA+ during the DB period (Weeks 0 – 16). Additional 11 (7.1%, 11/154) subjects became AAA+ in the OL period (Weeks 17 – 52).

Reviewer’s comment: *Because of the drug interference issue with the AAA assay, the AAA incidence reported for Study M10-467 may be underestimated. Refer to the Clinical Pharmacology Question-based Review regarding the AAA incidence in HS subjects and its impact on PK and efficacy.*

5.2. Study M10-313

5.2.1. Study Title:

- A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER I

5.2.2. Study Period:

- November 29, 2011 (first subject first visit) to January 28, 2014 (last subject last visit)

5.2.3. Test Product:

- Adalimumab 40 mg/0.8 mL, pre-filled syringes (Bulk Product Lot Numbers: 10-005762, 10-005763, 11-003870, 11-005882, 13-000648)

5.2.4. Study Design:

Study M10-313 included a 30-day screening period, a 12-week double-blind treatment period (Period A) and a 24-week double-blind treatment period (Period B) (Figure 5.2.4.1).

Period A:

- Period A is a 12-week double-blind, placebo-controlled treatment period during which subjects were randomized in a 1:1 ratio to receive adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg ew starting at Week 4 or matching placebo.

Period B:

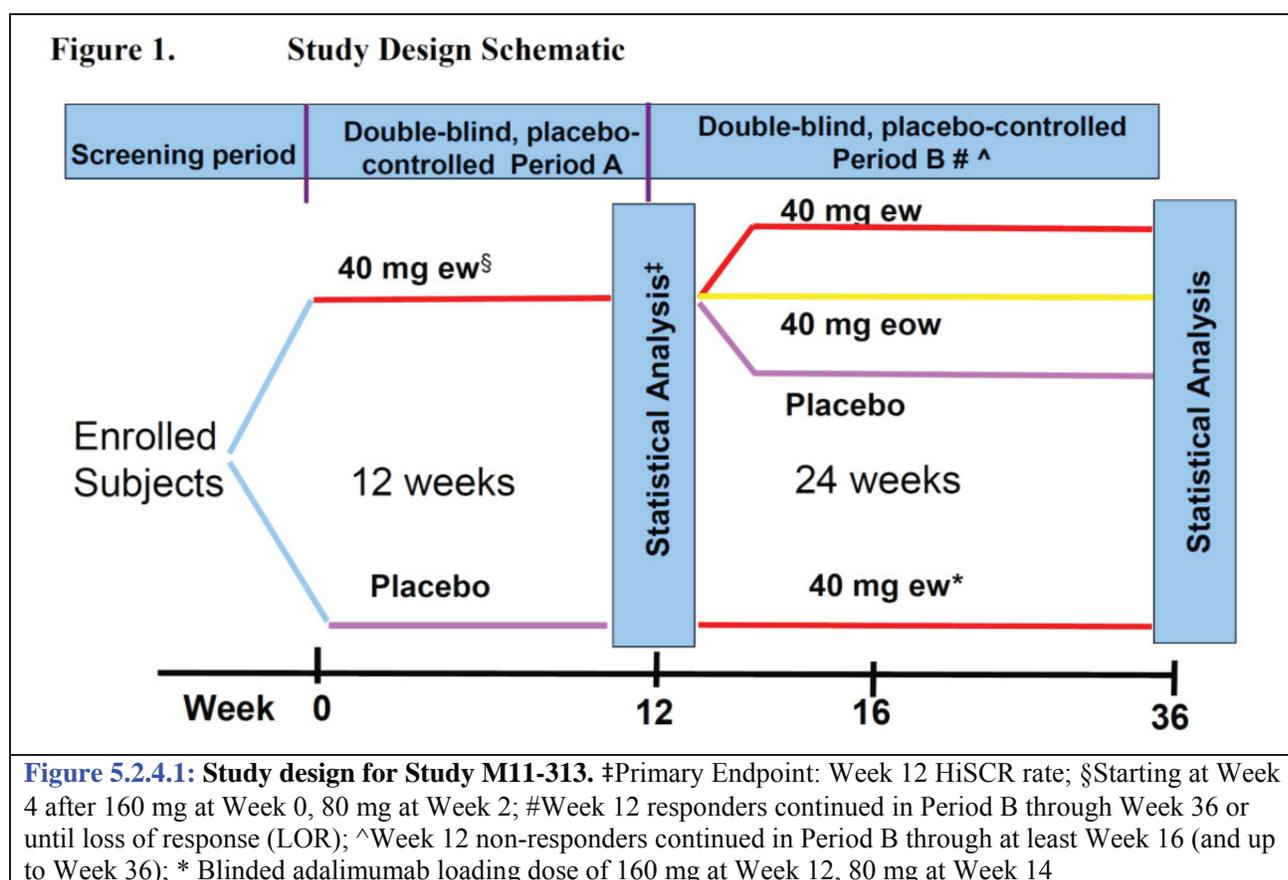
- Period B is a 24-week double-blind, placebo-controlled treatment period.
- Subjects randomized to adalimumab in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew, adalimumab 40 mg eow, or matching placebo from Week 12 to Week 35. Re-randomization was to be stratified by Week 12 Hidradenitis Suppurativa Clinical Response (HiSCR) response (responder versus non-responder) and by Baseline Hurley Stage

(II versus III). At Weeks 12 through 15, these subjects received matching placebo to blind the loading doses administered to subjects who had been randomized to placebo in Period A.

- Subjects from the placebo arm in Period A received adalimumab 160 mg at Week 12, 80 mg at Week 14, matching placebo at Week 13 and Week 15, and adalimumab 40 mg ew from Week 16 to Week 35.
- All subjects who achieved HiSCR at Week 12 continued in Period B through Week 36. Subjects who experienced a loss of response (LOR) in Period B, defined as an abscess and inflammatory nodule (AN) count that was greater than the average of AN counts at Baseline and Week 12, discontinued from the study and had the opportunity to enter the open-label extension (OLE) Study M12-555 to receive open-label adalimumab 40 mg ew.
- All subjects who did not achieve HiSCR at Week 12 continued in Period B through Week 36. Starting at or after Week 16, subjects who experienced a Worsening or Absence of Improvement (WOAI), defined as an AN count that was greater than or equal to the AN count at Baseline on 2 consecutive visits (excluding Week 12) that occurred at least 14 days apart, discontinued from the study and had the opportunity to enter the OLE Study M12-555 to receive open-label adalimumab 40 mg ew.

Starting at Week 4 or Week 8, if AN counts were greater-than-or equal-to 150% of Baseline AN counts, antibiotic rescue medication was permitted.

At Week 36, all subjects had the opportunity to enter the OLE Study M12-555 where they were to receive adalimumab 40 mg ew.



Primary efficacy endpoint

The primary efficacy variable was the proportion of subjects achieving HiSCR at Week 12.

HiSCR was defined as at least a 50% reduction in AN count (AN50) with no increase in abscess count and no increase in draining fistula count relative to Baseline.

5.2.5. Efficacy results

HiSCR at Week 12

A statistically significantly higher proportion of subjects in the adalimumab 40 mg ew group achieved HiSCR response at Week 12 compared to placebo. The HiSCR response rates were 41.8% and 26.0% for subjects in the adalimumab 40 mg ew treatment group and the placebo group, respectively (Table 5.2.5.1).

Table 5.2.5.1. Proportion of subjects achieving HiSCR at Week 12 in ITT-A population. Analysis was based on non-responder imputation (NRI). * $p < 0.01$; (Data source: Table 21, M11-313 CSR, R&D/13/1011.)

Baseline Hurley Stage	HiSCR Clinical Response at Week 12, n/N (%)	
	Placebo	Adalimumab 40 mg ew
All Stages	40/154 (26.0%)	64/153 (41.8%) *
Stage II	25/84 (29.8%)	37/83 (44.6%) *
Stage III	15/70 (21.4%)	27/70 (38.6%) *

HiSCR in ITT_B_R Population (HiSCR responders at Week 12) in Period B

ITT_B_R population included subjects who were randomized to adalimumab 40 mg ew in Period A and were re-randomized into Period B as HiSCR responders. All treatment groups in the ITT_B_R population showed reductions in the HiSCR response rates over time in Period B. By Week 36, the proportions of HiSCR responders were 27.3%, 50.0% and 52.4% in the ew/placebo, ew/eow and ew/ew treatment groups, respectively (Table 5.2.5.2).

Table 5.2.5.2. Proportion of subjects achieving HiSCR by visits in ITT_B_R population. Analysis was based on NRI. One subject (23902 in the ew/placebo group) who was a HiSCR non-responder at entry to Period B was randomized in the HiSCR responder stratum. (Data source: Table 39, M11-313 CSR, R&D/13/1011.)

Visit	ew/placebo (N=22) n (%)	ew/eow (N=20) n (%)	ew/ew (N=21) n (%)
Entry into period B	21 (95.5%)	20 (100%)	21 (100%)
Week 14	18 (81.8%)	16 (80.0%)	16 (76.2%)
Week 16	15 (68.2%)	15 (75.0%)	16 (76.2%)
Week 20	14 (63.6%)	13 (65.0%)	14 (66.7%)
Week 24	8 (36.4%)	11 (55.0%)	14 (66.7%)
Week 28	5 (22.7%)	11 (55.0%)	11 (52.4%)
Week 32	5 (22.7%)	10 (50.0%)	12 (57.1%)
Week 36	6 (27.3%)	10 (50.0%)	11 (52.4%)

Other efficacy endpoints based on AN counts in ITT_B_R population in Period B

Subjects in the adalimumab 40 mg ew/ew or ew/eow treatment group in general showed better clinical outcome at Week 36 across a number of efficacy endpoints including AN count of 0/1/2, AN50, AN75, and AN100. When comparing between the adalimumab 40 mg ew/eow and ew/ew treatment groups, 40 mg ew/ew showed numerically higher response rates for AN count of 0/1/2, AN75, and AN100 when compared with the 40 mg eow treatment group while ew/eow showed numerically higher response rate for AN50 (Table 5.2.5.3).

Table 5.2.5.3. Comparison of efficacy endpoints based on AN counts at Week 36 in ITT_B_R population.Analysis was based on NRI. * $p < 0.05$ vs ew/placebo. (Data source: Table 40, M11-313 CSR, R&D/13/1011.)

	ew/placebo (N=22) n (%)	ew/eow (N=20) n (%)	ew/ew (N=21) n (%)
AN count of 0/1/2	5 (22.7%)	6 (30.0%)	9 (42.9%)
AN50	7 (31.8%)	13 (65.0%)*	11 (52.4%)
AN75	5 (22.7%)	7 (35.0%)	8 (38.1%)
AN100	2 (9.1%)	3 (15.0%)	4 (19.0%)

HiSCR in ITT_B_NR population (HiSCR non-responders at Week 12) in Period B

The ITT_B_NR population included subjects who were randomized to adalimumab 40 mg ew in Period A and re-randomized in Period B as HiSCR non-responders. At Week 36, the proportions of subjects achieving HiSCR were 25.9%, 17.9% and 37.0% for ew/placebo, ew/eow and ew/ew treatment groups, respectively (Table 5.2.5.4). Only the 40 mg ew treatment regimen performed better than placebo in Period A non-responders. The results overall supported continuing adalimumab ew treatment beyond Week 12 in that some subjects achieved a HiSCR response in more than 12 weeks of treatment.

Table 5.2.5.4. Proportion of subjects achieving HiSCR over time in Period B in ITT_B_NR population.

Analysis was based on NRI. (Data source: Table 45, M11-313 CSR, R&D/13/1011.)

Visit	ew/placebo (N=27) n (%)	ew/eow (N=28) n (%)	ew/ew (N=27) n (%)
Entry into period B	1 (3.7%)	0 (0%)	1 (3.7%)
Week 14	6 (22.2%)	4 (14.3%)	4 (14.8%)
Week 16	5 (18.5%)	7 (25.0%)	5 (18.5%)
Week 20	6 (22.2%)	5 (17.9%)	6 (22.2%)
Week 24	5 (18.5%)	4 (14.3%)	6 (22.2%)
Week 28	6 (22.2%)	5 (17.9%)	9 (33.3%)
Week 32	7 (25.9%)	5 (17.9%)	8 (29.6%)
Week 36	7 (25.9%)	5 (17.9%)	10 (37.0%)

For the subset of ITT_B_NR patients who achieved a partial response of AN25 (defined as at least a 25% reduction in AN relative to baseline at the end of Period A), a statistically significantly higher response rate was observed in the ew/ew group than in the ew/eow and ew/placebo groups. Subjects who failed to achieve AN25 at the end of Period A and continued adalimumab treatment (ew or eow) did not show benefit over placebo treatment according to the observed HiSCR rate at Week 36 (Table 5.2.5.5).

Table 5.2.5.5. Proportion of subjects achieving HiSCR at Week 36 in ITT_B_NR population by status of AN25 response Week 12. Analysis was based on NRI. * $p < 0.05$ vs ew/eow and ew/placebo. (Data source: Table 47, M11-313 CSR, R&D/13/1011)

	AN25 Responders			AN25 Non-responders		
	ew/placebo (N=12) n (%)	ew/eow (N=7) n (%)	ew/ew (N=8) n (%)	ew/placebo (N=15) n (%)	ew/eow (N=21) n (%)	ew/ew (N=19) n (%)
Week 36	4 (33.3%)	3 (42.9%)	8 (100%)*	3 (20%)	2 (9.5%)	2 (10.5%)

Other efficacy endpoints based on AN counts in ITT_B_NR population in Period B

Adalimumab 40 mg ew/ew in general achieved better clinical outcomes at Week 36 compared to ew/eow or ew/placebo across a number of efficacy endpoints, including AN count of 0/1/2, AN50 and AN75 (Table 5.2.5.6).

Table 5.2.5.6. Comparison of other efficacy endpoints at Week 36 in ITT_B_NR population. Analysis was based on NRI. AN, abscess and inflammatory nodules. * $p < 0.05$ vs ew/eow. (*Data source: Table 48, M11-313 CSR, R&D/13/1011.*)

	ew/placebo (N=27) n (%)	ew/eow (N=28) n (%)	ew/ew (N=27) n (%)
AN count of 0/1/2	5 (18.5%)	3 (10.7%)	8 (29.6%)
AN50	8 (29.6%)	6 (21.4%)	12 (44.4%)
AN75	5 (18.5%)	2 (7.1%)	8 (29.6%)*

HiSCR in Period B

When evaluating HiSCR rate in Period B among all adalimumab ew subjects from Period A (combined ITT_B_R and ITT_B_NR populations), the response rate appeared to remain stable among subjects re-randomized to continue adalimumab ew, while the response rate was reduced over time in the ew/eow treatment group and in the ew/placebo treatment group (Table 5.2.5.7).

Table 5.2.5.7. Proportion of subjects achieving HiSCR over time in Period B in combined ITT_B_R and ITT_B_NR population. Analysis was based on NRI. (*Data source: Table 52, M11-313 CSR, R&D/13/1011.*)

Visit	ew/placebo (N=49) n (%)	ew/eow (N=48) n (%)	ew/ew (N=48) n (%)
Entry into period B	22 (44.9%)	20 (41.7%)	22 (45.8%)
Week 14	24 (49.0%)	20 (41.7%)	20 (41.7%)
Week 16	20 (40.8%)	22 (45.8%)	21 (43.8%)
Week 20	20 (40.8%)	18 (37.5%)	20 (41.7%)
Week 24	13 (26.5%)	15 (31.3%)	20 (41.7%)
Week 28	11 (22.4%)	16 (33.3%)	20 (41.7%)
Week 32	12 (24.5%)	15 (31.3%)	20 (41.7%)
Week 36	13 (26.5%)	15 (31.3%)	21 (43.8%)

HiSCR in ITT_B_PRR population (subjects achieved \geq AN25 at Week 12) in Period B

The ITT_B_PRR population included HiSCR responders at the end of Period A (i.e., the ITT_B_R population) and AN25 partial responders at the end of Period A in the ITT_B_NR population. In the ITT_B_PRR population, at Week 36 HiSCR was achieved in 65.5% of subjects re-randomized to the ew/ew group, as compared to 48.1% of subjects in the ew/eow group and 29.4% of subjects in the ew/placebo group (Table 5.2.5.8).

Table 5.2.5.8. Proportion of subjects achieving HiSCR over time in Period B in ITT_B_PRR population. Analysis was based on NRI. (*Data source: Table 53, M11-313 CSR, R&D/13/1011.*)

Visit	ew/placebo (N=34) n (%)	ew/eow (N=27) n (%)	ew/ew (N=29) n (%)
Entry into period B	22 (64.7%)	20 (74.1%)	22 (75.9%)
Week 14	23 (67.6%)	19 (70.4%)	19 (65.5%)
Week 16	19 (55.9%)	18 (66.7%)	21 (72.4%)
Week 20	19 (55.9%)	17 (63.0%)	18 (62.1%)
Week 24	9 (26.5%)	15 (55.6%)	18 (62.1%)
Week 28	8 (23.5%)	15 (55.6%)	16 (55.2%)
Week 32	8 (23.5%)	13 (48.1%)	16 (55.2%)
Week 36	10 (29.4%)	13 (48.1%)	19 (65.5%)

5.2.6. Pharmacokinetics and immunogenicity

Refer to the Clinical Pharmacology QBR for the PK and immunogenicity information in adalimumab HS Phase 3 trials.

5.3. Study M10-810

5.3.1. Study Title:

- A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER II

5.3.2. Study Period:

- December 28, 2011 (first subject first visit) to April 28, 2014 (last subject last visit)

5.3.3. Test Product:

- Adalimumab 40 mg/0.8 mL, pre-filled syringes (Bulk Product Lot Numbers: 10-005762, 11-003870, 11-005882, 13-000648)

5.3.4. Study Design:

Study M10-810 included a 30-day screening period, a 12-week double-blind treatment period (Period A) followed by an additional 24-week double-blind treatment period (Period B) (Figure 5.3.4.1).

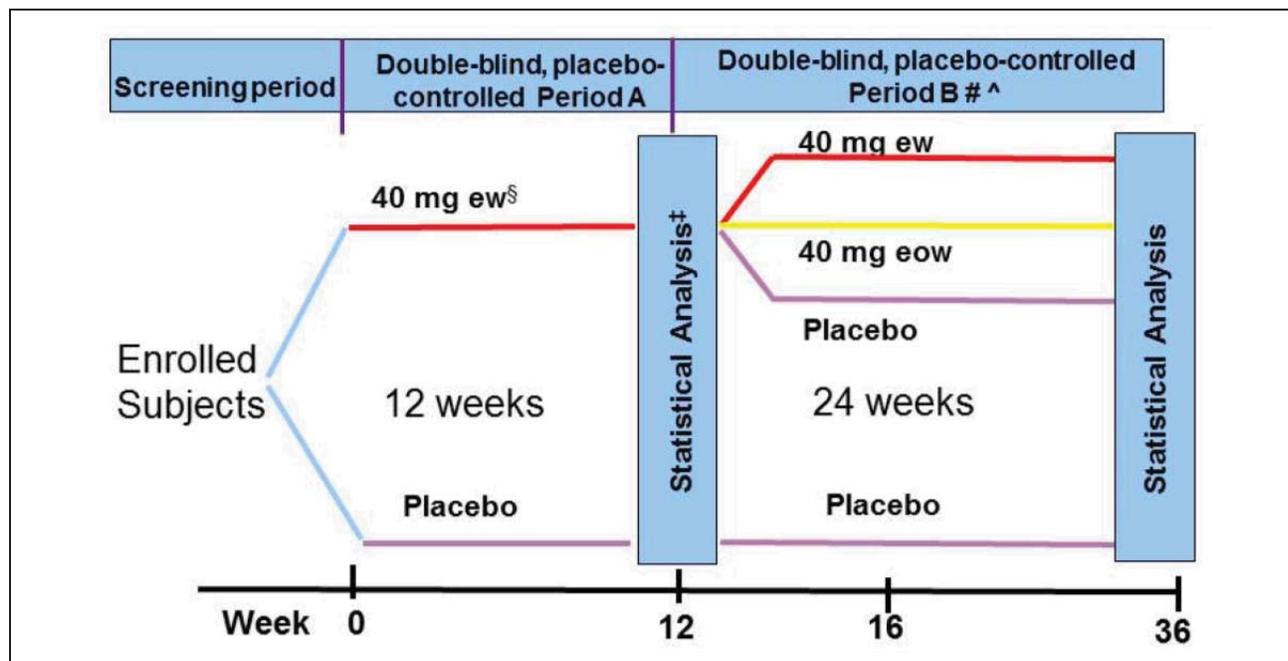


Figure 5.3.4.1. Study design for Study M11-810. †Primary efficacy endpoint: Week 12 HiSCR response rate; §Starting at Week 4 after 160 mg at Week 0 and 80 mg at Week 2; #Week 12 responders continued in Period B through Week 36 or until loss of response (LOR); ^Week 12 non-responders continued in Period B through at least Week 16 (and up to Week 36)

Period A:

- Period A is a 12-week double-blind, placebo-controlled treatment period during which subjects were randomized in a 1:1 ratio to receive adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg ew starting at Week 4 or matching placebo.

Period B:

- Period B is a 24-week double-blind, placebo-controlled treatment period.

- Subjects completed adalimumab treatment in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew, adalimumab 40 mg eow, or matching placebo from Week 12 to Week 35. Re-randomization was stratified by Week 12 HiSCR response (responder versus non-responder) and by Baseline Hurley Stage (II versus III).
- Subjects from the placebo group in Period A continued on blinded placebo from Week 12 to Week 35.
- All subjects who achieved HiSCR at Week 12 continued in Period B through Week 36. Subjects who experienced a loss of response (LOR) in Period B, defined as an abscess and inflammatory nodule (AN) count that was greater than the average of AN counts at Baseline and Week 12, discontinued from the study and had the opportunity to enter the open-label extension (OLE) Study M12-555 to receive open-label adalimumab 40 mg ew.
- All subjects who did not achieve HiSCR at Week 12 continued in Period B through Week 36. Starting at or after Week 16, subjects who experienced a Worsening or Absence of Improvement (WOAI), defined as an AN count that was greater than or equal to the AN count at Baseline on 2 consecutive visits (excluding Week 12) that occurred at least 14 days apart, discontinued from the study and had the opportunity to enter the OLE Study M12-555 to receive open-label adalimumab 40 mg ew.

At Week 36, all subjects had the opportunity to enter the OLE Study M12-555 where they received adalimumab 40 mg ew.

Primary Efficacy endpoint

The primary efficacy variable was the proportion of subjects achieving HiSCR at Week 12.

HiSCR was defined as at least a 50% reduction in AN count (AN50) with no increase in abscess count and no increase in draining fistula count relative to Baseline.

5.3.5. Efficacy results

HiSCR at Week 12

A statistically significantly higher proportion of subjects in the adalimumab 40 mg ew group achieved HiSCR response at Week 12 compared to placebo. The HiSCR response rates were 58.9% and 27.6% for subjects in the adalimumab 40 mg ew treatment group and the placebo group, respectively (Table 5.3.5.1).

Table 5.3.5.1. Proportion of subjects achieving HiSCR at Week 12 in ITT-A population. Analysis was based on non-responder imputation (NRI). *, p<0.001; (Data source: Table 20, M11-810 CSR, R&D/14/0252)

Baseline Hurley Stage	HiSCR Clinical Response at Week 12, n/N (%)	
	Placebo	Adalimumab 40 mg ew
All Stages	45/163 (27.6%)	96/163 (58.9%) *
Stage II	32/87 (36.8%)	53/85 (62.4%) *
Stage III	13/76 (17.1%)	43/78 (55.1%) *

HiSCR in ITT_B_R population (Period A HiSCR responders) in Period B

ITT_B_R population included subjects who were randomized to adalimumab 40 mg ew in Period A and were re-randomized into Period B as HiSCR responders. All treatment groups in the ITT_B_R population showed reductions in HiSCR response rate over time in Period B. By Week 36, the proportions of HiSCR responders were 35.5%, 43.8% and 45.2% in the ew/placebo, ew/eow and ew/ew treatment groups, respectively (Table 5.3.5.2).

Table 5.3.5.2. Proportion of subjects achieving HiSCR over time in Period B in the ITT_B_R population.

Analysis was based on NRI. (Data source: Table 35, M11-810 CSR, R&D/14/0252)

Visit	ew/placebo (N=31) n (%)	ew/eow (N=32) n (%)	ew/ew (N=31) n (%)
Entry into period B	31 (100%)	32 (100%)	31 (100%)
Week 14	24 (77.4%)	25 (78.1%)	22 (71.0%)
Week 16	20 (64.5%)	26 (81.3%)	21 (67.7%)
Week 20	16 (51.6%)	17 (53.1%)	24 (77.4%)
Week 24	13 (41.9%)	18 (56.3%)	18 (58.1%)
Week 28	14 (45.2%)	15 (46.9%)	15 (48.4%)
Week 32	9 (29.0%)	15 (46.9%)	15 (48.4%)
Week 36	11 (35.5%)	14 (43.8%)	14 (45.2%)

Other efficacy endpoints based on AN counts in ITT_B_R population in Period B

Adalimumab 40 mg ew/ew or ew/eow treatment group in general showed better clinical outcome at Week 36 across a number of efficacy endpoints including AN count of 0/1/2, AN50, AN75, and AN100 compared to placebo group. When comparing between the adalimumab 40 mg ew/eow and ew/ew treatment groups, ew/eow showed numerically higher response rates for AN count of 0/1/2, AN75 and AN100 while ew/ew showed numerically higher response rate for AN50 (Table 5.3.5.3).

Table 5.3.5.3. Efficacy results at Week 36 based on AN counts in the ITT_B_R population. Analysis was based on NRI. (Data source: Table 36, M11-810 Clinical Study Report, R&D/14/0252)

	ew/placebo (N=31) n (%)	ew/eow (N=32) n (%)	ew/ew (N=31) n (%)
AN count of 0/1/2	9 (29.0%)	13 (40.6%)	10 (32.3%)
AN50	13 (41.9%)	14 (43.8%)	14 (45.2%)
AN75	8 (25.8%)	12 (37.5%)	9 (29.0%)
AN100	3 (9.7%)	7 (21.9%)	3 (9.7%)

HiSCR in ITT_B_NR population (HiSCR non-Responders at Week 12) in Period B

The ITT_B_NR population included subjects who were randomized to adalimumab 40 mg ew in Period A and re-randomized in Period B as HiSCR non-responders. Some Week 12 HiSCR non-responders achieved HiSCR response in Period B. At Week 36, the HiSCR response rates were 20.0%, 9.5% and 40.0% for subjects in the ew/placebo, ew/eow and ew/ew treatment groups, respectively (Table 5.3.5.4). Only the 40 mg ew/ew treatment regimen performed better than ew/placebo in Period A non-responders. The results overall supported continuing adalimumab 40 mg ew treatment beyond Week 12 in that some subjects achieved a HiSCR response in more than 12 weeks of treatment.

Table 5.3.5.4. Proportion of subjects achieving HiSCR over time in Period B in ITT_B_NR population.

Analysis was based on NRI. (Data source: Table 41, M11-810 CSR, R&D/14/0252)

Visit	ew/placebo (N=20) n (%)	ew/eow (N=21) n (%)	ew/ew (N=20) n (%)
Entry into period B	20 (0%)	21 (0%)	20 (0%)
Week 14	2 (10.0%)	2 (9.5%)	8 (40.0%)
Week 16	3 (15.0%)	3 (14.3%)	5 (25.0%)
Week 20	2 (10.0%)	3 (14.0%)	7 (35.0%)
Week 24	4 (20.0%)	4 (19.0%)	6 (30.0%)
Week 28	3 (15.0%)	3 (14.3%)	10 (50.0%)
Week 32	4 (20.0%)	3 (14.3%)	10 (50.0%)
Week 36	4 (20.0%)	2 (9.5%)	8 (40.0%)

For the subset of ITT_B_NR patients who achieved a partial response of AN 25 defined as at least a 25% reduction in AN relative to baseline at the end of Period A, a numerically higher response rate was observed in the ew/ew group than in the ew/eow or ew/placebo group. Based on a limited number of subjects, subjects who failed to achieve AN 25 at the end of Period A and continued adalimumab (ew or eow) treatment did not show benefit over placebo treatment according to the observed HiSCR rate at Week 36 (Table 5.3.5.5).

Table 5.3.5.5. Proportion of subjects achieving HiSCR at Week 36 in ITT_B_NR population by status of Week 12 AN25 response. Analysis was based on NRI. (Data source: Table 43, M11-810 CSR, R&D/14/0252)

	AN25 Responders			AN25 Non-responders		
	ew/placebo (N=8) n (%)	ew/eow (N=11) n (%)	ew/ew (N=10) n (%)	ew/placebo (N=12) n (%)	ew/eow (N=10) n (%)	ew/ew (N=10) n (%)
HiSCR at Week 36	1 (12.5%)	1 (9.1%)	6 (60%)	3 (25%)	1 (10%)	2 (20%)

Other efficacy endpoints based on AN counts in ITT_B_NR population in Period B

Subjects who received the adalimumab 40 mg ew/ew treatment in general showed better clinical outcomes at Week 36 compared to subjects who received ew/eow or ew/placebo treatment when evaluated for efficacy endpoints including AN count of 0/1/2, AN50, and AN75 (Table 5.3.5.6).

Table 5.3.5.6. Efficacy results based on AN counts at Week 36 in ITT_B_NR population. Analysis was based on NRI. AN, abscess and inflammatory nodules. (Data source: Table 44, M11-810 CSR, R&D/14/0252)

	ew/placebo (N=20) n (%)	ew/eow (N=21) n (%)	ew/ew (N=20) n (%)
AN count of 0/1/2	2 (10.0%)	4 (19.0%)	6 (30.0%)
AN50	5 (25.0%)	5 (23.8%)	9 (45.0%)
AN75	2 (10.0%)	4 (19.0%)	5 (25.0%)

HiSCR in Period B

In the overall study population, all treatment groups showed reductions in HiSCR response rate over time in Period B. By Week 36 the HiSCR response rates were 29.4%, 30.2% and 43.1% for subjects in the ew/placebo, ew/eow and ew/ew treatment groups, respectively (Table 5.3.5.7).

Table 5.3.5.7. Proportion of subjects achieving HiSCR over time in Period B in combined ITT_B_R and ITT_B_NR populations. Analysis was based on NRI. (Data source: Table 48, M11-810 CSR, R&D/14/0252)

Visit	ew/placebo (N=51) n (%)	ew/eow (N=53) n (%)	ew/ew (N=51) n (%)
Entry into period B	31 (60.8%)	32 (60.4%)	31 (60.8%)
Week 14	26 (51.0%)	27 (50.9%)	30 (58.8%)
Week 16	23 (45.1%)	29 (54.7%)	26 (51.0%)
Week 20	18 (35.3%)	20 (37.7%)	31 (60.8%)
Week 24	17 (33.3%)	22 (41.5%)	24 (47.1%)
Week 28	17 (33.3%)	18 (34.0%)	25 (49.0%)
Week 32	13 (25.5%)	18 (34.0%)	25 (49.0%)
Week 36	15 (29.4%)	16 (30.2%)	22 (43.1%)

HiSCR in ITT_B_PRR population (subjects achieved AN \geq 25 at Week 12) in Period B

The ITT_B_PRR population included subjects in the ITT_B_R population and subjects who achieved a partial response (AN25) at the end of Period A in the ITT_B_NR Population. In the ITT_B_PRR population, all treatment groups showed reductions in HiSCR response rate over time in Period B. By Week 36, HiSCR response rates were 30.8%, 34.9% and 48.8% for subjects in the ew/placebo, ew/eow, ew/ew treatment groups, respectively (Table 5.2.5.8).

Table 5.2.5.8. Proportion of subjects achieving HiSCR over time in Period B in ITT_B_PRR population.

Analysis was based on on-responder imputation (NRI). (Data source: Table 49, M11-810 CSR, R&D/14/0252)

Visit	ew/placebo (N=39) n (%)	ew/eow (N=43) n (%)	ew/ew (N=41) n (%)
Entry into period B	31 (79.5%)	32 (74.4%)	31 (75.6%)
Week 14	25 (64.1%)	27 (62.8%)	29 (70.7%)
Week 16	22 (56.4%)	28 (65.1%)	26 (63.4%)
Week 20	17 (43.6%)	19 (44.2%)	30 (73.2%)
Week 24	15 (38.5%)	21 (48.8%)	22 (53.7%)
Week 28	15 (38.5%)	17 (39.5%)	22 (53.7%)
Week 32	10 (25.6%)	17 (39.5%)	22 (53.7%)
Week 36	12 (30.8%)	15 (34.9%)	20 (48.8%)

5.3.6. Pharmacokinetics and immunogenicity

Refer to the Clinical Pharmacology Question-based Review for the PK and immunogenicity information in adalimumab HS Phase 3 trials.

APPENDIX: Clinical Pharmacology Filing Review

1. Filing and review form

Office of Clinical Pharmacology			
Filing and Review Form			
<i>General Information About the Submission</i>			
BLA Number	125057/393	Brand Name	HUMIRA
OCP Division	DCP-3	Generic Name	Adalimumab
Medical Division	ODEIII/DDDP	Drug Class	Recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNF α).
OCP Reviewer	Jie Wang, Ph.D.	Indication(s)	The treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.
Pharmacometrics Team Leader	Jeffry Florian, Ph.D.	Dosage Form	Solution for injection presented in prefilled syringe or autoinjector (currently marketed formulation).
OCP Team Leader	Yow-Ming Wang, Ph.D.	Dosing Regimen	160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29.
Date of Submission	November 10, 2014	Route of Administration	Subcutaneous injection
Estimated Due Date of OCP Review	July 10, 2015	Sponsor	AbbVie Inc.
Medical Division Due Date	July 10, 2015	Priority Classification	Standard
PDUFA Due Date	September 10, 2015		

<i>Clinical Pharmacology and Biopharmaceutics Information</i>				
	“×” if included at filing	Number of studies submitted	Number of studies reviewed	Comments
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	×			
Tabular Listing of All Human Studies	×			
HPK Summary	×			
Labeling	×			
Reference Bioanalytical and Analytical Methods	×			<i>See section 3.2.</i>
I. Clinical Pharmacology				
Mass balance:				<i>n/a</i>
Isozyme characterization:				<i>n/a</i>
Blood/plasma ratio:				<i>n/a</i>
Plasma protein binding:				<i>n/a</i>
Pharmacokinetics (e.g., Phase 1)				
Healthy Volunteers-				<i>n/a</i>
single dose:				
multiple dose:				
Patients-				
single dose:				<i>n/a</i>
multiple dose:	×			Phase 2&3, Population PK
Dose proportionality -				
fasting / non-fasting single dose:				<i>n/a</i>
fasting / non-fasting multiple dose:				<i>n/a</i>
Drug-drug interaction studies -				<i>See section 3.4.</i>
In-vivo effects on primary drug:				<i>n/a</i>
In-vivo effects of primary drug:				<i>n/a</i>
In-vitro:				<i>n/a</i>
Subpopulation studies -				
ethnicity:				<i>Population PK</i>
gender:				<i>Population PK</i>
pediatrics:				<i>n/a</i>
geriatrics:				<i>Population PK</i>
renal impairment:				<i>n/a</i>
hepatic impairment:				<i>n/a</i>
PD -				
Phase 2:	×	1	1	
Phase 3:	×	2	2	
PK/PD -				
Phase 1 and/or 2:	×	1	1	
Phase 3 clinical trial:	×	2	2	

Population Analyses -				
Data rich:				
Data sparse:	×			
II. Biopharmaceutics				<i>See section 3.2.</i>
Absolute bioavailability				<i>n/a</i>
Relative bioavailability -				<i>n/a</i>
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				<i>n/a</i>
traditional design; single/multi dose:				
replicate design; single/multi dose:				
Food-drug interaction studies				<i>n/a</i>
Bio-waiver request based on BCS				<i>n/a</i>
BCS class				<i>n/a</i>
Dissolution study to evaluate alcohol induced dose-dumping				<i>n/a</i>
III. Other CPB Studies				
Genotype/phenotype studies				<i>n/a</i>
Chronopharmacokinetics				<i>n/a</i>
Pediatric development plan	×			<i>See section 3.7.</i>
Literature References	×			
Total Number of Studies		4	4	<i>See Appendix.1</i>

On **initial** review of the sBLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			×	<i>See section 3.2</i>
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			×	<i>See section 3.4</i>
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	×			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			×	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	×			<i>See section 3.3</i>
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	×			
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)?	×			
8	Did the applicant submit the module 2 summaries (e.g. Summary of Clinical Pharmacology and summary of Biopharmaceutics)?	×			
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?				
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 previously agreed to before the NDA submission?	×			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Content Parameter	Yes	No	N/A	Comment
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	×			
2	If applicable, are the pharmacogenomic datasets submitted in the appropriate format?			×	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	×			<i>See section 3.3.</i>
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)?	×			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	×			<i>See section 3.5.</i>
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?	×			<i>Review issue.</i>
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	×			<i>Review issue.</i>
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES.

Clinical Pharmacology Filing Memorandum

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2. Comments to the sponsor

There are no comments to be conveyed to the sponsor at this time.

3. Main clinical pharmacology findings on initial review of the submission

HUMIRA[®] (adalimumab) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNF α). HUMIRA was initially approved for the treatment of rheumatoid arthritis (RA) in December 2002 and subsequently approved for multiple indications, including for the treatment of psoriatic arthritis (October 2005), ankylosing spondylitis (August 2006), Crohn's Disease (February 2007), psoriasis (January 2008), juvenile idiopathic arthritis or JIA (February 2008), ulcerative colitis (September 2012), and pediatric Crohn's disease (September 2014).

The current efficacy supplement application is to include a new indication for HUMIRA for the treatment of active moderate to severe hidradenitis suppurativa (HiS or acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

The proposed dosing regimen is 160 mg initially on Day 1, and 80 mg on Day 15, followed by maintenance dose of 40 mg every week starting from Day 29. HUMIRA is administered by subcutaneous injection.

3.1. Overview of clinical trials and clinical pharmacology program

The sBLA (125507/393) is based on four clinical studies, i.e., Studies M10-467, M11-810, M11-313 and M12-555 (*see Appendix 1*). Study M10-467 was a Phase 2, placebo-controlled, dose-ranging study. Studies M11-810 and M11-313 had similar study design and were two randomized, double-blind, placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of adalimumab at Week 12 (Period A) and Week 24 (Period B). Study M12-555 was an open-label extension study evaluating efficacy and safety of adalimumab for the subjects rolled over from Studies M11-810 and M11-313 through additional 60 weeks. Studies M10-467, M11-810, and M11-313 have been completed. Study M12-555 is currently ongoing with data cutoff of 29 April 2014 for the efficacy and safety analyses in this submission.

3.2. Biopharmaceutics

HUMIRA is registered and marketed as solution for injection presented as single-use prefilled syringe (PFS) and prefilled pen for subcutaneous injection. The PFS presentation and the formulation of 40 mg adalimumab in 0.8 mL solution (50 mg/mL) used in HiS clinical trials were the same as the currently marketed presentation/formulation. Therefore, PK comparability data comparing the to-be-marketed product(s) and those used in the pivotal clinical trials are not needed to support the filing of the current sBLA.

3.3. Pharmacokinetics

The PK of adalimumab in HiS subjects was evaluated in the Phase 2 Study M10-467 and the two Phase 3 Studies M11-313 and M11-810 (see [Appendix 1](#)).

The following PK reports were submitted to support the sBLA.

- The *Summary of Clinical Pharmacology Studies* provided the PK summary across the HiS Phase 2 and Phase 3 studies. Additionally, the *Summary of Clinical Pharmacology Studies* also presented the PK data comparing the serum trough concentrations of adalimumab in subjects with HiS to those observed in subjects with UC, CD, or psoriasis in previous clinical trials.
- The *Study M10-467 PK report (R&D/11/528)*, *Study M11-313 PK report (R&D/13/1066)*, and *Study M11-810 PK report (R&D/14/0335)* provided the PK report for each individual study.
- Population PK analyses were performed using the combined data from Studies M10-467, M11-313 and M11-810. Population PK results were submitted in *Pharmacokinetic Report R&D/14/1054*.

Bioanalytical methods

Adalimumab concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) method. The applicant stated that the ELISA was the same as those provided in previous submissions. The assay validation was originally submitted and reviewed in the BLA application for RA. The bioanalytical report for the in-study performance of the ELISA method in each clinical study was provided in *Study M10-467 PK report (R&D/11/528)*, *Study M11-313 PK report (R&D/13/1066)*, and *Study M11-810 PK report (R&D/14/0335)*.

3.4. Drug-Drug interactions

The applicant did not conduct *in vitro* or *in vivo* studies to evaluate the drug-drug interactions (DDI) potential for adalimumab in subjects with HiS.

Reviewer's assessment: *HiS is a disease condition that involves altered expression of proinflammatory cytokines. Cytokines or cytokine modulators could modify the formation and activity of CYP enzymes and consequently affect the metabolism or PK of small molecule drugs that are substrates for P450 enzymes. The section 7.4 Cytochrome P450 Substrates of the HUMIRA product labeling contains the following general language "The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α , 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.” The currently available labeling language appears to be appropriate to imply the DDI potential for adalimumab in subjects with HiS; however, whether a dedicated clinical DDI study for adalimumab in subjects with HiS is needed or not would be a review issue.

3.5. Dose selection and exposure-response relationship

The Applicant submitted the following results to demonstrate the exposure-response (E-R) relationship for adalimumab in HiS clinical trials and to support the proposed dosing regimen:

- In Phase 3 Studies M11-313 and M11-810, at the end of Period A (Week 12), mean serum adalimumab concentrations were compared between HiSCR responders and non-responders (*Section 2.7.2.2. Summary of Clinical Pharmacology Studies*). HiSCR is the primary efficacy endpoint for the Phase 3 trials.
- Time-to-event (TTE) analyses were performed to explore the E-R relationship for the efficacy and safety of adalimumab during the withdrawal phase (Period B) of Phase 3 Studies M11-313 and M11-810. For efficacy, loss of response (LOR) in HiSCR responders at Week 12 and worsening or absence of improvement (WOAI) in HiSCR non-responders at Week 12 were evaluated.
- For safety, E-R for adverse events (AEs) of interests including infection was evaluated.
- The applicant conducted clinical trial simulations using the population pharmacokinetic model to justify an alternative initial dosing by administration of the 160 mg dose over 2 consecutive days, i.e., 2 injections of 40 mg per injection on Day 1 and 2 injections of 40 mg per injection on Day 2 (*Section 2.7.2.4.2, Summary of Clinical Pharmacology Studies*). The initial 160 mg dose on a single day requires 4 injections of 40 mg per injection.

3.6. Immunogenicity

Immunogenicity of adalimumab in the HiS population was assessed in Studies M10-467, M11-313 and M11-810. The immunogenicity summary was provided in the *Summary of Clinical Pharmacology Studies (section 2.7.2.4.1)*. The incidence of anti-drug antibodies (ADA) and the impacts of ADA on PK, efficacy and safety were reported.

The immunogenicity summary did not provide information regarding the neutralizing activity of ADA. However, the analysis of the ADA impact showed that ADA positive subjects were associated with lower serum adalimumab concentrations compared to ADA negative subjects and none of the ADA positive subjects achieved HiSCR response at Week 12 in Phase 3 studies indicating a negative impact of ADA on efficacy.

Immunogenicity Assay

The HiS program used the validated double-antigen ELISA method that only detects free (unbound) ADA in serum. The ELISA assay has been used since the original BLA application.

Reviewer’s assessment: *Due to the historical issue of drug interference of the ELISA method, ADA could be detected only when serum adalimumab levels were <2 mcg/mL. The applicant is currently developing an improved immunogenicity assay to fulfill PMR #3 listed in the FDA approval letter of BLA 125057/232 (UC indication) dated September 28, 2012. Due to the timing of the completion of the new assay validation, immunogenicity results using the improved assay were not available for the current sBLA. At the pre-sBLA meeting, the Agency has agreed that the absence of the immunogenicity*

data using the new assay would not be considered as a refuse-to-file issue in the sBLA submission provided that the applicant could commit to submit the immunogenicity data in a timely fashion. In the meeting discussion, the Applicant proposed to submit the immunogenicity data with the improved assay by the fourth quarter of 2015. The Agency responded that this proposed plan is reasonable and stated that a postmarketing requirement may be issued for submission of immunogenicity data from HiS clinical trials using the new immunogenicity assay. The comments and meeting discussion at the pre-sBLA meeting regarding the immunogenicity data submission are in the Meeting Minutes (08/05/2014) and are cited below.

“Response:

We recommend that you use the improved anti-adalimumab antibody assays with reduced sensitivity to product interference for immunogenicity assessment in your hidradenitis suppurativa Phase 3 trials. As described in PMR #3 of the FDA approval letter of BLA 125027/232 dated September 28, 2012, until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions.

Propose a timeline for submission of the immunogenicity data using the improved assays. We understand that you intend to submit the sBLA by the fourth quarter of 2014 and the immunogenicity data using the improved assay may not be available by then. We would not consider the absence of the immunogenicity data as a refuse-to-file issue in your sBLA submission provided that you commit to submit the immunogenicity data in a timely fashion. To allow sufficient time for review, submit the immunogenicity data no later than the date for submission of the 120-day safety update of the sBLA. Include the analysis results for assessment of the impact of immunogenicity on PK, efficacy and safety of your product for the treatment of HS in your immunogenicity data submission.

Meeting Discussion:

The sponsor indicated that they will need to perform indication-specific validation of their new immunogenicity assay. The results with the updated assay will therefore not be available by the 120 day safety update; instead they will submit the immunogenicity data using the old assay in the sBLA. The sponsor proposed to submit the immunogenicity assay data with the improved assay by the fourth quarter of 2015. The Agency responded that this proposed plan is reasonable and stated that a postmarketing requirement may be issued for submission of analysis of blood samples from clinical trials in hidradenitis suppurativa using the new immunogenicity assay. The sponsor indicated that they plan to update labeling based upon the results of the new immunogenicity assay. The Agency recommended that the sponsor consider also using the AAA titer in the analysis of immunogenicity impact.”

3.7. Proposed pediatric studies

The Applicant requested a partial waiver of studies in pediatric patients up to 12 years of age and a partial deferral of pediatric studies for adolescent patients from 12 to <17 years of age. The Applicant proposed to collect additional information on the natural history, treatment, and incidence and prevalence of HiS in adolescents, after which the request for a waiver for studies for adolescent patients 12 to <17 years of age will be reevaluated.

The agency has previously agreed with a partial waiver for pediatric studies in patients less than 12 years of age and recommended deferral of pediatric studies in patients 12 to 17 years of old during review of the initial pediatric study plan (*IND102320, Advice Letters dated on 04/21/2014 and 06/30/2014*).

Appendix 1: Clinical trials that support the sBLA.

Adalimumab PFS (40 mg/0.8 mL) was used in all the HiS clinical trials. ELISA, enzyme-linked immunosorbent assay; eow, every other week; ew, every week; HiS, Hidradenitis Suppurativa; PFS, prefilled syringe.

Clinical Trials	Study design, objectives, population (# of subjects)	Dosing regimen	PK	Immunogenicity
M10-467 (Phase 2)	<i>Design:</i> Double blind, randomized, placebo controlled <i>Primary objective:</i> To evaluate the safety and efficacy of adalimumab in subjects with moderate to severe HiS after 16 weeks of treatment. <i>Subjects:</i> HiS (154)	Period A (16 weeks) – Adalimumab 40 mg ew – Adalimumab 40 mg eow – Placebo Period B (36 additional weeks) – Adalimumab 40 mg eow, with possible dose-escalation to 40 mg ew at Week 28 or Week 31.	Baseline, Weeks 4, 8, 16, 28, 31, 39, 45 and 52.	Baseline, Weeks 4, 8, 16, 28, 31, 39, 45 and 52.
M11-313 (Phase 3)	<i>Design:</i> Randomized, Double Blind, Placebo Controlled <i>Primary objective:</i> To determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HiS after 12 weeks of treatment. <i>Subjects:</i> HiS (307)	Period A (12 weeks) – Adalimumab 40 mg ew – Placebo Period B (24 weeks) – Adalimumab 40 mg ew – Adalimumab 40 mg eow – Placebo	Baseline, Weeks 2, 4, 8, 12, 14, 16, 20, 24, 32, and 36.	Baseline, Weeks 4, 12, 16, 24, and 36.
M11-810 (Phase 3)	<i>Design:</i> Randomized, Double Blind, Placebo Controlled <i>Primary objective:</i> To determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HiS after 12 weeks of treatment. <i>Subjects:</i> HiS (326).	Period A (12 weeks) – Adalimumab 40 mg ew – Placebo Period B (24 weeks) – Adalimumab 40 mg ew – Adalimumab 40 mg eow – Placebo		
M12-555 (Open-label extension)	<i>Design:</i> Open-label extension <i>Objectives:</i> To evaluate the long term safety, tolerability, and efficacy of adalimumab in subjects with moderate to severe HiS who enter from a prior Phase 3 HiS study (Study M11-810 or Study M11-313)	Adalimumab 40 mg ew at Baseline, with possible dose reduction to 40 mg eow, depending on clinical response;	n/a	n/a

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/s/

JIE WANG
12/19/2014

JEFFRY FLORIAN
12/19/2014

YOW-MING C WANG
12/19/2014

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/s/

JIE WANG
07/10/2015

JEFFRY FLORIAN
07/10/2015

YOW-MING C WANG
07/10/2015

EDWARD D BASHAW
07/10/2015
Fully concur with both requested PMC/PMRs

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s393

OTHER REVIEW(S)

Table 1: Proposed Product Characteristics of Humira® (adalimumab).

Proprietary Name:	Humira®
Proper Name:	adalimumab
Indication:	Hidradenitis Suppurativa (HS)*, Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), and Plaque Psoriasis
Dose:	Dose ranges from 10 mg to 160 mg depending on indication. HS*: Initial dose 160 mg on day 1 or 80 mg for 2 consecutive days, then 80 mg (day 15), then 40 mg every week (day 29).
Route of Administration:	Subcutaneous
Dosage Form:	Injection
Strength and Container-Closure:	Pen: 40 mg/0.8 mL Prefilled syringe (PFS): 10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL Vial: 40 mg/0.8 mL
Storage and Handling:	Refrigerate 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. 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.

* Proposal for this supplement.

Materials Reviewed:

Carton Labeling for Starter Package (trade and sample)

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Review:

The Applicant's proposal to add the HS indication to the currently approved Starter Package for CD and UC is acceptable considering the proposed HS dosage for the initial and second doses is identical to CD and UC. Additionally, the use of the currently approved 40 mg PFS and Pen for the 40 mg every other week maintenance dose is appropriate.

The Applicant submitted updated carton labeling on February 9, 2015 that contains the updated storage instructions that allows for storage at room temperature to a maximum of 77°F (25°C) for a period of up to 14 days. These storage conditions were approved in sBLA 125057/280 on December 24, 2014.

Conclusions:

The carton labeling for Humira® (adalimumab) was 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/NF 38/33 [May 1, 2015 to July 31, 2015]. Labeling deficiencies were not identified. The carton labeling submitted on February 9, 2015 is acceptable.

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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 Medical Policy**

PATIENT LABELING REVIEW

Date: July 8, 2015

To: Kendall Marcus, MD
Acting Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Tara Turner, PharmD, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: 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: 393

Applicant: AbbVie Inc.

1 INTRODUCTION

On November 10, 2014, Abbvie, Inc. submitted for the Agency's review a Prior Approval Supplement to their Biologics Licensing Application (BLA) 125057/393 for HUMIRA (adalimumab) injection, for subcutaneous use. This efficacy supplement provides for a proposed new indication for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

HUMIRA (adalimumab) was originally approved on December 31, 2002 and 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
- Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older
- Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis
- Reducing signs and symptoms in adult patients with active ankylosing spondylitis
- 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 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.
- 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)
- 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 collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on March 4, 2015, for DMPP and OPDP 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 MG received on November 10, 2014, and received by DMPP and OPDP on June 25, 2015.
- Draft HUMIRA (adalimumab) injection IFU received on November 10, 2014, and received by DMPP and OPDP on June 25, 2015.
- Draft HUMIRA (adalimumab) injection Prescribing Information (PI) received on November 10, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 25, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes. Revisions to the IFU were not needed.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
07/08/2015

TARA P TURNER
07/08/2015

LASHAWN M GRIFFITHS
07/08/2015

BARBARA A FULLER
07/08/2015

MEMORANDUM

REVIEW OF LABEL AND LABELING

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)

Date of This Memorandum: June 26, 2015
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: BLA 125057/S-393
Product Name and Strength: Humira Pen (adalimumab) Injection, 40 mg/0.8 mL
Submission Date: November 10, 2014
Applicant/Sponsor Name: AbbVie Inc.
OSE RCM #: 2015-523
DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh
DMEPA Team Leader: Kendra Worthy, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products requested that we review the proposed carton labeling for Humira Pen (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

The applicant is only proposing the addition of the new indication (i.e. hidradentis supporativa) to the currently marketed Humira Pen 40 mg/0.8 mL Starter Pack (trade and sample). The proposed carton labeling is acceptable from a medication error perspective.

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/s/

CARLOS M MENA-GRILLASCA
06/26/2015

KENDRA C WORTHY
06/26/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 23, 2015

TO: Cristina Attinello, Regulatory Project Manager
Snezana Trajkovic, M.D., Medical Officer
Jane Liedtka, M.D., Medical Team Leader
Division of Dermatologic and Dental Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125057/393

APPLICANT: AbbVie, Inc.

DRUG: Humira (adalimumab)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of adults with hidradenitis suppurativa

CONSULTATION REQUEST DATE: January 9, 2015
 CLINICAL INSPECTION SUMMARY DATE: June 24, 2015
 DIVISION ACTION GOAL DATE: August 24, 2015
 PDUFA DATE: September 10, 2015

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Humira (adalimumab) for the treatment of subjects with hidradenitis suppurativa.

The pivotal studies M11-313 and M11-810 are both entitled, “A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa”, and were inspected in support of this application. These studies are identical in design to Protocol M11-313 for the first 12 weeks of the study. As such the primary and secondary endpoints of interest are also the same.

The following sites were selected for inspection because they had the highest subject enrollments and the highest treatment effects. Treatment effect for the primary and secondary endpoints for Study M11-810 was twice that reported for Study M11-313.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Jamie Weisman, MD Peachtree Dermatology Associates Research Center 3286 Northside Parkway, Suite 130 Northwest Atlanta, GA 30327	M11-313/ 36627/ 19	17 Mar-1 Apr 2015	NAI
Seth Forman, MD Forward Clinical Trials, Inc. 4915 Ehrlich Road Tampa, FL 33624	M11-810/ 37884/ 16	23-30 Mar 2015	NAI
Alma Cruz-Santana, MD Carolina Shopping Court, 6th Floor, Office 303 65th Infantry Avenue with Roberto Clemente St. Carolina, Puerto Rico 00985	M11-810/ 42801/ 11	30 Mar-16 Apr 2015	NAI

Key to 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 Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Jamie Weisman, MD

Atlanta Medical Dermatology Specialists, Inc.
875 Johnson Ferry Road, Suite 180
Atlanta, GA 30342

- a. **What was inspected:** At this site for Protocol M11-313, 30 subjects were screened, 19 subjects were enrolled, and 16 subjects completed at least 12 weeks of the study. The records of all 30 subjects screened for the study were reviewed. Records reviewed included, but were not limited to, informed consent, source documentation, adverse events, primary endpoints, test article accountability, sponsor and IRB communications, and protocol deviations.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. Please note that the study was performed at Peachtree Dermatology Associates while the inspection was conducted at Dr. Weisman's current address at Atlanta Medical Dermatology Associates.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Seth Forman, MD

Forward Clinical Trials, Inc.
4915 Ehrlich Road
Tampa, FL 33624

- a. **What was inspected:** At this site for Protocol M11-810, 24 subjects were screened, 16 subjects were enrolled, and 6 subjects completed the study. The records of the 16 subjects enrolled in the study were reviewed in detail. Records reviewed included, but were not limited to, source documentation, primary and secondary endpoints, adverse event reporting, concomitant medications, protocol deviations, laboratory certifications, sponsor, monitor, and IRB communications, financial disclosure, and test article accountability.
- b. **General observations/commentary:** Of the ten subjects not completing the study, three subjects quit the study because of lack of response, two subjects rolled over into the M12-255 study extension, two subjects withdrew because of adverse events, one subject was lost to follow-up, one subject moved out of state, and one subject quit due to worsening of the hidradenitis suppurativa. Informed consent was obtained from all screened subjects prior to the initiation of any study activities. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Alma Cruz-Santana, MD
Carolina Shopping Court, 6th Floor, Office 303
65th Infantry Avenue with
Roberto Clemente St.
Carolina, Puerto Rico 00985

- a. **What was inspected:** At this site for Protocol M11-810, 12 subjects were screened, 11 subjects were enrolled, and three subjects completed the study. The study records of all 12 subjects screened for the study were reviewed. Records reviewed included, but were not limited to, informed consent, source documents, inclusion/exclusion criteria, ECGs, concomitant medications, adverse events case report forms, the primary efficacy endpoint, regulatory communications including sponsor, monitor, and IRB correspondence, protocol deviations, training forms, licensures, financial disclosure forms, laboratory certificates, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed that the low number of subjects completing the study (3/12) was due to worsening of their condition or the absence of improvement at Week 28. The low rate of study completion was specifically addressed by the field investigator and was consistent with the protocol, source documents, and line listings.

With respect to informed consent, the first subject signed an informed consent form on January 9, 2012. Discussion with the field investigator indicated that the study (Version 1.0) was initially approved on October 6, 2011. There were several protocol amendments following the initial approval of the study in addition to several versions of the IRB-approved informed consent form. The most recent version of the protocol used at the site, Version 1.0 including Amendments 1, 2, and 3 (dated August 7, 2013) and an administrative change was approved by the IRB on September 10, 2013.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Weisman, Forman, and Cruz-Santana were inspected in support of this NDA. None of these sites were issued a Form FDA 483, and the final classification of the inspections of each of these sites was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by each of each of these sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
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/s/

ROY A BLAY
06/23/2015

JANICE K POHLMAN
06/23/2015

KASSA AYALEW
06/23/2015