CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125118Orig1s122

Trade Name: ORENCIA

Generic or Proper Name: abatacept

Sponsor: Bristol-Myers Squibb Company

Approval Date: 07/29/2011

Indication:

ORENCIA is a selective T cell costimulation modulator indicated for:

Adult Rheumatoid Arthritis (RA)

- moderately to severely active RA in adults. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Juvenile Idiopathic Arthritis

- moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Important Limitation of Use: should not be given concomitantly with TNF antagonists

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125118/122

SUPPLEMENT BLA APPROVAL
July 29, 2011

Bristol-Myers Squibb Company
P.O. Box 4000 (Mail Stop: D32-07)
Princeton, New Jersey 08543-4000

Attention: Ashley Pereira, Pharm.D.
Director, Global Regulatory Sciences

Dear Dr. Pereira:

Please refer to your Supplemental Biologics License Application (sBLA), dated October 4, 2010, received October 4, 2010, submitted under section 351 of the Public Health Service Act for Orencia (abatacept).

We acknowledge receipt of your amendments dated December 2, and 14, 2010, and February 3, and 4, March 1, 10, 14, and 17, April 8, and 25, May 31, June 13, and 22, and July 7, 11, 14, 25, and 26 (2), 2011.

This "Prior Approval" efficacy supplement to your biologics license application proposes the subcutaneous use of abatacept for Rheumatoid Arthritis.

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 are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 and text for the patient package insert,) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the

guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125118/122**."

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

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on July 25, 2011, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125118/122**." Approval of this submission by FDA is not required before the labeling is used.

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

We are waiving the pediatric study requirement for ages zero to 5 years because there is evidence strongly suggesting that the drug product would be ineffective and unsafe in this pediatric group. Given that the safety and efficacy of ORENCIA has not been established in pediatric patients below 6 years of age, ORENCIA is not recommended for use in this age group.

We are deferring submission of your pediatric study for ages 6 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be

reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

PMR#1: Conduct a PK/safety study of SC abatacept in polyaricular JIA patients ages 6 to 17 years of age.

Final Protocol Submission:	November 2012
Study Completion:	September 2017
Final Report Submission:	January 2018

Reports of this/these required pediatric postmarketing study(ies) must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC#1 Re-assess the bioburden action limits for the formulated drug product step (b) (4) based on the manufacturing scale data from 30 released drug product lots.

The timetable you submitted on July 7, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission:	December 2014

PMC#2 Collect bioburden data at the drug product (b) (4) step and set appropriate bioburden limits for this step.

The timetable you submitted on July 7, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission:	December 2014

PMC#3 Provide information and summary data on the product specific container closure integrity test (CCIT) method and provide an updated post-marketing stability protocol replacing the sterility test with CCIT.

The timetable you submitted on July 7, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2012

PMC#4 Re-evaluate the acceptance criteria for drug product specifications based on manufacturing data from at least 30 released commercial lots and data from lots used in clinical trials.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2015

PMC#5 Establish separate release and shelf-life limits and/or acceptance criteria for product attributes that are stability indicating and submit a PMC final report.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2012

PMC#6 Develop and validate a quantitative IEF specification using a method such as CE-IEF and submit a PMC final report.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: July 2013

PMC#7 Develop and validate a quantitative B7 binding specification that includes measurements of Keq and/or kd using a method such SPR and submit a PMC final report.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: July 2013

PMC#8 Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product based on the risks to product quality when stored under the approved conditions.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2013

PMC#9 Perform real time and accelerated stability studies on two additional batches of drug product produced from drug substance manufactured (b) (4) in accordance with the time points specified in the approved post-approval stability protocol and submit a PMC final report.

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: February 2015

PMC#10 Provide the results of the extractables analysis under the appropriate exaggerated conditions using the prefilled syringe components that come into contact with the drug (b) (4) .

Provide results of leachables analysis on one lot of the drug product in the assembled prefilled syringe unit using the Drug Product Vehicle with the Active Pharmaceutical Ingredient, as extraction medium. This data will include the real-time conditions 2°-8°C, as well as at the accelerated storage condition of 25°C/60% RH at multiple stability time-points throughout the shelf life of the product. Leachable analysis to employ validated methods of ICP-MS, LC-DAD and GC-FID. Provide a justification of the sample size used (i.e., number of lots and units within each lot).

The timetable you submitted on July 26, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: August 2012

Submit clinical protocols to your IND 9391 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), 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 Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

/Badrul A. Chowdhury, M.D., Ph.D./
Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

7/26/2011

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORENCIA safely and effectively. See full prescribing information for ORENCIA.

ORENCIA (abatacept)
for injection for intravenous use
injection, for subcutaneous use
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Dosage and Administration, Adult Rheumatoid Arthritis (2.1)	7/2011
Dosage and Administration, General Considerations for Subcutaneous Administration (2.4)	7/2011

INDICATIONS AND USAGE

ORENCIA is a selective T cell costimulation modulator indicated for:

Adult Rheumatoid Arthritis (RA) (1.1)

- moderately to severely active RA in adults. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists (1.1).

Juvenile Idiopathic Arthritis (1.2)

- moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. ORENCIA may be used as monotherapy or concomitantly with methotrexate (1.2).

Important Limitations of Use (1.3)

- should not be given concomitantly with TNF antagonists (1.3, 5.1).

DOSAGE AND ADMINISTRATION

Intravenous Administration for Adult RA (2.1)

Body Weight of Patient	Dose	Number of Vials
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than100 kg	1000 mg	4

Subcutaneous Administration for Adult RA (2.1)

- After a single intravenous infusion as a loading dose (as per body weight categories above), 125 mg administered by a subcutaneous injection should be given within a day, followed by 125 mg subcutaneously once a week.
- Patients who are unable to receive an infusion may initiate weekly injections of subcutaneous ORENCIA without an intravenous loading dose.
- Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Juvenile Idiopathic Arthritis (2.2)

- Pediatric patients weighing less than 75 kg receive 10 mg/kg intravenously based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).

General Dosing Information for Intravenous Administration (2.1)

- Administer as a 30-minute intravenous infusion (2.1)
- Following initial dose, give at 2 and 4 weeks, then every 4 weeks (2.1)
- Prepare ORENCIA using only the silicone-free disposable syringe (2.3)
- Use only sterile water to reconstitute the powder (2.3)
- The reconstituted product must be administered using a filter (2.3)

DOSAGE FORMS AND STRENGTHS

- 250 mg lyophilized powder in a single-use vial for intravenous infusion (3)
- 125 mg/mL solution in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Concomitant use with a TNF antagonist can increase the risk of infections and serious infections (5.1)
- Hypersensitivity, anaphylaxis, and anaphylactoid reactions (5.2)
- Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections (5.3, 8.5)
- Discontinue if a serious infection develops (5.3)
- Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating ORENCIA (5.3)
- Live vaccines should not be given concurrently or within 3 months of discontinuation (5.4)
- Patients with juvenile idiopathic arthritis should be brought up to date with all immunizations prior to ORENCIA therapy (5.4)
- Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations (5.4)
- COPD patients may develop more frequent respiratory adverse events (5.5)

ADVERSE REACTIONS

Most common adverse events (≥10%) are headache, upper respiratory tract infection, nasopharyngitis, and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

USE IN SPECIFIC POPULATIONS

- Pregnancy: Registry available. Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adult Rheumatoid Arthritis (RA)

ORENCIA® 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. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

1.2 Juvenile Idiopathic Arthritis

ORENCIA is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).

1.3 Important Limitations of Use

ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Rheumatoid Arthritis

For adult patients with RA, ORENCIA may be administered as an intravenous infusion or a subcutaneous injection.

ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

For pediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used [see *Dosage and Administration (2.2)*].

Intravenous Dosing Regimen

ORENCIA intravenous should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous administration,

an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 1: Dose of ORENCIA for Intravenous Infusion in Adult RA Patients

Body Weight of Patient	Dose	Number of Vials[a]
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1000 mg	4

[a] Each vial provides 250 mg of abatacept for administration.

Subcutaneous Dosing Regimen

Following a single intravenous loading dose (as per body weight categories listed in Table 1), the first 125 mg subcutaneous injection of ORENCIA should be given within a day, followed by 125 mg subcutaneous injections once weekly.

Patients who are unable to receive an infusion may initiate weekly injections of subcutaneous ORENCIA without an intravenous loading dose.

Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.2 Juvenile Idiopathic Arthritis

The recommended dose of ORENCIA for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg intravenously calculated based on the patient's body weight at each administration. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA should be administered as a 30-minute intravenous infusion. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded.

2.3 Preparation and Administration Instructions for Intravenous Infusion

Use aseptic technique.

ORENCIA is provided as a lyophilized powder in preservative-free, single-use vials. Each ORENCIA vial provides 250 mg of abatacept for administration. The ORENCIA powder in each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP, using *only the silicone-free disposable syringe provided with each vial* and an 18- to 21-gauge needle. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL. If the ORENCIA powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

If the *silicone-free disposable syringe* is dropped or becomes contaminated, use a new *silicone-free disposable syringe* from inventory. For information on obtaining additional *silicone-free disposable syringes*, contact Bristol-Myers Squibb 1-800-ORENCIA.

1) Use 10 mL of Sterile Water for Injection, USP to reconstitute the ORENCIA powder. To reconstitute the ORENCIA powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial with gentle swirling to minimize foam formation, until the contents are completely dissolved. Do not shake. Avoid prolonged or vigorous agitation.

2) Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 mL). The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

3) The reconstituted ORENCIA solution must be further diluted to 100 mL as follows. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the reconstituted ORENCIA solution required for the patient's dose. Slowly add the reconstituted ORENCIA solution into the infusion bag or bottle using the same *silicone-free disposable syringe provided with each vial*. Gently mix. *Do not shake the bag or bottle*. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 10 mg/mL. Any unused portions in the vials must be immediately discarded.

4) Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discoloration. Discard the solution if any particulate matter or discoloration is observed.

5) The entire, fully diluted ORENCIA solution should be administered over a period of 30 minutes and must be administered with an infusion set and a *sterile, non-pyrogenic, low-protein-binding filter* (pore size of 0.2 µm to 1.2 µm).

6) The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of reconstitution of the ORENCIA vials. The fully diluted ORENCIA solution may be stored at room temperature or refrigerated at 2°C to 8°C (36°F to 46°F) before use. Discard the fully diluted solution if not administered within 24 hours.

7) ORENCIA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of ORENCIA with other agents.

2.4 General Considerations for Subcutaneous Administration

ORENCIA Injection, 125 mg/syringe is not intended for intravenous infusion.

ORENCIA Injection is intended for use under the guidance of a physician or healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject with ORENCIA if a physician/healthcare practitioner determines that it is appropriate. Patients should be instructed to follow the directions provided in the Instructions for Use for additional details on medication administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use ORENCIA prefilled syringes exhibiting particulate matter or discoloration. ORENCIA should be clear and colorless to pale yellow.

Patients using ORENCIA for subcutaneous administration should be instructed to inject the full amount in the syringe (1 mL), which provides 125 mg of ORENCIA, according to the directions provided in the Instructions for Use.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

3 DOSAGE FORMS AND STRENGTHS

- **Lyophilized Powder for Intravenous Infusion**

  250 mg single-use vial

- **Solution for Subcutaneous Injection**

  125 mg/mL single-dose prefilled glass syringe

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Concomitant Use with TNF Antagonists

In controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) [see *Adverse Reactions (6.1)*]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

5.2 Hypersensitivity

Of 2688 patients with adult RA treated with ORENCIA intravenously in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see *Adverse Reactions (6.1, 6.3)*].

5.3 Infections

Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing

treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection [see *Adverse Reactions (6.1)*]. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA [see *Warnings and Precautions (5.1)*].

Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

Antirheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

5.4 Immunizations

Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. The efficacy of vaccination in patients receiving ORENCIA is not known. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy.

5.5 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with RA and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status [see *Adverse Reactions (6.1)*].

5.6 Immunosuppression

The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses.

The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood [see *Adverse Reactions (6.1)*]. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience in Adult RA Patients Treated with Intravenous ORENCIA

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

The data described herein reflect exposure to ORENCIA administered intravenously in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with ORENCIA, 134 with placebo).

The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: methotrexate, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

The most serious adverse reactions were serious infections and malignancies.

The most commonly reported adverse events (occurring ≥10% of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Infections

In the placebo-controlled trials, infections were reported in 54% of ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia [see *Warnings and Precautions (5.3)*].

Serious infections were reported in 3.0% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis [see *Warnings and Precautions (5.3)*].

Malignancies

In the placebo-controlled portions of the clinical trials (1955 patients treated with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers [see *Warnings and Precautions (5.6)*]. The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V [see *Clinical Studies (14.1)*] were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and <1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure,

and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

Of 2688 patients treated with ORENCIA in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see *Warnings and Precautions (5.2)*].

Adverse Reactions in Patients with COPD

In Study V [see *Clinical Studies (14.1)*], there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with ORENCIA and 17 COPD patients who were treated with placebo. The COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]) [see *Warnings and Precautions (5.5)*].

Other Adverse Reactions

Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients during placebo-controlled RA studies are summarized in Table 2.

Table 2: Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in ORENCIA-Treated Patients During Placebo-Controlled RA Studies

Adverse Event (Preferred Term)	ORENCIA (n=1955)[a] Percentage	Placebo (n=989)[b] Percentage
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with ORENCIA. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity.

No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays. 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

medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

Clinical Experience in Methotrexate-Naive Patients

Study VI was an active-controlled clinical trial in methotrexate-naive patients [see *Clinical Studies (14.1)*]. The safety experience in these patients was consistent with Studies I-V.

6.2 Clinical Experience in Adult RA Patients Treated with Subcutaneous ORENCIA

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

Study SC-I was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to methotrexate (MTX-IR) [see *Clinical Studies (14.1)*]. The safety experience and immunogenicity for ORENCIA administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated in Study SC-I and two other smaller studies discussed in the sections below.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA

Study SC-I compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA

Study SC-I compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with

previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous ORENCIA Administration as Monotherapy without an Intravenous Loading Dose

Study SC-II was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous ORENCIA upon Withdrawal (Three Months) and Restart of Treatment

Study SC-III in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous ORENCIA throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

6.3 Clinical Studies Experience in Juvenile Idiopathic Arthritis

In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients [see *Warnings and Precautions (5)*, *Adverse Reactions (6)*].

ORENCIA has been studied in 190 pediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis. Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36% [see *Clinical Studies (14.2)*]. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient pediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with ORENCIA.

Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults.

Upon continued treatment in the open-label extension period, the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with juvenile idiopathic arthritis following repeated treatment with ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies.

The presence of antibodies was generally transient and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum

concentrations of abatacept. For patients who were withdrawn from ORENCIA during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of ORENCIA therapy.

6.4 Postmarketing Experience

Adverse reactions have been reported during the post-approval use of ORENCIA. 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 ORENCIA. Based on the postmarketing experience with ORENCIA in adult RA patients, the adverse event profile of ORENCIA does not differ from that listed/discussed above in Section 6.1 in adults.

7 DRUG INTERACTIONS

7.1 TNF Antagonists

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended [see *Warnings and Precautions (5.1)*].

7.2 Other Biologic RA Therapy

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra, and therefore such use is not recommended.

7.3 Blood Glucose Testing

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA through intravenous administration, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of ORENCIA use in pregnant women. Abatacept has been shown to cross the placenta in animals, and in animal reproduction studies alterations in immune function occurred. ORENCIA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Abatacept was not teratogenic when administered to pregnant mice at doses up to 300 mg/kg and in pregnant rats and rabbits at doses up to 200 mg/kg daily representing approximately 29 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve).

Abatacept administered to female rats every three days during early gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg, representing 3 times the exposure associated with the MRHD of 10 mg/kg based on AUC. However, at 200 mg/kg, 11 times the MRHD exposure, alterations in immune function were observed consisting of a 9-fold increase in T-cell dependent antibody response in female pups and thyroid inflammation in one female pup. It is not known whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept. However, exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [see *Nonclinical Toxicology (13.2)*].

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ORENCIA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether ORENCIA is excreted into human milk or absorbed systemically after ingestion by a nursing infant. However, abatacept was excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

ORENCIA is indicated for reducing signs and symptoms in pediatric patients with moderately to severely active polyarticular juvenile idiopathic arthritis ages 6 years and older. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Studies in juvenile rats exposed to ORENCIA prior to immune system maturity have shown immune system abnormalities including an increase in the incidence of infections leading to death as well as inflammation of the thyroid and pancreas [see *Nonclinical Toxicology (13.2)*]. Studies in adult mice and monkeys have not demonstrated similar findings. As the immune system of the rat is undeveloped in the first few weeks after birth, the relevance of these results to humans greater than 6 years of age (where the immune system is largely developed) is unknown.

ORENCIA is not recommended for use in patients below the age of 6 years.

The safety and effectiveness of ORENCIA in pediatric patients below 6 years of age have not been established. The safety and efficacy of ORENCIA in pediatric patients for uses other than juvenile idiopathic arthritis have not been established.

8.5 Geriatric Use

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

10 OVERDOSAGE

Doses up to 50 mg/kg have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

ORENCIA® (abatacept) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge,

CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA lyophilized powder for intravenous infusion is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of ORENCIA provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration.

ORENCIA solution for subcutaneous administration is supplied as a sterile, preservative-free, clear, colorless to pale yellow solution with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, dibasic sodium phosphate anhydrous (0.838 mg), monobasic sodium phosphate monohydrate (0.286 mg), poloxamer 188 (8 mg), sucrose (170 mg), and quantity sufficient to 1 mL with water for injection. Unlike the intravenous formulation, ORENCIA solution for subcutaneous administration contains no maltose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and are found in the synovium of patients with RA.

In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon-γ. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

12.2 Pharmacodynamics

In clinical trials with ORENCIA at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNFα. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

12.3 Pharmacokinetics

Healthy Adults and Adult RA - Intravenous Administration

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see Table 3).

Table 3: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 (1 to 66) mcg/mL. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

Juvenile Idiopathic Arthritis

In patients 6 to 17 years of age, the mean (range) steady-state serum peak and trough concentrations of abatacept were 217 (57 to 700) and 11.9 (0.15 to 44.6) mcg/mL. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept

increased with baseline body weight. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 (0.20 to 1.12) mL/h/kg. After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Study SC-II was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load. When the intravenous loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing.

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies produced exposures 0.8, 2.0, and 3.0 times higher, respectively, than the exposure associated with the maximum recommended human dose (MRHD) of

10 mg/kg based on AUC (area under the time-concentration curve). The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (producing 9 times the MRHD exposure based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* bacterial reverse mutation (Ames) or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays with or without metabolic activation, and no chromosomal aberrations were observed in human lymphocytes treated with abatacept with or without metabolic activation.

Abatacept had no adverse effects on male or female fertility in rats at doses up to 200 mg/kg every three days (11 times the MRHD exposure based on AUC).

13.2 Animal Toxicology and/or Pharmacology

A juvenile animal study was conducted in rats dosed with abatacept from 4 to 94 days of age in which an increase in the incidence of infections leading to death occurred at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed.

In studies of adult mice and monkeys, inhibition of TDAR was apparent. However, infection and mortality, altered T-helper cells, and inflammation of thyroid and pancreas were not observed.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The efficacy and safety of ORENCIA for intravenous administration were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled)

in patients ≥18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study V did not require any specific number of tender or swollen joints. ORENCIA or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter in intravenous Studies I, II, III, IV, and VI. The safety and efficacy of ORENCIA for subcutaneous administration were assessed in Study SC-I, which was a randomized, double-blind, double-dummy, non-inferiority study that compared abatacept administered subcutaneously and intravenously in 1457 subjects with rheumatoid arthritis (RA), receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate (MTX-IR).

Study I evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept. In Study II and Study III, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to methotrexate and who were continued on their stable dose of methotrexate. In Study IV, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to a TNF blocking agent, with the TNF blocking agent discontinued prior to randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. Patients in Study V were not excluded for comorbid medical conditions. In Study VI, the efficacy and safety of ORENCIA were assessed in methotrexate-naive patients with RA of less than 2 years disease duration. In Study VI, patients previously naive to methotrexate were randomized to receive ORENCIA plus methotrexate or methotrexate plus placebo. In Study SC-I, the goal was to demonstrate the efficacy and safety of ORENCIA subcutaneous relative to ORENCIA intravenous administration in subjects with moderate to severely active RA and experiencing inadequate response to methotrexate, using a non-inferiority study design.

Study I patients were randomized to receive one of three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive ORENCIA 2 or 10 mg/kg or placebo for 12 months. Study III, IV, V, and VI patients were randomized to receive a dose of ORENCIA based on weight range or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg. In Study SC-I, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive ORENCIA 125 mg subcutaneous injections weekly, after a single intravenous loading dose of ORENCIA based on body weight or ORENCIA intravenously on Days 1, 15, 29, and every four weeks thereafter. Subjects continued taking their current dose of methotrexate from the day of randomization.

Clinical Response

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, IV, and VI are shown in Table 4. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients and within 29 days versus methotrexate in Study VI. In Studies II, III, and VI, ACR response rates were maintained to 12 months in ORENCIA-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II. In Study III, ORENCIA-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

In Study VI, a greater proportion of patients treated with ORENCIA plus methotrexate achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 at 12 months compared to those treated with methotrexate plus placebo (Table 4). Of patients treated with ORENCIA plus methotrexate who achieved DAS28-CRP less than 2.6, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

In Study SC-I, the main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of −7.5%. As shown in Table 4, the study demonstrated non-inferiority of ORENCIA administered subcutaneously to intravenous infusions of ORENCIA with respect to ACR 20 responses up to 6 months of treatment. ACR 50 and 70 responses are also shown in Table 4. No major differences in ACR responses were observed between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown).

Table 4: Clinical Responses in Controlled Trials

	Percent of Patients									
	Intravenous Administration								Subcutaneous Administration	
	Inadequate Response to DMARDs		Inadequate Response to Methotrexate (MTX)		Inadequate Response to TNF Blocking Agent		MTX-Naive		Inadequate Response to MTX	
	Study I		Study III		Study IV		Study VI		Study SC-I	
Response Rate	ORN[a] n=32	PBO n=32	ORN[b] +MTX n=424	PBO +MTX n=214	ORN[b] + DMARDs n=256	PBO + DMARDs n=133	ORN[b] +MTX n=256	PBO +MTX n=253	ORN[e] SC +MTX n=693	ORN[e] IV +MTX n=678
ACR 20										
Month 3	53%	31%	62%‡	37%	46%‡	18%	64%*	53%	68%	69%
Month 6	NA	NA	68%‡	40%	50%‡	20%	75%†	62%	76%§	76%
Month 12	NA	NA	73%‡	40%	NA	NA	76%‡	62%	NA	NA
ACR 50										
Month 3	16%	6%	32%‡	8%	18%†	6%	40%‡	23%	33%	39%
Month 6	NA	NA	40%‡	17%	20%‡	4%	53%‡	38%	52%	50%
Month 12	NA	NA	48%‡	18%	NA	NA	57%‡	42%	NA	NA
ACR 70										
Month 3	6%	0	13%‡	3%	6%*	1%	19%†	10%	13%	16%
Month 6	NA	NA	20%‡	7%	10%†	2%	32%†	20%	26%	25%
Month 12	NA	NA	29%‡	6%	NA	NA	43%‡	27%	NA	NA
Major Clinical Response[c]	NA	NA	14%‡	2%	NA	NA	27%‡	12%	NA	NA
DAS28-CRP <2.6[d]										
Month 12	NA	NA	NA	NA	NA	NA	41%‡	23%	NA	NA

* p<0.05, ORENCIA (ORN) vs placebo (PBO) or MTX.

† p<0.01, ORENCIA vs placebo or MTX.

‡ p<0.001, ORENCIA vs placebo or MTX.

§ 95% CI: **−4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%).**

a 10 mg/kg.

b Dosing based on weight range [see *Dosage and Administration (2.1)*].

c Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

d Refer to text for additional description of remaining joint activity.

e Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively.

The results of the components of the ACR response criteria for Studies III, IV, and SC-I are shown in Table 5 (results at Baseline [BL] and 6 months [6 M]). In ORENCIA-treated patients,

greater improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

Table 5: Components of ACR Responses at 6 Months

	Intravenous Administration								Subcutaneous Administration			
	Inadequate Response to Methotrexate (MTX)				Inadequate Response to TNF Blocking Agent				Inadequate Response to MTX			
	Study III				Study IV				Study SC-I[c]			
	ORN +MTX n=424		PBO +MTX n=214		ORN +DMARDs n=256		PBO +DMARDs n=133		ORN SC +MTX n=693		ORN IV +MTX n=678	
Component (median)	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M
Number of tender joints (0-68)	28	7‡	31	14	30	13‡	31	24	27	5	27	6
Number of swollen joints (0-66)	19	5‡	20	11	21	10‡	20	14	18	4	18	3
Pain[a]	67	27‡	70	50	73	43†	74	64	71	25	70	28
Patient global assessment[a]	66	29‡	64	48	71	44‡	73	63	70	26	68	27
Disability index[b]	1.75	1.13‡	1.75	1.38	1.88	1.38‡	2.00	1.75	1.88	1.00	1.75	1.00
Physician global assessment[a]	69	21‡	68	40	71	32‡	69	54	65	16	65	15
CRP (mg/dL)	2.2	0.9‡	2.1	1.8	3.4	1.3‡	2.8	2.3	1.6	0.7	1.8	0.7

† $p<0.01$, ORENCIA (ORN) vs placebo (PBO), based on mean percent change from baseline.

‡ $p<0.001$, ORENCIA vs placebo, based on mean percent change from baseline.

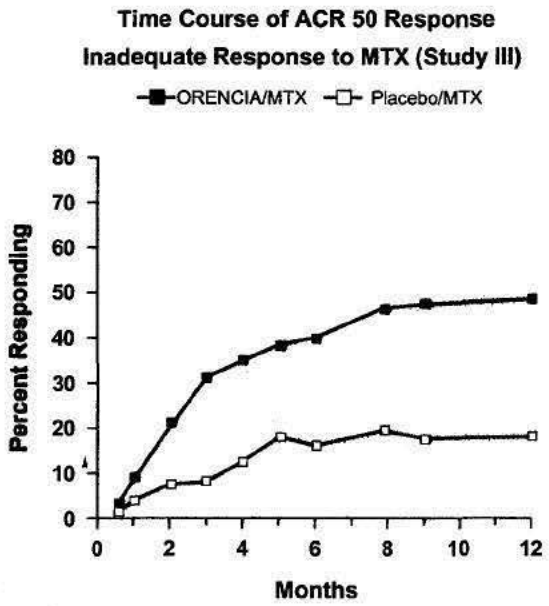
a Visual analog scale: 0 = best, 100 = worst.

b Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

c SC-I is a non-inferiority study. Per protocol data is presented in table.

The percent of patients achieving the ACR 50 response for Study III by visit is shown in Figure 1. The time course for the ORENCIA group in Study VI was similar to that in Study III.

Figure 1: Percent of Patients Achieving ACR 50 Response by Visit* (Study III)



*The same patients may not have responded at each time point.

The percent of patients achieving the ACR 50 response for Study SC-I in the ORENCIA subcutaneous (SC) and intravenous (IV) treatment arms at each treatment visit was as follows: Day 15—SC 3%, IV 5%; Day 29—SC 11%, IV 14%; Day 57—SC 24%, IV 30%; Day 85—SC 33%, IV 38%; Day 113—SC 39%, IV 41%; Day 141—SC 46%, IV 47%; Day 169—SC 51%, IV 50%.

Radiographic Response

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. ORENCIA/methotrexate slowed the progression of structural damage compared to placebo/methotrexate after 12 months of treatment as shown in Table 6.

Table 6: Mean Radiographic Changes in Study III[a] and Study VI[b]

Parameter	ORENCIA/MTX	Placebo/MTX	Differences	P-value[d]
Study III				
First Year				
TSS	1.07	2.43	1.36	<0.01
ES	0.61	1.47	0.86	<0.01
JSN score	0.46	0.97	0.51	<0.01
Second Year				
TSS	0.48	0.74[c]	-	-
ES	0.23	0.22[c]	-	-
JSN score	0.25	0.51[c]	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

[a] Patients with an inadequate response to MTX.
[b] MTX-naive patients.
[c] Patients received 1 year of placebo/MTX followed by 1 year of ORENCIA/MTX.
[d] Based on a nonparametric ANCOVA model.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/methotrexate and 65% of patients initially randomized to placebo/methotrexate were evaluated radiographically at Year 2. As shown in Table 6, progression of structural damage in ORENCIA/methotrexate-treated patients was further reduced in the second year of treatment.

Following 2 years of treatment with ORENCIA/methotrexate, 51% of patients had no progression of structural damage as defined by a change in the TSS of zero or less compared with baseline. Fifty-six percent (56%) of ORENCIA/methotrexate-treated patients had no progression during the first year compared to 45% of placebo/methotrexate-treated patients. In their second year of treatment with ORENCIA/methotrexate, more patients had no progression than in the first year (65% vs 56%).

Physical Function Response and Health-Related Outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, ORENCIA demonstrated greater improvement from baseline versus placebo in Studies II-V and versus methotrexate in Study VI. In Study SC-I, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous administration. The results from Studies II and III are shown in Table 7. Similar results were observed in Study V compared to placebo and in

Study VI compared to methotrexate. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

Table 7: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate			
	Study II		Study III	
HAQ Disability Index	ORENCIA[a] +MTX (n=115)	Placebo +MTX (n=119)	ORENCIA[b] +MTX (n=422)	Placebo +MTX (n=212)
Baseline (Mean)	0.98[c]	0.97[c]	1.69[d]	1.69[d]
Mean Improvement Year 1	0.40[c],***	0.15[c]	0.66[d],***	0.37[d]

*** p<0.001, ORENCIA vs placebo.

[a] 10 mg/kg.

[b] Dosing based on weight range [see *Dosage and Administration (2.1)*].

[c] Modified Health Assessment Questionnaire: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[d] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of ORENCIA were assessed in a three-part study including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). Patients 6 to 17 years of age (n=190) with moderately to severely active polyarticular JIA who had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included Oligoarticular (16%), Polyarticular (64%; 20% were rheumatoid factor positive), and Systemic (20%). At study entry, 74% of patients were receiving methotrexate (mean dose, 13.2 mg/m^2 per week) and remained on a stable dose of methotrexate (those not receiving methotrexate did not initiate methotrexate treatment during the study).

In Period A (open-label, lead-in), patients received 10 mg/kg (maximum 1000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as **≥30% improvement in at least 3 of the 6** JIA core set variables and **≥30% worsening in not more than 1 of the 6 JIA core set variables.** Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA was less than one-third than that for patients withdrawn from ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders has remained consistent for 1 year.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ORENCIA® (abatacept) lyophilized powder for intravenous infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe, providing 250 mg of abatacept in a 15-mL vial: NDC 0003-2187-10.

For Subcutaneous Injection

ORENCIA® (abatacept) injection solution for subcutaneous administration is supplied as a single-dose disposable prefilled glass syringe with flange extender. The Type I glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall, ½-inch needle) covered with a rigid needle shield. The prefilled syringe provides 125 mg of abatacept in 1 mL and is provided in a pack of 4 syringes: NDC 0003-2188-31.

Storage

ORENCIA lyophilized powder supplied in a vial should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use.

ORENCIA solution supplied in a prefilled syringe should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the prefilled syringe. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe to freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

17.1 Concomitant Use With Biologic Medications for RA

Patients should be informed that they should not receive ORENCIA treatment concomitantly with a TNF antagonist, such as adalimumab, etanercept, and infliximab because such combination therapy may increase their risk for infections [see *Indications and Usage (1.3)*, *Warnings and Precautions (5.1)*, and *Drug Interactions (7.1)*], and that they should not receive ORENCIA concomitantly with other biologic RA therapy, such as anakinra because there is not enough information to assess the safety and efficacy of such combination therapy [see *Indications and Usage (1.3)*, *Drug Interactions (7.2)*].

17.2 Hypersensitivity

Patients should be instructed to immediately tell their healthcare professional if they experience symptoms of an allergic reaction during or for the first day after the administration of ORENCIA [see *Warnings and Precautions (5.2)*].

17.3 Infections

Patients should be asked if they have a history of recurrent infections, have underlying conditions which may predispose them to infections, or have chronic, latent, or localized infections. Patients should be asked if they have had tuberculosis (TB), a positive skin test for TB, or recently have been in close contact with someone who has had TB. Patients should be instructed that they may be tested for TB before they receive ORENCIA. Patients should be informed to tell their healthcare professional if they develop an infection during therapy with ORENCIA [see *Warnings and Precautions (5.3)*].

17.4 Immunizations

Patients should be informed that live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. Caregivers of patients with juvenile idiopathic arthritis should be informed that the patient should be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy and to discuss with their healthcare provider how best to handle future immunizations once ORENCIA therapy has been initiated [see *Warnings and Precautions (5.4)*].

17.5 Pregnancy and Nursing Mothers

Patients should be informed that ORENCIA has not been studied in pregnant women or nursing mothers so the effects of ORENCIA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare professional if they are pregnant, become pregnant, or are thinking about becoming pregnant [see *Use in Specific Populations (8.1)*]. Patients should be instructed to tell their healthcare professional if they plan to breast-feed their infant [see *Use in Specific Populations (8.3)*].

17.6 Blood Glucose Testing

Intravenous Administration

Patients should be asked if they have diabetes. Maltose is contained in ORENCIA for intravenous administration and can give falsely elevated blood glucose readings with certain blood glucose monitors on the day of ORENCIA infusion. If a patient is using such a monitor, the patient should be advised to discuss with their healthcare professional methods that do not react with maltose [see *Drug Interactions (7.3)*].

Subcutaneous Administration

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

PATIENT INFORMATION

ORENCIA® (oh-REN-see-ah)
(abatacept)
Lyophilized Powder for Intravenous Infusion

ORENCIA® (oh-REN-see-ah)
(abatacept)
Injection, Solution for Subcutaneous Administration

Read this Patient Information before you start using ORENCIA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ORENCIA?

ORENCIA is a prescription medicine that reduces signs and symptoms in:

- adults with moderate to severe rheumatoid arthritis (RA), including those who have not been helped enough by other medicines for RA. ORENCIA may prevent further damage to your bones and joints and may help your ability to perform daily activities. In adults, ORENCIA may be used alone or with other RA treatments other than tumor necrosis factor (TNF) antagonists.
- children and adolescents 6 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (JIA). ORENCIA may be used alone or with methotrexate.

It is not known if ORENCIA is safe and effective in children under 6 years of age.

It is not known if ORENCIA is safe and effective in children for uses other than juvenile idiopathic arthritis.

What should I tell my healthcare provider before using ORENCIA?

Before you use ORENCIA, tell your healthcare provider if you:

- have any kind of infection even if it is small (such as an open cut or sore), or an infection that is in your whole body (such as the flu). If you have an infection when taking ORENCIA, you may have a higher chance for getting serious side effects.
- have an infection that will not go away or an infection that keeps coming back.
- are allergic to abatacept or any of the ingredients in ORENCIA. See the end of this leaflet for a list of the ingredients in ORENCIA.

- have or have had inflammation of your liver due to an infection (viral hepatitis). Before you use ORENCIA, your healthcare provider may examine you for hepatitis.
- have had a lung infection called tuberculosis (TB), a positive skin test for TB, or you recently have been in close contact with someone who has had TB. Before you use ORENCIA, your healthcare provider may examine you for TB or perform a skin test. Symptoms of TB may include:
    - a cough that does not go away
    - weight loss
    - fever
    - night sweats
- are scheduled to have surgery.
- recently received a vaccination or are scheduled for a vaccination. If you are receiving ORENCIA, and for 3 months after you stop receiving ORENCIA, you should not receive live vaccines.
- have a history of a breathing problem called chronic obstructive pulmonary disease (COPD).
- have diabetes and use a blood glucose monitor to check your blood sugar (blood glucose) levels. ORENCIA for intravenous infusion (given through a needle placed in a vein) contains maltose, a type of sugar that can give false high blood sugar readings with certain types of blood glucose monitors, on the day of ORENCIA infusion. Your doctor may tell you to use a different way to monitor your blood sugar levels.
- ORENCIA for subcutaneous injection (injected under the skin) does not contain maltose. You do not need to change your blood sugar monitoring if you are taking ORENCIA subcutaneously.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if ORENCIA can harm your unborn baby.

  Bristol-Myers Squibb Company has a registry for pregnant women exposed to ORENCIA. The purpose of this registry is to check the health of the pregnant mother and her child. Women are encouraged to call the registry themselves or ask their doctors to contact the registry for them by calling 1-877-311-8972.
- are breast-feeding or plan to breast-feed. It is not known if ORENCIA passes into your breast milk. You and your healthcare provider should decide if you will use ORENCIA or breast-feed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

ORENCIA may affect the way other medicines work, and other medicines may affect the way ORENCIA works causing serious side effects.

Especially tell your healthcare provider if you take other biologic medicines to treat RA or JIA that may affect your immune system, such as:

- Enbrel® (etanercept)
- Humira® (adalimumab)
- Remicade® (infliximab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Simponi® (golimumab)
- Cimzia® (certolizumab pegol)
- Actemra® (tocilizumab)

You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines for your RA or JIA.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new prescription.

How should I use ORENCIA?

- You may receive ORENCIA given by a healthcare provider through a vein in your arm (IV or intravenous infusion). It takes about 30 minutes to give you the full dose of medicine. You will then receive ORENCIA 2 weeks and 4 weeks after the first dose and then every 4 weeks.
- You may also receive ORENCIA as an injection under your skin (subcutaneous). If your healthcare provider decides that you or a caregiver can give your injections of ORENCIA at home, you or your caregiver should receive training on the right way to prepare and inject ORENCIA. Do not try to inject ORENCIA until you have been shown the right way to give the injections by your healthcare provider.
- Your healthcare provider will tell you how much ORENCIA to use, and when to use it.
- **See the Instructions for Use at the end of this Patient Information leaflet for instructions about the right way to prepare and give your ORENCIA injections at home.**

What are the possible side effects of ORENCIA?

ORENCIA can cause serious side effects including:

- **infections.** ORENCIA can make you more likely to get infections or make the infection that you have get worse. Call your healthcare provider right away if you have any symptoms of an infection. Symptoms of an infection may include:
    - fever

- feel very tired
- have a cough
- have flu-like symptoms
- warm, red, or painful skin

- **allergic reactions.** Allergic reactions can happen to people who use ORENCIA. Call your healthcare provider or go to the emergency room right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction may include:
    - hives
    - swollen face, eyelids, lips, or tongue
    - trouble breathing
- **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 ORENCIA. Your healthcare provider may do a blood test before you start treatment with ORENCIA while you use ORENCIA.
- **vaccinations.** You should not receive ORENCIA with certain types of vaccines (live vaccines). ORENCIA may also cause some vaccinations to be less effective. Talk with your healthcare provider about your vaccination plans.
- **breathing problems in patients with Chronic Obstructive Pulmonary Disease (COPD).** Some people may get certain respiratory problems more often if you receive ORENCIA and have COPD. Symptoms of respiratory problems include:
    - COPD that becomes worse
    - cough
    - trouble breathing
- **cancer (malignancies).** Certain kinds of cancer have been reported in people using ORENCIA. It is not known if ORENCIA increases your chance of getting certain kinds of cancer.

Common side effects of ORENCIA include:

- headache
- upper respiratory tract infection
- sore throat
- nausea

In children and adolescents, other side effects may include:

- diarrhea
- cough
- fever
- abdominal pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ORENCIA. For more information, ask your healthcare provider or pharmacist.

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

How should I store ORENCIA?

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Keep ORENCIA and all medicines out of the reach of children.

General information about the safe and effective use of ORENCIA

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not use ORENCIA for a condition for which it was not prescribed. Do not give ORENCIA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ORENCIA. If you would like more information, talk to your healthcare provider.

You can ask your pharmacist or healthcare provider for information about ORENCIA that is written for health professionals.

For more information, go to www.ORENCIA.com or call 1-800-ORENCIA.

What are the ingredients in ORENCIA?

Active ingredient: abatacept

Intravenous inactive ingredients: maltose, monobasic sodium phosphate, sodium chloride for administration

Subcutaneous inactive ingredients: sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection

This Patient Information has been approved by the U.S. Food and Drug Administration.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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1292618 Rev July 2011

Instructions for Use
ORENCIA® (oh-REN-see-ah)
(abatacept)
Prefilled Syringe

Read and follow these Instructions for Use that come with your ORENCIA prefilled syringe before you start using it and each time you get a refill. Before you use ORENCIA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

Do not remove the needle cover (the cap) until you are ready to inject ORENCIA.

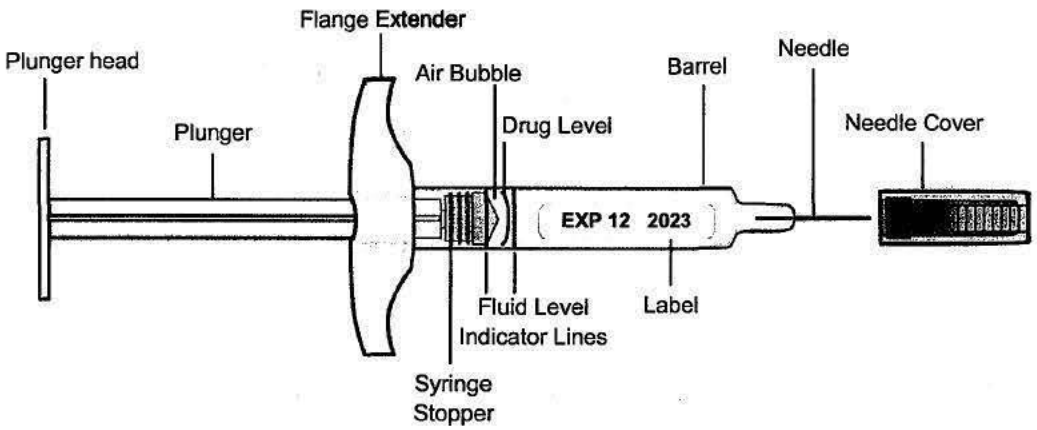

Figure A

- The ORENCIA prefilled syringe has a flange extender that makes it easier to hold the syringe and inject **(see Figure A)**.

Supplies needed for your ORENCIA Prefilled Syringe Injection (see Figure B):

- a new ORENCIA prefilled syringe
- alcohol swab
- cotton ball or gauze
- adhesive bandage
- puncture resistant container (sharps container)

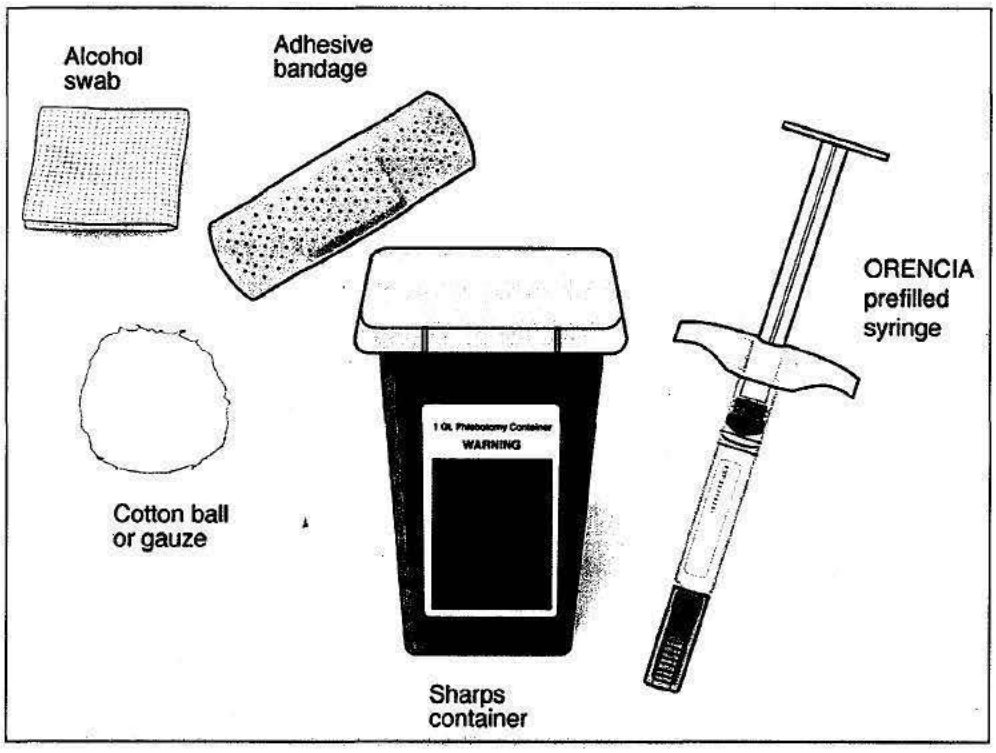

Figure B

STEP 1: Preparing for an ORENCIA Injection

Find a comfortable space with a clean, flat, working surface.

- Check the expiration date on the ORENCIA prefilled syringe (**see Figure A**). **Do not** use it if the expiration date has passed. Throw it away and get a new one.
- Remove 1 single-use ORENCIA prefilled syringe from the refrigerator and let it warm up for 30 to 60 minutes to allow it to reach room temperature.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.

Do not remove the needle cover while allowing ORENCIA prefilled syringe to reach room temperature.

- Keep your unused syringes in their original carton and keep in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not** freeze.
- Hold your ORENCIA prefilled syringe by the barrel with the covered needle pointing down (**see Figure C**).

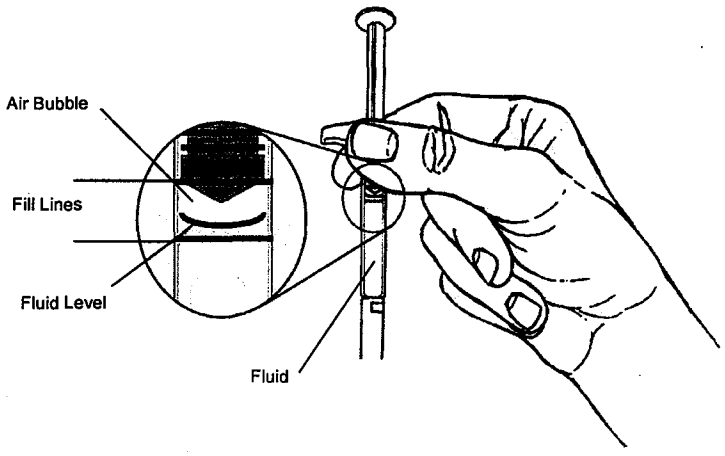

Figure C

- Check the liquid in the ORENCIA prefilled syringe. It should be clear and colorless to pale yellow. **Do not** inject ORENCIA if the liquid is cloudy, discolored, or has lumps or particles in it. Throw the syringe away and get a new one.
- Check that the amount of liquid in your ORENCIA prefilled syringe is the correct amount. The liquid should be between the two lines on the syringe barrel (**see Figure C**).
- **Do not** inject ORENCIA if it does not have the correct amount of liquid. Throw the ORENCIA prefilled syringe away and get a new one. It is normal to see an air bubble. There is no reason to remove it.
- Wash your hands well with soap and water.

STEP 2: Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh is a recommended injection area. You may use your abdomen except for the 2-inch area around your navel (**see Figure D**).
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself (**see Figure E**).

Rotate Injection Site

- Choose a different injection site for each new injection. You may use the same thigh for weekly injections, as long as each injection is at least 1 inch away from the last area you injected.
- Do not inject into areas where your skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

Areas for self-injection and caregiver injection

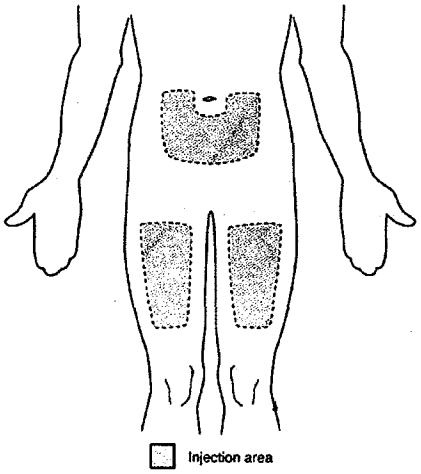

Figure D

Additional injection area for caregivers only

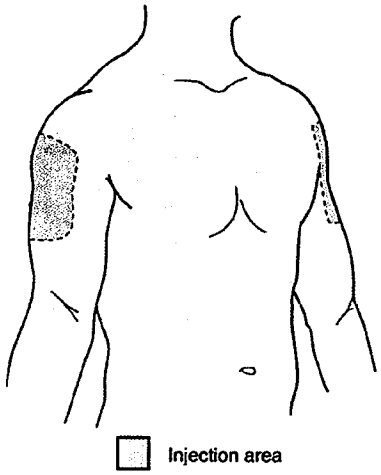

Figure E

Prepare the Injection Site

- Wipe the injection site with an alcohol swab in a circular motion and let it air dry. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

STEP 3: Inject ORENCIA

- Hold the barrel of the ORENCIA prefilled syringe with one hand and pull the needle cover straight off with your other hand (**see Figure F**). **Do not** touch the plunger while you remove the needle cover.

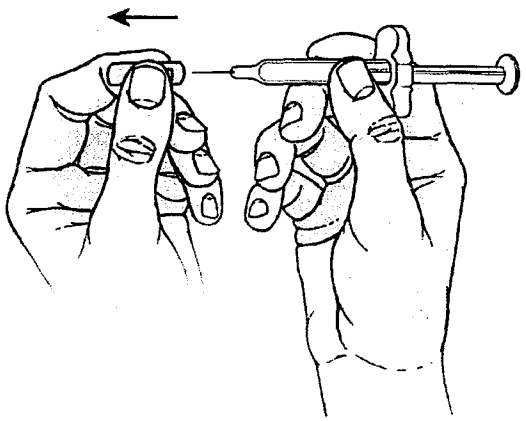

Figure F

- Throw away the needle cover in your household trash.
- There may be a small air bubble in the ORENCIA prefilled syringe barrel. You do not need to remove it.
- You may notice a drop of fluid leaving the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.
- Hold the barrel of your ORENCIA prefilled syringe in one hand between the thumb and index finger (**see Figure G**).

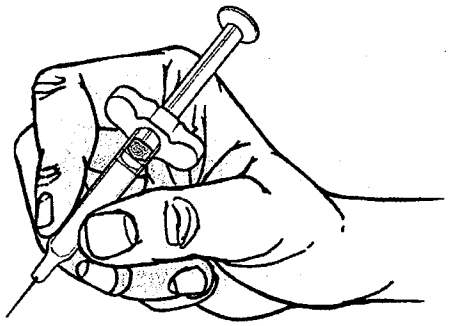

Figure G

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at a 45° angle (**see Figure H**).

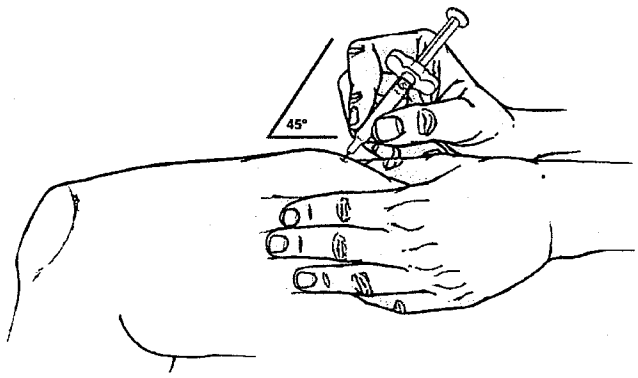

Figure H

- To inject all of the medicine, use your thumb to push down on the plunger head until the plunger head is pushed in as far as it will go (**see Figure I**).

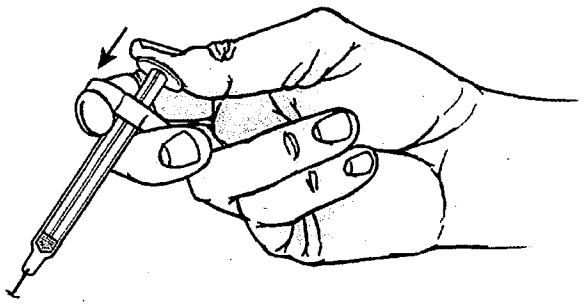

Figure I

- Remove the needle from the skin and let go of the surrounding skin.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

STEP 4: Disposal and Recordkeeping

- The ORENCIA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container (see "**How do I throw away used syringes?**").
- **Do not** put the needle cover back on the needle.
- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

Check with your healthcare provider or pharmacist for instructions about the right way to throw away used syringes. There may be special local or state laws about how to throw away used syringes.

- **Do not** throw away used syringes in the household trash and do not recycle them.
- Put used and empty ORENCIA prefilled syringes in a biohazard container made specifically for disposing of used syringes (called a "sharps" container) or in a hard plastic container with a screw-on cap (such as an empty detergent bottle) or in a metal container with a plastic lid (such as a coffee can). Sharps containers can be purchased at your local pharmacy or many retail outlets.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Keep ORENCIA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Frequently Asked Questions

Injecting with the ORENCIA prefilled syringe

I feel a little bit of burning or pain during injection. Is this normal?

- When giving yourself an injection, you may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. This may happen and the discomfort should be mild to moderate. If you have any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider.

Traveling with ORENCIA prefilled syringes

How should I keep my prefilled syringes cool while traveling?

- If you need to take your prefilled syringes with you, store them in a cool carrier between 36°F to 46°F (2°C to 8°C) until you are ready to use.
- **Do not** freeze ORENCIA.
- Keep ORENCIA in the original carton and protected from light. Your healthcare provider may know about special carrying cases for injectable medicines.

Can I take my prefilled syringes on an airplane?

- Generally you are allowed to carry ORENCIA prefilled syringes with you on an airplane. **Be sure to carry the prefilled syringes with you on board the plane, and do not put them in your "checked" luggage.** You should carry ORENCIA prefilled syringes with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C) until you are ready to use.
- Keep ORENCIA in the original carton, with its original preprinted labels and protected from light.

What if my syringe does not stay cool for an extended period of time? Is it dangerous to use?

- Contact 1-800-ORENCIA (1-800-673-6242) for details.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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

1292618 Rev July 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	July 29, 2011
From:	Badrul A. Chowdhury Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125-118, supplement 122
Applicant Name:	Bristol-Myers Squibb Company
Date of Submission:	October 4, 2010
PDUFA Goal Date:	August 4, 2011
Proprietary Name:	Orencia
Established Name:	Abatacept
Dosage form:	250 mg lyophilized powder for use in single-use vial for intravenous infusion (approved) 125 mg/mL solution in a single-dose prefilled syringe for subcutaneous administration (current application)
Strength:	125 mg/mL (current application)
Proposed Indications:	Moderately severe active rheumatoid arthritis (RA) in adults either as monotherapy or concomitantly with disease modifying anti rheumatic drugs (DMARDs) other than TNF antagonists (b) (4)
Action:	Approval

1. Introduction

Bristol-Myers Squibb (BMS) submitted this BLA supplement for Orencia (abatacept) to support marketing of a 125 mg solution formulation for fixed dose subcutaneous administration in patients with rheumatoid arthritis (RA). The proposed indication for the fixed dose subcutaneous formulation is the same as the currently approved RA indication for Orencia. Orencia was originally approved in December 2005 for the treatment of moderately to severely active RA in adults, and later in April 2008 for the treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients 6 years of age and older. Orencia is currently marketed as lyophilized powder for intravenous infusion (250 mg/vial) with a weight-tiered dosing regimen for RA and JIA. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease modifying anti rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-

inflammatory and analgesic effects. Corticosteroids are versatile agents with potent anti-inflammatory effects, but their use is limited by long-term toxicity. DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression or produce a disease-modifying effect by retarding radiographic progression of joint damage. Approved DMARDs and some of their features are listed in Table 1 and Table 2. Methotrexate is the most commonly used DMARD because of its proven efficacy, and well-understood long-term effects. Large molecule biologic products are considered to be DMARDs when they have been shown to inhibit progression of joint damage, which is the case for most of them (Table 2). In the treatment of RA, methotrexate is often the initial DMARD used and then combined with other DMARDs, commonly biologics, to enhance clinical effect.

Table 1. Small molecule DMARDs approved for marketing in the United States

Product Name (Trade Name) [Sponsor]	**Mechanism of Action in RA**	**Year of First Approval for RA**
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing (?)	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998

Table 2. Large molecule biologic DMARDs approved for marketing in the United States

Product Name (Trade Name) [Sponsor] {year} *	**Presentation and *ROA*** †	**Description and *MOA*** §	**Claims for adult RA** #
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 100 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2002}	Prefiled syringe 40 mg/0.8 mL Prefilled syringe 20 mg/0.4 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion* *SC injection* **	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen]	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb	Clinical response Physical function response

Product Name (Trade Name) [Sponsor] {year} *	Presentation and *ROA* †	Description and *MOA* §	Claims for adult RA #
{2006}		*Anti CD20, B cell depletor*	Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefiled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL *SC injection*	Humanized Fab fragment *TNF inhibitor*	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Vial 20 mg/mL *IV infusion*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	Clinical response Major clinical response Radiographic response Physical function response

*Year = Year of first approval for RA
†ROA = Route of administration
§MOA= Mechanism of action
#Claims: Clinical response (or reducing signs and symptoms) assessed by ACR 20, 50, and 70 response over at least 3-6 month; Major clinical response defined as achieving ACR 70 response continuously over 6 months period; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) over at least 6 month period; Radiographic response (or inhibiting progression of structural damage) assessed radiographically by Total Sharp Score (TSS) and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over at least 12 months
** **Subject of the current application**

The clinical efficacy and safety data that supported the original approval of Orencia for the claim of reducing signs and symptoms (clinical response), inhibiting progression of structural damage (radiographic response), and improving physical function and health related outcomes in RA were from six controlled clinical studies in patients 18 years of age and older with active RA. These studies are described in the currently approved Orencia product label. The current submission to support approval of subcutaneous administration of Orencia is based on one non-inferiority clinical study comparing intravenous and subcutaneous dosing (Study SC-I), and three safety studies. New pharmacokinetic studies were also conducted to assess the clinical pharmacokinetics of abatacept following subcutaneous administration.

3. Chemistry, Manufacturing, and Controls

Abatacept drug substance is a human, recombinant, soluble fusion protein comprised of the extracellular domain of human CTLA-4 and a modified hinge-CH2-CH3 fragment of the human IgG1 Fc domain. Abatacept is a selective costimulation modulator of T-cells that derives its mechanism of action by inhibiting the interaction of CD80 and CD86 with their receptor CD28. This interaction normally provides a costimulatory signal necessary for full activation of T cells.

Abatacept drug substance to be used in the [redacted] (b) (4) [redacted]. The Orencia solution for subcutaneous administration contains 125 mg/mL abatacept, 170 mg/mL sucrose, 8 mg/mL poloxamer 188, [redacted] (b) (4) [redacted], and is adjusted to pH of 6.8 to 7.4. The Orencia injection solution for subcutaneous administration is supplied as a single-dose disposable prefilled glass syringe with flange extender. The glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall, ½-inch

needle) covered with a rigid needle shield. The prefilled syringe provides 125 mg of abatacept in 1 mL and is provided in a pack of 4 syringes. The finished drug product will be manufactured in the BMS facility in Manati, Puerto Rico. All manufacturing and testing facilities associated with this application have acceptable inspection status. An expiry period of (b) (4) months from (b) (4) is proposed and supported by submitted data.

There are seven CMC related post-marketing commitment studies that are listed in the action letter.

4. Nonclinical Pharmacology and Toxicology

Information regarding the toxicology profile of abatacept was submitted and reviewed with the original application to support chronic intravenous administration for the approved adult RA indications. This supplement includes three nonclinical studies that provided support for the change in the route of administration from intravenous to subcutaneous administration. These nonclinical studies provide adequate support of safety the new route of administration in RA patients.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology data were submitted and reviewed with the original application to support chronic intravenous administration for the approved adult RA indications. To support this application, two new clinical pharmacology studies were conducted. The clinical pharmacology studies included a single-dose study in health adults (IM101013) and a multiple-dose, parallel-group, placebo-controlled study in adult subjects with active RA (IM101063).

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) values for C_{min} and C_{max} at steady state observed after 85 days of treatment were 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration. Consistent with intravenous data, population pharmacokinetic analysis for subcutaneous abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance.

The selection of the 125 mg fixed dose regimen for subcutaneous administration was based on the objective of obtaining steady-state trough serum concentrations of abatacept of at least 10 mcg/mL for patients of all body weights. This target concentration was based on in-vitro cell-based assays and nonclinical models that suggested concentrations of at least 10 mcg/mL provided maximal T-cell inhibition as measured by T-cell proliferation and cytokine responses, as well as on the intravenous abatacept experience,

where Cmin concentrations above 10 mcg/mL were associated with clinical efficacy, whereas steady-state trough concentrations of 5 mcg/mL were associated with suboptimal efficacy responses. Trough concentrations up to 30 mcg/mL were observed in the intravenous clinical development program with acceptable safety. Therefore a fixed dose that would target trough concentrations from 10 to 30 mcg/mL across the body weight ranges was selected.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical development program to support fixed dose subcutaneous administration of Orencia in patients with RA included four clinical studies. The studies included a non-inferiority study that compared subcutaneous and intravenous Orencia (IM101174 or SC-I), a study to support safety of subcutaneous Orencia as monotherapy (IM101173 or SC-II), a study to show safety of subcutaneous Orencia after prolonged treatment interruption (IM101167 or SC-III), and a study to show safety of subcutaneous Orencia after switching from intravenous Orencia (IM101185). The non-inferiority study was the only study providing efficacy data to support the current submission. The three safety studies were done to address the concern of immunogenicity associated with subcutaneous route of administration of Orencia. The clinical development program was discussed with BMS at end-of-phase 2 meeting and pre-sBLA meeting and was determined to be acceptable.

b. Design and conduct of the studies

Non-inferiority study (IM101174 or SC-I):

Study SC-I was a randomized, double-blind, active-controlled parallel group global study (242 sites worldwide that included 82 sites in the US) conducted in patients with active RA having an inadequate response to methotrexate (MTX). After meeting eligibility criteria, 1464 patients were randomized in a 1:1 ratio (1457 patients ultimately received study treatment) to receive either Orencia 125 mg subcutaneously weekly plus intravenous loading dose on Day 1 (with intravenous placebo at Day 15, Day 29, and every 28 days thereafter) or abatacept intravenous weight-tiered dosing on Days 1, 15, 29 and every 28 days thereafter with a subcutaneous placebo weekly. Patients were stratified by weight (<60 kg, 60 to 100 kg, >100 kg) and remained on their background dose of MTX and concomitant folate. Primary efficacy endpoint was the proportion of patients achieving ACR20 response at day 169, with the primary analysis being a comparison between the intravenous and subcutaneous Orencia in the per protocol population. The subcutaneous formulation was pre-specified to be non-inferior to the intravenous formulation if the lower limit of a two sided 95% CI of the difference in ACR20 response rates between subcutaneous and intravenous formulations were greater

than or equal to the non-inferiority margin of -7.5%. This non-inferiority margin was based on two previous intravenous Orencia studies conducted by BMS and selected to ensure that the ACR20 response in the SC group preserves at least 70% of the minimum effect seen with the intravenous formulation when compared with placebo. Other efficacy endpoints included ACR50 and ACR70 responses, physical function characterized by HAQ-DI, and changes in DAS28-CRP. Safety assessment in the study included recording of adverse events, vital signs, clinical laboratory measures, physical examination, and development of antibody to abatacept. Assessment of autoantibodies and PK assessment were also done.

Monotherapy safety study (IM101173 or SC-II):

Study SC-II was a 4-month open-label study in 100 RA patients (49 on monotherapy and 51 on concomitant MTX) who had not previously receive abatacept or other CTLA-4 targeted products, with a primary objective to evaluate the immunogenicity and safety of subcutaneous abatacept in the absence of an intravenous loading dose, when given as monotherapy vs. with concomitant MTX, and to assess whether the use of concomitant MTX influenced the development of immunogenicity.

Treatment interruption safety study (IM101167 or SC-III):

Study SC-III was a 9-month 3 period study designed to evaluate the impact on immunogenicity and safety of interruption and reintroduction of subcutaneous Orencia, with or without an intravenous loading dose of Orencia in patients with active RA treated concomitantly with MTX who had an initial response to subcutaneous Orencia. Period 1 was 3-month open-label run in to induce a clinical response to subcutaneous Orencia (n=167 RA patients); period 2 was a 3-month randomized withdrawal period (n=120 responders); and period 3 was a 12-week open-label re-start in the patients who completed Period 2 (n=119).

Intravenous to subcutaneous switching safety study (IM101185):

Study IM101185 was an open-label study in 123 RA patients designed to evaluate the safety of conversion from intravenous to subcutaneous Orencia treatment. Patients enrolled in this study were RA patients who were participating in open-label long-term extension studies from the original intravenous Orencia program in RA.

c. Efficacy findings and conclusions

The submitted clinical program showed that fixed dose subcutaneous administration of Orencia was not inferior to intravenous administration of Orencia in patients with RA. Table 3 shows results of the primary efficacy endpoint and two selected secondary endpoints. Various subgroup analyses, including analysis by body weight grouping showed consistent efficacy across body weights. Patients with lower body weight, both in intravenous and subcutaneous dosing groups, tended to have numerically higher proportion of responders. The data is supportive of fixed dosing regimen of subcutaneous Orencia.

Table 3. Clinical response in study SC-I on day 169, per protocol patients

		Orencia SC N=693	Orencia IV N=678
ACR 20, per protocol patients	Number of patients (%)	527 (76.0%)	514 (75.8%)
	95% CI	(72.9, 79.2)	(72.6, 79.0)
	Estimate of difference (95% CI)	0.3 (-4.2, 4.8)	N/A
ACR 50, ITT patients	Number of subjects (%)	368 (50.2%)	348 (48.6%)
	95% CI	(46.6, 53.8)	(44.9, 52.3)
	Estimate of Difference (95% CI)	1.6 (-3.5, 6.8)	N/A
ACR 70, ITT patients	Number of subjects (%)	189 (25.8%)	173 (24.2%)
	95% CI	(22.6, 29.0)	(21.0, 27.3)
	Estimate of Difference (95% CI)	1.6 (-2.9, 6.1)	N/A
For PP: n=693, 678 for SC and IV; For ITT: n=733, 716 for SC and IV			

8. Safety

a. Safety database

New safety data submitted with this application are from the four studies discussed above. Overall 1879 patients received subcutaneous Orencia and 819 patients received treatment for 12 months or longer.

b. Safety findings and conclusion

The new safety data do not raise any new safety concerns for subcutaneous Orencia. The safety findings for subcutaneous Orencia were generally similar to that of intravenous Orencia. There were no new or unique safety findings with subcutaneous Orencia.

One specific safety concern with subcutaneous Orencia was regarding immunogenicity relating to switch from intravenous to subcutaneous Orencia. Immunogenicity was assessed in study SC-I and three other specific safety studies to assess immunogenicity as discussed above. Results of these studies did not show specific immunogenicity concern with subcutaneous Orencia or with switching from intravenous to subcutaneous Orencia. The immunogenicity frequency noted in study SC-I was 1.1% and 2.3% for the intravenous and subcutaneous groups, respectively. The frequencies were generally within the range observed in previous studies with Orencia. In study SC-II, which was conducted to determine the effect of subcutaneous Orencia monotherapy, no patients in either group developed anti-product antibody. In study SC-III, which was conducted to determine the effect of withdrawal and retreatment with subcutaneous Orencia, also did not show any findings of concern. At the end of period 3, when all patients were treated with subcutaneous Orencia, the immunogenicity frequency was 2.6% and 2.7% for the group that received subcutaneous Orencia throughout and the group that received placebo during the withdrawal period, respectively.

c. REMS/RiskMAP

Approved intravenous Orencia does not have a REMS. The data submitted to support subcutaneous Orencia do not show any new safety signal that would warrant a REMS.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Efficacy and safety findings in the clinical program for fixed dose subcutaneous Orencia were consistent with findings in the intravenous Orencia experience and did not warrant discussion at an advisory committee meeting.

10. Pediatric

Orencia administered by intravenous route is already approved for juvenile idiopathic arthritis (JIA) in patients 6 to 17 years of age based on one randomized withdrawal study in 190 JIA patients. Studies in patients under 6 years of age were previously waived because juvenile animal studies suggested that abatacept treatment in a developing immune system led to profound immunosuppression, and there was evidence of increasing frequency of thyroiditis with decreasing animal age. BMS requested a deferral of PREA-required pediatric studies in JIA studies. (b) (4) BMS's deferral request was discussed at a Pediatric Review Committee PeRC) meeting held on June 29, 2011. The PeRC agreed with the Division's position to defer Orencia subcutaneous pediatric studies in JIA patients 6 to 17 years of age, and waive studies in patients below 6 years of age to stay consistent with the decision for intravenous Orencia. There are no new data to support safety of Orencia in children below 6 years of age. It was agreed that PREA study requirement for subcutaneous Orencia could possibly be met with a PK study to identify an age appropriate dose and a safety study with that dose in the appropriate age group.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit of study sites was done as part of the original BLA. No further audit was conducted for this submission. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Orencia was previously reviewed and found to be acceptable. The product is currently marketed under the trade name Orencia.

b. Physician Labeling

The labeling of Orencia was reviewed previously with the original approval of the product in 2005 for RA and later in 2008 with approval of JIA indicaton. With this application the existing label will be updated to include the new information regarding the Orencia subcutaneous formulation and data from the new studies. The main changes are in the following sections of the label - Dosage and Administration, Dosage Forms and Strengths, Adverse Reactions, Description, Clinical Pharmacology, and Clinical Studies. The Division and BMS have agreed on the final labeling language.

c. Carton and Immediate Container Labels

New carton and container labels were submitted for the single-dose prefilled syringe with flange extender proposed for marketing. These were reviewed by various disciplines of this Division, OBP, and DMEPA, and were found to be acceptable with some revisions.

d. Patient Labeling and Medication Guide

There are no data that warrant changes to the currently approved patient labeling. As discussed in section 8c above, there is no Medication Guide for Orencia.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Orencia (abatacept) 125 mg solution formulation for fixed dose subcutaneous administration in patients with RA. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of Orencia for fixed dose subcutaneous administration in patients with RA. The submitted data show that the benefit of Orencia administered by subcutaneous route is not inferior to that of the intravenous route. The safety of Orencia administered by subcutaneous route does not show any new or unique safety findings.

c. Post-marketing Risk Management Activities

The data submitted with this application do not suggest any new safety signal for Orencia. A REMS is not warranted for Orencia.

d. Post-marketing Study Commitments

This application triggers a study requirement on the basis of the Pediatric Research Equity Act (PREA). The applicant will be required to conduct a PK/safety study of SC

abatacept in JIA patients 6 to 17 years of age. The Office of Biotechnology Products (OBP) has various post-marketing commitment studies that are listed in the action letter.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

OFFICER/EMPLOYEE LIST

Consent for the Officer Employee List for BLA 125118 s122

Badrul Chowdhury
Sarah Yim
Molly Topper
Sandy Barnes
Joan Buenconsejo
Thomas Permutt
Carol Holquist
Roberta Szydlo
Colette Jackson
Lawrence Leshin
Jack Ragheb
Susan Kirshner
Kalavati Suvarna
Liang Zhao
Zachary Oleszczuk
Manizheh Siahpoushan
LaShawn Griffiths
Robin Duer
Shawna Hutchins
Jacqueline Ryan
Nikhil Thakur
Isabel Tejero
Kiya Hamilton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 14, 2011
From	Sarah Okada-Yim M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	sBLA 125118/ 122
Applicant	Bristol Myers Squibb
Date of Submission	October 4, 2010
PDUFA Goal Date	August 4, 2011
Proprietary Name / Established (USAN) names	Orencia® / abatacept
Dosage forms / Strength	Pre-filled syringe/125 mg
Proposed Indication(s)	1. Moderately to Severely Active Rheumatoid Arthritis in Adults (same as IV formulation)
Recommended:	*Approval, with revisions to proposed labeling*

1. Introduction

Abatacept was first approved in December 2005 for the treatment of moderately to severely active RA in adults with inadequate response to one or more DMARDS; the requirement for inadequate response to one or more DMARDS was later dropped as a result of additional studies. It was approved in April 2008 for the treatment of moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children 6 years of age and older. Abatacept is in a unique class as an immunomodulator targeting prevention of the second co-stimulatory signal required for T-cell activation. It is a recombinant soluble fusion protein comprised of the extracellular domain of human CTLA-4 and the hinge CH2-CH3 regions of the Fc domain of human IgG1, further modified to prevent complement fixation and antibody dependent cellular cytotoxicity (which might result in unintended T-cell depletion). Abatacept is currently marketed as lyophilized powder for intravenous infusion (250 mg/vial), to be reconstituted in sterile water for injection, diluted in normal saline, and infused over 30 minutes. Current IV dosing is weight-tiered (500 mg for patients <60 kg, 750 mg for patients 60 to 100 kg, and 1000 mg for patients over 100 kg) and given every 2 weeks for the first 3 doses, then every 4 weeks thereafter.

This efficacy supplement consists of data to support the applicant's proposed marketing of abatacept as a fixed dose (125 mg) subcutaneous injection in pre-filled syringes for weekly administration.

2. Background

Expectations for the subcutaneous clinical development program were discussed at an End of Phase 2 (EOP2) meeting with the Division of Anesthesia, Analgesics and Rheumatology Products (DAARP) on 27-Nov-2007. Key items included:

- FDA requested that BMS enroll an adequate number of subjects weighing > 100 kg in IM101174 (~10% of the overall study population) and provide subgroup analyses of efficacy, safety, and immunogenicity data based on weight quartiles.
- FDA suggested using a more stringent (-7.5%) NIM in ACR 20 response in IM101174 if the applicant wanted to extrapolate all of the IV efficacy claims to the SC product. Accordingly, BMS modified the NIM in IM101174 such that SC abatacept would preserve at least 70% of IV abatacept's benefit over placebo.
- Because the FDA was concerned about the potential for increased immunogenicity associated with the SC route of administration, FDA requested data regarding the safety of subcutaneous abatacept in anticipated scenarios of clinical use, including as monotherapy, when switching from IV to SC route of administration, and when re-starting SC administration after temporary treatment interruptions. In order to address these concerns, BMS conducted Study IM101173 (SC abatacept monotherapy), Study IM101167 (SC abatacept following treatment interruption), and Study IM101185 (switching from long-term IV to SC abatacept) (See Table 1 below).

Table 1: Summary of SC Abatacept Clinical Studies

Summary of Clinical Studies in the Subcutaneous Abatacept Development Program				
Study	**Design**	**Number of subjects**	**Population**	**Efficacy Endpoint**
IM101174: SC vs IV non-inferiority; 242 sites world-wide	6-month double-blind, double-dummy, SC ABA, 125 mg weekly (single weight-tiered IV ABA loading dose on Day 1) vs. weight-tiered IV ABA	SC ABA n = 696; IV ABA n = 683; total 1379	MTX-inadequate responders	Primary: ACR 20, NI Margin -7.5%
IM101173: SC Monotherapy safety study; 22 sites world-wide	4- month open-label SC ABA, 125 mg weekly (no IV loading dose), monotherapy vs. with concomitant MTX	SC ABA monotherapy, n=49; with concomitant MTX, n = 51	MTX Naïve or off MTX for at least 4 weeks prior to study or receiving stable MTX	Descriptive DAS28 and HAQ DI
IM101167: SC withdrawal and re-start safety study; 32 sites world-wide	Randomized double-blind withdrawal study: 12 week OL run in (period I), 12 week withdrawal period in responders (period II), 12 week OL re-start (period III)	Period I, n=167; Period II, n=120; Period III, n=119	MTX-inadequate responders	Descriptive DAS28 and HAQ DI
IM101185: IV to SC switch safety study	Open-label extension switching from IV ABA to SC abatacept, 125 mg weekly (no IV loading dose) for a period of 1 year.	n = 123	RA patients tolerating at least 5 years of IV abatacept in long-term extension studies IM101102 or IM101029	Descriptive DAS28 and HAQ DI

Source: Table 1.2 of Module 2.7.3

At the pre-sBLA meeting the applicant held with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on June 3, 2010, additional discussion surrounded expectations for data to support approval of (b) (4) a PFS with a flange extender. The applicant stated that the device constituent of this (b) (4) was previously cleared in the (b) (4). CDRH verified that the syringe was cleared through the 510 (k) submission process. As such, the applicant could reference these submissions in support of the current product, provided that they have written authorization by (b) (4) to reference the testing that was performed in the

original 510 (k) submission. The applicant was advised that this information alone may not sufficiently address the specific performance, biocompatibility and human factors aspects associated with the delivery of abatacept through the (b) (4) and that this performance data to demonstrate that the user can manipulate the device to safely and effectively deliver the subcutaneous abatacept injection would be expected in the sBLA.

3. CMC/Device

Primary product quality reviewer: Jack Ragheb, M.D. Ph.D.
Product quality team leader: Susan Kirshner, Ph.D.

- **General product quality considerations**

This supplement is for approval of a 125 mg/ml pre-filled ready-to-use syringe (PFS) dosage form for subcutaneous administration of abatacept. The currently approved dosage form is a 250 mg lyophilized cake in a vial for intravenous administration following reconstitution. No changes to the approved drug substance manufacturing process were proposed; therefore drug substance manufacture and characterization were not reviewed as part of this sBLA submission.

Unless appropriately formulated, abatacept forms insoluble filamentous particulates when it comes in contact with silicone. The formulation of the lyophilized presentation of abatacept does not protect drug product from the effects of silicone. Therefore the lyophilized dosage form is marketed with an unsiliconized syringe. (b) (4) A summary comparison of the formulations may be found in Table 2 below.

Table 2: Comparison of SC and IV abatacept formulations

Component	Function	125 mg/ml	250 mg/vial
Abatacept	Active ingredient	x	x
Sucrose	(b) (4)	x	
(b) (4)			
Poloxamer	(b) (4)	x	
(b) (4)			
Sodium phosphate dibasic, anhydrate	(b) (4)	x	
Sodium chloride	(b) (4)		x
(b) (4)			
Water for injection	(b) (4)	x	x
(b) (4)	(b) (4)		

Source: Dr. Kirshner's review

The subcutaneous (SC) ready-to-use (RTU) injection formulation contains 125 mg/mL abatacept, 170 mg/mL sucrose, 8 mg/mL Poloxamer 188, (b) (4),

and is pH (b) (4) The excipients in the SC formulation have been used in other injectable products. Abatacept with sucrose in the absence of surfactant formed particulates in syringes in less than an hour whereas in the presence of surfactant the syringes remain free of particulates throughout the requested shelf-life of (b) (4) months. The product quality team concurs with the applicant's choice of excipients.

The drug product will be supplied in a pre-filled syringe with flange extender. Review of the syringe and flange extender was performed by CDRH and is discussed below. The container closure is a 1-ml long glass barrel syringe with fill line markings with a 29 gauge thin wall (b) (4) needle and rigid needle shield and stoppered with (b) (4) coated (b) (4) stopper. A (b) (4) was requested to account for needle and syringe loss; the product quality team determined that the (b) (4) is justified, as it does not exceed USP recommendations and needle volume should be taken into consideration to help ensure proper dosing.

The Sponsor requested a categorical exclusion from the preparation of an environmental assessment based on 21 CFR 25.21(a) and (b). The product quality team recommends they be granted the categorical exclusion per 21 CFR 25.31(c) as the proposed change will not significantly change the distribution of the active compound in the environment.

Adequate data were provided to support the requested dating period of (b) (4) months from final filtration when stored at 2-8°C and protected from light and freezing.

- **Facilities review/inspection**

Abatacept SC drug substance is the same drug substance used for abatacept IV formulation. Therefore the drug substance sites were up to date with respect to facilities inspection and were not re-inspected with this submission. The drug product manufacturing facilities included:

Bristol-Myers Squibb Holdings Pharma, LTD.
P.O. Box 301000
Road 686, KM. 2.3
Manati, Puerto Rico 00674-3000
Establishment Number: 2650089
Short summary of manufacturing activities performed: *Manufacturing, Microbiological Control Testing, Packaging, Labeling, Release, and Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by SJN-DO February 23-March 28, 2011 and classified VAI. This was a GMP inspection to verify corrective actions following the Warning Letter issued on August 30, 2010. The CTL, SVS, SVL, and TRP profiles were updated and are acceptable.

Bristol-Myers Squibb Company
6000 Thompson Road
East Syracuse, New York 13057

Establishment number: 1317461
Short summary of manufacturing activities performed: *DS and DP Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by NYK-DO August 16-20, 2010 and classified NAI. The CTL profile was updated and is acceptable.

- **Other notable issues (resolved or outstanding)**

Device Evaluation

The Division consulted the Center for Devices and Radiological Health (CDRH) to assist in the review of the PFS (b) (4) The applicant submitted (b) (4)

CDRH review raised the following issues, which were sent to the applicant for clarification:
1. According to Drawing No DMC6506550503 (Created February 14, 2003, Revision 2), the thickness of the (b) (4) atop the glass syringe barrel is (b) (4) millimeters. ISO 11040 states that the minimum thickness for this (b) (4) should be 1.9 millimeters. In your submission, you state that the Orencia pre-filled syringe will be equipped with a "flange extender" that (b) (4) Please clarify whether the "flange extender" will be attached to all new Orencia pre-filled syringes.
Sponsor Response: The proposed abatacept injection prefilled syringe with flange extender product presentation proposed in the sBLA is comprised of a prefilled syringe with flange extender which will be fully assembled prior to release to the market. In addition, as stated in ISO 11040-4:2007 Table 1 - "Barrel dimensions': the glass finger flange thickness for a 1mL long syringe barrel has a nominal specification of 1.9 mm with a tolerance of +/- 0.5 mm. The vendor drawing DMC6506550503 states a minimum glass finger flange thickness of (b) (4) mm, thus the syringe meets the minimum requirement as stated in the ISO standard.

2. Additionally, regarding the flange extender, you have provided human factors simulated use testing to demonstrate that the user can successfully manipulate the Orencia prefilled syringe with the flange extender attached. However, it was unclear whether the testing assessed whether the user (b) (4) Please demonstrate that the (b) (4) (b) (4) please demonstrate that the glass barrel syringe meets collar thickness requirement under ISO 11040.
Sponsor Response: The abatacept injection prefilled syringe with flange extender presentation will be fully assembled at the manufacturing site prior to release to the market. (b) (4) *under normal handling and shipping this does not happen. Since the product is provided fully assembled and the Instructions for Use indicate the flange extender in the diagrams, it is expected that users will use the product* (b) (4) *as intended. As described in the response to Question 1, the glass finger flange thickness of the syringe which is minimally* (b) (4) *mm meets*

the minimum requirement as stated in ISO 11040-4. Every syringe batch BMS has tested has passed the minimum flange thickness of 1.4 mm.

3. There was no description on whether the Hydrolytic Resistance and Annealing Quality testing was performed on the glass barrel of the prefilled syringe. CDRH notes that the syringe is manufactured by (b) (4) However, since the pre-filled syringe will be approved under the sBLA 125118, it is your responsibility to ensure that the syringe is safe and effective for its intended use. Please demonstrate that the (b) (4) pre-filled syringe has been subjected to the Hydrolytic Resistance and Annealing Quality testing.
Sponsor Response: Per USP <660> and Ph. Eur.3.2. 1, hydrolytic resistance testing is performed as one of the physicochemical tests listed in the BMS syringe specifications (please refer to Table 3.2.P.7.1. 1.T01 of Section 3.2.P.7.1.1 Packaging Components Specifications Abatacept Injection Prefilled Syringe in the initial sBLA). Every batch BMS has tested for hydrolytic resistance has passed. The results from one representative batch of syringes, 9M39750 are presented in Table Q3. T01. BMS has been informed by (b) (4) that the syringe barrels go through the annealing step (b) (4) during manufacturing I. After the annealing step, a (b) (4) Every syringe batch BMS has tested has passed this (b) (4) inspection

4. Within sBLA 125118, it appears that you have made a promissory note to assess container closure integrity during manufacturing. Whereas it relevant to ensure that devices that are manufactured meet the leak testing performance criteria as part of the validation of the manufacturing process, it is more critical to demonstrate that the syringe that is selected for the delivery of Orencia is free of leaks and prevents any ingress of foreign matter within the pre-filled syringe barrel. Please demonstrate that leak testing has been performed on the prefilled Orencia syringe.
Sponsor Response: To mitigate the possibility of the prefilled syringe leaking, the primary components are subjected to a leak test as part of the incoming inspection. Every batch tested by BMS to date has passed the leak test. In addition, during the development of the primary container system, CCIT testing was performed and the results were provided in section 3.2.P.2.5, "Pharmaceutical Development - Microbiological Attributes" of the initial sBLA. Also as part of the assembly validation and shipping qualification activities CCIT testing was performed. CCIT summaries are being provided in response to questions 1 and 3 received from FDA on March 8, 2011.

CDRH consultants determined these responses to be acceptable.

The applicant also submitted the results of a human factors/design validation study that involved 31 participants with RA, ages 28 to 63, of whom 91 % had a moderate to severe form of the disease, 61 % were presently self-injecting a medication, and 80% were female. The applicant conducted a user failure mode and effects analysis to identify the critical tasks for device operation. If a study subject was unsuccessful at prioritizing and performing critical steps as defined by the complete product use sequence, then additional training, including passive and/or active learning, was provided by the moderator. In validation testing, CDRH

prefers that participant failure be followed by exploration with the participant of the root cause of the problem to identify and understand any hazards that might require mitigation. Generally this would take the form of an interview with open-ended questions. However, given that the study participants failed to complete the critical tasks in only 1 of 62 trials, it appears that moderator actions after a failure caused little valuable data to be lost. Therefore, CDRH determined the Human Factors study to be acceptable.

Product Quality PMCs:

1. Re-evaluate the acceptance criteria for drug product release specifications based on data from at least 30 commercial lots and submit a PMC final report. The specifications established for DP release testing are based on a limited data set and in some instances are broader than the limits for the abatacept injection intravenous presentation. The submission should include the proposed specifications and a justification that includes manufacturing data and data from lots used in the clinical trials.

2. Establish separate release and shelf-life limits and/or acceptance criteria for product attributes that are stability indicating and submit a PMC final report.

3. Develop and validate a quantitative IEF specification using a method such as CE-IEF and submit a PMC final report.

4. Develop and validate a quantitative B7 binding specification that includes measurements of Keq and/or kd using a method such SPR and submit a PMC final report.

5. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

6. Perform real time and accelerated stability studies on 2 additional batches of DP produced from DS manufactured with (b) (4)

7. Conduct extractables and leachables studies. Extractables analysis should be peroformed under the appropriate exaggerated conditions using the prefilled syringe components that come into contact with the drug (b) (4) Extractables studies should include a spectrum of (b) (4) Supplier data can be used as a starting point, or in place, of the extractables study when sufficiently representative.

   Leachables analysis should be conducted on the assembled prefilled syringe unit under the real-time conditions and should include multiple stability time- points throughout the dating period of the product using the Drug Product Vehicle with (b) (4) the Active Pharmaceutical Ingredient, as extraction media.

Where studies of leachables have not been performed under the conditions encountered during the licensed manufacturing process, repeat the studies under the relevant conditions or provide a justification why it is not necessary to do so. In addition to (b) (4) studies should test for the presence of (b) (4) Studies should employ methods (e.g. ICP-DRC-MS) that permit chemical identification and quantitation (e.g., ppb, ppm) of each compound and report the same. A justification of the sample size used (i.e., number of lots and units within each lot) should be provided.

Submit a PMC final report(s) with the results of these studies.

Submission dates for the above 7 PMCs were still under negotiation at the time of this review, and will be captured in the final action letter.

Product Quality Microbiology PMCs:

1. The applicant set the bioburden action limits for the process based on bioburden data of (b) (4) in the process. The bioburden data from 10 lots in the submission suggests that the action limits can be lowered to (b) (4) The applicant stated that the (b) (4) bioburden limits would be reevaluated as they gain commercial manufacturing experience.

PMC: To reassess the bioburden action limits for the formulated drug product step (b) (4) based on the manufacturing scale data from 30 lots and submit the final report by December 31, 2013.

2. The applicant performed bioburden testing to support (b) (4)

PMC: To collect bioburden data at the (b) (4) step and set appropriate bioburden limits for this step. The final study report should be submitted by December 31, 2013.

3. The applicant performed container closure integrity testing with water for injection. The Agency recommends container closure integrity test in lieu of sterility test for the stability program.

PMC: To develop a container closure integrity test for use in lieu of sterility in the stability program. The final study report should be submitted by December 31, 2013.

No product quality-related postmarketing requirements are recommended. The product quality teams recommended approval of the sBLA based on the data in this submission.

4. Nonclinical Pharmacology/Toxicology

Primary pharmacology/toxicology reviewer: Lawrence "Steve" Leshin, D.V.M.
Pharmacology/toxicology supervisor: Molly Topper, Ph.D.

The bulk of the information regarding the toxicologic profile of abatacept are derived from the nonclinical program conducted to support chronic intravenous (IV) administration for the approved adult rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) indications. This supplement presented 3 nonclinical studies that provided support for the change in the route of administration from intravenous to subcutaneous administration. There are no changes to the indication or patient population in this supplement. There are no nonclinical changes to the label.

The presence and formation of high molecular weight (HMW) impurities were studied under various pHs and temperature conditions to minimize their levels. A drug product stability study found that the rates of HMW species formation and deamidation of abatacept increases as pH decreases; however, the rate of deamidation decreases as formulation pH decreases. At pH of about 7.2 (formulation B), the rate of deamidation is slower than at pH 7.65 (formulation A) with little impact on HMW formation. Therefore, a SC formulation at the target pH of 7.2 (formulation B) was selected for Phase IIb and Phase III clinical studies and is the final drug product intended for commercialization.

To evaluate the potential for local irritation of the SC formulation, 2 studies were conducted with the clinical SC formulation in rats at different pH levels (pH 7.6/Study DS05129, or pH 7.2/Study DS07088) to assess local tolerance following the intended SC route of administration and 1 study in rabbits at pH 7.2 (Study DS08084) to assess local tolerance following accidental exposure via the IV, intraarterial, paravenous, or intramuscular route of administration. No significant injection-site irritation was observed following a single subcutaneous dose to rats of 1 mL of the abatacept RTU SC formulation at pH 7.6 or pH 7.2. In a local tolerance study in rabbits, abatacept subcutaneous RTU clinical formulation was not significantly irritating when administered by intravenous, intraarterial, paravenous, or intramuscular injection.

As there were no toxicologically significant effects in any of the three nonclinical subcutaneous administration studies and both formulations had been used in clinical studies, and High Molecular Weight (HMW) impurities are within acceptable product quality specifications, the pharmacology/toxicology team reports no concerns at this time with the HMW impurities in the formulation B intended for commercialization.

- **General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).**

For the SC formulation systemic toxicity, the applicant is relying on the nonclinical safety studies previously conducted to support the marketing applications for abatacept IV administration. As systemic exposure (based on area under the concentration-time curve [AUC] values) in humans is 43% lower when administered by the recommended SC dose (approximately 2 mg/kg SC weekly) as compared to the approved monthly IV dose

(approximately 10 mg/kg IV monthly), safety multiples derived from exposures in the nonclinical studies are 1.8-fold higher with the SC route.

In the IV program, abatacept was well tolerated in mice following SC treatment for up to 6 months (9-fold human SC exposure based on AUCs) and monkeys following IV treatment for 1 year (16-fold human SC exposure). All findings were generally related to the pharmacology of the drug (e.g., decreased serum immunoglobulin levels and germinal center activity) with no clinical manifestations of opportunistic or other infections, no dose-limiting or significant target-organ toxicities, and were reversible following clearance of the drug. This was in contrast to findings in rats (juveniles or adults) following up to 3 months of exposure with abatacept (≥7-fold human SC exposures), which demonstrated unique altered immunological parameters and target-organ toxicities suggestive of autoimmunity (inflammation of the pancreatic islet cells and thyroid), which increased during the dose-free period.

- **Carcinogenicity**

No evidence of genetic toxicity was observed in a battery of in vitro tests. In a 20- month carcinogenicity study in mice in which abatacept was administered subcutaneously, the major findings were increased incidences of lymphomas and mammary tumors (≥1.8-fold human SC exposure). These findings were attributed to decreased control of murine leukemia virus and mouse mammary tumor viruses in the presence of long-term immunomodulation. In addition, no drug-related SC inflammation was observed in the carcinogenicity study.

- **Reproductive and developmental toxicology**

The reproductive and developmental toxicity of abatacept was characterized in conjunction with approval of the abatacept IV formulation. This evaluation included fertility and early embryonic development in rats, embryonic and fetal development in mice, rats, and rabbits, and pre- and postnatal development in rats. Results are already incorporated in approved labeling. Abatacept was not teratogenic when administered to pregnant mice at doses up to 300 mg/kg and in pregnant rats and rabbits at doses up to 200 mg/kg daily, representing approximately 29 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC. Abatacept had no adverse effects on male or female fertility in rats at doses up to 200 mg/kg every 3 days (11 times the MRHD exposure based on AUC). Juvenile animal studies in rats dosed with abatacept from 4 to 94 days of age showed an increased incidence of infections leading death at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed, as were inhibition of T-cell dependent antibody responses. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed. Because these findings could represent more profound immunosuppression and/or perturbed tolerance resulting in autoimmunity with abatacept exposure in the developing immune system, PREA-required studies in young children (children less than 6 years of age, who had not yet been studied in clinical trials) were waived. See section 10 for further details.

- **Other notable issues (resolved or outstanding)**

The pharmacology/toxicology review team has determined that the submitted information is adequate to support approval of this sBLA. No postmarketing requirements, postmarketing commitments, or labeling changes are recommended from a nonclinical standpoint.

5. Clinical Pharmacology/Biopharmaceutics

Primary Clinical Pharmacology/Pharmacometrics Reviewer: Liang Zhao, Ph.D.
Clinical Pharmacology Supervisor: Suresh Doddapaneni, Ph.D.
Pharmacometrics Team Leader: Yaning Wang, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The studies including a PK component were IM101013, IM101063, IM101174, IM101167, IM101063, and IM101185. A summary of the PK parameters for the IV and SC abatacept dose regimens may be found in Table 3 below, derived from Study IM101174 PK data. The bioavailability of SC abatacept was identified to be 78.6% from trial IM101174.

Table 3: Mean (Range) Pharmacokinetic Parameter Estimates for Abatacept Following Either SC or IV Multiple Dose Administration in RA Subjects

PK Parameter	SC Abatacept	IV Abatacept
CL (mL/h/kg) [a]	0.28 (0.03, 0.58)	0.29 (0.11, 0.71)
Vss (L/kg) [a]	0.11 (0.02, 0.17)	0.11 (0.03, 0.36)
T-HALF (days) [a]	14.3 (9.19, 24.5)	14.2 (4.69, 79.1)
AUC (TAU) (μg•h/mL) [b,c]	5875.5 (1261.0, 13068.4)	41981.5 (18315.6, 88991.5)
Observed Cmax (μg/mL) [b]	48.1 (9.8, 132.4)	231.6 (123.1, 458.9) [d]
Observed Cmin (μg/mL) [b,e]	32.5 (6.6, 113.8)	22.3 (1.2, 80.6)

[a] Population PK model estimate from IM101174
[b] Observed Mean (range) from IM101174
[c] TAU = 7 days for SC and TAU = 28 days for IV
[d] The PK sample for Cmax was taken 30 minutes after the end of infusion and represents an approximation
[e] Observed Mean (range) Cmin on Day 85 from IM101174
Source: Summary of Clinical Pharmacology, Table 3.2.1[22]

Population PK and exposure-response analysis

No covariates except for body weight had a major effect on PK parameters. Trough concentrations at steady state (Cminss) following subcutaneous (SC) injection were comparable or higher than the Cminss values following intravenous (IV) administration for all weight categories (<60 kg, 60-100 kg, and >100 kg).

The applicant provided an exposure-response analysis showing a positive relationship between the Cminss values and the magnitude of DAS28 reduction at Month 6. The relationship has been characterized by an Emax-Tmax exposure-efficacy response model. DAS reduction reaches a plateau when Cminss exceeds approximately 10 μg/mL. This relationship was the basis for the identification of the 125 mg SC weekly fixed-dose. Events of infection and serious infection were used as safety endpoints in the exposure-response model. Analyses performed did not reveal any significant exposure-safety response correlations with either IV or SC dosing.

Dose Selection Rationale

The selection of the 125 mg fixed dose regimen was based on the objective of obtaining steady-state trough serum concentrations of abatacept of at least 10 μg/mL for patients of all body weights. This target concentration was based on in-vitro cell-based assays and nonclinical models that suggested concentrations of at least 10 μg/mL provided maximal T-cell inhibition as measured by T-cell proliferation and cytokine responses, as well as on the IV abatacept experience, where Cminss concentrations above 10 μg/mL were associated with clinical efficacy, whereas steady-state trough concentrations of 5 μg/mL were associated with suboptimal efficacy responses. Trough concentrations up to 30 μg/mL were observed in the IV clinical development program with acceptable safety. Therefore a fixed dose that would target trough concentrations from 10 to 30 μg/mL across the weight ranges was selected.

- **Drug-drug interactions**

No formal drug-drug interaction studies were conducted with SC abatacept. However, population PK analysis demonstrated that there was no effect of concomitant medications on the PK of SC abatacept.

- **Pathway of elimination**

As a large protein molecule, abatacept is most likely cleared by reticuloendothelial system.

- **Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

There was no effect of age or gender on the PK of SC abatacept. Limited data on patients with renal or hepatic impairment revealed no clear effect on the PK of SC abatacept. As with IV abatacept, the clearance of SC abatacept increases with increasing body weight.

- **Thorough QT study or other QT assessment**

As a macromolecule, unlikely to affect the cardiac conduction system, a thorough QT study was not required for the IV abatacept program or the SC abatacept program.

- **Other notable issues (resolved or outstanding)**

The clinical pharmacology/pharmacometrics review team believes the information submitted is adequate to support approval of this sBLA.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Keith Hull, M.D., Ph.D.
Primary statistical reviewer: Kiya Hamilton, Ph.D.
Statistical Team Leader: Joan Buenconsejo, Ph.D.

Overview of Study Design

The pivotal study supporting the efficacy of SC abatacept was Study IM101174. Study IM101174 was a randomized, double-blind, double-dummy, active-controlled, parallel-group 6-month comparison of efficacy of SC and IV abatacept in 1457 adults with active RA having an inadequate response (IR) to methotrexate (MTX). This study also allowed for a direct comparison of the safety, immunogenicity, and pharmacokinetic (PK) profile of abatacept, administered via the SC and IV routes, and permitted assessment of a single fixed-dose for SC abatacept irrespective of body weight. Patients received either abatacept 125 mg SC weekly + IV loading dose on Day 1 (with IV placebo at Day 15, Day 29, and every 28 days thereafter) or abatacept IV weight-tiered dosing on Days 1, 15, 29 and every 28 days thereafter with a SC placebo weekly. Patients were stratified by weight (<60 kg, 60 to 100 kg, >100 kg) and remained on their background dose of MTX and concomitant folate. Study IM101174 was designed to demonstrate non-inferiority of SC abatacept to IV abatacept with a pre-specified non-inferiority margin of 7.5%, which would preserve roughly 70% of the treatment effect observed with IV abatacept. The effect size of IV abatacept in previous placebo-controlled studies using the proportion of patients achieving ACR20 responses at 6 months was 26 to 28%. This non-inferiority margin was selected in agreement with previous Agency advice to the applicant.

Study Conduct

The study was conducted at 242 sites worldwide (82 sites in the US). A total of 2472 subjects were screened, with 1464 being randomized and 1457 actually receiving study treatment in IM101174. The treatment groups were well-balanced with respect to demographics, disease characteristics, and concomitant medications (see Table 4 below).

Table 4: Baseline Characteristics—Selected Demographics, Disease Characteristics, and Concomitant Medications

	ABATACEPT SC N=696	ABATACEPT IV N=683
Age (years); mean ± SD	50±13	50±13
Weight (kg); mean ± SD	72±18	72±18
Weight Category, n(%)		
<60 kg	176 (25)	158 (23)
60-100 kg	464 (67)	475 (68)
>100 kg	56 (8)	50 (7)
Gender, n(%)		
Female	586 (84)	549 (80)
Male	110 (16)	134 (20)
Race, n(%)		
White	516 (74)	505 (74)
Asian	63 (9)	72 (11)
Black	26 (4)	24 (4)
American Indian	5 (1)	1 (<1)
Other	86 (12)	81 (12)
Region, n(%)		
North America	129 (19)	111 (16)
South America	338 (49)	340 (50)
Europe	123 (18)	123 (18)
ROW	106 (15)	109 (16)
Duration of Disease (yr)		
mean ± SD	8±8	8±8
DAS-28		
mean ± SD	6.3±0.8	6.2±0.8
(+) RF Status, n (%)	582 (85)	583 (87)
MTX dose (mg Qwk), n	696	683
mean ± SD	16±4	17±4
Corticosteroids, n (%)	496 (71)	507 (74)
Oral dose, mean ± SD	5±4	5±7

Sources: Tables 2, 3, and 4 of Dr. Hull's review

Ninety-four percent of patients in the IV and the SC treatment groups completed the 6-month controlled period. The reasons for discontinuation were similar between treatment groups, with the most common reason for discontinuation being adverse events in both groups (3% of patients in the SC group and 4% of patients in the IV group).

A similar proportion of protocol violations were reported in each treatment group (approximately 5% of patients). Ten patients in the abatacept SC treatment group and 12 patients in the abatacept IV treatment group received parenteral or high dose oral corticosteroids within 28 days of the final assessments for disease activity. Because the

number/type of protocol violations was small and generally balanced between treatment groups, they were not felt to bias or adversely affect the overall study results.

Efficacy Results

The primary efficacy endpoint was ACR20 response at Day 169, with the primary analysis being a comparison between the IV and SC abatacept per protocol populations. The SC formulation was pre-specified to be non-inferior to the IV formulation if the lower limit of a two sided 95% CI of the difference in ACR20 response rates between SC and IV were greater than or equal to the non-inferiority margin of -7.5%. This non-inferiority margin was selected to ensure that the ACR20 response in the SC group preserves at least 70% of the minimum effect seen with the IV formulation when compared with placebo.

Table 5: Summary of Primary and Key Secondary Efficacy Variables for IM101174

	PP Population		ITT Population	
Efficacy Variable at Day 169	**SC Aba + MTX N = 696**	**IV Aba + MTX N = 683**	**SC Aba + MTX N = 736**	**IV Aba + MTX N = 721**
ACR 20 Response (Primary variable)				
No. Responders (%)	530 (76.1%)	517 (75.7%)	551 (74.9%)	535 (74.2%)
95% CI	(73.0, 79.3)	(72.5, 78.9)	(71.7, 78.0)	(71.0, 77.4)
Estimate of difference (95% CI)	0.3 (-4.2, 4.8)	N/A	0.5 (-4.0, 5.0)	N/A
ACR 50 Response				
No. Responders (%)	358 (51.4%)	343 (50.2%)	369 (50.1%)	350 (48.5%)
95% CI	(47.7, 55.1)	(46.5, 54.0)	(46.5, 53.7)	(44.9, 52.2)
Estimate of difference (95% CI)	1.2 (-3.2, 6.1)	N/A	1.4 (-3.7, 6.6)	N/A
ACR 70 Response				
No. Responders (%)	183 (26.3%)	170 (24.9%)	189 (25.7%)	173 (24.0%)
95% CI	(23.0, 29.6)	(21.6, 28.1)	(22.5, 28.8)	(20.9, 27.1)
Estimate of difference (95% CI)	1.4 (-3.2, 6.1)	N/A	1.6 (-2.8, 6.1)	N/A
HAQ Response				
No. Responders (%)	486 (69.8%)	444 (65.0%)	503 (68.3%)	459 (63.7%)
95% CI	(66.4, 73.2)	(61.4, 68.6)	(65.0, 71.7)	(60.2, 67.2)
Estimate of difference (95% CI)	5.0 (0.0, 10.0)	N/A	4.8 (-0.1, 9.7)	N/A

Source: IM101174 CSR, Tables 6.3.2, S.5.1.1B, S.5.3.1A, S.5.3.1B, S.5.2.1A, S.5.2.1B

N/A = not applicable

Source: Module 2.5, Table 4.1

A summary of the results of the primary and key secondary efficacy variables for Study IM101174 may be found in Table 5 above, for both per-protocol and ITT analyses. Results of the per-protocol and ITT analyses were similar. Results for SC abatacept and IV abatacept were essentially the same for ACR20/50/70 responders and in the proportion of patients

achieving an improvement of at least 0.3 units in the HAQ-DI (annotated as "HAQ Response"). The pre-specified non-inferiority margin was met, with the lower bound of the 95% confidence interval of the difference in ACR20 responders being -4.2.

Subgroup Analyses

One concern regarding the transition to a single fixed-dose regimen for all weight groups is the potential for differential effects at the extremes of weight. As shown in Table 6 below, lower body weight (<60 kg) did appear to be associated with a somewhat higher proportion of responders compared to patients of higher body weight (>100 kg); however this pattern was also noted with the IV weight-tiered dosing.

Table 6: Selected Subgroup Analyses of ACR20 and HAQ Responses at Day 169

Selected Subgroup Analyses of ACR20 and HAQ Responses at Day 169				
	ACR 20 Response No. Subjects n/N (%) (95% CI)		HAQ Response* No. Subjects n/N (%) (95% CI)	
PP population Subgroup	SC Abatacept N = 696	IV abatacept N = 683	SC Abatacept N = 696	IV Abatacept N = 683
Baseline Weight				
<60 kg	139/176 (79) (73, 85)	130/158 (82) (76, 88)	118/176 (67) (60, 74)	103/158 (65) (58, 73)
60 to 100 kg	352/464 (76) (72, 80)	355/475 (75) (71, 79)	336/464 (72) (68, 76)	311/475 (65) (61, 70)
>100 kg	39/56 (70) (58, 82)	32/50 (64) (51, 77)	32/56 (57) (44, 70)	30/50 (60) (46, 74)
Age				
<65 years	475/606 (78) (75, 82)	458/604 (76) (72, 79)	437/606 (72) (68, 76)	398/604 (66) (62, 70)
≥65 years	55/90 (61) (51, 71)	59/79 (75) (65, 84)	49/90 (54) (44, 65)	46/79 (58) (47, 69)
≥75 years	6/13 (46) (19, 73)	7/14 (50) (24, 76)	4/13 (31) (6, 56)	7/14 (50) (24, 76)
Geographic Region				
North America	82/129 (64) (55, 72)	72/111 (65) (56, 74)	73/129 (57) (48, 65)	61/111 (55) (46, 64)
South America	294/338 (87) (83, 91)	278/340 (82) (78, 86)	275/338 (81) (77, 86)	252/340 (74) (70, 79)
Europe	80/123 (65) (57, 74)	86/123 (70) (62, 78)	72/123 (58) (50, 67)	64/123 (52) (43, 61)
Rest of World	74/106 (70) (61, 79)	81/109 (74) (66, 82)	66/106 (62) (53, 72)	67/109 (62) (52, 71)

Source: Table 6.3.5 of IM101174 CSR
*HAQ Response defined as ≥0.3 units improvement from baseline

With respect to subgroups by age and geographic region, the pattern of responders continued to be similar between SC and IV treatment arms for each subgroup. The pattern of responders also appeared to be consistent with that seen in other RA clinical trials, with a lower proportion of responders in the elderly and in North America.

Subgroup analyses by gender, race, disease duration, history of TNF inhibitor use, high baseline DAS-CRP score (above or below 5.1), and baseline RF status likewise did not suggest a difference between SC and IV abatacept with respect to the ACR20 or HAQ endpoints (data not shown).

- **Discussion of the statistical review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed**

The clinical and statistical review teams are in agreement that the data provided were adequate to provide substantial evidence that SC abatacept 125 mg SC weekly is non-inferior to the currently approved IV abatacept weight-tiered dosing.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

There were no notable efficacy issues.

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any**

The safety database for the SC abatacept clinical development program included:

i. **IM101063:** a phase 2 PK study in 68 RA patients with a main study period of 12 weeks;
ii. **IM101174:** the pivotal non-inferiority study in 1457 RA patients with a main study period of 6 months;
iii. **IM101173:** a 4-month open-label study in 100 RA patients (49 on monotherapy and 51 on concomitant MTX), with a primary objective to evaluate the immunogenicity and safety of SC abatacept in the absence of an IV loading dose, when given as monotherapy vs. with concomitant MTX, and to assess whether the use of concomitant MTX influenced the development of immunogenicity;
iv. **IM101167:** a 9-month study (3 periods—Period 1, 12-week open-label run in, in 167 RA patients, Period 2, 12-week randomized withdrawal period in 120 responders, and Period 3, 12-week open-label re-start in the 119 patients who completed Period 2), designed to evaluate the impact on immunogenicity and safety, of interruption and reintroduction of SC abatacept, with or without an IV loading dose, in subjects with active RA treated concomitantly with MTX who had an initial response to SC abatacept; and
v. **IM101185:** an open-label study in 123 RA patients who had tolerated at least 5 years of IV abatacept in long-term extension studies IM101102 or IM101029, designed to evaluate the safety of conversion from chronic IV abatacept use to SC abatacept.

All studies had a long-term extension period. Data from all 5 studies were pooled to allow a cumulative assessment of the safety profile. The single-dose SC PK study IM101013 was not

included in the pooled analysis. The comparative safety of SC vs. IV formulations of abatacept are derived from 6-month controlled period of IM101174. The cumulative SC safety data includes a mean duration of exposure of approximately 13 months. Eight-hundred ninety-six subjects received >12 months of SC abatacept. Overall 1879 patients received SC abatacept for a total exposure of approximately 1946 patient-years. The IV abatacept safety experience includes up to 9 years of continued exposure, including over 12,000 patient-years exposure in 1165 patients with at least 5 years exposure, and pharmacovigilance monitoring under market usage with over 60,000 patient-years exposure. The safety database submitted in the sBLA provided adequate data to support the safety of SC abatacept.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

As shown in Table 7 below, there was very little difference between the SC and IV abatacept groups with respect to the incidence of deaths, serious adverse events (SAEs), adverse events (AEs), adverse events leading to discontinuation, and AE of special interest.

There were a total of 15 deaths reported during all periods of the submitted studies. During the controlled period of IM101174, 5 deaths occurred in patients receiving IV abatacept and 2 deaths occurred in patients receiving SC abatacept; the remainder died during the open-label, long-term extension periods from Studies IM101063, IM101167, and IM101174 (and were therefore receiving SC abatacept).

Deaths appeared to be related to known abatacept-associated toxicities, such as serious infection, or were consistent with morbidities seen in the underlying patient population such as cardiovascular events (subarachnoid hemorrhage and bowel infarction) or malignancy. Deaths in the long-term extensions were of similar etiologies. The types of SAEs and discontinuations due to AEs reported followed a similar pattern, with infections being the most commonly reported etiology.

Overall, no new safety signals were identified with SC abatacept treatment. Detailed evaluation of the immunogenicity of the SC route of administration is discussed in further detail below.

Table 7: Overview of Safety in IM101174 6-month Controlled Period

	Number (%) of Subjects		
	SC Abatacept N = 736		**IV Abatacept N = 721**
Deaths	2 (0.3)		5 (0.7)
Relative Risk (95% CI)		N/A	
SAEs	31 (4.2)		35 (4.9)
Relative Risk (95% CI)		*0.87 (0.54, 1.39)*	
AEs	493 (67.0)		470 (65.2)
Relative Risk (95% CI)		*1.03 (0.95, 1.11)*	
AEs Leading to Discontinuation	15 (2.0)		25 (3.5)
Relative Risk (95% CI)		*0.59 (0.31, 1.11)*	
AE of Special Interest			
Infections and Infestations	234 (31.8)		221 (30.7)
Relative Risk (95% CI)		*1.04 (0.89, 1.21)*	
Serious Infections and Infestations	5 (0.7)		10 (1.4)
Relative Risk (95% CI)		*0.49 (0.17, 1.43)*	
Malignancies	3 (0.4)		5 (0.7)
Relative Risk (95% CI)		*0.59 (0.14, 2.45)*	
Autoimmune events	7 (1.0)		6 (0.8)
Relative Risk (95% CI)		*1.14 (0.39, 3.38)*	
Systemic Injection Reaction	56 (7.6)		56 (7.8)
Relative Risk (95% CI)		*0.98 (0.69, 1.40)*	
Local Injection Site Reaction	19 (2.6)		18 (2.5)
Relative Risk (95% CI)		*1.03 (0.55, 1.95)*	

Source: Summary of Clinical Safety, Overview section,[30] SCS-A - Appendix 16.23[30] Table 5.1 of Module 2.5

- **Immunogenicity**

As previously discussed, one of the Agency's primary concerns about the switch from IV to SC abatacept pertained to the possible increase in immunogenicity to abatacept. The underlying concern that an immunogenic response to abatacept could lead to an autoimmune response against endogenous CTLA-4 has thus far not been borne out in the experience with IV abatacept. In the course of clinical development of the SC formulation, the Agency requested that the immunogenicity of SC abatacept be assessed in likely clinical scenarios of 1) interruption of SC dosing (assessed by Study IM101167), 2) initiation of SC dosing with or without concomitant MTX and with or without an IV loading dose (assessed by Study IM101173), and 3) switch from IV abatacept to SC abatacept (assessed by Study IM101185). The immunogenicity of SC vs. IV abatacept was assessed in the pivotal study, IM101174.

Study IM101174: Immunogenicity of SC vs. IV abatacept

As discussed above, Study IM101174 was a 6-month, randomized, double-blind, placebo-controlled, double-dummy study designed to evaluate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with MTX. Serum samples were collected from subjects on Study Days 1, 85, and 169 during the short-term period of Study IM101174. Subjects who were receiving the SC formulation and discontinued prematurely during this period had serum samples collected 7, 28, 56, and 85 days after their last SC injection. Subjects who were receiving the IV formulation and discontinued prematurely had serum samples collected 28, 56, 85, and 113 days after their last IV infusion.

As shown in Table 8 below, while on therapy, a total of 5 out of 681 (0.7%) subjects receiving SC abatacept developed anti-abatacept or anti-CTLA4-T antibodies by Study Day 169 compared to 8 out of 658 (1.2%) subjects treated with IV abatacept during the same period. Data from subjects who discontinued therapy demonstrated that anti-product antibodies developed in 3 out of 28 (10.7%) subjects treated with SC abatacept compared to 7 out of 31 (22.6%) IV-abatacept treated subjects.

Table 8: Proportion of Patients with Positive Anti-Abatacept or Anti-CTLA4-T Responses (ELISA Assays) Over Time During the Controlled Period of IM101174

Treatment Group	Study Day	Anti-abatacept n/m (%)	Anti-CTLA4-T n/m (%)	Total n/m (%)
SC Abatacept	Day 85	0/700	0/705	0/706
	Day 169	3/671 (0.4%)	2/681 (0.3%)	5/681 (0.7%)
	Overall On Trt Visits	3/707 (0.4%)	2/716 (0.3%)	5/716 (0.7%)
	28 days post last dose	0/18	0/20	0/20
	56 days post last dose	0/19	1/19 (5.3%)	1/19 (5.3%)
	85 days post last dose	0/12	2/13 (15.4%)	2/13 (15.4%)
	Overall Post Visits	0/26	3/28 (10.7%)	3/28 (10.7%)
	Overall	3/714 (0.4%)	5/725 (0.7%)	8/725 (1.1%)
IV Abatacept	Day 85	2/682 (0.3%)	0/689	2/689 (0.3%)
	Day 169	4/648 (0.6%)	4/658 (0.6%)	8/658 (1.2%)
	Overall On Trt Visits	5/691 (0.7%)	4/702 (0.6%)	9/702 (1.3%)
	28 days post last dose	0/25	2/27 (7.4%)	2/27 (7.4%)
	56 days post last dose	0/22	1/23 (4.3%)	1/23 (4.3%)
	85 days post last dose	0/15	5/15 (33.3%)	5/15 (33.3%)
	Overall Post Visits	0/29	7/31 (22.6%)	7/31 (22.6%)
	Overall	5/698 (0.7%)	11/710 (1.5%)	16/710 (2.3%)

n = Number of patients who are positive; m = Number of patients who are evaluated
Source: Sponsor Table 6.6.1.1, IM101174 CSR

The rate of immunogenicity in subjects on and off therapy in both treatment arms is consistent with what has been reported during the IV abatacept clinical program and post-marketing data. Overall, the data from Study IM101174 suggests that the proposed dosing of the SC formulation of abatacept is no more immunogenic than the approved IV formulation.

Because the SC regimen is also a fixed dose, an analysis of immunogenicity by weight category was also performed, as shown in Table 9 below. The proportion of patients with positive anti-product antibody assays was generally similar for IV and SC abatacept in each weight category. Consistent with previous experience, a higher proportion of patients tested

positive in the post-treatment period. With the largest patients on the SC fixed dose, only 1 of 56 patients tested was positive; this did not suggest that the lower potential exposure associated with the SC fixed-dose would be likely to increase immunogenicity risk.

Table 9: Study IM101174 Immunogenicity by Weight, IV vs. SC Groups

Immunogenicity by Weight, IV vs. SC Groups, Study IM101174			
Weight Category	**Treatment**	**IV Abatacept**	**SC Abatacept**
<60 kg	On treatment	1/164 (0.6%)	1/181 (0.6%)
	Post-treatment	2/10 (20%)	2/8 (25%)
	Overall	3/164 (1.8%)	3/184 (1.6%)
60-100 kg	On treatment	8/481 (1.7%)	3/480 (0.6%)
	Post-treatment	5/15 (33.3%)	1/16 (6.3%)
	Overall	13/489 (2.7%)	4/485 (0.8%)
>100 kg	On treatment	0/57	1/55 (1.8%)
	Post-treatment	0/6	0/4
	Overall	0/57	1/56 (1.8%)

Source: IM101174 CSR Table 6.6.1.3A

Study IM101167: Immunogenicity of interrupted SC dosing

Study IM101167 was a 9-month, multicenter, randomized, double-blind, withdrawal study designed to evaluate the effect of interruption and reintroduction on the immunogenicity and safety of SC abatacept, with or without an IV loading dose, in subjects with active RA who have had an initial clinical response to SC abatacept. The trial was organized in three, 12-week periods. A total of 167 patients were treated with SC abatacept (IV loading dose followed by 125 mg SC weekly) in Period 1. Of these, 120 patients were identified as responders (had a decrease in DAS28-CRP of at least 0.6 units) and entered into Period 2 where they were randomized to continue receiving SC abatacept therapy or SC placebo. At the end of 12-weeks, patients entered Period 3 and either continued to receive SC abatacept or were restarted on SC abatacept with or without an IV loading dose. Data were available for all 120 subjects during the withdrawal period of the study. During the reintroduction period data were available for 119 subjects with one subject in the SC placebo group who withdrew consent on Day 197.

As shown in Table 10 below, at the end of the withdrawal period (Study Day 169), immunogenicity testing showed that none of the 38 subjects who received continuous SC abatacept had developed anti-product antibodies compared to 7 out of 73 (10%) subjects who had their SC abatacept withdrawn during this period.

Following reintroduction of SC abatacept therapy during Period 3, 1 out of 38 (3%) subjects who had continued to receive SC abatacept through Periods 2 and 3 developed anti-product antibodies compared to 2 out of 73 (3%) subjects who reinitiated SC abatacept therapy following a 12-week hiatus from therapy during Period 2.

Overall, Study IM101167 demonstrated that immunogenicity was not significantly increased upon withdrawal of SC abatacept for 12 weeks. Also, there were no obvious changes in clinical efficacy or safety when SC abatacept therapy was reintroduced after temporary withdrawal.

Table 10: Proportion of Patients with Anti-Abatacept or Anti-CTLA4-T Responses in Study IM101167

Proportion of Patients with Anti-Abatacept or Anti-CTLA4-T Responses by ELISA					
Study Day	**Analyte**		**Period II SC Aba N = 40**	**Period II SC Pbo N = 80**	**Total N = 120**
Day 169 (End of Period II)	Anti-abatacept	No. Subjects n/m (%)	0/37	1/71 (1.4)	1/108 (0.9)
		95% CI	n/a	(0.0, 4.1)	(0.0, 2.7)
		Estimate of diff (95% CI)	1.41 (-3.39, 6.21)	n/a	n/a
	Anti-CTLA4-T	No. Subjects n/m (%)	0/38	6/73 (8.2)	6/111 (5.4)
		95% CI	n/a	(1.9, 14.5)	(1.2, 9.6)
		Estimate of diff (95% CI)	8.22 (-0.08, 16.52)	n/a	n/a
	Total	No. Subjects n/m (%)	0/38	7/73 (9.6)	7/111 (6.3)
		95% CI	n/a	(2.8, 16.3)	(1.8, 10.8)
		Estimate of diff (95% CI)	9.59 (0.83, 18.34)	n/a	n/a
Day 253 (End of Period III)	Anti-abatacept	No. Subjects n/m (%)	0/38	0/73	0/111
		95% CI	n/a	n/a	n/a
		Estimate of diff (95% CI)	n/a	n/a	n/a
	Anti-CTLA4-T	No. Subjects n/m (%)	1/38 (2.6)	2/73 (2.7)	3/111 (2.7)
		95% CI	(0.0, 7.7)	(0.0, 6.5)	(0.0, 5.7)
		Estimate of diff (95% CI)	0.11 (-8.21, 8.43)	n/a	n/a
	Total	No. Subjects n/m (%)	1/38 (2.6)	2/73 (2.7)	3/111 (2.7)
		95% CI	(0.0, 7.7)	(0.0, 6.5)	(0.0, 5.7)
		Estimate of diff (95% CI)	0.11 (-8.21, 8.43)	n/a	n/a

n = Number of patients who are positive, m = Number of patients tested; n/a = not applicable
Sources: Tables 12 and 13 of Immunogenicity Summary; Tables 6.6.1.1A and 6.6.1.1D of IM101167 CSR

Study IM101173: Immunogenicity of No IV Loading Dose and as Monotherapy

Study IM101173 was a 4-month, open-label, multicenter trial designed to assess the immunogenicity of SC abatacept with or without concomitant MTX and absent of an IV loading dose of abatacept.

As shown in Table 11 below, none of the 95 subjects (50 subjects in the SC abatacept + MTX treatment arm and 45 in SC abatacept monotherapy treatment arm) were positive for anti-product antibodies at the end of the short-term treatment period of Study IM101173. Positive antibody responses were infrequently observed at earlier time points during the short-term treatment period or during the follow-up for subjects who did not enter the long-term period; however, these positive antibody responses were of low titer, transient, and generally occurred prior to Study Day 85. During the short-term treatment period, a total of 2 of 49 (4%) subjects treated with SC abatacept monotherapy were positive for anti-product antibodies compared to 2 out of 51 (4%) subjects treated with SC abatacept + MTX. There did not appear to be any correlation of the development of antibodies with clinical safety or efficacy findings.

Table 11: Proportion of Patients with Anti-Abatacept or Anti-CTLA4-T Responses (ELISA Method) in Study IM101173

Treatment Cohort	Study Day	Anti-abatacept n/m (%)	Anti-CTLA4-T n/m (%)	Total n/m (%)
SC Aba + MTX	Day 15	0 / 50	0 / 51	0 / 51
	Day 29	1 / 49 (2.0%)	1 / 50 (2.0%)	2 / 50 (4.0%)
	Day 43	1 / 49 (2.0%)	1 / 50 (2.0%)	2 / 50 (4.0%)
	Day 57	0 / 49	1 / 50 (2.0%)	1 / 50 (2.0%)
	Day 85	0 / 49	0 / 50	0 / 50
	Day 113	0 / 49	0 / 50	0 / 50
	Overall on Trt Visits	1 / 50 (2.0%)	1 / 51 (2.0%)	2 / 51 (3.9%)
	28 Days post last dose	0 / 2	0 / 2	0 / 2
	56 days post last dose	0 / 2	0 / 2	0 / 2
	85 days post last dose	0 / 4	0 / 4	0 / 4
	Overall Post Visits	0 / 4	0 / 4	0 / 4
	Overall	1 / 50 (2.0%)	1 / 51 (2.0%)	2 / 51 (3.9%)
SC Aba Only	Day 15	0 / 47	0 / 47	0 / 47
	Day 29	0 / 48	0 / 48	0 / 48
	Day 43	0 / 48	0 / 48	0 / 48
	Day 57	0 / 47	1 / 47 (2.1%)	1 / 47 (2.1%)
	Day 85	0 / 47	0 / 47	0 / 47
	Day 113	0 / 45	0 / 45	0 / 45
	Overall on Trt Visits	0 / 49	1 / 49 (2.0%)	1 / 49 (2.0%)
	28 Days post last dose	0 / 3	0 / 3	0 / 3
	56 days post last dose	0 / 3	0 / 3	0 / 3
	85 days post last dose	0 / 4	1 / 4 (25.0%)	1 / 4 (25.0%)
	Overall Post Visits	0 / 4	1 / 4 (25.0%)	1 / 4 (25.0%)
	Overall	0 / 49	2 / 49 (4.1%)	2 / 49 (4.1%)

n = Number of patients who are positive; m = Number of patients who are evaluated
Source: Table 11 of Immunogenicity Summary and Table 10.1.2.1 of IM101073 CSR

Overall, results from Study IM101173 suggested that SC abatacept monotherapy did not induce more immunogenicity compared to subjects treated with SC abatacept + MTX. While these results support the safety of SC abatacept as monotherapy regarding the development of immunogenicity, the study was not powered to adequately assess the efficacy of monotherapy abatacept compared to IV abatacept.

Study IM101185: Immunogenicity of switching from IV to SC abatacept

Study IM101185 was a 12-month, multicenter, open-label, single treatment arm study evaluating the safety of abatacept in subjects switching from IV to SC abatacept therapy. The study enrolled subjects with RA who were participating in open-label long-term extension trials of studies from the core IV abatacept program in RA.

As shown in Table 12 below, a total of 8 out of 122 (7%) subjects developed anti-product antibodies during the first 3 months after switching from IV to SC abatacept. There was no apparent relationship between the anti-product antibodies and efficacy or safety results during this period. One subject who had developed a positive anti-CTLA4 antibody titer during this period developed sarcoidosis on Day 131 that was serious and resulted in treatment discontinuation; however, a causative relationship cannot be determined with the limited data. Abatacept-induced immunogenicity, based on the ECL assay, was not observed in any subject during the first 3 months (Day 85) and for 1 subject (0.8%) during the cumulative treatment

period. Overall, the risk of immunogenicity following switching to SC abatacept therapy from long-term IV therapy does not appear to be increased over the background rate of immunogenicity observed with abatacept treatment.

Table 12: Proportion of Patients with Anti-Abatacept or Anti-CTLA4-T Responses in IM101185

Proportion of Patients with Anti-Abatacept or Anti-CTLA4-T Responses (ELISA Method) During the First 3 Months of IM101185			
Study Day	Anti-Abatacept n/m (%)	Anti-CTLA4-T n/m (%)	Total n/m (%)
Day 29	7/83 (8.4)	0/120	7/120 (5.8)
Day 57	5/82 (6.1)	1/118 (0.8)	6/118 (5.1)
Day 85	6/84 (7.1)	1/121 (0.8)	7/121 (5.8)
Overall on Treatment Visits	7/85 (8.2)	1/122 (0.8)	8/122 (6.6)
28 days post last dose	0/2	0/2	0/2
56 days post last dose	0/2	0/2	0/2
85 days post last dose	0/2	0/2	0/2
Overall Post Visits	0/2	0/2	0/2
Overall	7/85 (8.2)	1/122 (0.8)	8/122 (6.6)

n = Number of patients who are positive; m = Number of patients who were tested
Source: Table 16 of Immunogenicity Summary and Table 10.1.1A of IM101185 CSR

- **Special safety concerns**

As previously mentioned, the fixed dose SC regimen raises questions regarding whether there might be differential efficacy or safety at extremes of weight. Thus an analysis of adverse events by weight category was performed, as shown in Table 13 below. Overall, it did not appear that the proportion of patients experiencing deaths, SAEs, AEs, or discontinuations due to SAEs or AEs was very different in the various weight categories for either SC or IV abatacept.

Table 13: Summary of AEs by Weight Category, IM101174 Controlled Period

Summary of AE by Weight Category, IM101174 Controlled Period		
	SC Abatacept	IV Abatacept
Baseline Weight <60 kg	**N = 185**	**N = 166**
Deaths	0	3 (2)
SAEs	9 (5)	10 (6)
Discontinuations due to SAEs	1 (<1)	7 (4)
AEs	129 (70)	106 (64)
Discontinuations due to AEs	2 (1)	9 (5)
Baseline Weight 60 to 100 kg	**N = 494**	**N = 498**
Deaths	1 (<1)	2 (<1)
SAEs	19 (4)	21 (4)
Discontinuations due to SAEs	6 (1)	7 (1)
AEs	319 (65)	320 (64)
Discontinuations due to AEs	12 (2)	14 (3)
Baseline Weight >100 kg	**N = 57**	**N = 57**
Deaths	1 (2)	0
SAEs	3 (5)	4 (7)
Discontinuations due to SAEs	1 (2)	0
AEs	45 (79)	44 (77)
Discontinuations due to AEs	1 (2)	2 (4)

Source: Table 6.4.7.1A, IM101174 CSR

- **Discussion of primary reviewer's comments and conclusions**

Dr. Hull has concluded that the safety profile of SC abatacept was similar to IV abatacept, and that there is no apparent difference in risk for the lowest weight patients (who would experience the highest exposure from the fixed-dose of 125 mg weekly). Dr. Hull also concluded that the immunogenicity risk associated with SC abatacept does not appear to be obviously different from that seen with IV abatacept, even in situations that could be associated with more immunogenicity risk, such as with treatment interruption, or when given as monotherapy. Therefore, he has concluded that the safety profile of SC abatacept is acceptable for approval.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

I concur with Dr. Hull's conclusions.

- **Discussion of notable safety issues (resolved or outstanding)**

No additional safety issues were identified.

9. Advisory Committee Meeting

Not applicable. No issues warranting Advisory Committee input were identified in this application.

10. Pediatrics

- **Rationale for extrapolation, if applicable**—Not applicable.
- **Peds exclusivity board review - PPSR/WR**—Not applicable.
- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

Abatacept by intravenous infusion is already approved for polyarticular juvenile idiopathic arthritis (JIA) patients ages 6 to 17 years of age, on the basis of a single randomized withdrawal study in 190 patients (Study IM101033). Because of evidence from juvenile animal studies suggested that abatacept exposure in a developing immune system could be deleterious—more profound immunosuppression, and thyroiditis (with incidence and severity increasing with decreasing age of exposure)—the Agency waived pediatric studies in children less than 6 years of age. Ages 5 and under were waived because they had not yet been studied, and it is not clear from available data when the human immune system would be considered sufficiently mature to not correlate with the juvenile animal study findings. In this sBLA, the applicant has requested a deferral of pediatric studies required by the Pediatric Research Equity Act (PREA) in JIA patients, (b) (4) In a parallel submission distinct from the sBLA, the (b) (4)

[redacted]

A pediatric ethics consult was obtained to provide input regarding the use of [redacted]

The applicant's deferral request, and the [redacted], was discussed at the meeting of the Pediatric Review Committee (PeRC) on June 29, 2011. The PeRC agreed with the Division's recommendation to defer SC pediatric studies in JIA patients ages 6 to 17 years, and waive studies in JIA patients under 6 years of age, because these were the actions taken for the IV pediatric clinical development program and there are no new data available to provide reassurance of the safety of human exposure under 6 years of age. PeRC also agreed with a PREA study requirement calling for a PK/safety study.

- **Consults**

A pediatrics ethics consult was obtained for a separate submission for the [redacted], as described above.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—No issues identified.
- **Exclusivity or patent issues of concern**—No issues identified.
- **Financial disclosures**—No conflicts identified that were likely to have affected overall study results.
- **Other GCP issues**

An error in the analyses dataset regarding stratification classification by baseline body weight (<60 kg, 60 to 100 kg, and >100 kg) was identified for Study IM101174 after finalization of the initial report; however, the stratified randomization for the study was conducted correctly. Datasets were revised accordingly, as were efficacy, safety and PK analyses. However, these did not affect the overall study results. Additionally, the sponsor identified a non-compliance issue regarding Good Clinical Practice (GCP) regulations for Study IM101174 Site 229 in [redacted] resulting in the exclusion of all eight subjects from the study site from the efficacy analyses. These revisions did not affect the overall conclusions of Study IM101174.

- **DSI audits**

A DSI audit was not performed for this sBLA. The efficacy study IM101174 was conducted at 242 sites and enrolled 1457 patients. Any given site would have enrolled a very small fraction of the overall study population. Furthermore, approval of this sBLA would not be expected to result in a significant expansion of the population of abatacept users. Therefore, the review team did not believe that inspection of the clinical sites would be optimal use of DSI resources.

- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—No other issues identified.

12. Labeling

- **Proprietary name**—No change to the proprietary name "Orencia" is proposed.
- **DDMAC and OSE Division Comments**

The main issue raised by OSE/DMEPA (Office of Surveillance and Epidemiology/Division of Medication Error, Prevention and Analysis) and DDMAC (Division of Drug Marketing, Advertising, and Communication) pertained to potential confusion regarding the (b) (4) An information request was sent to the applicant to better describe how they intended to ensure that confusion between the (b) (4) did not occur. In response, the applicant decided (b) (4) (b) (4)

- **Physician labeling**

The primary labeling issue pertained to the applicant's proposal that SC dosing be allowed with or without an IV load. The large noninferiority trial that serves as the basis of the determination of comparative efficacy and safety (IM101174) utilized an IV loading dose for patients in the SC treatment group. The applicant proposes that the IV load be optional, on the basis of Studies IM101167 and IM101173. Study IM101167 included experience with approximately 40 patients who resumed SC abatacept without an IV load and 40 patients who resumed SC abatacept with an IV load, after a randomized withdrawal period. Study IM101173 was a 4- month open-label trial in 100 patients who were randomized to either receive SC abatacept monotherapy or SC abatacept with MTX. Patients in this trial were not given an IV loading dose of abatacept. Neither of the latter trials was designed to assess efficacy; thus the conclusion that SC abatacept is the same as IV abatacept clinically only applies to the situation studied in IM101174, where SC patients received an IV abatacept loading dose. Therefore the Division believes the IV load should be the primary recommended dosing. However, Studies IM101167 and IM101173 are adequate support to add a clause that patients who are unable to receive an IV load may safely begin SC dosing without it. The primary efficacy concern from a lack of IV load would be a delay in efficacy. Based on PK data from IM101173, a Cmin above the target concentration of 10 μg/mL would be achieved by 2 weeks, if an IV loading dose is not used.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

Final labeling has not been completed at the time of this CDTL review, however no major issues of disagreement are anticipated.

- **Carton and immediate container labels (if problems are noted)**

Final review of carton and container labels is pending, however no major issues are anticipated.

- **Patient labeling/Medication guide (if considered or required)**

Orencia does not currently have a medication guide. The safety data that have accrued in IV postmarketing and that were submitted in this sBLA are consistent with the known safety profile of Orencia. Thus a medication guide was not considered to be warranted. The Patient Information sheet was reworded and reformatted by the Division of Risk Management (DRISK), OSE. (b) (4) patient instructions for use (PIFU) were submitted, (b) (4) for the PFS with flange extender. The PIFU for the (b) (4) Additional edits from DDMAC and DMEPA regarding the PIFU were relayed to the applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application, provided that agreement can be reached on labeling.

- **Risk Benefit Assessment**

The data provided in this application provided adequate evidence that the abatacept SC formulation and route of administration is not inferior to the abatacept IV formulation and route of administration with respect to efficacy and safety. Consistent with the Agency's previous conclusion that the risk:benefit profile of IV abatacept is favorable, the data support that SC abatacept has a similar risk:benefit profile, and therefore may also be approved.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The data in this application do not suggest any new safety signals. Abatacept IV does not have a REMS and a REMS is not warranted for the SC formulation.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing Requirements:
1) This application triggers PREA. The applicant will be required to conduct a PK/safety study of SC abatacept in polyarticular JIA patients ages 6 to 17. Studies in polyarticular JIA patients under 6 years of age will be waived. See Section 10 above for further details. Applicant-proposed milestones of November 2012 for submission of the final protocol, September 2017 for completion of the study, and January 2018 for submission of the final study report are acceptable.

Postmarketing Commitments:
Ten product-quality-related postmarketing commitments are being requested. See Section 3 above for further details.

- **Recommended Comments to Applicant**

Not applicable.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental BLA
Application Number(s)	125118/122
Priority or Standard	S
Submit Date(s)	December 3, 2010
Received Date(s)	October 4, 2010
PDUFA Goal Date	August 4, 2011
Division / Office	DPARP/ODE2
Reviewer Name(s)	Keith M Hull, MD, PhD
Review Completion Date	June 30, 2011
Established Name	Abatacept
(Proposed) Trade Name	ORENCIA
Therapeutic Class	Fusion Protein
Applicant	Bristol-Myers Squibb
Formulation(s)	Subcutaneous injection
Dosing Regimen	125 mg SC Qwk
Indication(s)	Treatment of Rheumatoid Arthritis
Intended Population(s)	Adult patients with moderate to severe rheumatoid arthritis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The intravenous (IV) formulation of abatacept (Orencia) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) was initially approved in 2005. This supplemental biologic licensing application seeks approval of the subcutaneous (SC) formulation of abatacept and to extend the indication and claims of the approved IV formulation to the SC formulation.

The primary focus of the current review was Study IM101174, a large, non-inferiority trial designed to demonstrate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with methotrexate (MTX). The trial was well designed and used a stringent non-inferiority margin that preserved 70% of the treatment effect size of the IV formulation. Three additional studies (IM101167, IM101173, and IM101185) provided further safety data regarding the potential immunogenicity of the SC abatacept formulation.

The review of Study IM101174 demonstrated that the study met the prespecified primary endpoint with an estimated difference between the two treatment arms, assessed by the proportion of subjects achieving an ACR 20 at Day 169, of 0.3% (95% CI: -4, 5). Alternatively expressed, 76% of subjects in both treatment arms achieved an ACR 20 at Day 169. These data were further supported by sensitivity analyses and major secondary endpoints. Pooled analyses of the four clinical studies did not demonstrate an increased safety risk or difference in the development of immunogenicity with the SC formulation compared to IV abatacept. Overall, no new safety signals for the SC formulation were identified.

The current data also provides evidence for adequate directions for use of the proposed product based on the study designs that provided subjects with instructions on how to administer SC self-injections. Subjects were provided pre-filled glass syringes containing abatacept 125 mg/syringe or placebo for weekly SC injections. Overall, subject compliance was high and the SC dosing was well tolerated. Of note, the sponsor is planning on marketing the pre-filled glass syringes with an attached flange extender, which was not used in the four major clinical studies; however, after consultation with the Center for Devices and Radiological Health, who evaluated the proposed marketed combination device, the prefilled glass syringe with flange extender has been deemed acceptable.

Based on data from Studies IM101167, IM101173, and IM 101185, the sponsor has proposed language to the Dosage and Administration section of the Package Insert to

allow SC abatacept to be initiated with or without an IV loading dose and with or without concomitant MTX. While these studies have provided evidence of safety in regards to SC abatacept, they were not designed, or powered, to assess the efficacy of these dosing regimens compared to the IV formulation. Consequently, it is my opinion that only the dosing regimen used in Study IM101174, namely initiation of SC abatacept following an IV abatacept loading dose, should be included in the new Package Insert.

Based upon my review of the clinical data as a whole, I recommend approval of the SC abatacept formulation for the treatment of patients with moderately to severely active RA.

1.2 Risk Benefit Assessment

The risk-benefit assessment of SC abatacept is in favor of approval for the current application given the adequacy of the clinical studies, the magnitude of the clinical efficacy response observed in Study IM101174, and the overall similar safety profile of SC abatacept compared to IV abatacept. Approval of the SC formulation of abatacept will provide an alternative route of administration for patients who may be unable to commit to monthly IV infusions with the currently marketed product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no current clinical recommendations for postmarket risk evaluation and mitigation strategies for SC abatacept.

1.4 Recommendations for Postmarket Requirements and Commitments

While there are no current clinical recommendations for postmarket requirements and commitments for SC abatacept, this application triggers the Pediatric Research Equity Act (PREA), and a pediatric study in patients with polyarticular juvenile idiopathic arthritis (JIA) will be required. In accordance with the PREA-required study of the IV formulation of abatacept, and due to juvenile animal study findings which suggest more potent immunosuppression and autoimmunity could occur with abatacept exposure in a developing immune system, testing in children ages 5 and under will be waived. The sponsor has submitted a study proposal to assess the development of SC abatacept in children with juvenile idiopathic arthritis (JIA). The Division is in discussion with the sponsor regarding study design and clinical endpoints.

2 Introduction and Regulatory Background

2.1 Product Information

Abatacept (Orencia) is a fully human, recombinant, soluble fusion protein comprised of the extracellular domain of human CTLA-4 and the hinge-CH2-CH3 domain fragment of the Fc domain of human IgG1. Abatacept is a selective costimulation modulator of T-cells that derives its mechanism of action by inhibiting the interaction of CD80 and CD86 with their receptor CD28. This interaction normally provides a costimulatory signal necessary for full activation of T cells.

The currently proposed product consists of abatacept 125 mg/syringe as a single dose, disposable, ready-to use subcutaneous solution packaged in a 1-mL long glass syringe with fill line markings and is stoppered with a (b) (4)-coated (b) (4) stopper. Although subjects were provided with pre-filled (b) (4) during the Phase 3 development program, the sponsor is planning to market the pre-filled syringe with a flange extender. Our Division consulted the Center for Devices and Radiological Health (CDRH) to request evaluation of the combination drug/device product for delivering abatacept by SC injection.

Nikhl Thakur, Combination Products Team Leader of the General Hospital Devices Branch in CDRH, reviewed the consult and product information and concluded that the sponsor had performed an acceptable Human Factors study for this product. In his review, Mr. Thakur identified several deficiencies that were satisfactorily addressed by the sponsor. These relevant deficiencies and sponsor's answers are summarized below:

1. The Agency inquired whether the flange extender would be attached to all new Orencia pre-filled syringes. The sponsor answered that the proposed Orencia pre-filled syringes will be comprised of a pre-filled syringe with flange extender fully assembled prior to release to the market.

2. The Agency inquired whether the (b) (4) . Since the product is provided fully assembled and the Instructions for Use indicate the flange extender in the diagrams, it is expected that users will use the product (b) (4) as intended.

Mr. Thakur concluded the consult by stating that the sponsor has adequately addressed all deficiencies and that the final product was acceptable.

2.2 Currently Available Treatments for Proposed Indications

Pharmacologic therapy for RA depends on the severity of disease and may include a combination of DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), and/or corticosteroids. While corticosteroids and NSAIDS are commonly used in the management of RA, they do not tend to alter the course of the disease, as do the non-biologic and biologic RA DMARD therapies. Since abatacept is of the latter category, we will limit our discussion to the DMARDs that are available for treatment of RA. DMARD therapies for RA can be divided into 2 categories: non-biologic RA therapies and biologic RA therapies.

2.2.1 Non-Biologic RA Therapies

The non-biologic RA therapies commonly used in the treatment of RA include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide. Less commonly utilized are azathioprine (AZA), D-penicillamine, gold salts, minocycline, and cyclosporine. These medications suppress immune function to varying degrees and are used alone or in combination. Controlled clinical trials have demonstrated the clinical benefit of some of the non-biologic DMARDs (e.g., leflunomide) to improve the signs and symptoms of joint involvement, improve functional status and health-related quality of life, and inhibit structural damage as evidenced by decreased progression of erosions on radiographs. Which particular drug(s) are used depends on the physician and the needs of the individual patient but includes relative efficacy, convenience of administration, cost of the medication and monitoring, frequency of monitoring for adverse events, and the toxicity profile of the drug. Many rheumatologists choose MTX as the initial drug because of its favorable risk-benefit ratio.

2.2.2 Biologic RA Therapies

The FDA approved biologic RA therapies include the TNF-blockers (Enbrel®, Remicade®, Humira®, Simponi®, and Cimzia®), the IL-1 blocker, Kineret®, the anti-CD20 monoclonal antibody Rituxan®, the anti-IL-6R monoclonal antibody Actemra®, and the IV formulation of Orencia®. The biologic RA therapies are generally used in subjects with moderate to severe RA who have failed non-biologic RA therapies; however, Enbrel®, Humira®, Cimzia®, Actemra®, and IV Orencia® can be used in combination with MTX or alone, while Remicade®, Simponi®, and Rituxan® are to be administered in combination with MTX. Controlled trials have demonstrated the biologic RA drugs with concomitant MTX to be superior to MTX alone as measured by a greater proportion of subjects demonstrating improved signs and symptoms, improved physical function, and in most cases, inhibition of structural damage. The major concerns with the biologic RA therapies are the adverse events (e.g., infections, possible increased rate of lymphoma) and cost of therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Orencia is currently available in the US as a lyophilized powder in preservative-free, single-use vials. Each Orencia vial provides 250 mg of abatacept for IV administration, which is to be administered as a 30-minute intravenous infusion. The IV dosage is dependent on patient body weight as follows:

- <60 kg: Orencia 500 mg
- 60 kg-100 kg: Orencia 750 mg
- >100 kg: Orencia 1000 mg

Abatacept is approved for the treatment of adults with RA and children with JIA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were adequate. The amount of missing data was small and did not interfere with reaching conclusions on the safety and efficacy of the product. Issues regarding data quality and integrity of the studies are described below.

An error in the analyses dataset regarding stratification classification by baseline body weight (<60 kg, 60 to 100 kg, and >100 kg) was identified for Study IM101174 after finalization of the sponsor's initial report; however, the stratified randomization for the study was conducted correctly. These corrected datasets resulted in revised efficacy, safety and PK analyses. Additionally, the sponsor identified a non-compliance issue regarding Good Clinical Practice (GCP) regulations for Study IM101174 Site 229 in (b) (4) resulting in the exclusion of all eight subjects from the study site from the efficacy analyses. Overall, these revisions had a minimal impact on the overall conclusions of Study IM1010174.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with the ethical principles in the Declaration of Helsinki and Good Clinical Practice. The studies were conducted in compliance with the prespecified protocols. Informed consent, protocol amendments, and administrative letters for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

3.3 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry. There were 2 investigators identified with potential conflict of interest.

(b) (6) owns 2500 shares of Bristol-Myers Squibb stock valued at $63,000, however, it is unlikely that his participation in Study IM101174 adversely impacted the outcome of the study given that (b) (6) study site enrolled (b) (4) subjects out of the total 1464. Potential for bias was further minimized by using a randomized, double-blind, placebo-controlled study design.

(b) (6) received in excess of $25,000 for speaking and consulting engagements in both 2007 and 2008. (b) (6) was a principle investigator at (b) (6) for Study IM101174 and IM101185. For Study IM101174, (b) (6) site enrolled (b) (6) subjects out

total of 1464 and given that the study was randomized, double-blind, and placebo-controlled it is unlikely that the results biased the outcome of the study. (b) (6) participation in Study IM101185 is also unlikely to affect the overall conclusions drawn from the study, and submission as a whole, as Study IM101185 was designed as a safety study assessing the safety and tolerability of switching subjects from long-term IV abatacept to SC abatacept.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There were no significant efficacy or safety issues related to other review disciplines for the current submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. Table of Clinical Studies

Study #:	Trial Design	Treatment Arms	Subjects (n) Entered/Completed	Efficacy Endpoints
		Efficacy Trials		
IM101174: Non-inferiority Study	**ST:** 6-month, DB, DD, PC, MC, NI study comparing SC and IV ABA in RA subjects with an inadequate response to MTX **LT:** MC, OLE	**ST:** SC ABA: ABA 125 mg SC Qwk with initial IV loading dose on Day 1 then PBO IV Days 15, 29, then Q28d IV ABA: IV dosing on Days 1, 15, 29, then Q28d. PBO SC Qwk **LT:** ABA 125 mg SC Qwk	**ST:** SC ABA: 736/693 IV ABA: 721/676 **LT:** 1357/1301 (ongoing)	**Primary:** ACR 20 @ 6-months **Secondary:** ACR 50, ACR 70, HAQ response
		Safety Trials		
IM101167 A 3-Period Withdrawal/Restart Immunogenicity and Safety Study	**ST:** Period 1: 12-wk, OL Induction Period Period 2: DB, R, PC, withdrawal in responders Period 3: 12-wk, OL, reintroduction **LT:** MC, OLE	**ST:** Period 1: ABA 125 mg SC Qwk with initial IV loading dose Period 2: ABA: ABA 125 mg SC Qwk PBO: PBO SC Qwk Period 3: Period 2 SC ABA continued with 125 mg SC Period 2 SC PBO changed to ABA 125 mg SC Qwk with initial IV loading dose or ABA 135 mg SC only **LT:** ABA 125 mg SC Qwk	**ST:** Period 1: 167/157 Period 2: ABA: 40/40 PBO: 80/79 Period 3: Period 2 ABA: 40/40 Period 2 PBO: -SC and IV ABA: 35/35 -SC and IV PBO: 44/42 **LT:** 150/138 (ongoing)	**Primary:** DAS28
IM101173 Monotherapy Immunogenicity and Safety Study	**ST:** 16-week, MC OL study **LT:** MC, OLE	**ST:** Monotherapy: PBO + ABA 125 mg SC Qwk (no IV loading dose) Concomitant Therapy: MTX + ABA 125 mg SC Qwk (no IV loading dose) **LT:** ABA 125 mg SC Qwk	**ST:** SC ABA: 51/50 IV ABA: 49/46 **LT:** 90/75 (ongoing)	**Primary:** DAS28
IM101185 IV to SC Switching Immunogenicity and Safety Study	**ST:** 12-month, MC OL study assessing switch from long-term IV abatacept to SC **LT:** MC, OLE	**ST:** Subjects on long-term IV ABA changed to ABA 125 mg SC Qwk **LT:** ABA 125 mg SC Qwk	**ST:** SC ABA: 123/120 **LT:** 123/112 (ongoing)	**Primary:** DAS28

DB: double-blind; DD: double-dummy; PC: placebo-controlled; MC: multicenter; NI: non-inferiority; SC: subcutaneous; IV: intravenous; RA: rheumatoid arthritis; ABA: abatacept; PBO: placebo; MTX: methotrexate; ST: Short-Term Period; LT: Long-Term Period OL: open-label; OLE: open-label extension.

5.2 Review Strategy

The primary focus of the current review is Study IM101174, a large, non-inferiority trial designed to demonstrate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with MTX. The trial was well designed and used a stringent non-inferiority margin that preserved 70% of the treatment effect size of the IV formulation. Overall, Study IM101174 was adequately powered and had an appropriate primary endpoint from which conclusions could be drawn allowing the data from this study to be considered adequate to assess the sponsor's proposed indications and claims. Consequently, the efficacy data submitted for Studies IM101167, IM10173, and IM101185, which were primarily designed to assess the safety and immunogenicity of SC abatacept, will not be reviewed to further support Study IM101174 as the efficacy endpoints were secondary and not statistically powered to assess the non-inferiority of SC abatacept compared to the IV formulation.

The safety review is largely based on the comparative data from the short-term period of Study IM101174, which allows for the comparison of safety data between the SC and IV formulations of abatacept. Additional data is derived from Studies IM101167, IM10173, and IM101185 that were conducted with the primary objective of assessing the safety and immunogenicity of SC abatacept. Together, these 4 studies provided an adequate amount of drug exposure for evaluation of the safety of abatacept in adult subjects with RA.

The SC formulation of abatacept is a fixed-dose of 125 mg weekly, and although the overall systemic exposure is lower than the IV dosing, serum trough concentrations vary with body weight. For example, subjects with body weights <60 kg achieve almost twice the trough concentration of abatacept as do subjects weighing >100 kg. Consequently, to assess the potential for differences in safety and efficacy of SC abatacept across the subject population, additional subgroup analyses were performed using the same body weight tiers as those employed in the approved IV dosing recommendations, namely subjects weighing <60 kg, 60-100 kg, and >100 kg.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study IM101174 (Efficacy Trial)

Study IM101174 is the principal clinical trial providing efficacy data for the current submission. The study was a 6-month, randomized, double-blind, placebo-controlled, double-dummy study designed to evaluate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with MTX (Figure 1).

Figure 1. Study IM101174 Design Overview

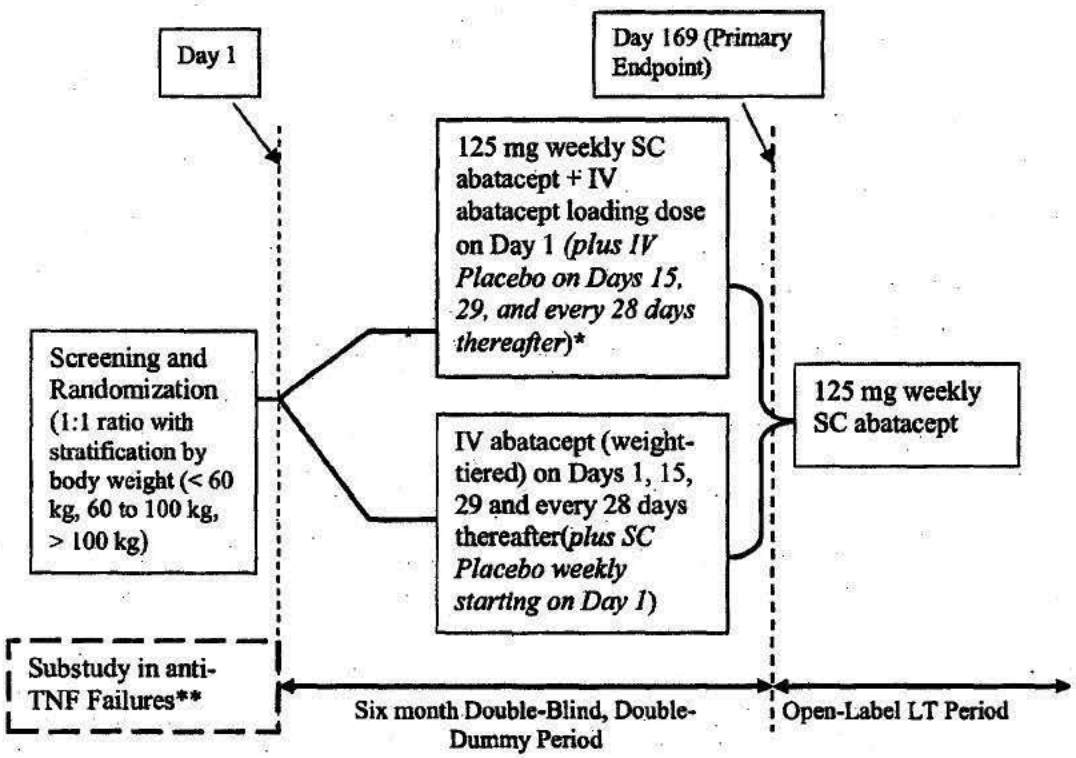

*Figure adapted from sponsor's submission.

The double-blind period of the study (Study Days 1 through 169) is referred to in this review as the short-term (ST) period and the subsequent open-label extension period starting from Day 170 as the long-term (LT) period. The study was conducted at 242 sites worldwide, of which 82 sites were in the US, 69 sites in Europe, 34 sites in South America, 13 sites in Canada, 13 sites in Mexico, 7 sites in India, 7 sites in South Africa, 6 sites in Australia, 6 sites in Taiwan, and 5 sites in South Korea.

All subjects were required to meet the following inclusion criteria at screening:

- Diagnosis of RA (1987 ACR criteria) >1 year
- RA functional classes I, II, or III
- Treated with MTX (≥15 mg weekly) ≥3 months and at stable doses for ≥28 days prior to study treatment.
- Discontinuation of all DMARDs except MTX ≥4 weeks prior to study treatment
  - Discontinuation of leflunomide ≥4 weeks prior to enrollment
  - Stable doses of oral corticosteroids (≤10 mg prednisone daily or equivalent) and NSAIDs ≥28 days prior to study treatment
- Active disease despite current DMARD therapy
  - MTX Monotherapy

- ≥10 swollen joints (66 joint count)
- ≥12 tender joints (68 joint count)
- CRP ≥0.8 mg/dL

- After washout and stabilization of DMARDS and at randomization (Day 1)
  - ≥10 swollen joints
  - ≥12 tender joints
  - CRP ≥0.8 mg/dL

Major exclusion criteria included:

- Women of child bearing potential who were unwilling or unable to use an acceptable method to avoid pregnancy for the entire study duration and 10 week thereafter
- Women who were pregnant or breastfeeding
- Subjects with active major medical illness or impairment
- Subjects with history of malignancy other than non-melanoma skin cancer within the previous 5 years
- Subjects with active or history of recurrent infection(s) including HAV, HBV, HCV, HIV, TB
- Subjects with HgB ,8.5 g/dL, WBC <3,000/mm^3, Platelets < 100,00/mm^3, Scr > 2x ULN, ALT or AST >2x ULN
- Subjects could not have received treatment with rituximab or prior exposure to abatacept
- Subjects currently, or ≤3 months, receiving treatment with azathioprine, gold, leflunomide, immunoadsorption columns, mycophenylate mofetil, cyclosporine A or other calcineurin inhibitors, or D-Penicillamine.
- Subjects who had received discontinued treatment with a TNF antagonist due to lack of efficacy
- Subjects exposed to ≥2 or more TNF antagonist therapies
- Subjects treated with anakinra at the time of enrollment unless they underwent a 4 week washout period

Subjects meeting these criteria were randomized 1:1 with stratification by body weight based on the weight tiers used for the approved IV abatacept dosing, (i.e., <60 kg, 60 to 100 kg, >100 kg) to receive one of the following treatments:

- Subcutaneous Abatacept Treatment Arm
  - On Day 1 of the Study, subjects received an IV loading dose of abatacept based on the approved dosing regimen and abatacept 125 mg SC. For the remainder of the study, subjects randomized to this treatment arm received weekly, self-administered abatacept 125 mg SC injections and placebo IV infusions on Days 15, 29, and every 28 days thereafter.

Subcutaneous abatacept injections, and matching placebo, were ready-to-use liquid products provided in glass syringes for SC administration.

- Intravenous Abatacept Treatment Arm
  - On Day 1 of the Study, subjects received an initial IV dose of abatacept (based on the approved dosing regimen) and a placebo SC injection. These subjects received IV abatacept infusions on Days 15, 29, and every 28 days thereafter and weekly SC doses of placebo for the 6-month double-blind period.

All subjects continued to be treated with their entry-level dose of MTX and concomitant folate supplementation throughout the double-blind period of the trial. At the end of the 6-month period all eligible subjects who enrolled into the long-term period received open-label abatacept 125 mg SC weekly without additional IV abatacept infusions.

Based on the FDA guidance document and regulatory advice from our Division, Study IM101174 was designed to demonstrate non-inferiority of SC abatacept compared to IV abatacept by showing that the SC formulation preserves at least 70% of the treatment effect size observed with the IV formulation using the proportion of subjects achieving an ACR 20 at 6 months as the primary endpoint. Previous placebo-controlled studies with IV abatacept have demonstrated the effect size in ACR 20 response at 6 months to be between 25.6% and 28.2%. Therefore, 25% constituted the minimum expected benefit of IV abatacept over placebo. The non-inferiority margin that leads to 70% preservation of the minimum effect of abatacept IV is 7.5%. The point estimate of the maximum difference between the ACR 20 response of the two formulations would then be -2.1% (-7.5%, 3.2%). The major secondary endpoints, ACR 50, ACR 70, and HAQ response were assessed in a manner similar to the primary endpoint.

Sample size calculations determined that 685 subjects in each treatment arm (1370 subjects total) would yield a power of 80% to conclude that the ACR 20 response from SC-treated subjects was not inferior to IV-treated subjects at 0.025 significant level, which is equivalent to the lower limit of a 2-sided 95% CI of the difference in ACR 20 response rates greater or equal to the non-inferiority margin of -7.5%.

5.3.2 Study IM101167 (Safety Trial)

Study IM101167 was a 9-month, multicenter, randomized, double-blind, withdrawal study designed to evaluate the effect on immunogenicity and safety of interruption and reintroduction of SC abatacept, with or without an IV loading dose, in subjects with active RA who have had an initial clinical response to SC abatacept. Major inclusion criteria included subjects ≥18 years of age, fulfillment of the 1987 ARA diagnostic criteria for RA, and a DAS28-CRP score ≥3.2 to ≤5.1 despite receiving stable doses of MTX ≥10 mg weekly for ≥3 months. The trial was organized in three, 12-week periods:

- Period 1: this period served as an open-label run-in period designed to induce a clinical response in subjects with SC abatacept. All subjects received a single loading dose of IV abatacept based on the approved dosing regimen and abatacept 125 mg SC. For the remainder of Period 1, subjects received weekly self-administered abatacept 125 mg SC injections through Day 85. Clinical response was assessed on Day 78 and was defined as a decrease of ≥0.6 points from baseline in their DAS28-CRP score. Subjects classified as responders were entered into Period 2, while non-responders were entered into the open-label extension portion of the trial.

- Period 2: responders from Period 1 were randomized 2:1 to receive either placebo SC or abatacept 125 mg SC. Subjects who experienced a flare in their disease during this period could receive symptomatic treatment, e.g., NSAIDS and/or two high doses of corticosteroids. Subjects whose RA symptoms persisted or worsened could proceed to Period 3 provided that they met 2 or more of the following criteria:

    - Doubling of tender or swollen joint counts from Day 78 assessment
    - Increased DAS-CRP score ≥1.2 from Day 78 assessment
    - Investigator's clinical judgment after discussion with Medical Monitors

- Period 3: At the start of Period 3, all subjects entering from Period 2 received a single double-blind IV loading dose of abatacept or placebo. Subjects who were assigned to the SC abatacept-treatment arm in Period 2 received a single placebo IV loading dose prior to continuing open-label SC abatacept. Subjects assigned to the SC placebo-treatment arm in Period 2 were randomized 1:1 to receive a single IV loading dose of abatacept or placebo prior to restarting open-label abatacept. Weekly, self-administered open-label SC abatacept injections continued through Day 253.

Eligible subjects completing Period 3 could enter the open-label, long-term extension study where they continued to receive abatacept 125 mg SC weekly. Period 1 non-responders who directly enrolled into the long-term portion of this study continued to

receive weekly SC abatacept; however, if a clinical response was not achieved at the end of 12-weeks, the subject was discontinued from the study. Figure 2 illustrates the clinical trial design of Study IM101167.

Figure 2. Study IM101167 Design Overview

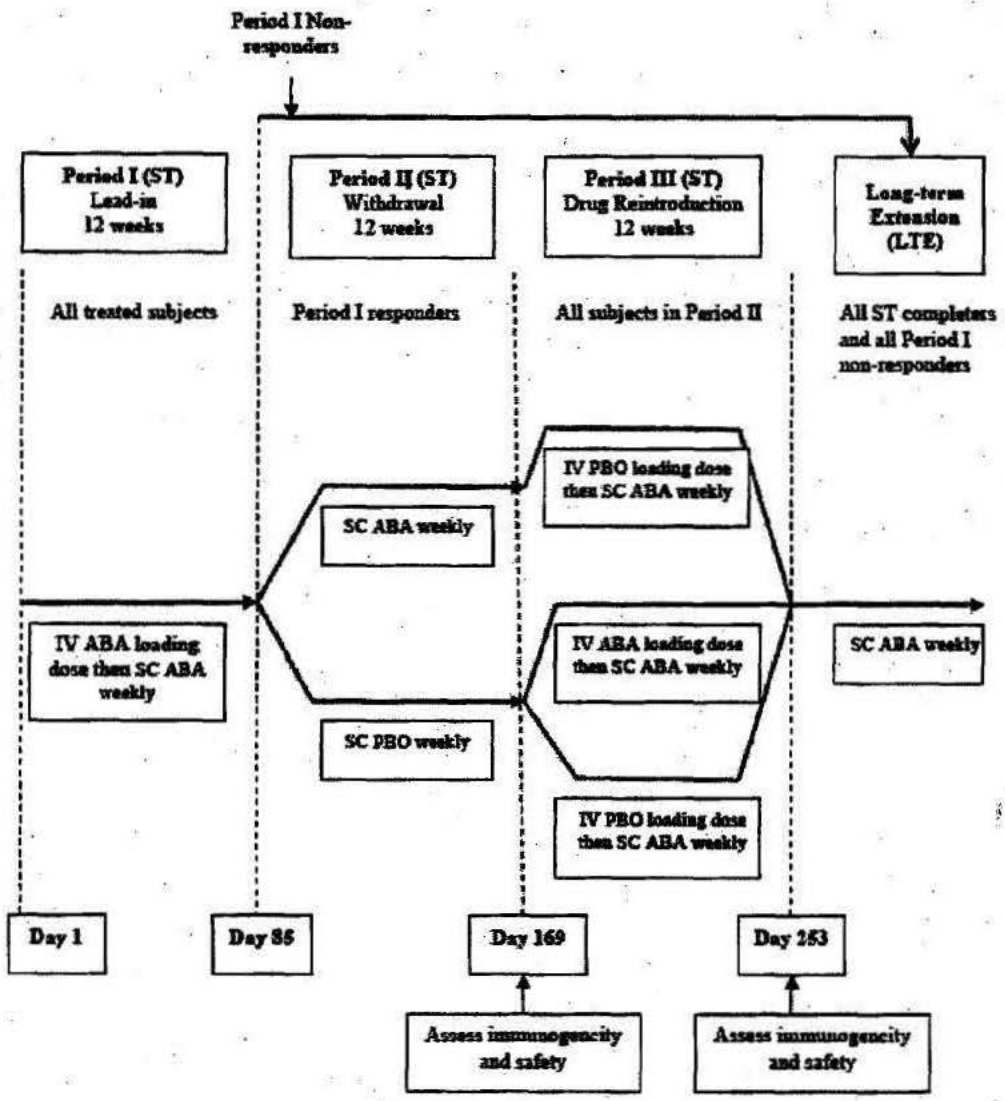

*Figure adapted from sponsor's submission.

The primary objective of Study IM101167 was to assess the safety and immunogenicity in subjects with RA, who after having achieved a clinical response to SC abatacept, had the drug withdrawn for 12-weeks and restarted either with or without an IV loading dose.

A major secondary objective was to assess RA disease activity in subjects at the different time periods using DAS28-CRP scores.

Statistical testing was provided for immunogenicity using the ITT population. All CI were 2-sided, 95%. Within-group CI's provided for proportions were based on normal approximation and within-group CI's provided for mean changes were based on t-distribution. Between-group CI's provided for proportions were based on normal approximation with continuity correction. Since efficacy endpoints were secondary in this study, analyses were performed based on as-observed data. Within-group 95% CI's were provided for each efficacy endpoint at each time point of the analysis. No between-group CI's were provided for any of the efficacy endpoints.

Study IM101167 enrolled 120 subjects who were very similar in baseline demographics and disease characteristics as those of Study IM101174. Treatment arms were similarly balanced and the majority of subjects were white and female with a mean age of 49 years and a mean DAS28-CRP score at baseline of 4.8 units. The subject population of Study IM101167 as a whole was representative of the US population of patients with RA.

5.3.3 Study IM101173 (Safety Trial)

Study IM101173 was a 4-month, open-label, multicenter trial designed to assess the immunogenicity of SC abatacept with or without concomitant MTX and absent of an IV loading dose of abatacept. Major inclusion criteria included subjects ≥18 years of age, fulfillment of the 1987 ARA diagnostic criteria for RA, a Subject Global Assessment VAS score >20 mm, and requiring a new therapeutic treatment for their RA disease. Adults meeting the entry criteria were randomized and stratified 1:1 into 2 treatment arms based on their current use of MTX. Subjects not receiving MTX were either MTX-naïve or had discontinued MTX ≥4 weeks prior to Study Day 1 due to lack of efficacy or tolerability. Subjects receiving MTX were to be on a stable dose of ≥10 mg weekly for ≥1 month prior to Study Day 1 and maintain this dose of MTX throughout the 4-month period. All subjects received weekly, self-administered abatacept 125 mg SC. At the completion of the 4-month open-label period, subjects were eligible to continue in the open-label, long-term extension period.

Figure 3 illustrates the clinical trial design of Study IM101167.

Figure 3. Study IM101173 Design Overview

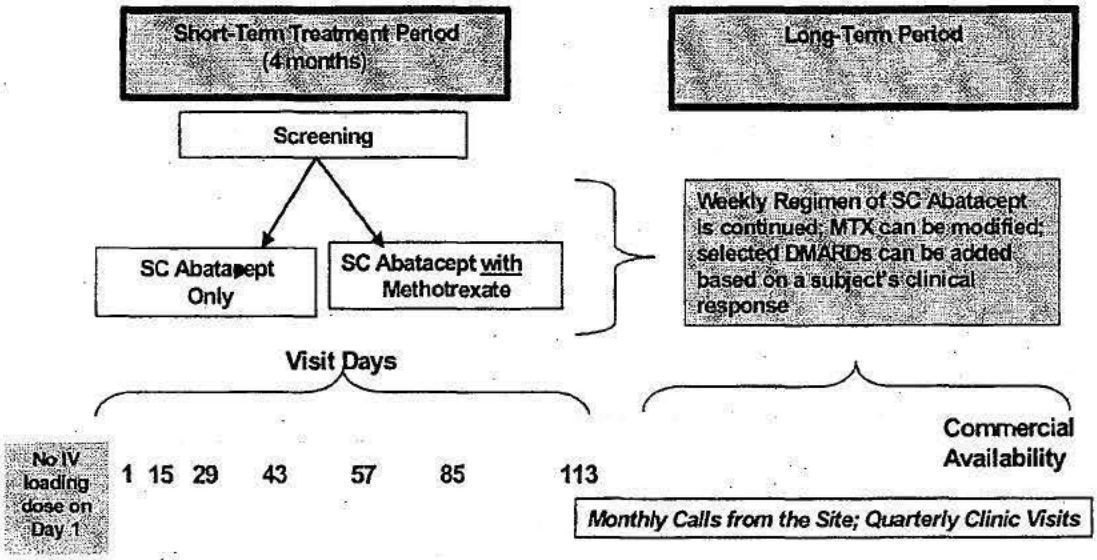

*Figure adapted from sponsor's submission.

The primary endpoint of Study IM101173 evaluated the immunogenicity of SC abatacept, as either monotherapy or with concomitant MTX, by assessing the proportion of subjects with positive antibody (anti-abatacept and anti-CTLA4-T) response at the end of 4-months (Day 113) using the sponsor's validate ELISA. A continuity-corrected Chi-square test was used to compare the immunogenicity rate of the 2 cohorts at 4-months using a 2-sided 5% significance level. Major secondary endpoints evaluated efficacy as the mean change from baseline in DAS28-CRP score, HAQ-DI score, and the proportion of subjects with ≥1.2 unit reduction from baseline in DAS28-CRP at 4-months.

Study IM101173 enrolled 100 subjects who were very similar in baseline demographics and disease characteristics as those of Study IM101174. Treatment arms were similarly balanced and the majority of subjects were white and female with a mean age of 54 years. The subject population of Study IM101173 as a whole was representative of the US population of patients with RA.

5.3.4 Study IM101185 (Safety Trial)

Study IM101185 was a 12-month, multicenter, open-label, single treatment arm study evaluating the safety of abatacept in 123 subjects switching from IV to SC abatacept therapy. The study enrolled subjects with RA who were participating in open-label long-term extension trials of studies from the core IV abatacept program in RA. The subjects initially enrolled in the IV studies had an inadequate response to MTX and/or TNF antagonists and had received ≥4 years of treatment with IV abatacept. For Study IM101185, subjects had up to 4 weeks to complete their Day 1 visit following completion of their previous IV abatacept infusion. Stable doses of concomitant DMARDs, corticosteroids, and NSAIDs were continued through Day 85, after which, adjustments were permitted based on the individual subjects needs.

Formal statistical testing was not performed on any data. Descriptive statistics were used for analyses of safety, PK/PD, and efficacy.

Study IM101185 enrolled 123 subjects who were very similar in baseline demographics and disease characteristics as those of Study IM101174. Treatment arms were similarly balanced and the majority of subjects were white and female with a mean age of 54 years. The subject population of Study IM101185 as a whole was representative of the US population of patients with RA.

6 Review of Efficacy

Efficacy Summary

The primary efficacy data derives from Study IM101174, a large, non-inferiority trial designed to demonstrate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with MTX. The trial was well designed and used a strict non-inferiority margin that preserved 70% of the treatment effect size of the IV formulation. Review of the data demonstrated that the study met the prespecified primary endpoint with an estimated difference between the two treatment arms, assessed by the proportion of subjects achieving an ACR 20 at Day 169, of 0.3% (95% CI: -4, 5). These data were further supported by sensitivity analyses and major secondary endpoints.

Although use of the ACR 20 may lack sensitivity in certain applications, its use as primary endpoint in the current study was adequate given that the same drug product is used in both the SC and IV formulations and that a known effect size of abatacept compared to placebo has been previously established allowing for proper statistical testing to be performed. Overall, Study IM101174 was well designed and conducted as prespecified in the sponsor's protocol.

According to my review of the clinical data as a whole, I recommend approval of the SC abatacept formulation for the treatment of patients with moderately to severely active RA. Approval of the SC formulation of abatacept will provide an alternative route of administration for patients who may be unable to commit to monthly IV infusions with the currently marketed product.

6.1 Indication

The proposed indication for SC abatacept is identical to that in the current approved label for IV abatacept (ORENCIA) for RA:

- *ORENCIA® 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. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.*

  ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy, such as anakinra.

6.1.1 Methods

Refer to Section 5.3 for discussion of the Study IM101174 trial design.

6.1.2 Demographics

The baseline subject demographics for Study IM101174 were similar across both treatment arms and are shown in Table 2. The majority of subjects were white and female with a mean age of 50 years and a mean weight of 72 kg. The subject population as a whole was representative of the US population of patients with RA.

Table 2. Study IM101174 Baseline Demographics

	ABATACEPT SC N=696	ABATACEPT IV N=683
Age (years); mean ± SD	50±13	50±13
Weight (kg); mean ± SD	72±18	72±18
Weight Category, n(%)		
<60 kg	176 (25)	158 (23)
60-100 kg	464 (67)	475 (68)
>100 kg	56 (8)	50 (7)
Gender, n(%)		
Female	586 (84)	549 (80)
Male	110 (16)	134 (20)
Race, n(%)		
White	516 (74)	505 (74)
Asian	63 (9)	72 (11)
Black	26 (4)	24 (4)
American Indian	5 (1)	1 (<1)
Other	86 (12)	81 (12)
Region, n(%)		
North America	129 (19)	111 (16)
South America	338 (49)	340 (50)
Europe	123 (18)	123 (18)
ROW	106 (15)	109 (16)

The baseline disease characteristics of the study subjects are shown in

Table 3. Subjects had active RA despite receiving an average of 16 mg of MTX weekly as demonstrated by the number of swollen joints (~21), tender joints (~30), CRP (~2.7 mg/dL), and DAS-28 score (~6.3 units). The mean duration of RA was approximately 8 years. Overall, the treatment arms were balanced.

Table 3. Study IM101174 Baseline Disease Characteristics

	ABATACEPT SC N=696	ABATACEPT IV N=683
Duration of Disease (yr); n	696	683
mean ± SD	8±8	8±8
Duratiion of Disease Categorty		
≤2 years	229 (33)	206 (30)
2-≤5 years	144 (21)	145 (21)
5-≤10 years	134 (19)	155 (23)
>10 years	189 (27)	177 (26)
Tender Joint Count, n	695	683
mean ± SD	30±14	30±13
Swollen Joint Count, n	695	683
mean ± SD	21±9	20±9
Subject Pain Assessment (VAS 100), n	696	683
mean ± SD	68±20	67±21
Physical Function (HAQ-DI), n	696	683
mean ± SD	1.7±0.7	1.7±0.7
Subject Global Assessment (VAS 100), n	696	683
mean ± SD	67±20	65±20
Physician Global Assessment (VAS 100), n	696	683
mean ± SD	64±17	63±16
hsCRP (mg/dL), n	694	683
mean ± SD	2.7±3	2.7±3
DAS-28, n	693	683
mean ± SD	6.3±0.8	6.2±0.8
(+) RF Status, n (%)	582 (85)	583 (87)
MTX dose (mg Qwk), n	696	683
mean ± SD	16±4	17±4

Similar proportions of subjects in both treatment arms were receiving concomitant MTX, corticosteroids, and/or NSAIDS as shown in (Table 4). All subjects were receiving MTX and approximately 80% of subjects were receiving concomitant NSAIDs and a mean dose of 5 mg/day of prednisone.

Table 4. Study IM101174 Concomitant Drugs at Baseline

	ABATACEPT SC N=696	ABATACEPT IV N=683
Corticosteroids, n (%)	496 (71)	507 (74)
Oral dose, mean ± SD	5±4	5±7
NSAIDS	562 (81)	544 (80)
DMARDS		
MTX	696 (100)	683 (100)
CsA	1 (<1)	1 (<1)
HCQ	0	2 (<1)
CQ	0	1 (<1)
SSZ	0	1 (<1)

6.1.3 Subject Disposition

A total of 2472 subjects were enrolled with 1464 subjects being randomized and 1457 subjects receiving study drug in Study IM101174 (Figure 4). The most frequent reason for not being randomized was subjects no longer meeting study entry criteria. A total of 7 subjects were randomized but no treated as a result of 4 subjects no longer fulfilling study criteria, 2 subjects withdrew consent, and 1 subject was randomized in error.

Figure 4. Study IM101174 Subject Disposition

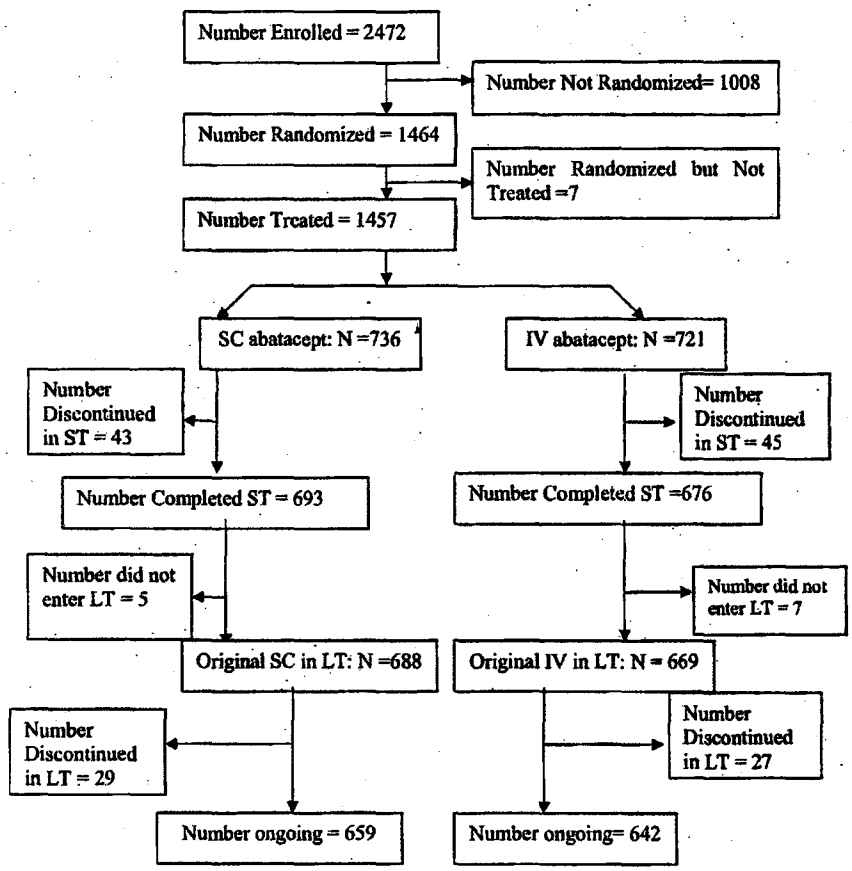

*Figure adapted from sponsor's submission.

Similar proportions of subjects in both treatment arms (94%) completed the study through Study Day 169 (Table 5). Adverse events were the most common reason for discontinuation from the study in both groups.

Table 5. Study IM101174 Reasons for Discontinuation from Study during Short-Term Period

	ABATACEPT SC N=736	ABATACEPT IV N=721
Subjects Discontinued; n (%)	43 (6)	45 (6)
Reason for Discontinuation; n (%)		
Adverse Event	17 (3)	25 (4)
Withdrawal of Consent	11 (2)	5 (1)
Lost to Follow-up	0	6 (1)
Administrative Reasons	1 (<1)	0
Death	1 (<1)	1 (<1)
Not Meeting Study Criteria	2 (<1)	1 (<1)
Lack of Efficacy	6 (1)	1 (<1)
Non-Compliance	3 (<1)	0
Other	2 (<1)	6 (1)
Subjects Completing Period; n (%)	693 (94)	676 (94)

A similar proportion of subjects in both treatment arms (96%) remained participating in the study at the time the database was locked (Table 6). Lack of Efficacy was the most common reason cited for discontinuation from the study during this period in both treatment arms.

Table 6. Study IM101174 Reasons for Discontinuation from Study During Long-Term Period

	ABATACEPT SC N=688	ABATACEPT IV N=669
Subjects Discontinued; n (%)	29 (4)	27 (4)
Reason for Discontinuation; n (%)		
Adverse Event	6 (1)	7 (1)
Withdrawal of Consent	2 (<1)	5 (1)
Lost to Follow-up	1 (<1)	3 (<1)
Death	3 (<1)	1 (<1)
Lack of Efficacy	13 (2)	10 (2)
Non-Compliance	1 (<1)	0
Other	3 (<1)	1 (<1)
Subjects Completing Period; n (%)	659 (96)	642 (96)

On the whole, relatively few subjects discontinued the study and the number of subjects, and reasons for discontinuation, were similar between treatment arms. The number of discontinuations is not expected to affect the interpretation of the results of the study.

6.1.3.1 Protocol Violations

During the 6-month short-term period of Study IM101174 a total of 78 subjects were identified who had met ≥1 protocol deviation criteria

- 40 (5%) subjects randomized to the ABA-SC treatment arm reported ≥1 protocol deviation (note some subjects may have had >1 protocol deviation):
  - 14 subjects had a CRP that was <0.5 mg/dL at their screening visit
  - 10 subjects received an intra-articular/intra-muscular/intravenous injection of corticosteroid or high-dose oral corticosteroids within 28 days of the final assessments for disease activity
  - 6 subjects did not meet the required number of swollen and/or tender joints
  - 5 subjects had been treated with ≥2 TNF inhibitors prior to enrollment
  - 4 subjects had an increase of ≥ 5mg/week above baseline weekly dose at Day 169
  - 2 subjects were enrolled with an ACR Functional Class IV
  - 1 subject received a prohibited non-biologic DMARD between Study Days 1 to 169
  - 1 subject received > 2 intra-articular injections between Study Days 1 to 169
  - 1 subject missed ≥2 IV doses of abatacept between Study Days 1 to 169

- 38 (5%) subjects randomized to the ABA-IV treatment arm (note some subjects may have had >1 protocol deviation):
  - 12 subjects received an intra-articular/intra-muscular/intravenous injection of corticosteroid or high-dose oral corticosteroids within 28 days of the final assessments for disease activity
  - 11 subjects did not meet the required number of swollen and/or tender joints
  - 5 subjects had a CRP that was <0.5 mg/dL at their screening visit
  - 5 subjects had been treated with ≥2 TNF inhibitors prior to enrollment
  - 3 subjects subject missed ≥5 consecutive SC doses of abatacept between Study Days 1 to 169
  - 2 subjects received inadequate washout for a biologic DMARD or leflunomide prior to Study Day 1
  - 1 subject received ≤5 mg MTX weekly for ≥ 1 week during the screening period prior to Study Day 1

- 1 subject had an increase of ≥ 5mg/week above baseline weekly dose at Day 169

The most common protocol deviation during this period of the trial, experienced by 22 subjects, was receiving an intra-articular/intra-muscular/intravenous injection of corticosteroid or high-dose oral corticosteroids within 28 days of the final assessments for disease activity at Day 78. The majority of these subjects were early discontinuations due to lack of efficacy. The next most common protocol deviation involved 19 subjects who's CRP was <0.5 mg/dL at their screening visit. This error likely occurred in part from confusion among investigators relating to the conversion of results to international standard units of mg/L from the sponsor's central laboratory. The third most common protocol deviation involved 17 subjects not meeting the required number of swollen and tender joints. Upon review of the case report forms, it appears that these subjects had a relatively high number of either swollen or tender joints but not the other and that the site investigators considered the subject to have sufficient disease activity to enter the study despite no meeting this specific eligibility criterion. Overall, the total number of subjects from each group with protocol violations was small and relatively balanced between treatments arms. Consequently, these subjects were included in all analyses and are not expected to adversely affect the conclusions drawn from the study.

6.1.3.2 Unblinding

There was an accidental unblinding of study drug during the double-blind period of the study for 2 subjects. Since there were 1457 subjects treated in the study, inclusion of these 2 subjects is not expected to adversely bias the outcome of the study.

6.1.3.3 Extent of Exposure and Treatment Compliance

Subjects in the SC abatacept treatment arm received on average 167±15 days of exposure to abatacept during the double-blind period of the study compared to 166±18 days for subjects receiving IV abatacept. Determination of treatment compliance was determined by the number of injections received compared to the number of injections expected during the double-blind period of the study. A total of 615/736 (84%) abatacept SC-treated subjects received all of the expected 24 SC injections, and 87/736 (12%) only missed a single injection. No subject missed more than 4 SC injections in this treatment arm. All abatacept SC-treated subjects received the loading IV infusion of abatacept on Day 1 and 700/736 (95%) did not miss a single IV placebo infusion. No subject in this treatment arm missed more than 2 IV placebo infusions during the double-blind period. A total of 688/721 (95%) abatacept IV-treated subjects did not miss a single IV abatacept infusion during the double-blind period and no subject missed >3 IV infusions. A total of 585/721 (81%) subjects in this treatment arm received all SC placebo injections and only 4 (<1%) subjects missed ≥5 SC injections.

Overall, the data demonstrate that subjects in both treatment arms received similar exposure to abatacept and that the majority of subjects were compliant with receiving study drug.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint of Study IM101174 was the comparison of the proportions of subjects achieving an ACR 20 response at Day 169. The SC abatacept formulation was prespecified to be non-inferior to IV abatacept formulation if the lower limit of a 2-sided 95% CI of the difference in ACR 20 response rates between the two treatment arms were greater than or equal to the non-inferiority margin of -7.5%, which was chosen to preserve ≥70% of the minimum effect observed with the IV abatacept when compared to placebo.

As shown in Table 7, the primary objective of Study IM101174 using the per-protocol population was met with the estimated difference between the two treatment arms, assessed by the proportion of subjects achieving an ACR 20 at Day 169, of 0.3% (95% CI: -4, 5). Seventy-six percent of subjects in both treatment arms achieved an ACR 20 at Day 169. As a measure of sensitivity, analysis of the data using the ITT population demonstrated similar results to the primary endpoint (Table 7). These analyses support that the SC abatacept formulation is non-inferior to the IV abatacept formulation.

Table 7. Study IM101174: ACR 20 Response at Day 169

	PER-PROTOCOL POPULATION		ITT POPULATION	
Efficacy Measure	ABATACEPT SC (n=696)	ABATACEPT IV (n=683)	ABATACEPT SC (n=736)	ABATACEPT IV (n=721)
ACR20				
N (%)	530 (76)	517 (76)	551 (75)	535 (74)
95% CI	(73, 79)	(73, 79)	(72, 78)	(71, 77)
Est. Diff (95% CI)	0.3 (-4, 5)	N/A	0.5 (-4, 5)	N/A

6.1.5 Analysis of Secondary Endpoints(s)

The proportion of subjects achieving an ACR 50, ACR 70, and HAQ Response were prespecified as the major secondary endpoints in the statistical analysis plan for Study IM101174 using the same non-inferiority margin as that for the primary endpoint. Consequently, for the purposes of this review, only the analyses of the ACR 50, ACR 70, and HAQ Response Rate will be reviewed as supportive evidence of the primary endpoint.

6.1.5.1 ACR 50 and ACR 70 Response Rates

The ACR 50 and ACR 70 responses at Day 169 were analyzed in a manner similar to the primary efficacy endpoint. As shown in Table 8, subjects treated with SC abatacept demonstrated ACR 50 and ACR 70 response rates of 50% and 26%, respectively, compared to abatacept IV-treated subjects 49% and 24%, respectively. Overall, these data support the conclusion that the SC formulation is non-inferior to the IV formulation of abatacept.

Table 8. Study IM101174: ACR 50 & ACR 70 Response at Day 169

ACR Response	ABATACEPT SC (n=733)	ABATACEPT IV (n=716)
ACR 50; n (%) (95% CI)	368 (50) (47, 54)	348 (49) (45, 52)
ACR 70; n (%) (95% CI)	189 (26) (23, 29)	173 (24) (21, 27)

6.1.5.2 HAQ Response Rate

Improvement in physical function was characterized by the HAQ response whereby a reduction of ≥0.3 units in HAQ score from baseline represents a clinically meaningful improvement. At Day 169, the HAQ response rates were similar between the SC abatacept group and the IV abatacept group, 70% and 65%, respectively (Table 9). These data further support the conclusion that the SC formulation is non-inferior to the IV formulation of abatacept.

Table 9. Study IM101174: HAQ Response at Day 169

HAQ Response	ABATACEPT SC (n=693)	ABATACEPT IV (n=678)
HAQ Response; n (%) (95% CI)	483 (70) (66, 73)	442 (65) (62, 69)

6.1.6 Other Endpoints

No other efficacy endpoints are discussed in this review.

6.1.7 Subpopulations

The fixed-dose SC abatacept formulation results in different serum trough concentrations of abatacept in patients of differing body weights. Consequently, additional analyses were performed to assess the proportion of subjects achieving an ACR 20 response at Day 169 based on the body weight tiers used for dosing IV abatacept, i.e., <60 kg, 60-100 kg, and >100 kg. As shown in Table 10, subjects in both treatment arms achieved similar ACR 20 response rates at each baseline weight tier.

The subgroup analysis was performed using the per-protocol population and were not powered to detect differences between the treatment groups but rather to determine consistency of results across the subpopulations. These data suggest that the SC abatacept formulation induces similar ACR 20 responses as IV abatacept at each weight tier analyzed and that there appears to be no apparent difference in efficacy due to the fixed-dosing of the SC formulation as compared to the IV formulation.

Table 10. Study IM101174: ACR 20 Response at Day 169 by Subject Body Weight Tier

	ACR20 RESPONSE	
Baseline Weight	**ABATACEPT SC (n=693)**	**ABATACEPT IV (n=678)**
<60 kg; n (%) (95% CI)	141/173 (82) (76, 87)	138/168 (82) (76, 88)
60-100 kg; n (%) (95% CI)	349/463 (75) (72, 79)	347/463 (75) (71, 79)
>100 kg; n (%) (95% CI)	37/57 (65) (53, 77)	29/47 (62) (48, 76)

Additional subgroup analyses of ACR 20 responses at day 169 were performed by age, gender, race, baseline weight quartiles, geographic location, duration of RA, use of previous TNF antagonist therapy, baseline DAS-28, and RF status was performed using descriptive statistics and no imbalances were identified (data not shown).

7 Review of Safety

Safety Summary

The safety review is largely based on the comparative data from the short-term period of Study IM101174, which allows for the comparison of safety data between the SC and IV formulations of abatacept. Additional data is derived from Studies IM101167, IM10173, and IM101185 that were conducted with the primary objective of assessing the safety and immunogenicity of SC abatacept. Together, these 4 studies provided an adequate amount of drug exposure for evaluation of the safety of abatacept in adult subjects with RA.

Based on my review of the data, the overall safety of the SC formulation of abatacept is similar to the currently approved IV formulation. No new safety signals were identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The subject pool for the safety analyses is largely derived from the four Phase 3 efficacy, safety, and immunogenicity studies (IM1011174, IM101167, IM101173, IM101185) outlined in Section 5.1, and to a lesser extent, a single clinical pharmacology trial IM1011063 (

Figure 5). The double-blind period of Study IM101174 provides data directly comparing the safety data between the SC and IV formulations of abatacept and pooled data from the Phase 3 studies were used for the cumulative assessment of the SC formulation. Cumulative incidence rates per 100 patient-years from these data were compared with the cumulative incidence rates per 100 patient-years of the established IV abatacept database, which is based on data of up to 9 years of continued abatacept exposure. Lastly, the safety profile of SC abatacept was also assessed under clinical scenarios that could potentially increase the development of immunogenicity, e.g., no IV loading dose, monotherapy without concomitant MTX, prolonged withdrawal of SC therapy and subsequent restarting, and switching from IV to SC formulation).

Figure 5. Clinical Studies Contributing to the Subject Safety Pool

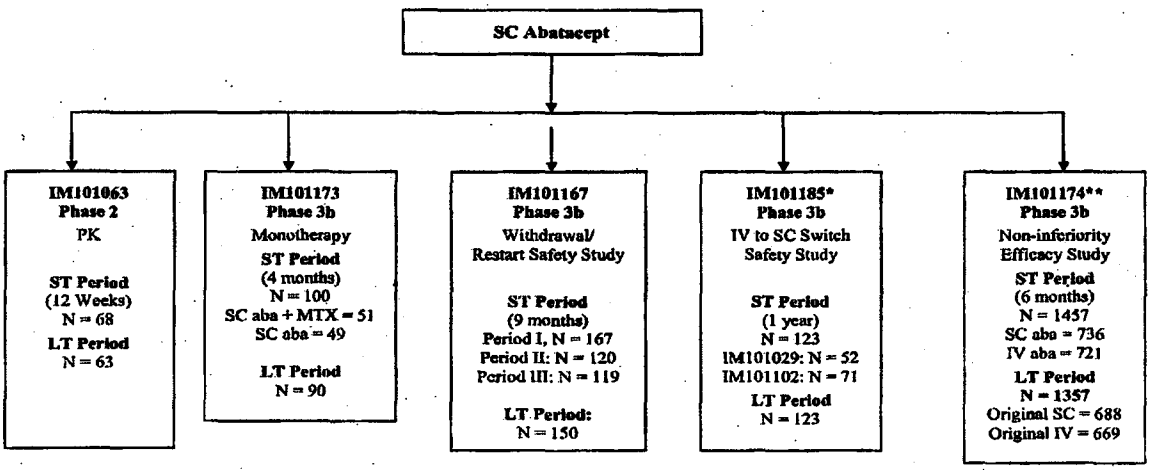

*Figure adapted from sponsor's submission.

7.1.2 Categorization of Adverse Events

All safety evaluations were conducted and reported according to Good Clinical Practice guidelines with data collected for AEs, clinical laboratory test results, and vital signs. Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries and pre-defined lists of preferred terms (PTs) were developed by the sponsor and used to analyze the data for safety events.

Adverse events were included in the safety analysis if the onset date was on or after the first dose start date of a specified period, and up to the 56 days post the last dose in a specified period, or up to the first dose date in the next period. Subject listings included all AEs, even those that occurred more than 56 days after the last dose of study medication.

All AEs were coded and grouped into PTs by system organ class (SOC), using the most current version of the MedDRA (MedDRA 12.1). Unless specified otherwise, listings and summaries were based on SOCs and PTs using the primary path.

Adverse event frequency summaries were based on proportions represented by the number of subjects with AEs divided by the total number of subjects in the population. Incidence rates per 100 p-y and associated 95% Poisson confidence intervals were calculated for the cumulative SC period. The numerator was the number of subjects with an event occurrence; the denominator was the overall total exposure.

7.2 Adequacy of Safety Assessments

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

The Phase 3 studies that comprise the majority of the safety data enrolled subjects with RA who had comparable baseline demographics and disease characteristics to those of the targeted patient population in the US. Additionally, each of the studies utilized abatacept 125 mg SC weekly, which is the proposed marketed dose. Overall, these studies provide adequate data in regards to drug exposure in the targeted patient population to support the safety of SC abatacept.

7.2.2 Explorations for Dose Response

The sponsor utilized abatacept 125 mg SC weekly for all Phase 3 trials and did not conduct a dose-ranging study. However, because the SC formulation is a fixed-dose product, additional subgroup analyses were performed to assess the safety of SC abatacept in subjects based on body weight utilizing the weight-tiers used for the approved IV formulation, i.e., <60 kg, 60-100 kg, and >100kg.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of 15 deaths reported during all periods of the submitted studies; 6 subjects died during the short-term period of Study IM101174 (Table 11) and 9 subjects died during the open-label, long-term extension periods from Studies IM101063, IM101167, and IM101174 (Table 12).

Comparative data between the SC and IV formulations during the short-term period of Study IM101174 demonstrated that 5 deaths occurred in subjects treated with the IV formulation compared to 1 subject treated with the SC formulation (Table 11). Three of the deaths appeared to be related to known abatacept-associated toxicities, namely serious infection and the remaining three were due cardiovascular events (subarachnoid hemorrhage and bowel infarction) or malignancy. Overall, there does not appear to be a new safety signal in regards to death associated with the SC formulation.

Table 11. Deaths Occurring During the Short-Term Period of Study IM101174

Study Subject # (age/sex)	Abatacept Treatment	Cause of Death/Narrative	Death Study Day
IM101174-113-563 (76/F)	IV	On Study Day 30 the subject developed Grade II urinary tract infection treated with antibiotics. Study Day 42 developed Grade IV pneumonia that progressed to sepsis, multisystem organ failure and death on Study Day (b) (6)	(b) (6)
IM101174-126-766 (51/F)	IV	On Study Day 15 the subject experienced a subarachnoid hemorrhage and ischemic cerebral vascular accident. Subject died on Study Day (b) (6)	
IM101174-206-652 (64/F)	IV	On Study Day 170 the subject was hospitalized for abdominal pain, distention, vomiting, and fever. She was diagnosed with adenocarcinoma of the gallbladder with metastasis. Subject died on Study Day (b) (6)	
IM101174-215-252 (49/M)	IV	On Study Day 27 the subject presented with non-productive cough and shortness of breath for which she received treatment with an oral antibiotic. On Study Day 19 the subject was admitted to the hospital with severe dyspnea and hypoxia. The subject was intubated and developed multisystem organ failure due to nectrotizing pneumonia. Subject died on Study Day (b) (6)	
IM101174-217-1661 (67/M)	IV	On Study Day 81 the subject, with medical history significant for atherosclerosis, presented with acute gastric pain and shortness of breath and was diagnosed with an acute bowel infarction. The subject died on Study Day (b) (6)	
IM101174-219-1418 (66/F)	SC	On Study Day 145 the subject had blood cultures positive for staphylococcus aureus and was diagnosed with staphylococcal septicemia. The subject died on Study Day (b) (6)	

Reasons for death in the long-term periods of the clinical studies were largely due to serious infections (Table 12).

Table 12. Deaths Occurring During the Long-Term Extension Periods

Study Subject # (age/sex)	Abatacept Treatment	Cause of Death	Death Study Day
IM101063-6-5 (57/F)	SC	On Study Day 877 the subject developed shortness of breath and was diagnoses with bronchitis subsequent diagnostic evaluation demonstrated pseudomonas aeruginosa pneumonia. Subject was discharged on Study Day 968 but returned to hospital on Study Day 995 with declining health status and ultimately died due to cardiac arrest on Study Day (b) (6)	(b) (6)
IM101063-11-13 (79/M)	SC	On Study Day 1041 the subject was diagnosed with pneumonia and acute renal failure. Subject died at home on Study Day (b) (6) due to unknown causes.	
IM101063-16-5 (51/M)	SC	On Study Day 447 subject was diagnosed with pneumonia and prescribed oral antibiotics. On Study Day 449 returned to emergency room with respiratory failure, staphylococcal sepsis, and multisystem organ failure. The subjects was intubated and admitted to the ICU but conditioned worsened. Subject died on Study Day (b) (6)	
IM101167-41-175 (70/F)	SC	On Study Day (b) (6) the subject died due to acute upper gastrointestinal hemorrhage.	
IM101167-52-259 (55/F)	SC	On Study Day 52 the subject was hospitalized for lower extremity cellulitis contracted following a bicycling injury. Subject was discontinued from the study and treated with oral antibiotics. Investigator follow-up with subject revealed death due to pulmonary embolism on Study Day (b) (6)	
IM101174-130-646 (74/M)	SC	On Study Day (b) (6) the subject died due to motor vehicle accident.	
IM101174-162-635 (49/F)	SC	On Study Day (b) (6) the subject died of reported respiratory failure.	
IM101174-232-2040 (56/M)	SC	On Study Day (b) (6) the subject died of acute myocardial infarction.	
IM101174-258-2244 (50/M)	SC	Subject's symptoms started in ST period of study but died in LT period of study due to unknown causes on Study Day (b) (6)	

Overall, the reasons and number of deaths observed during the clinical trials associated with the SC abatacept program are consistent with data from the IV abatacept clinical program and post-marketing data and no new safety signals are identified.

7.3.2 Nonfatal Serious Adverse Events

During the short-term period of Study IM101174, for which comparisons can be made between the SC and IV formulations, 31 (4%) SAEs were reported in SC-abatacept – treated subjects compared to 35 (5%) subjects treated with IV abatacept (Table 13). The majority of SAEs occurred in single subjects and were related to infections in both treatment arms. Overall there were a similar number and type of SAEs in both treatment arms, which were consistent with what has been reported in the IV abatacept clinical program. No new safety signals were identified with the SC formulation.

Table 13. SAEs during the Short-Term Period of Study IM101174

System Organ Class (SOC) % Preferred Term (PT) %	Abatacept SC N=736	Abatacept IV N=721
Total Subjects with SAE	31 (4)	35 (5)
Infections & Infestations	5 (1)	10 (1)
Pneumonia	1 (<1)	3 (<1)
Gastroenteritis	1 (<1)	1 (<1)
UTI	0	2 (<1)
Appendicitis	0	1 (<1)
Bronchitis	0	1 (<1)
Infective tenosynovitis	0	1 (<1)
Pneumonia primary atypical	1 (<1)	0
Pyelonephritis acute	0	1 (<1)
Salpingitis	1 (<1)	0
Staphylococcal sepsis	1 (<1)	0
Varicella	0	1 (<1)
Gastrointestinal Disorders	3 (<1)	7 (1)
Abdominal pain	2 (<1)	1 (<1)
Nausea	0	2 (<1)
Aphthous stomatitits	1 (<1)	0
Crohn's Disease	0	1 (<1)
Intestinal infarction	0	1 (<1)
Pancreatitis	0	1 (<1)
Vomiting	0	1 (<1)
Musculoskeletal & Connective Tissue d/o	5 (1)	2 (<1)
Osteoarthritis	1 (<1)	1 (<1)
Rheumatoid arthritis	1 (<1)	0
Arthritis	1 (<1)	0
Back pain	1 (<1)	0
Intervertebral disk protusion	0	1 (<1)
Osteoporotic fracture	1 (<1)	0
Neoplasms, Benign, Malignant, & Unspec.	2 (<1)	5 (1)
Basal Cell CA	1 (<1)	0
B-cell Lymphoma	1 (<1)	1 (<1)
Cervix CA Stage 0	0	1 (<1)
Colon neoplasm	0	1 (<1)
Gallbladder cancer metastatic	0	1 (<1)
Squamous cell CA of skin	0	1 (<1)
Respiratory, Thoracic, & Mediastinal Disorders	5 (1)	2 (<1)
Pleural effusion	1 (<1)	1 (<1)
Asthma	1 (<1)	0
Dyspnea	1 (<1)	0
Interstitial lung disease	1 (<1)	0
Lung d/o	0	1 (<1)
Pulmonary toxicity	1 (<1)	0

Table 13. SAEs during the Short-Term Period of Study IM101174 (continued)

System Organ Class (SOC) % Preferred Term (PT) %	Abatacept SC N=736	Abatacept IV N=721
Total Subjects with SAE	31 (4)	35 (5)
Nervous System Disorders	2 (1<)	4 (1)
Headache	1 (<1)	2 (<1)
Convulsion	1 (<1)	0
Encephalitis	0	1 (<1)
Subarachnoid Hemorrhage	0	1 (<1)
Cardiac Disorders	3 (<1)	1 (<1)
Myocardial infarction	3 (<1)	0
Atrial flutter	0	1 (<1)
Pericarditis	1 (<1)	0
Sinus tachycardia	0	1 (<1)
General Disorders & Administrative	2 (<1)	2 (<1)
Chest pain	0	1 (<1)
Death	1 (<1)	0
Pyrexia	1 (<1)	0
Reproductive System & Breast Disorders	2 (<1)	1 (<1)
Metrorrhagia	1 (<1)	1 (<1)
Cervical dysplasia	1 (<1)	0
Blood & Lymphatic System Disorders	2 (<1)	0
Anemia	1 (<1)	0
Hemolysis	1 (<1)	0
Ear & Labyrinth Disorders	0	2 (<1)
Deafness	0	1 (<1)
Vertigo	0	1 (<1)
Eye Disorders	2 (<1)	0
Cataract	1 (<1)	0
Maculopathy	1 (<1)	0
Immune System Disorders	1 (<1)	1 (<1)
Anaphylactic Reaction	1 (<1)	1 (<1)
Injury Poisoning & Procedural Complication	0	2 (<1)
Femoral neck fracture	0	1 (<1)
Lower limb fracture	0	1 (<1)
Psychiatric Disorders	2 (<1)	0
Anxiety	1 (<1)	0
Schizophrenia	1 (<1)	0
Congenital, Familial, & Genetic Disorders	1 (<1)	0

Gastrointestinal angiodysplasia hemorrhagic	1 (<1)	0
Hepatobiliary Disorders	1 (<1)	0
Cholecystitis	1 (<1)	0
Metabolism & Nutrition Disorders	1 (<1)	0
Dehydration	1 (<1)	0
Vascular Disorders	1 (<1)	0
Deep Vein Thrombosis	1 (<1)	0

A total of 161 SAEs were reported for subjects in the open-label and long-term extension studies with an incident rate of 9 events/100 patient-years of exposure. Overall, the types of SAEs experienced by subjects were consistent with those seen in the short-term period of Study IM101174 and the IV abatacept program, namely Infections & Infestations (2%), Musculoskeletal and Connective Tissue Disorders (2%), Neoplasms, Benign, Malignant and Unspecified (1%), Most individual SAEs were reported for <1% of subjects. No new safety signals were identified during the open-label and long-term extension studies.

Overall, the frequency and type of SAEs observed during the clinical trials associated with the SC abatacept program are consistent with data from the IV abatacept clinical program and post-marketing data and no new safety signals were identified.

7.3.3 Dropouts and/or Discontinuations

Comparative data between the SC and IV formulations during the short-term period of Study IM101174 demonstrated that on the whole, the rate of discontinuation from the study was low with 15 SC-abatacept-treated subjects (2%) discontinuing from the study compared to 25 (4%) subjects treated with the IV formulation (Table 14). Eight (1%) subjects treated with SC abatacept discontinued from the study compared to 14 (2%) subjects treated with IV abatacept.

Table 14. Discontinuations Due to AE During the Short-Term Period of Study IM101174

System Organ Class (SOC) % Preferred Term (PT) %	Abatacept SC N=736	Abatacept IV N=721
Total Subjects with AE Discontinuing from Study	15 (2)	25 (4)
Infections & Infestations	3 (<1)	10 (1)
Pneumonia	0	3 (<1)
UTI	0	2 (<1)
Arthritis Infective	0	1 (<1)
Brochopneumonia	1 (<1)	0
Cellulitis	0	1 (<1)
Device related infection	0	1 (<1)
Herpes Zoster	0	1 (<1)
Infected skin ulcer	0	1 (<1)
Sinusitis	1 (<1)	0
Upper respiratory tract infection	1 (<1)	0
Varicella	0	1 (<1)
Gastrointestinal Disorders	0	4 (1)
Aphthous stomatitits	0	1 (<1)
Crohn's Disease	0	1 (<1)
Intestinal infarction	0	1 (<1)
Peptic ulcer	0	1 (<1)
Neoplasms, Benign, Malignant, & Unspec.	1 (<1)	3 (<1)
B-cell Lymphoma	1 (<1)	0
Cervix CA Stage 0	0	1 (<1)
Colon neoplasm	0	1 (<1)
Gallbladder cancer metastatic	0	1 (<1)
Reproductive System & Breast Disorders	2 (<1)	2 (<1)
Breast calcifications	1 (<1)	0
Breast edema	0	1 (<1)
Cervical Dysplasia	1 (<1)	0
Metrorrhagia	0	1 (<1)
Skin and Subcutaneous Tissue Disorders	1 (<1)	2 (<1)
Drug Eruption	0	1 (<1)
Rash	1 (<1)	0
Urticaria	0	1 (<1)
Blood and Lymphatic System Disorders	1 (<1)	1 (<1)
Hemolysis	1 (<1)	0
Lymphopenia	0	1 (<1)
Immune System Disorders	1 (<1)	1 (<1)
Anaphylactic reaction	0	1 (<1)
Hypersensitivity	1 (<1)	0

Table 14. Discontinuations Due to AE During the Short-Term Period of Study IM101174 (continued)

System Organ Class (SOC) % Preferred Term (PT) %	Abatacept SC N=736	Abatacept IV N=721
Total Subjects with AE Discontinuing from Study	15 (2)	25 (4)
Injury, Poisoning and Procedural Complications	0	2 (<1)
Femoral neck fracture	0	1 (<1)
Wound complication	0	1 (<1)
Investigations	2 (<1)	0
Liver function test abnormal	1 (<1)	0
Smear cervix abnormal	1 (<1)	0
Nervous system disorders	0	2 (<1)
Encephalitis	0	1 (<1)
Headache	0	1 (<1)
Respiratory, Thoracic & Mediastinal Disorders	2 (<1)	0
Interstitial lung disease	1 (<1)	0
Pulmonary toxicity	1 (<1)	0
Cardiac Disorders	1 (<1)	0
Myocardial Infarction	1 (<1)	0
General Disorders a& Administration Site	1 (<1)	0
Influenza like illness	1 (<1)	0
Metabolism & Nutrition Disorders	0	1 (<1)
Metabolic syndrome	0	1 (<1)
Musculoskeletal & Connective Tissue Disorders	1 (<1)	0
Muscular Weakness	1 (<1)	0
Myalgia	1 (<1)	0
Psychiatric Disorders	1 (<1)	0
Schizophrenia	1 (<1)	0
Renal & Urinary Disorders	0	1 (<1)
Hematuria	0	1 (<1)
Vascular Disorders	1 (<1)	0
Deep vein thrombosis	1 (<1)	0

A total of 46 (2%) subjects receiving SC abatacept discontinued from the open-label or long-term extension studies due to an AE. This corresponds to an incidence rate of 2 events/100 patient-years of exposure. The most common AE leading to discontinuation was cellulitis (3 subjects). Serious adverse events led to the discontinuation of 24 (1%) subjects with an incident rate 1 event/100 patient-years of exposure.

The discontinuation rates observed in the clinical program for SC abatacept are similar to the discontinuation rates observed in the clinical program for IV abatacept. No new safety signals are identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the short-term period of Study IM101174, 493 (67%) SC-abatacept–treated subjects reported an AE compared to 470 (65%) IV-abatacept-treated subjects (Table 15). Adverse events that reported in ≥5% of subjects in either treatment arm included headache, nasopharyngitis, upper respiratory tract infections, diarrhea, and nausea. The majority of the reported AEs were of mild to moderate intensity in both treatment groups and severe AEs were reported in 35 (5%) subjects in the SC abatacept group and 24 (3%) subjects in the IV abatacept group. Overall, there were a similar number and type of AEs in both treatment arms, which were consistent with what has been reported in the IV abatacept clinical program. No new safety signals were identified with the SC formulation.

Table 15. Most Frequently Reported AEs ≥5% of Subjects During the Short-Term Period of Study IM101174

Preferred Term (PT) %	Abatacept SC N=736	Abatacept IV N=721
Total Subjects with AE	493 (67)	470 (65)
Headache	44 (6)	55 (8)
Nasopharyngitis	41 (6)	42 (6)
Upper Respiratory Tract Infection	35 (5)	37 (5)
Diarrhea	30 (4)	41 (6)
	39 (5)	22 (3)

Adverse events occurring during the cumulative SC period were reported for a total of 1267 (67%) subjects with an incidence rate of 144 events/100 patient-years of exposure. Adverse events occurring in ≥5% of subjects included upper respiratory tract infection (8%), nasopharyngitis (7%), UTI (6%), bronchitis 96%), sinusitis (5%), and headache (5%). The majority of AEs were of mild to moderate intensity.

Overall, the rates and types of AEs reported in the SC abatacept development program are similar to those observed in the IV abatacept and postmarketing experience. No new safety signals were identified.

7.4.2 Laboratory Findings

Overall, abatacept was not associated with clinically significant changes on hematology and chemistry laboratory parameters. No new safety signals were identified.

7.4.3 Vital Signs

Overall, abatacept was not associated with clinically significant changes vital sign. No new safety signals were identified.

7.4.5 Special Safety Studies/Clinical Trials

See Section 7.4.6 for discussion of immunogenicity

7.4.6 Immunogenicity

Along with the immunogenicity data collected from Study IM101174, the sponsor conducted 3 additional clinical studies to assess the immunogenicity of SC abatacept under different potential clinical scenarios (individual study designs are discussed in Section 5.3).

- Study IM101167 assessed immunogenicity in subjects who had clinically responded to SC abatacept but then had SC abatacept treatment discontinued for 12 weeks and subsequently restarted with or without an IV loading dose.
- Study IM101173 assessed immunogenicity in subjects who initiated SC abatacept as monotherapy versus in combination with MTX and an IV abatacept loading dose.
- Study IM101185 assessed immunogenicity in subjects who had been receiving IV abatacept long-term and switched to SC abatacept.

Immunogenicity data from each study will be discussed separately below.

7.4.6.1 Study IM101174: Immunogenicity

As discussed above, Study IM101174 was a 6-month, randomized, double-blind, placebo-controlled, double-dummy study designed to evaluate that weekly SC injections of abatacept 125 mg were non-inferior to the approved IV dosing regimen of abatacept in subjects with active RA despite treatment with MTX. Serum samples were collected from subjects on Study Days 1, 85, and 169 during the short-term period of Study IM101174. Subjects who were receiving the SC formulation and discontinued prematurely during this period had serum samples collected 7, 28, 56, and 85 days after

their last SC injection. Subjects who were receiving the IV formulation and discontinued prematurely had serum samples collected 28, 56, 85, and 113 days after their last IV infusion.

While on therapy, a total of 5 out of 681 (0.7%) subjects receiving SC abatacept developed anti-abatacept or anti-CTLA4-T antibodies by Study Day 169 compared to 9 out of 702 (1.3%) subjects treated with IV abatacept (Table 16) during the same period. Data from subjects who discontinued therapy demonstrated that anti-product antibodies developed in 3 out of 28 subjects treated with SC abatacept compared to 7 out of 28 IV-abatacept treated subjects.

Table 16. Immunogenicity Data for Study IM101174

Treatment Group	Study Day	Anti-Abatacept n/m (%)	Anti-CTLA4-T n/m (%)
SC Abatacept	Day 85	0/700	0/705
	Day 169	3/671 (0.4)	2/681 (0.3)
	Overall on treatment	3/707 (0.4)	2/716 (0.3)
	28 Days after last dose	0/18	0/20
	56 Days after last dose	0/19	1/19 (5)
	85 Days after last dose	0/12	2/13 (15)
	Overall after treatment	0/26	3/28
	Overall	3/714 (0.4)	5/725 (0.7)
IV Abatacept	Day 85	2/682 (0.3)	0/689
	Day 169	4/648 (0.6)	4/658 (0.6)
	Overall on treatment	5/691 (0.7)	4/702 (0.6)
	28 Days after last dose	0/25	2/27 (7)
	56 Days after last dose	0/22	1/23 (4)
	85 Days after last dose	0/15	5/15 (33)
	Overall after treatment	0/29	7/31 (23)
	Overall	5/698 (0.7)	11/710 (1.5)

The rate of immunogenicity in subjects on and off therapy in both treatment arms is consistent with what has been reported during the IV abatacept clinical program and post-marketing data. Overall, the data from Study IM101174 demonstrates that the proposed dosing of the SC formulation of abatacept is no more immunogenic than the approved IV formulation.

7.4.6.2 Study IM101167: Immunogenicity

Study IM101167 was a 9-month, multicenter, randomized, double-blind, withdrawal study designed to evaluate the effect on immunogenicity and safety of interruption and reintroduction of SC abatacept, with or without an IV loading dose, in subjects with

active RA who have had an initial clinical response to SC abatacept. The trial was organized in three, 12-week periods: Period 1 was an open-label run in period. Subjects responding to SC abatacept therapy during Period 1 entered Period 2 where they were randomized to continue receiving SC abatacept therapy or SC placebo. At the end of 12-weeks, all subjects entered Period 3 and either continued to receive SC abatacept or were restarted on SC abatacept with or without an IV loading dose. Data were available for all 120 subjects during the withdrawal period of the study. During the reintroduction period data were available for 119 subjects with one subject in the SC placebo group who withdrew consent on Day 197.

At the end of the withdrawal period (Study Day 169), immunogenicity rates showed that none of the 38 subjects who received continuous SC abatacept had developed anti-product antibodies compared to 7 out of 73 (10%) subjects who had their SC abatacept withdrawn during this period. The pre-specified point estimate (95% CI) of the treatment difference was 10% (0.8, 18) and was not statistically significant.

Following reintroduction of SC abatacept therapy during Period 3, 1 out of 38 (3%) subjects who had continued to receive SC abatacept through Periods 2 and 3 developed anti-product antibodies compared to 2 out of 73 (3%) subjects who reinitiated SC abatacept therapy following a 12-week hiatus from therapy during Period 2. The pre-specified point estimate (95% CI) of the treatment difference was 0.1% (-8, 8).

Overall, Study IM101167 demonstrated that immunogenicity was not significantly increased upon withdrawal of SC abatacept for 12 weeks. Furthermore, subsequent analysis showed that there were no changes in clinical efficacy or safety when SC abatacept therapy was reintroduced after temporary withdrawal.

7.4.6.3 Study IM101173: Immunogenicity

Study IM101173 was a 4-month, open-label, multicenter trial designed to assess the immunogenicity of SC abatacept with or without concomitant MTX and absent of an IV loading dose of abatacept.

None of the 95 subjects (50 subjects in the SC abatacept + MTX treatment arm and 45 in SC abatacept monotherapy treatment arm) were positive for anti-product antibodies at the end of the short-term treatment period of Study IM101173. Positive antibody responses were infrequently observed at earlier time points during the short-term treatment period or during the follow-up for subjects who did not enter the long-term period; however, these positive antibody responses were of low titer, transient, and generally occurred prior to Study Day 85. During the short-term treatment period, a total of 2 of 49 (4%) subjects treated with SC abatacept monotherapy were positive for anti-product antibodies compared to 2 out of 51 (4%) subjects treated with SC abatacept + MTX. There did not appear to be any correlation of the development of antibodies with clinical safety or efficacy findings.

Overall, Study IM101173 demonstrated that SC abatacept monotherapy did not induce more immunogenicity compared to subjects treated with SC abatacept + MTX. While these results support the safety of SC abatacept as monotherapy regarding the development of immunogenicity, the study was not powered to adequately assess the efficacy of monotherapy abatacept compared to IV abatacept. Therefore, the results of Study IM101173 do not support a labeling change to the Product Insert recommending SC abatacept monotherapy under Dosage and Administration.

7.4.6.4 Study IM101185: Immunogenicity

Study IM101185 was a 12-month, multicenter, open-label, single treatment arm study evaluating the safety of abatacept in subjects switching from IV to SC abatacept therapy. The study enrolled subjects with RA who were participating in open-label long-term extension trials of studies from the core IV abatacept program in RA.

A total of 8 out of 122 (7%) subjects developed anti-product antibodies during the first 3 months after switching from IV to SC abatacept. There was no apparent relationship between the anti-product antibodies and efficacy or safety results during this period. One subject who had developed a positive anti-CTLA4 antibody titer during this period developed sarcoidosis on Day 131 that was serious and resulted in treatment discontinuation; however, a causative relationship cannot be determined with the limited data. Abatacept-induced immunogenicity, based on the ECL assay, was not observed in any subject during the first 3 months (Day 85) and for 1 subject (0.8%) during the cumulative treatment period. Overall, there does not appear to be a serious risk of developing immunogenicity following switching to SC abatacept therapy following long-term IV therapy.
In summary, the sponsor has conducted a full and adequate assessment of the immunogenic potential of SC abatacept under a number of different clinical scenarios. In all studies, the risk of immunogenicity with the SC abatacept formulation does not appear to be greater than that of the currently approved IV formulation. Furthermore, although the data is limited due to the relatively few subjects who developed anti-product antibodies, the presence of anti-abatacept antibodies and/or anti-CTLA4-T antibodies were not correlated with clinical outcomes.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Additional analyses were performed to evaluate the safety profile of SC abatacept across different body weights in light of the fact that the subcutaneous formulation of abatacept is a fixed dose regimen. These safety analyses were performed using the same body weight tiers used in the IV dosing regimen, namely <60 kg, 60 to 100 kg,

and >100 kg. Additionally, baseline weight quartiles for comparative SC and IV treatment arms were analyzed.

In the short-term period of IM101174, approximately 68% of subjects weighed between 60 to 100 kg, 24% weighed <60 kg, and 9% weighed >10 kg. As shown in Table 17, Deaths, SAEs, AEs, and SAEs/AEs resulting in discontinuation were generally similar between the three weight tiers as well as between the SC and IV treatment arms within weight tiers. The most common AE experienced in all three weight tiers was Infections and Infestations and occurred at similar frequencies between the SC and IV formulation treatment arms (data not shown). There was a higher incidence of injection site reactions in subjects <60 kg (4%) compared to the 60 to 100 kg (2%) and >100 kg (2%) body weight tier treatment arms (data not shown). This clinical significance of differences in injection site reactions is difficult to interpret given the small number of subjects in each treatment arm. Overall, these data suggest that the fixed dose of SC abatacept does not present a greater risk to subjects with lower body weights, compared to those of higher body weights, despite attaining an almost doubling of the serum trough of abatacept.

Table 17. Safety Data by Body Weight Tier during the Short-Term Period of Study IM101174

Baseline Weight <60 kg		**Abatacept SC N=185**	**Abatacept IV N=168**
	Deaths	0	3 (2)
	SAE	9 (5)	10 (6)
	Discontinued due to SAE	1 (1)	7 (4)
	AEs	129 (70)	106 (64)
	Discontinued due to AE	2 (1)	9 (5)
Baseline Weight 60-100 kg		**Abatacept SC N=494**	**Abatacept IV N=498**
	Deaths	1 (<1)	2 (<1)
	SAE	19 (4)	21 (4)
	Discontinued due to SAE	6 (1)	7 (1)
	AEs	319 (65)	320 (64)
	Discontinued due to AE	12 (2)	14 (3)
Baseline Weight >100 kg		**Abatacept SC N=57**	**Abatacept IV N=57**
	Deaths	1 (2)	0
	SAE	3 (5)	4 (7)
	Discontinued due to SAE	1 (2)	0
	AEs	45 (79)	44 (77)
	Discontinued due to AE	1 (2)	2 (4)

Since the lowest weight subjects are expected to have higher exposures to abatacept, additional analyses were performed for subjects <40 kg, ≥40-<50 kg, ≥50-<60 kg (Table

18). While the number of subjects was small in each of the subgroups analyzed, overall, AEs and SAEs were similar between SC and IV treatment arms in each weight group. These data support the general findings of safety discussed above.

Table 18. Safety Data by Body Weight Tier for Subjects Weighing Less Than 60 kg During the Short-Term Period of Study IM101174

Baseline Weight <40 kg		**Abatacept SC N=4**	**Abatacept IV N=2**
	AEs	4 (100)	2 (100)
	SAEs	2 (50)	0
	Discontinued due to AE	0	0
	Infections & Infestations	1 (25)	1 (50)
Baseline Weight ≥40-<50 kg		**Abatacept SC N=39**	**Abatacept IV N=42**
	AEs	27 (69)	23 (55)
	SAEs	4 (10)	3 (7)
	Discontinued due to AE	1 (3)	2 (5)
	Infections & Infestations	8 (21)	12 (29)
Baseline Weight ≥50-<60kg		**Abatacept SC N=142**	**Abatacept IV N=122**
	AEs	98 (69)	81 (66)
	SAEs	3 (2)	7 (6)
	Discontinued due to AE	1 (1)	7 (6)
	Infections & Infestations	51 (36)	45 (37)

Subgroup analyses by body weight for subjects receiving SC abatacept during the open-label/long-term extension trials were generally similar across body weight-tiers and no new safety signals were identified. Additional safety subgroup analyses including race, age, gender, and geographic region demonstrated similar safety data as that for the IV abatacept development program. Overall, there were no new safety signals identified.

8 Postmarket Experience

Postmarketing experience is not applicable for SC abatacept; however, approximately (b) (4) patients have been exposed to IV abatacept since the time of its approval in December 2005 through September 2010. During this period of time the types and rates of AEs have been consistent with what was reported at the time of approval.

9 Appendices

9.1 Literature Review/Reference

No scientific literature was reviewed to support the efficacy and safety of this application.

9.2 Major Labeling Recommendations

The SC formulation of abatacept should receive the same clinical indication as the IV formulation, namely for the "treatment of moderately to severely active RA in adults".

Additionally, it is my opinion that only the dosing regimen used in Study IM101174, namely initiation of SC abatacept following an IV abatacept loading dose, should be included in the new Package Insert. Although data from Studies IM101167, IM101173, and IM 101185, provided evidence of safety in regards to initiation of SC abatacept as either monotherapy or with concomitant MTX and with or without an IV loading dose, the studies were not designed, or powered, to assess the efficacy of these dosing regimens compared to the IV formulation.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was conducted for the current application.

SIGNATURES/DISTRIBUTION LIST

Primary Clinical Reviewer_____
Keith M Hull, M.D., Ph.D.

Concurring Clinical Team Leader_____
Sarah Yim, M.D.

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Clinical overview [2.5]	Y	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	
❑ Biopharmaceutics and associated analytical methods	Y	
❑ Clinical pharmacology [includes immunogenicity]	Y	
❑ Clinical Efficacy [for each indication]	Y	
❑ Clinical Safety	Y	
❑ Synopses of individual studies	Y	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y	
Tabular Listing of all clinical studies [5.2]	Y	
Study Reports and related information [5.3]	Y	
❑ Biopharmaceutic	Y	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	
❑ Pharmacokinetics (PK)	Y	
❑ Pharmacodynamic (PD)	Y	
❑ Efficacy and Safety	Y	
❑ Postmarketing experience	Y	
❑ Case report forms	Y	
❑ Individual patient listings (indexed by study)	Y	
o electronic datasets (e.g. SAS)	Y	
Literature references and copies [5.4]	Y	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y	
❑ legible	Y	
❑ English (or certified translation into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	Y	
❑ protocols for clinical trials present	Y	
❑ all electronic submission components usable	Y	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	Y	
❑ conducted in compliance with requirements for informed consent	Y	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	
drug interaction studies communicated as during IND review as necessary are included	Y	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	
comprehensive analysis of safety data from all current world-wide knowledge	Y	

Examples of Filing Issues	Yes?	If not, action & status
of product		
data supporting the proposed dose and dose interval	Y	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y	
adequate characterization of product specificity or mode of action	Y	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
IM101174	Y	Y	Y	Y
IM101173	Y	NR	Y	NR
IM101167	Y	NR	Y	NR
IM101185	Y	NR	Y	NR
IM101013	Y	NR	Y	NR
IM101063	Y	NR	Y	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None.

Is clinical site(s) inspection (BiMo) needed?

No.

Is an Advisory Committee needed?

No.

Recommendation (circle one): **File** RTF

Reviewer: [signature] 11/22/10 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] Division. Director: _____
(signature/ date) (signature/ date)
11-22-10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From:	**Susan L Kirshner, Ph.D.** **Division of Therapeutic proteins (DTP)**
Through:	**Barry Cherney, Ph.D. Deputy Director, DTP**
BLA Number:	**125118/122**
Product:	**Orencia (abatacept)**
Sponsor:	**Bristol-Myers Squibb**
Date of Review:	**July 6, 2011**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does recommend approval of STN125118/122 for abatacept injection, 125 mg/ml manufactured by Bristol Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of abatacept injection, 125 mg/ml is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

- Abatacept is produced via recombinant DNA technology and therefore will not be on Lot Release.
- Manufacturing sites:
  Drug product manufacture, QC testing, release testing, labeling and assembly, secondary packaging, market-life stability:
  Bristol-Myers Squibb Holdings Pharma, LTD.
  P.O. Box 30100
  Road 686, KM 2.3
  Manati, Puerto Rico 00674

  Drug product QC testing, market-life stiblity testing:
  Bristol-Myers Squibb Company
  600 Thompson Road
  East Syracuse, NY 12057

- USAN and marketed names: abatacept/ Orencia
- The dating period will be (b) (4) months from final filtration
- Storage: 2-8°C protected from light and freezing.
- The (b) (4) stability protocol for the purpose of (b) (4) and the (b) (4) stability protocol.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

PMCs

1. (b) (4)

(b) (4)

Final Report Submission: [Sponsor to fill in date]

2. Establish separate release and shelf-life limits and/or acceptance criteria for product attributes that are stability indicating and submit a PMC final report.

   Final Report Submission: [Sponsor to fill in date]

3. Develop and validate a quantitative IEF specification using a method such as CE-IEF and submit a PMC final report.

   Final Report Submission: [Sponsor to fill in date]

4. Develop and validate a quantitative B7 binding specification that includes measurements of Keq and/or kd using a method such SPR and submit a PMC final report.

   Final Report Submission: [Sponsor to fill in date]

5. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product based on the risks to product quality when stored under the approved conditions.

   Final Report Submission: [Sponsor to fill in date]

6. Perform real time and accelerated stability studies on 2 additional batches of DP produced from DS manufactured with (b) (4)

   Final Report Submission: [Sponsor to fill in date]

7. (b) (4)

(b) (4)

Final Report Submission: [Sponsor to fill in date]

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no deficiencies to be communicated.

V. EXECUTIVE SUMMARY

A. Description of abatacept injection 125 mg/ml

This supplement is for approval of a 125 mg/ml pre-filled ready-to-use syringe (PFS) dosage form for subcutaneous administration of abatacept by patients outside of a clinical setting. The currently approved dosage form is a 250 mg lyophilized cake in a vial for intravenous administration following reconstitution. No changes to the approved drug substance manufacturing process are proposed. Therefore drug substance manufacture and characterization are not reviewed as part of this submission.

Unless appropriately formulated, abatacept forms insoluble filamentous particulates when it comes in contact with silicone. The formulation of the lyophilized presentation of abatacept does not protect drug product from the effects of silicone. Therefore the lyophilized dosage form is marketed with an unsiliconized syringe. (b) (4)

The table below summarizes the two formulation.

Component	Function	125 mg/ml	250 mg/vial
Abatacept	Active ingredient	x	x
Sucrose	(b) (4)	x	
(b) (4)	(b) (4)		(b
Poloxamer	(b) (4)	x	
(b) (4)			
Sodium phosphate	(b) (4)	x	

dibasic, anhydrate			
Sodium chloride	(b) (4)		x
(b) (4)	(b) (4)		(b
Water for injection	Solvent	x	x
(b) (4)	(b) (4)		

The Sponsor provided formulation development data supporting their selection of excipients. In particular, abatacept with sucrose in the absence of surfactant formed particulates in syringes in less than an hour whereas in the presence of surfactant the syringes remain free of particulates throughout the requested shelf-life of (b) (4) months. We concur with the Sponsor's choice of excipients.

- How supplied – Pre-filled syringe with flange extender (the review of the syringe and flange extender was performed by CDRH).
- Container closure – "1-ml long glass barrel syringe with fill line markings with a 29 gauge thin wall (b) (4) needle and rigid needle shield;…stoppered with (b) (4) coated (b) (4) stopper."
- (b) (4) is requested to account for needle and syringe loss. The overfill is justified as it does not exceed USP recommendations and needle volume should be taken into consideration to help ensure proper dosing.
- Storage conditions – see section on approval letter comments.
- The Sponsor requested a categorical exclusion from the preparation of an environmental assessment based on 21 CFR 25.21(a) and (b). We recommend they be granted the categorical exclusion per 21 CFR 25.31(c) as the proposed change will not significantly change the distribution of the active compound in the environment.

B. Specifications

Drug product specifications are summarized in the table below:

Test	Method	Limits
Appearance		
Color	Ph. Eur.	Colorless to pale yellow solution
Opalescence	Ph. Eur.	Clear to slightly opalescent solution
Particulate matter	Ph. Eur.	Essentially free of particulate matter
Volume in container	USP, Ph. Eur., JP	>=1.0 ml
pH	USP, Ph. Eur., JP	6.8 – 7.4
Osmolality	USP, Ph. Eur.	(b) (4)
Identification	Capillary electrophoresis	Samples positively identified, consistent with reference standard
Protein content	UV A280 nm	(b) (4)
Peptide mapping	Tryptic mapping with quantitation by UPLC	
Profile		Consistent with reference standard
Asp deamidation		(b) (4)

Met oxidation		(b) (4)
Isoelectric focusing	IEF	
pI range 4.2 – 5.6		(b) (4)
pI range 4.3 – 5.3		(b) (4)
pI range 4.5 – 5.2		(b) (4)
pI range 4.5 – 5.2		(b) (4)
pI 4.5 or proximity		(b) (4) d
Size homogeneity monomer	SE-HPLC	(b) (4)
Size homogeneity HMW	SE-HPLC	(b) (4)
Size homogeneity LMW	SE-HPLC	(b) (4)
SDS-PAGE	Coomassie stain reduced	
Abatacept major band		(b) (4)
Each individual unexpected new band		(b) (4)
SDS-PAGE	Coomassie stain non-reduced	
Abatacept major band		(b) (4)
Each individual unexpected new band		(b) (4)
B7 binding	Surface plamon resonance	(b) (4)
Human cell IL-2 inhibition assay	Bioassay	(b) (4)
Particulate matter	HIAC - USP, Ph. Eur., JP	Must comply with harmonized USP, EP and JP requirements
Sterility	USP, Ph. Eur., JP	Must comply with harmonized USP, EP and JP requirements
Endotoxins	USP, Ph. Eur., JP	(b) (4)

The Specifications are adequate to ensure consistent clinical efficacy and safety. For the most part they supported by clinical experience. The firm has limited manufacturing history with abatacept injection PFS and so has in a number of instances requested slightly broader limits than are currently approved for abatacept injection IV. Therefore we recommend a post-marketing commitment (PMC) to reassess (b) (4) once the Sponsor has manufactured additional commercial lots. Thirty los is generally sufficient for establishing specification limits. We have specific concerns about the following specifications:

- Human IL-2 inhibition assay – the requested limits are (b) (4) of reference activity. Currently approved limits for abatacept injection IV are (b) (4) of reference activity. During much of abatacept's clinical development the upper biopotency limit was (b) (4) of reference activity. The clinical safety and efficacy profile indicate that the drug is safe and effective at 150% of reference. Therefore we recommend approval of these limits. However, the need for the higher upper limit should be re-evaluated after a sufficient number of commercial batches have been

produced. This should be a post-marketing commitment PMC (see PMC #).

- SDS-PAGE reduced and non-reduced – the requested limit for the abatacept major band is (b) (4) The currently approved limit is (b) (4) As unexpected new bands are controlled there is little risk to lowering the limit for the major band. However, the need for the reduced lower limit should be re-evaluated after a sufficient number of commercial batches have been produced. This should be a PMC (see PMC #).
- SE-HPLC HMW species – the requested upper limit is (b) (4) whereas the approved limit for abatacept injection IV is (b) (4) Abatacept injection IV has separate limits for HMW species at release and on stability because HWM species increase slightly over time. The Sponsor is proposing to have the same limits for release and stability for abatacept injection PFS. We find that having tighter release specifications for an attribute known to change on stability is a best practice as it prevents the release of drug product that may go out of specification during its shelf life. However because the change in HMW species over time is slight and manufacturing history is well within the proposed limit (no higher than (b) (4) with 15 batches), this concern may be addressed as a PMC (see PMC #).
- Oxidation and deamidation by peptide mapping – Abatacept injection IV has separate limits for oxidized and deamidated species at release and on stability because these species increase over time. The Sponsor is proposing to have the same limits for release and stability for abatacept injection PFS. We find that having tighter release specifications for an attribute known to change on stability is a best practice as it prevents the release of drug product that may go out of specification during its shelf life. However the change in oxidized and deamidated species over time is slight and manufacturing history is well within the proposed limit (no higher than (b) (4) for oxidized species and (b) (4) for deamidates species with 12 batches. These analyses were not performed on three batches.) Therefore this concern may be addressed as a PMC (see PMC #).
- The Sponsor is developing a quantitative method for isoelectric focusing to allow for tighter control over charge variants. This method should be applied to abatacept injection PFS as well. This may be performed as a PMC (see PMC #).
- The Sponsor is developing a quantitative method (measuring the equilibrium and dissociate constants) for B7 binding to have a more informative assay. With the exception of high temperature almost no forced degradation method showed changes to B7 binding by the current method. Therefore this method does not provide useful information about product quality. This method should be applied to abatacept injection PFS as well. This may be performed as a PMC (see PMC #).
- The Sponsor is developing methods for the assessment of subvisible particles in the (b) (4) for abatacept injection IV. The Sponsor currently assesses particles smaller than (b) (4) (SE-HPLC) and greater than (b) (4) (HIAC). Thus there is a gap in their

analysis of particulates. This method should be applied to abatacept injection PFS as well. This may be performed as a PMC (see PMC #).

C. Stability

The Sponsor provided data demonstrating that abatacept injection PFS is stable under recommended storage conditions for up to 30 months. Drug should be stored protected from light and freezing.

Summary of study results

No new degradation pathways were identified for abatacept injection PFS. The degradation pathways for abatacept injection IV are oxidation (b) (4)), deamidation (b) (4) formation of high molecular weight (HMW) species and glycation. Oxidation and deamidation are monitored by peptide mapping. Formation of HMW species is measured by size exclusion-high performance liquid chromatography. Abatacept injection IV is susceptible to glycation since it is formulated with maltose, which has a reducing form. Abatacept injection PFS is formulated with sucrose, which is not a reducing sugar. Therefore glycation is not an expected degradation pathway for the proposed PFS presentation.

In the initial BLA for abatacept injection IV, increased HMW species were detected under stressed, accelerated and photostability conditions. Increased HMW species are associated with increased activity in the bioassay. Consistent with this, in the present submission it is reported that after 6 mo storage at 25°C (either horizontal or upright), samples showed ~5% increase in HMW species and 20 – 40% increase in activity in the bioassay. Similar to results reported in the original BLA, binding to B7 as detected by Surface Plasmon Resonance (SPR) was not impacted by the formation of HMW species.

Exposure to high pH or oxidant in forced degradation studies resulted in product deamidation and oxidation respectively. Oxidized and deamidated product were less active in the potency assay. Binding to B7 as detected by SPR was not impacted.

Both the PFS and IV formulations show increased HMW species and activity in the bioassay when exposed to light. The PFS formulation showed an ~1% increase in oxidized product in photostress studies following conditions recommended in ICH guidance. Oxidation was not reported for the IV formulation in the original BLA and side-by-side forced degradation studies were not performed. Since approval of the license application, the peptide mapping method was optimized for more accurate reporting of oxidized species, which may account for this difference. Data provided in the submission show that the container closure system adequately protects the PFS presentation from degradation by light. The proposed labeling includes a statement that DP should be stored protected from light. Given the limited impact to product quality when

the product is exposed to intense light, the limited exposure to light when the product is administered, in use photo studies are not necessary. No further action is required.

Drug product was subjected to up to seven freeze/thaw cycles. No changes to product quality were observed. However the Sponsor proposes the labeling to include a "Do not freeze" statement because they are concerned about the potential for stopper movement during freeze/thaw cycling. This rationale is appropriate to support the proposed labeling.

The Sponsor provided long term stability data on a single DP lot manufactured from DS produced using the (b) (4). The (b) (4) has recently been approved and is replacing the process (b) (4) Therefore, to provide a more robust stability database for the (b) (4), the Sponsor should place two additional lots on long term stability once they have been manufactured. This may be done as a PMC as DS manufactured by (b) (4) was found to be comparable.

The company performed shipping validation studies that included simulated (b) (4) testing for packaging integrity, as well as (b) (4) studies for large and small quantity shipments designed to ensure shipping conditions will maintain the product in appropriate environmental conditions. Review of these studies is the purview of BMAB.

The firm did not perform formal shipping stability studies to assess the impact of shipment on drug quality. However the firm performed shaking studies as part of formulation development. The studies covered protein concentrations of 100 or 125 mg/mL (proposed formulation contains 125mg/mL), poloxamer 188 concentrations of 6 or 8 mg/mL (proposed formulation contains 8mg/mL), sucrose concentrations ranging from 100 to 210 mg/mL (proposed formulation contains 170 mg/mL). The formulations were placed in 5cc tubing glass vials on a wrist-action shaker in a 5°C cold-room and shaken for 62 days. At the conclusion of the study, no visible particulates were present in the vials and the increase in soluble aggregates was less than 0.15%. In addition, for the long term stability studies drug product was shipped from Manati, PR where it was manufactured, to New Brunswick, NJ where the stability storage chamber are and then back to Manati, PR for testing. The long term stability studies show that drug product quality is not negatively impacted by shipping throughout the requested shelf-life of the product. These data indicate that drug product is stable when shipped or shaken if cold chain is properly maintained. No further testing is required.

The container compatibility studies performed by the firm were incomplete in that the Sponsor did not assess for leachables under the appropriate conditions. The stability data provided by the Sponsor indicate that drug product is stable in the proposed container closure system. Therefore, risk to patients is very low.

However, formal leachables studies should be performed to fill this gap in knowledge. This will be requested as a post-marketing commitment (see PMC #).

Summary of study conditions and methods used

The stability of abatacept injection PFS was assessed via long term long-term (5°C), accelerated (25°C/60%RH), stress (30°C and 40°C) and photostability studies. Data were provided from 3 primary batches (30 months) and two supporting batch (24 months and 36 months). The supporting stability studies had fewer tests and some tests were performed on a different schedule than the primary studies. One supporting batch was filled in the same container closure system, but using a syringe barrel (b) (4) with a 27 gauge needle instead of a 29 gauge needle. Eighteen months of data on one batch (9G47899) of abatacept injection PFS manufactured from drug substance using the (b) (4) are provided in this submission.

The analytical procedures used to assess stability were: appearance (color, opalescence and visible particles), pH, protein concentration (mg/ml and % of label), size homogeneity (SE-HPLC – monomer, high and low molecular weight species), B7 binding, tryptic peptide mapping (HPLC and UPLC) SDS-PAGE (reduced and non-reduced), isoelectric focusing, human cell IL-2 inhibition assay, particulate matter (HIAC), capillary electrophoresis, sterility[1], endotoxin[1], volume in container, breakloose force (b) (4) [1], glideability ((b) (4)) [1]. These methods are all validated and were shown to be suitable for detecting abatacept degradation products.

[1] These tests were not performed as part of the supporting stability studies protocols.

D. Complexity

The following text is copied from the Executive Summary of the original abatacept BLA. Begin copied text.

General: Abatacept is the USAN name for Bristol-Myers Squibb's CTLA4Ig product. a fusion protein comprised of the extracellular domain of the human Cytotoxic T-lymphocyte Antigen-4 (CTLA-4) fused by genetic engineering to human IgG1 immunoglobulin heavy chain Fc sequence including the hinge, CH2 and CH3 domains. IgG1 disulfides were eliminated by the introduction of three Cys→Ser mutations into the IgG1 hinge region sequence. An inter-chain disulfide bond between sequence in the CTLA4 portion of the molecule creates a CTLA4Ig homodimer. This covalent homodimer is referred to as Abatacept "monomer". The C120-C120 disulfide bond is the inter-chain disulfide bond which joins the 2 abatacept polypeptide chains to create the covalently linked homodimer. The predicted MW based on the Abatacept cDNA sequence is 78,800 Daltons. However, the MW obtained by MALDI-TOF is 92,300 Daltons. The 13,500 Dalton difference is due to glycosylation. There are three N-linked

glycosylation sites confirmed by peptide mapping to occur at asparagines 76, 108 (both in the CTLA4 region) and 207 (Fc region). Two O-linked glycosylation sites have been identified at Ser 129 and 139.

Complexity: As described above, product is a complex mixture of different isoforms due to post-translational modifications, particularly glycosylation. Glycosylation differences have been shown to impact the pharmacokinetics and clearance of the product. The product is also (b) (4)

Studies in the BLA demonstrate that (b) (4)

...

Critical Product Attributes

i. (b) (4)

ii.

iii.

iv.

End copied material.

E. Homology to Other Products

The CTLA4 portion of abatacept is derived from the native sequence of human CTLA4. The Fc portion is homologous to human IgG1, but contains mutations as described above in section D.

F. Mechanism of Action

The following text is copied from the Executive Summary of the original abatacept BLA. Begin copied text.

Biological activity: Abatacept functions to selectively block costimulatory signals required for optimal activation of T lymphocytes. Full activation of mature T cells and robust expression of IL-2 requires engagement of the T cell receptor (TCR) by antigen (Signal 1) as well as signaling through a costimulatory receptor (Signal 2) such as CD28. CD28 signaling occurs as the result of engagement of CD80 (B7-1) and CD86 (B7-2) on antigen presenting cells (APCs) and can be blocked by CTLA4-Ig which binds specifically to B7-1 and -2. Presumably, when used to treat patients with rheumatoid arthritis, CTLA4Ig inhibits activation of the T lymphocytes found in the synovium of affected joints.

Potency Assays to Measure Activity. The product is designed to inhibit B7-CD28 mediated costimulation. Two assays are used. The first assay is a binding assay in which surface plasmon resonance (SPR) is used to detect binding of Abatacept to recombinant B7-Ig on sensor chips. Activity is measured as concentration as a percent of reference standard binding. This assay is a good indicator of activity of the CTLA4 region to bind appropriate ligands. The second assay is a bioassay in which a Jurkat T cells line has been engineered to express luciferase under control of the human IL-2 promoter. If cells are activated (by anti-CD3 and B7) they will express luciferase at high levels. The addition of Abatacept blocks B7 signals. The assay is a good indicator of the ability of the molecule to inhibit a critical T cell function response i.e. generation of IL-2. While the molecule has been shown incapable of effectively fixing complement, it is possible that the ability of the molecule to bind FcR could contribute to its activity. The sponsor has not investigated this possibility and will be requested as a PMC.

End copied material.

G. Manufacturing Process

This submission is for a new drug product presentation. No changes were made to the drug substance manufacturing process. Therefore drug substance manufacturing will not be discussed in this memo.

The manufacturing process for abatacept injection PFS is summarized in the Sponsor's flow diagrams below. The Sponsor provided data to demonstrate the process is adequately controlled for consistent manufacture. The review of the facilities (b) (4) and microbiology are the purview of Biotech Manufacturing Assessment Branch.

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(b) (4)

[redacted]

H. Comparability

There is no difference between the clinical trial and to be marketed materials.

I. Immunogenicity

The immunogencity of subcutaneously administered abatacept was assessed in five different studies.

- Study IM101174, a Phase 3b study, was "a randomized double blind, double dummy, active-controlled, parallel group 6 month comparison of efficacy of sc and iv abatacept in adults with active RA having an inadequate response (IR) to methotrexate (MTX)". This was the primary study to assess comparability of sc and iv abatacept with regards to clinical safety and efficacy.
- "Study IM101173 was a 4 month open label study with a primary objective of evaluating the immunogenicity and safety of SC abatacept in the absence of an IV loading dose, when given as monotherpay versus with concomitant MTX."
- "Study IM101167 was a 9-month study designed to evaluate the impact on immunogenicity and safety of interruption and reintroduction of SC abatacept with or without IV loading dose, in subjects with active RA an don background MTX with an initial response to the SC abatacept."

- "Study IM101185 was designed to evaluate the safety of SC abatacept during the first 3 months following the switch from multi-year use of IV abatacept to SC abatacept."
- Study IM101063 was a multi-dose PK study.

The overall rate for the development of anti-drug antibodies (ADA) was similar whether given SC or IV. ADA were detected in 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. Previous studies with abatacept IV showed a 1.7 % (34/1993) rate for the development of ADA. No effect of immunogenicity on pharmacokinetics, safety, or efficacy was seen.

No ADA were seen after 4 months when Orencia was administered SC in the presence (n=51) or absence (n=49) of MTX. However given the low rate of ADA formation, the small sample size and the short duration of the study these data should be interpreted with caution.

The frequency of ADA increased when patients were withdrawn from Orencia for three months. Thus 7/73 (9.6%) of patients who withdrew from Orencia had ADA at the end of the withdrawl period (day 169), whereas 0/38 patients who were maintained on Orencia had ADA on day 169. After Orencia treatment was reintroduced 2/73 patients (2.7%) had detectable ADA. In the control group 1/38 patients (2.6%) had detectable ADA. It is unclear whether the increase in ADA after withdrawl is because ADA develop after the immunosuppressive effects of the drug wear off, on-board drug interferes with the detection of ADA, or both. The rate of increase in ADA detection after withdrawl from Orencia SC is similar to that seen with the IV presentation.

The data presented above are based on the results of an electrochemiluminescent (ECL) based assay that detects anti-CTLA4-Ig antibodies. The assay validation was reviewed previously and therefore is not part of this submission.

VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Barry Cherney, Ph,D. Deputy Director, Division of Therapeutic Proteins	Barry Cherney 7-15-11
Susan L. Kirshner, Ph.D. Associate Chief, Laboratory of Immunology, Division of Therapeutic Proteins	Susan L. Kirshner 7/15/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science

CMC Review Cover Sheet

Division of Therapeutic Proteins

Jack A. Ragheb, M.D. Ph.D. HFD-122
Susan Kirshner, Ph.D. HFD-122

Name and Title	Signature and Date
Jack A. Ragheb, M.D. Ph.D. Senior Regulatory Research Office Division of Therapeutic Proteins	MD PhD 7/6/2011
Susan L. Kirshner, Ph.D. Associate Chief, Laboratory of Immunology, Division of Therapeutic Proteins	Susan L. Kirshner 7/6/2011

Recommendations and Conclusions on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of STN125118/122 for SC Orencia (Abatacept Injection, 125 mg/Syringe) manufactured by Bristol-Myers Squibb for human use (under conditions specified in the package insert). The data submitted in this application are adequate to support the conclusion that the manufacture of SC Orencia is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved.

The dating period for SC Orencia (Abatacept Injection, 125 mg/Syringe) shall be (b) (4) months from the date of manufacture when stored at 2 – 8 °C protected from light and freezing.

PMC

Specifications

1. The specifications established for DP release testing do not appear to provide appropriate control of critical product attributes. Based on 30 manufacturing lots:
   a. (b) (4)
   b. Establish separate release and shelf-life specifications for product attributes that are stability indicating.
2. Develop and report quantitative IEF specifications using a method such as CE-IEF
3. Develop and report quantitative B7 binding specifications including Keq and/or kd using a method such SPR.
4. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

Stability

The stability data from a single lot of DP produced from DS manufactured with (b) (4) is not sufficient to establish that such DP is comparable to that produced from DS manufactured with conventional (b) (4). Perform real time and accelerated stability studies on 2 additional batches of DP produced from DS manufactured with (b) (4)

Leachables and Extractables

The studies performed to assess syringe and contact equipment compatibility were either not performed, or not performed under conditions reflective of the manufacturing process (e.g. temperature), or did not report leachables and extractables where it would have been appropriate to do so. In addition, where leachables and extractables were reported, data on metals was not presented.

Extractables analysis should be conducted under the appropriate exaggerated conditions using the prefilled syringe components that come into contact with the drug (b) (4) Extractables studies are expected to include a spectrum of chemistries ranging from organic to inorganic, from highly volatile to non-volatile, and from highly polar to

non-polar. Supplier data can be used as a starting point, or in place, of the extractables study when sufficiently representative.

Leachables study should be conducted on the assembled prefilled syringe unit under the real-time conditions and should include multiple stability time- points throughout the dating period of the product using the Drug Product Vehicle with and without (i.e., placebo) the Active Pharmaceutical Ingredient, as extraction media.

Where studies of leachables have not been performed under the conditions encountered during the licensed manufacturing process, repeat the studies under the relevant conditions or provide a justification why it is not necessary to do so. In addition to metals, studies should test for the presence of non-volatile, semi-volatile and volatile leachables. Stuides should employ methods (e.g. ICP-DRC-MS) that permit chemical identification and quantitation (e.g., ppb, ppm) of each compound and report the same. A justification of the sample size used (i.e., number of lots and units within each lot) should be provided.

Reviewer's Preface

Throughout this product review, all black text is taken directly, paraphrased, or otherwise condensed/summarized from the sponsor's submission. By contrast, reviewer comments/findings are in *italicized text, either blue or red for emphasis*. Data that is the immediate subject of reviewer comments/findings are presented within the body of the review unless the data is so lengthy, or in a format (e.g. landscape orientation) that inclusion in the body of the review would disrupt its flow, in which case the data is presented in an Appendix. For emphasis, I have highlighted some data provided by the sponsor. Additional data is presented in the Appendixes simply for ease of reference. Unless stated otherwise, I concur with the sponsor's conclusions in the BLA.

DRUG PRODUCT

(b) (4)

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3.2.P.6 Reference Standards

The reference material used for the qualification of abatacept injection drug product is the same reference material used for the qualification of the abatacept drug substance and the qualification of the abatacept IV drug product.

3.2.P.7 Container Closure

The abatacept injection, 125 mg/mL is packaged in a 1-mL long glass syringe barrel with fill line marking with a 29 gauge thin wall (b) (4) needle and rigid needle shield; it is stoppered with (b) (4) coated (b) (4) (b) (4) stopper (prefilled syringe). The syringe barrel and the (b) (4) stopper are sterile and ready-to-use components of the prefilled syringe. The prefilled syringe is a component of the following (b) (4)

- (b) (4)
- Abatacept injection prefilled syringe with flange extender

Primary Packaging Components

Submission materials related to the primary container (i.e. syringes) were reviewed by CDRH.

Secondary Packaging Components - The abatacept injection prefilled syringe with flange extender (b) (4) is placed in a tray. The tray is placed inside a paperboard carton, which completes the secondary container. This secondary packaging structure provides the functional protection during shipping and protection from light. The suitability of the packaging system for commercialization is supported by the stability and photo-stability studies reported in Section, 3.2.P.8, "Stability."

3.2.P.8 Stability

Forced Degradation (3.2.P.2.2.5)

Abatacept injection drug product Lot Numbers 6E19096, 8C46123 and Lot Number 9B48222 (spiked with (b) (4) were stressed under various conditions of acidic pH, basic pH, heat, oxidation, irradiation (UV, Fluorescence), and agitation as listed in Table 3.2.P.2.2.5.T01 below.

Table 3.2.P.2.2.5.T01: Degradation Conditions

Stress Factor	pH			Temp.	Oxidation	Irradiation (UV)	Irradiation (Fluorescent)	Agitation
Condition	pH 4.0	pH 7.0	pH 8.0	5°C and 25°C	1.4% (w/w) H_2O_2	UV (4 W /m^2)	Fluorescent (1200 Lux)	5 rpm
Time Point (s)	1 hr	8, 27 days	8, 27 days	28 days	5 min	45 min	48 and 72 hr	3, 12 days
Stress Temp.	RT	25°C	25°C	5°C and 25°C	RT (dark)	11°C	25°C	RT

[a] RT =Room Temperature

[b] UV =Ultra Violet

Physical, biochemical, and biological properties of these samples were evaluated using various release and extended characterization methods. This study was also intended to compare the degradation pathways and impurity profiles of abatacept injection formulation to the commercial IV formulation.

Stressed samples and controls were analyzed using the following release methods: Appearance, Protein Concentration (A_{280}), pH, Peptide Map (LC/UV), isoelectric focusing (IEF) gel electrophoresis, SDS-PAGE, tandem SE-HPLC and surface plasmon resonance (SPR) binding to B7.1 and potency bioassay. Results of forced degradation for lot# 6E19096 are shown in Appendix I and discussed below.

Results for lot # 9B48222, formulated at pH 7.2 was spiked with (b) (4) to investigate the presence of traces (b) (4) in syringe tips on degradation pathways. In general, the results were similar to the other 2 lots except under oxidizing conditions where degradation was accelerated/increased by the presence of (b) (4) It's interesting that independent of

(b) (4) there was some variability among the lots. For example, after 12 days of agitation lot# 6E19096 met release specifications in the bioassay but the other 2 lots were OOS.

Interestingly, relative to Abatacept IV DP, the SC formulation did not show higher glycation at 5 °C & 25 °C 28 days, presumably as a consequence of the use of sucrose in the SC DP formulation rather than maltose. Oxidation was the only condition shown to have an impact using these orthogonal characterization methods. Oxidized DP disulfides were not comparable to reference material. The oxidized samples containing (b) (4) showed higher HPAEC domain I, ranging from 36.2% to 38.0% but is within specification.

The degradation pathways determined for abatacept injection are oxidation, deamidation, and the formation of high molecular weight (HMW) species.

Given the impact on HMW species, it would have been relevant to include (b) (4) characterization in these studies, however BMS is still developing methods for (b) (4) testing. This will be addressed as a post-marketing commitment.

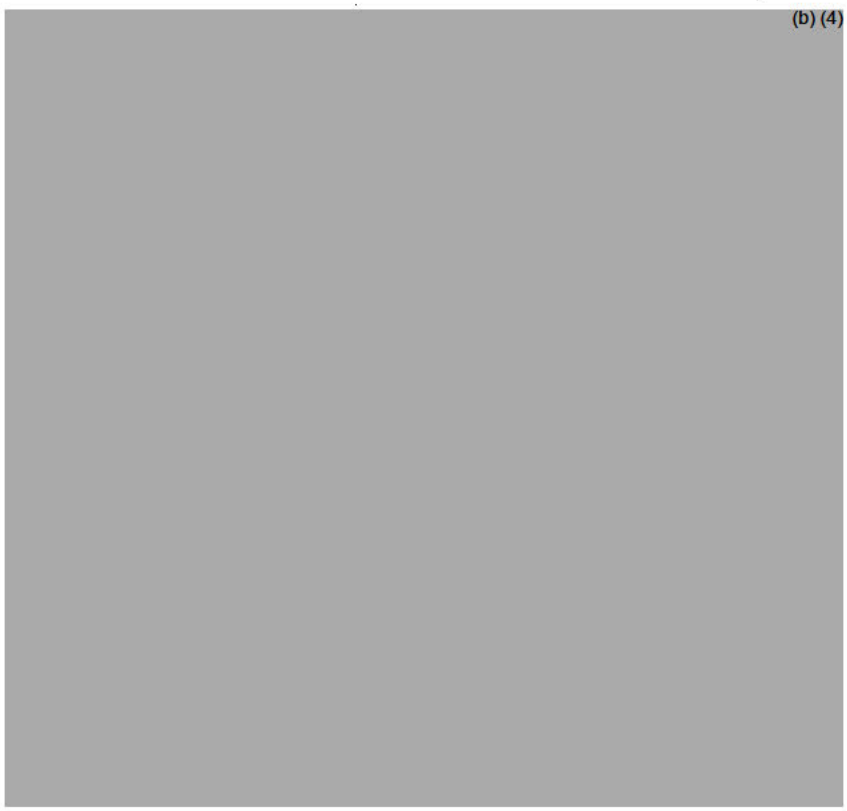
Oxidation - treatment with hydrogen peroxide for 5 minutes induced oxidation (%T6ox ranged from (b) (4). For all the other stressed conditions, the %T6ox was below the quantitation level indicating that these stress conditions did not impact oxidation.

These results are consistent with the degradation profile seen with abatacept IV.

Deamidation - drug product samples exposed to pH 8.0 were found to have increase in %T26deam1 level. There is very little impact of other stressed conditions on deamidation.

These results are consistent with the degradation profile seen with abatacept IV.

HMW and LMW Species - forced degradation from UV light, pH at 4.0, pH 7.0 (8 and 28 days), pH 8.0 (8 and 28 days) and oxidation resulted in significant increases of HMW species with corresponding decrease in monomer for abatacept drug product when compared with reference standard. This increase in HMW included both dimeric and multimeric species. The most prevalent HMW species observed in forced degradation samples was dimmer, but HMW species (b) (4) were also present except in the oxidized sample. Stressed drug product samples that had been oxidized contained LMW species (SDS-PAGE purities in the range of (b) (4) in reduced conditions and (b) (4) in non-reduced conditions), as did 2 samples exposed to UV radiation (SDS-PAGE purities of (b) (4) in reduced conditions and (b) (4) in non-reduced conditions), which also contained HMW species (Figure 3.2.P.2.2.5.F02 below).



The most predominant degradation pathway of abatacept was aggregation upon prolonged exposure (days) to pH 7.0 and pH 8.0, and short exposure to UV light, pH 4.0, and oxidants. The presence of (b) (4) increased aggregation of abatacept (b) (4) upon oxidation.

Under the forced degradation conditions that resulted in increased HMW and deamidated species, there was no impact on the ability of the stressed abatacept to bind to B7.1-Ig. However, oxidation of abatacept reduced its bind to B7.1-Ig and its potency in a cell-based bioassay.

Note that while conditions that resulted in increased HMW species hand no impact on B7 binding, many were OOS in the bioassay (b) (4). *As seen previously, there is generally a poor correlation between B7 binding activity and the IL-2 bioassay. These results are consistent with results obtained with abatacept IV.*

Stability Studies (3.2.P.8)

The sBLA includes stability data from long-term (5°C), accelerated (25°C/60%RH), photostability, freeze-thawing, as well as 30°C and 40°C stress conditions studies to support excursions due to typical shipping and handling, and justify the recommended label storage condition of 2°-8°C with protection from light and from freezing. To support shipping stability, during product development BMS also performed a shaking study in which DP in various formulations were placed in 5cc tubing glass vials, placed on a wrist-action shaker in a 5C cold-room and shaken for a period of 62 days. At the conclusion of the study, no visible particulates were present in the vials and the increase in soluble aggregates (by SEC) was less than (b) (4)

To justify a shelf life of (b) (4) months under the recommended conditions for abatacept injection prefilled syringe 125 mg/mL, data through 30 months from three primary batches and data through 24 months on one supporting batch and through 36 months on a 2nd supporting batch were submitted. One supporting batch was filled in the same container closure system, but using a syringe barrel staked with a 27 gauge needle instead of a 29 gauge needle. Accelerated data are available through 6 months on each supporting batch and stress data for the conditions below for supporting batch 7F25817.

- -20°C for up to 24 months
- seven freeze/thaw temperature cycles (between -20°C and 25°C/60%RH minimally for 24 hours at each temperature)
- 30°C/75%RH for up to 2 weeks
- 40°C/75%RH for up to 1 week

In addition, 18 months of data on one batch (9G47899) of abatacept injection prefilled syringe manufactured from drug substance using the new (b) (4) are provided in this submission.

The LTS studies are based on the ICH Guidelines Q1A (R2) "Stability Testing of New Drug Substances and Products," Q1B "Photostability Testing of New Drug Substances and Products", and Q5C, "Stability Testing of Biotechnological/Biological Products." Testing is being performed on the prefilled syringes using stability-indicating assays which include appearance, size exclusion HPLC, SDS-PAGE (reduced and non-reduced), tryptic peptide mapping, B7 binding Surface Plasmon Resonance (SPR) assay, human cell IL-2 inhibition assay, particulate matter (HIAC), and pH. The drug product is also being tested for, protein concentration (A_{280}), isoelectric focusing, sterility, bacterial endotoxins, capillary electrophoresis, and deliverable volume. The analytical procedures used in abatacept injection, 125 mg/Syringe (125 mg/mL), stability studies are listed in Table 3.2.P.8.1.T08 and Table 3.2.P.8.1.T09 below.

Table 3.2.P.8.1.T08: Analytical Procedure Groups for Primary Stability Study

Test Group	Test
a	Appearance (Color, Opalescence and Visible Particles)
	pH
	Protein Concentration (A280) reported in mg/mL and % of label
	Size Homogeneity (SE-HPLC):
	-Monomer
	-High MW Species
	-Low MW Species
	B7 Binding Assay (Surface Plasmon Resonance)
	Tryptic Peptide Mapping HPLC and UPLC[1]
	SDS-PAGE (Reduced and Non-Reduced)
	Isoelectric Focusing (IEF)
	Human Cell IL-2 Inhibition Assay
b	Particulate Matter (HIAC)
c	Capillary Electrophoresis
d	Sterility
	Bacterial Endotoxin
e	Volume in Container
f	Breakloose Force (Instron)
	Glideability (Instron)

[1] The HPLC Tryptic Peptide Mapping was used for all timepoints during the study. In addition, a new RP-UPLC method (Method 250362) was used to test 5°C samples starting at the 18-month timepoint. Only the HPLC method was used to analyze samples for the supporting batches.

Table 3.2.P.8.1.T09: Analytical Procedure Groups for Supporting Stability Studies

Test Group	Test
a	Appearance of Solution
	pH
	Protein Concentration (A280) reported in mg/mL and % of label
	Size Homogeneity (HPLC):
	-Monomer
	-High MW Species
	-Low MW Species
	SDS-PAGE (Coomassie Stain, Reduced and Non-reduced)
	B7 Binding (SPR) Assay
	Tryptic Peptide Mapping(HPLC)
b	Particulate Matter (HIAC)
c	Capillary Electrophoresis
	Volume in Container
d	Isoelectric Focusing
	Human Cell IL-2 Inhibition Assay

Note that the TPM UPLC method only became available for use beginning with the 18-month LTSS time point and is being used for the duration of the LTSS. There will be 18, 21 and 24-month UPLC data available at least three months prior to the PDUFA Action Date. The HPLC method is continuing to be used in the LTSS program for the primary stability batches, as well.

BMS is evaluating test methodology to study sub-visible particulate matter below (b) (4) in the abatacept injection 125 mg/Syringe, prefilled syringe and will determine any required testing at the conclusion of the evaluation.

Independent of BMS conclusions, the results of this study should be reported as a PMC.

The stability conditions and data available from the stability studies for the primary and supporting batches of Abatacept Injection are provided in Table 3.2.P.8.1.T01 of sBLA Amendment 9.

Each primary LTSS drug product batch was prepared with a different batch of abatacept drug substance. The batch information and packaging components for the primary stability batches manufactured in support of the BLA are summarized in Table 3.2.P.8.1.T02 below. Supporting batch information is summarized in Table 3.2.P.8.1.T03 and T04 below. The primary and the supporting batches were manufactured using the intended commercial process and with the same formulation as the intended commercial product but at a (b) (4) batch scale. A post approval commitment to study the stability of manufacturing scale batches is included in Section 3.2.P.8.2 "Post-Approval Stability Protocol and Stability Commitment".

Also included in this submission is 18 months of stability data for 1 PV batch (9G47899) of abatacept injection, 125 mg/Syringe (125 mg/mL) produced using DS manufactured with the new (b) (4) For comparative purposes, 18 months of stability data from two other PV batches (9C55084, 9C55085) manufactured from DS made using conventional (b) (4) are included. The batch information for all 3 lots is only provided in the stability summary tables (see BLA Amendment 9 Tables 3.2.P.8.3.T27-29).

It's unclear why 18 months of data for PV batches 9C55084 and 9C55085 has been included since the sBLA already contains data from such batches (i.e. the primary and supporting LTSS batches).

Table 3.2.P.8.1.T02: Batch Information for Primary Stability Studies (Prefilled Syringe)

Manufacturing Batch Number	8A44629	8C42809	8C42810
Drug Substance Batch Number	7Z070	7Z102	7Z031
Drug Substance Manufacturing Date	July 2007	August 2007	October 2006
Drug Substance Process	F	F	F
Drug Substance Manufacturing Site	Lonza Biologics, Inc., Portsmouth, New Hampshire		
Date of Drug Product Manufacture	March 2008	April 2008	April 2008
Batch Size (liters)	20	20	20
Batch Size (syringes)	12,643	11,004	11,509
Date on Stability	April 2008	May 2008	May 2008
Manufacturing Site	Bristol-Myers Squibb, Manati, Puerto Rico		
Stability Storage Site	Bristol-Myers Squibb, New Brunswick, New Jersey		
Stability Testing Sites	Bristol-Myers Squibb, Manati, Puerto Rico Bristol-Myers Squibb, East Syracuse, New York (b) (4) (Functionality testing)		
Packaging Components[1]			
Syringe	(b) (4) 1-mL long, Type I glass syringe barrel (b) (4) with 29G stainless steel needle with rigid needle shield		
Stopper	(b) (4) coating on product contact side		

[1] Packaging components are described in Section 3.2.P.7 "Container Closure System". Unmarked syringe barrels were used for the stability batches.

Table 3.2.P.8.1.T03: Batch Information for Supporting Stability Studies

Manufacturing Batch Number	7F25817
Drug Substance Batch Number	48200
Drug Substance Manufacturing Date	October 2006
Drug Substance Process	F
Drug Substance Manufacturing Site	Lonza Biologics, Portsmouth, New Hampshire
Date of Drug Product Manufacture	June 2007
Batch Size (liters)	20
Batch Size (syringes)	11,030
Date on Stability	August 2007
Manufacturing Site	Bristol-Myers Squibb, Candiac, Canada
Stability Storage Site	Bristol-Myers Squibb, New Brunswick, New Jersey
Stability Testing Site	Bristol-Myers Squibb, Hopewell, New Jersey Bristol-Myers Squibb, East Syracuse, New York
Packaging Components	
Syringe	Becton-Dickinson 1-mL long, Type I glass syringe barrel (unmarked) (b) (4) with 27G stainless steel needle with rigid needle shield
Stopper	(b) (4) coating on product contact side

Table 3.2.P.8.1.T04: Batch Information for Supporting Stability Studies

Manufacturing Batch Number	7K24254
Drug Substance Batch Number	48200
Drug Substance Manufacturing Date	October 2006
Drug Substance Process	F
Drug Substance Manufacturing Site	Lonza Biologics, Portsmouth, New Hampshire
Date of Drug Product Manufacture	October 2007
Batch Size (liters)	20
Batch Size (syringes)	12,000
Date on Stability	December 2007
Manufacturing Site	Bristol-Myers Squibb, Manati, Puerto Rico
Stability Storage Site	Bristol-Myers Squibb, New Brunswick, New Jersey
Stability Testing Site	Bristol-Myers Squibb, Hopewell, New Jersey Bristol-Myers Squibb, East Syracuse, New York (b) (4)
Packaging Components	
Syringe	(b) (4) 1-mL long, Type I glass syringe barrel (unmarked) (b) (4) with 29G stainless steel needle with rigid needle shield
Stopper	(b) (4) coating on product contact side

The protocol employed for the long-term stability studies is provided in Table 3.2.P.8.1.T05 and protocols for supporting batches are in Table 3.2.P.8.1.T06 (Appendix J). Samples were randomly distributed at each storage condition.

The protocol employed for the 1 batch of abatacept injection, 125 mg/Syringe (125 mg/mL) produced using DS manufactured with the new (b) (4), and the 2 comparative batches produced using DS manufactured with conventional (b) (4), follows the general stability protocol except that in addition, there is a 1-month time point for the 5°C and 25°C/60%RH conditions.

Summary of Pertinent DP[1] Stability Test Results (1)

Trends were observed in HMW and deamidation results at the 5°C conditions. Although HMW and deamidation values increased with time, the data support a 30-month shelf life. No definite trend in human cell IL-2 inhibition results have been confirmed at the 5°C condition, however, the IL-2 results from samples stored for 6 months at 25°C/60%RH were above the proposed upper acceptance criteria (Batches 8A44629 and 8C42810). The full data set is presented in Table 3.2.P.8.1.T10, T11 and T12 of the sBLA Amendment 9.

The results are what would be expected based on prior experience with Abatacept IV and Belatacept. All 3 primary stability lot samples stored for 6 months at 25°C/60%RH were above

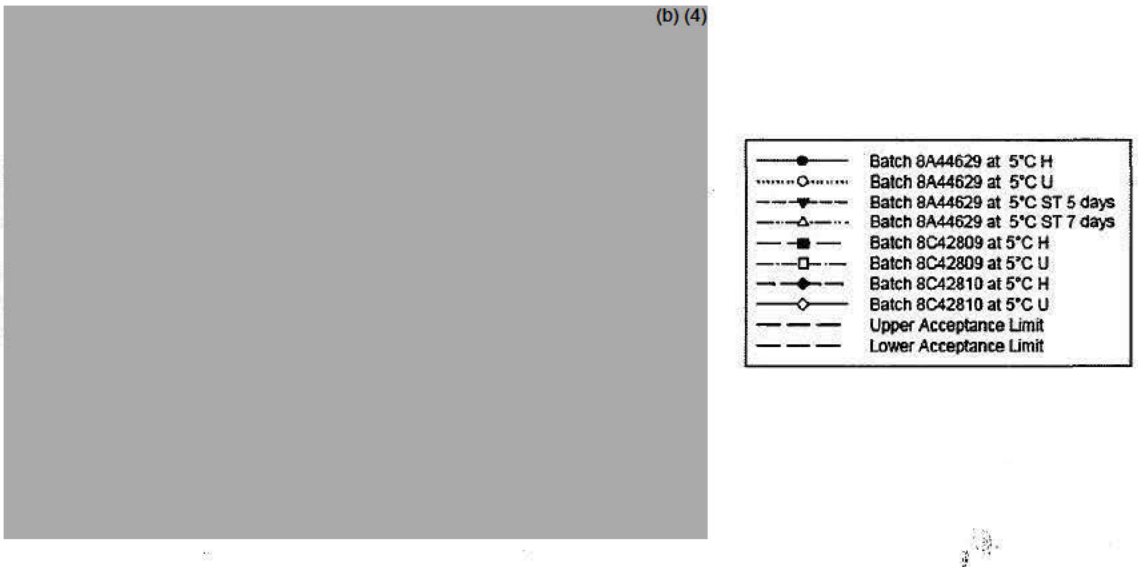
[1] DP manufactured from DS produced from conventional (b) (4)

the proposed upper acceptance criteria for deamidation and HMW (with a corresponding decrease in Monomer).

As for the 3 primary stability lot samples stored for 6 months at 25°C/60%RH, the 2 supporting stability lot samples were above the proposed upper acceptance criteria for HMW (with a corresponding decrease in Monomer) and deamidation. In addition, they were below the proposed lower acceptance criteria for SDS-PAGE Non-Reduced (Major Band). There is also a decreasing trend for SDS-PAGE Reduced (Major Band) but it remained within limits. Similar trends are observed at 40°C/75%RH and 30°C/65%RH.

Select results and figures from this submission are summarized and discussed below:

Figure 3.2.P.8.1.F03: B7-SPR Binding Assay for the Primary Batches of Abatacept Injection, 125 mg/Syringe at 5°C H/U and 5°C ST (Stressed at RT/RL)



In the original submission, 2 of the 3 primary batches (Figure 3.2.P.8.1.F03 above) and one supporting batch (Figure 3.2.P.8.1.F27 below) appeared to show a downward trend in B7-SPR Binding at 5°C between 12 and 18 months that projected to be OOS at 24 months. This trend did not appear to be related to the orientation of the syringe (H=Horizontal; U=Upright). However, additional stability data through 30-36 months that was subsequently submitted did not reflect such a trend.

Figure 3.2.P.8.1.F27: B7-SPR Binding Assay for Abatacept Injection, 125 mg/Syringe, Supporting Batch 7F25817

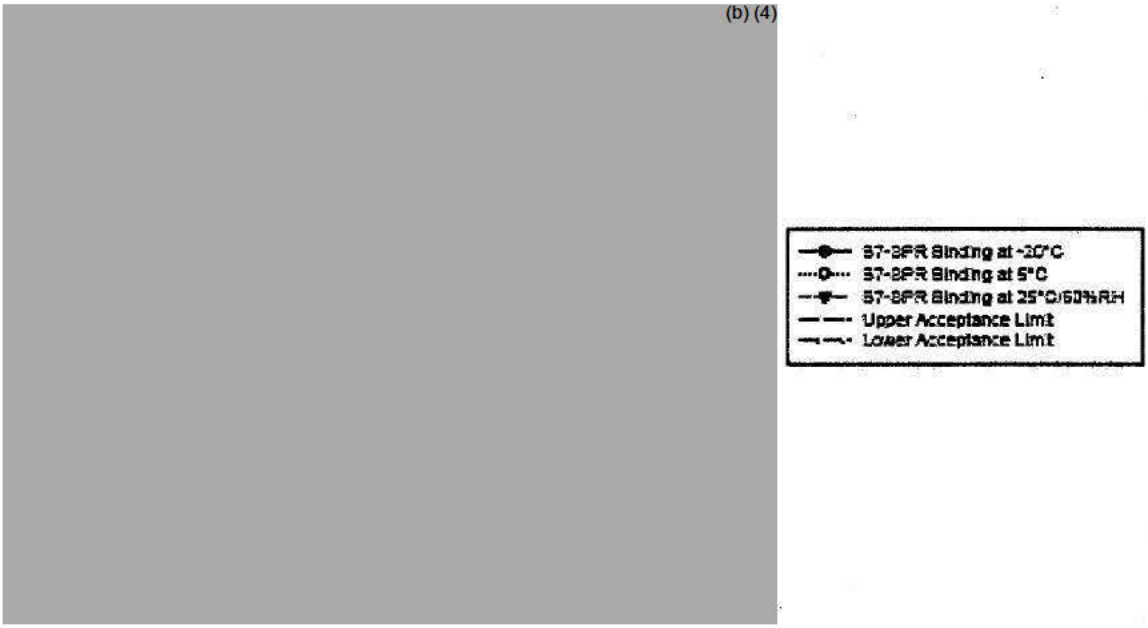


Figure 3.2.P.8.1.F28: B7-SPR Binding Assay for Abatacept Injection, 125 mg/Syringe, Supporting Batch 7K24254

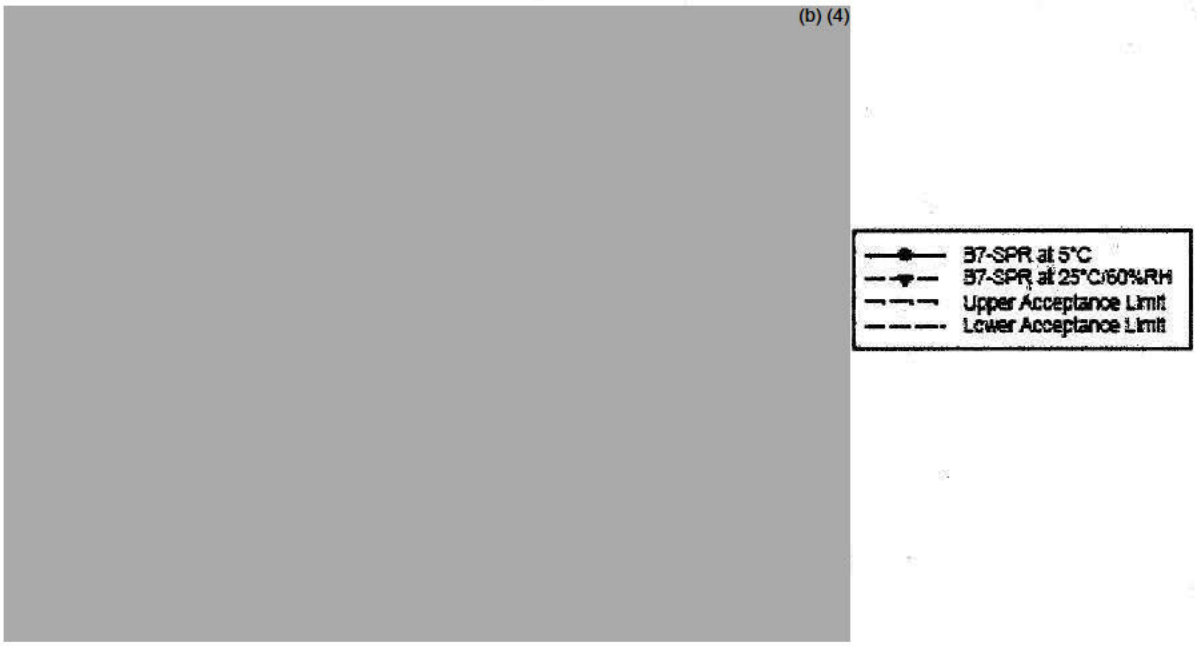
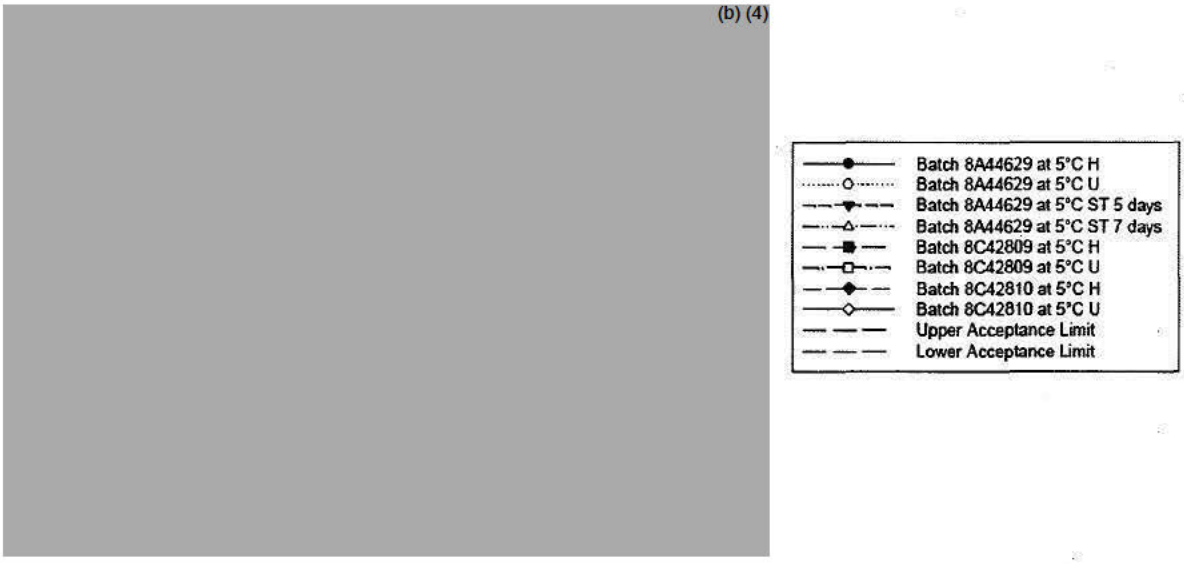


Figure 3.2.P.8.1.F05:Human Cell IL-2 Inhibition Assay for the Primary Batches of Abatacept Injection, 125 mg/Syringe at 5°C H/U and 5°C ST (Stressed at RT/RL)



In the original submission all 3 of the primary batches showed an upward trend in the Human Cell IL-2 Inhibition Assay at the 5°C condition between 12 and 18 months that for 2 of 3 batches appears to be heading OOS (Figure 3.2.P.8.1.F05 above). Additional stability data through 30 months that was subsequently submitted did not reflect such a trend, though data on Batch 8C42810 in the upright position (U) beyond 24 months was not submitted.

A similar upward trend was not apparent in the 2 supporting batches until 18 months but remains within the proposed specification at 24 and 36 months respectively (Figure 3.2.P.8.1.F29 & F30 below).

Figure 3.2.P.8.1.F29: Human Cell IL-2 Inhibition Assay for Abatacept Injection, 125 mg/Syringe, Supporting Batch 7F25817

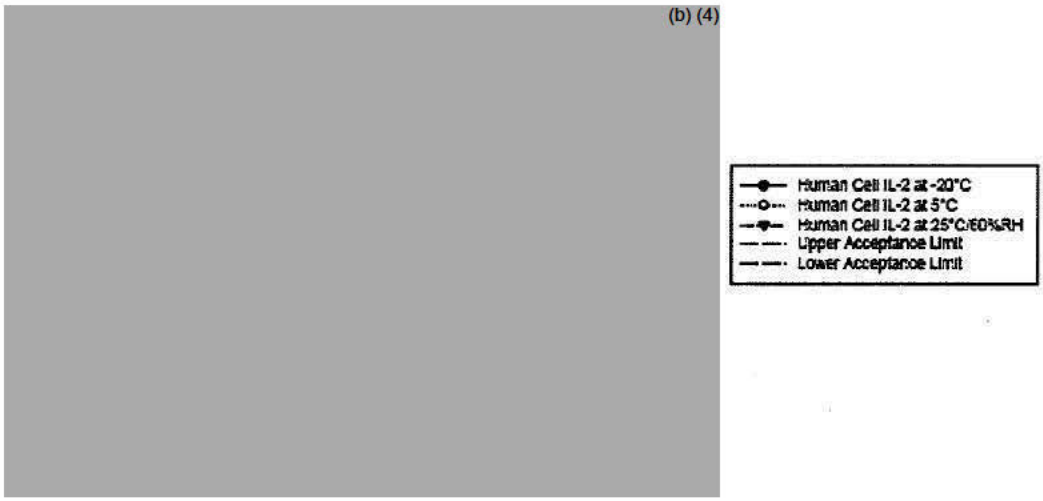
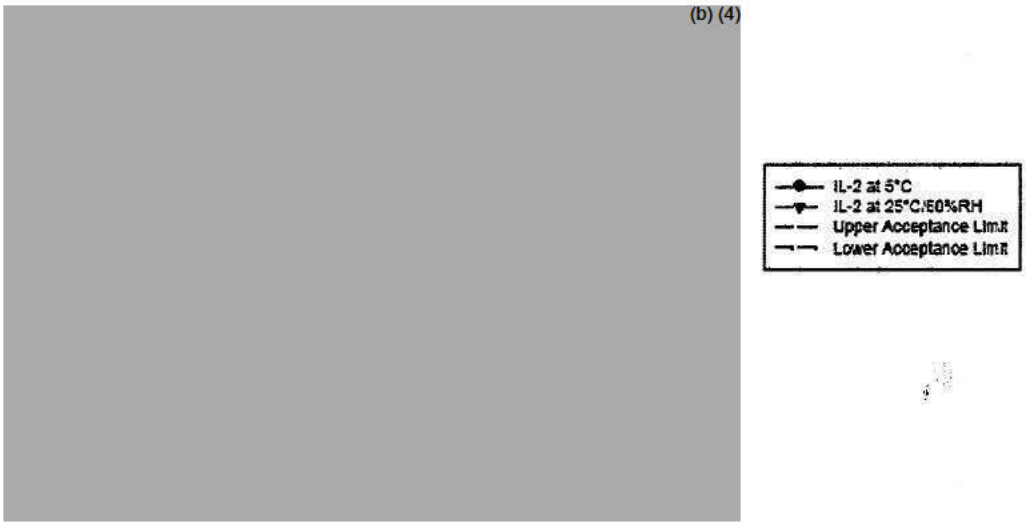


Figure 3.2.P.8.1.F30: Human Cell IL-2 Inhibition Assay for Abatacept Injection, 125 mg/Syringe, Supporting Batch 7K24254



It's interesting to note that in contrast to Aba IV and Belat, there is essentially no particulate matter in the SC formulation (data not shown, see Figure 3.2.P.8.1.F21 & F22 in the sBLA).

Stress and Photostability Studies

The results from the stress and photostability studies on primary and supporting batches are presented in Table 3.2.P.8.1.T11 and T12 of sBLA Amendment 9 and summarized below.

Lot 8A44629, was subjected at RT (25°C/60%RH) to approximately 500 lux of room light (RL) stress exposures (RT/RL E) for 48 hours, then subjected to an additional 3 or 5 day of room temperature exposure (total of 5 or 7 days at 25°C) protected from light (RT/RL P), before

placing on long-term stability at 5°C in a Horizonatal (H) orientation. After 18 months, results from these stressed samples were comparable to results of samples stored at the long-term 5°C H storage condition.

Lot 8C42809 samples, were tested and evaluated after storage for 1 week at 30°C/75%RH, or 1 day at 40°C/75%RH to determine the impact of stress temperatures on the stability of the product. These samples showed increasing levels of HMW species indicating protein aggregation due to heat stress. However, after 1 week at 30°C/75%RH the product met all of the proposed acceptance criteria. Supportive batch samples stored at 40°C/75%RH which showed a steady decline in B7 binding over the course of 1 week from an initial value of 86% down to 65%.

Samples tested and evaluated after storage for 4 days at the minimum exposure of high-intensity fluorescent, visible light and ultraviolet A irradiation (HIL/UVA E) in accordance with ICH Q1B showed large increases in HMW species (up to 16%), increases in oxidation levels, and decreases in the SDS-PAGE major bands, with associated increases in minor bands. There was no apparent change in B7 binding, however, the IL-2 value increased from (b) (4) initially to (b) (4) after exposure. The photostability results indicate that the product should be protected from light. Samples exposed to the same HIL/UVA exposure, but protected in a folded paperboard carton (HIL/UVA P), met all the proposed acceptance criteria.

Supporting Stability Studies

In addition to the studies described above, product from supporting batch 7F25817 was stored at -20°C and then exposed to seven freeze/thaw cycles of -20°C for at least 24 hours, and then stored at 25°C/60%RH for 24 hours. Test results (see Table 3.2.P.8.1.T12 of sBLA Amendment 9) for showed essentially no change from the initial values. However, due to the potential for stopper movement during freeze/thaw cycling, the intended labeling for the product will include "Do not freeze".

Summary of Pertinent DP[2] Stability Test Results (2)

Stability data, 6 months at 25°C/60%RH and 18 months at 5°C, for the one PV batch (9G47899) of abatacept injection, 125 mg/Syringe (125 mg/mL) produced using DS manufactured with the new (b) (4), as well as 2 PV batches produced using DS manufactured with conventional (b) (4) is provided (see BLA Amendment 9 Tables 3.2.P.8.3.T27-29).

As for the primary and supporting LTSS lot samples stored for 6 months at 25°C/60%RH, under these conditions DP samples produced from the new (b) (4), showed upward trends in deamidation and HMW species (with a corresponding decrease in Monomer). However, unlike the primary and supporting LTSS lot samples, or the two additional PV DP lot samples provided for comparative purposes, lot 9G47899 did not exceed the proposed upper acceptance criteria for HMW. Unlike the LTSS batches at 6 months, one of the PV lots (9C55084) was above the proposed upper acceptance criteria for oxidation. However, it is unclear whether this is a valid result as the 1 and 3 month samples of this lot were <QL for oxidation.

[2] DP manufactured from DS produced from (b) (4)

While oxidized abatacept/belatacept is a known forced degradation product, I don't recall ever previously seeing oxidation at 25°C/60%RH or other accelerated stability conditions. However, the significance of this isolated finding is unclear, and as mentioned above may be spurious.

At the 5°C condition, DP samples produced from the new (b) (4) *showed no apparent upward trend in deamidation or in HMW species across the 18 month stability study.*

Based on prior experience with IV Abatacept and Belatacept, the stability results at 5°C for abatacept injection, 125 mg/Syringe (125 mg/mL) produced using DS manufactured with the new (b) (4) *are surprising. The data provided in this sBLA suggest that the stability profile of SC abatacept produced from DS manufactured with* (b) (4) *is likely comparable to or better than that of IV abatacept/belatacept DP produced from DS manufactured with conventional* (b) (4).

Statistical Analyses

BMS undertook a full model Statistical Analyses (b) (4)) to predict stability results for B7 binding, human cell IL-2, protein concentration, deamidation, and HMW at 24 months based on data from the three primary stability batches of abatacept injection, 125 mg/Syringe, (125 mg/mL) drug product stored at 5°C for eighteen months.

The results of this analysis are not pertinent to the stability review.

Sponsor's Conclusions

• The stability data from the primary and supporting batches demonstrate that abatacept injection, 125 mg/Syringe (125 mg/mL), is stable for at least 30 months at the recommended storage condition of 2°-8°C, when packaged into a 1-mL glass syringe (b) (4) with a 29G thin wall stainless steel needle and stoppered with a (b) (4) stopper (plunger) of which the product contact surface is coated with (b) (4) with protection from light.

• Stability data from the supporting batches demonstrate that abatacept injection, 125 mg/Syringe, remains stable for up to 36 months at 5°C, when stored in the same or essentially the same primary packaging (1-mL glass syringe staked with a 27G or 29G thin wall stainless steel needle and stoppered with a (b) (4) stopper (plunger) of which the product contact surface is coated with (b) (4), with protection from light.

• Stability data from 25°C/60%RH, 30°C/75%RH and 40°C/75%RH indicate the product is sensitive to higher temperatures and the product should be stored refrigerated.

• The 5°C and 25°C/60%RH stability data from the upright and horizontal orientations demonstrate that there is no difference in syringe orientation during long-term storage. Either orientation may be used to study future batches.

I concur with the sponsor's conclusion, since there is not a bubble in the syringe, the downward orientation need not be studied.

• The photostability study results indicate that the drug product is sensitive to exposure to high-intensity fluorescent visible light/ultraviolet-A irradiation and should be protected from light. A paperboard carton provides adequate protection from exposure to light.

• Stability data from stress studies on the primary batches demonstrate that the product is not sensitive to room light for at least 48 hours or room temperature for at least seven days (cumulative exposure out of refrigeration). The data demonstrate that the product is stable for one week at temperatures up to 30°C. Due to the potential for stopper movement during freezing and thawing, the product should be protected from freezing.

• Stability studies support a shelf life of 30 months at 2°-8°C, protected from freezing and protecting the prefilled syringe from light.

• Stability data on the batch of abatacept injection prefilled syringe manufactured from drug substance produced using the new (b) (4) demonstrate that the product is stable for at least 18 months when stored at 2°-8°C. Data collected through 18 months indicate that it is reasonable to expect that the product made with the new (b) (4) will have the same stability, and therefore same shelf life, as the product made with drug substance produced with the original media.

While it is likely that DP produced from DS manufactured with (b) (4) will have a similar stability profile as that produced from conventional (b) (4), and BMS has provided a commitment (below) to provide (b) (4) of stability data on the one lot, given the limited experience with this new DS manufacturing process, stability data from 2 additional lots of DP produced from DS manufactured with (b) (4) should be secured through a PMC.

Post-Approval Stability Protocol and Stability Commitment

Bristol-Myers Squibb commits to the completion of all on-going stability studies for the Abatacept Injection Prefilled Syringe in the long-term stability study program and to monitoring on-going stability studies in accordance with the assigned stability protocols. Studies on the prefilled syringe process validation batches, manufactured in April and August 2009, including the batch manufactured with drug substance produced with the new (b) (4), will also continue according to the assigned protocols.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: BLA 125118\122 Supplement
Abatacept (Orencia)
Submitted October 4, 2010

FROM: Molly E. Topper, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Pulmonary, Allergy and Rheumatology Products

DATE: May 26, 2011

Bristol-Myers Squibb, Co. submitted a supplement to their Biological License Application (BLA) 125118\122 on October 4, 2010 for Orencia (abatacept) for a change in route of administration from intravenous (IV) to subcutaneous (SC) and a modified clinical formulation. There are no proposed changes to the approve indication for this supplement. The approved indication is for the reduction of 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.

In support of the safety of the proposed new route of administration, the applicant submitted three nonclinical toxicology studies to assess local irritation and tolerance for the SC formulation. The primary pharmacology/toxicology reviewer, Lawrence Leshin, DVM, PhD, completed a review of these studies and concluded that these nonclinical studies provide adequate support of safety for the new route of administration in patients. No changes to the nonclinical sections of the label are recommended. I concur with Dr. Leshin's conclusions. From the nonclinical perspective, an approval of this BLA supplement (122) is recommended.

Molly E. Topper 5/24/2011
Molly E. Topper, Ph.D.
Pharmacology/Toxicology Supervisor

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:	**125118**
Supporting document/s:	**S122**
Applicant's letter date:	Oct 4, 2010
CDER stamp date:	Oct 4, 2010
Product:	Orencia® (abatacept)
Indication:	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.
Applicant:	Bristol-Myers Squibb Co.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	L. Steven Leshin, D.V.M., Ph.D.
Supervisor:	Molly E. Topper, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Colette Jackson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125118 are owned by Bristol-Myers Squibb Co. or are data for which Bristol-Myers Squibb Co. has obtained a written right of reference. Any information or data necessary for approval of BLA 125118 that Bristol-Myers Squibb Co. 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Bristol-Myers Squibb Co. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA 125118.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From the pharmacology-toxicology perspective, the Application may be approved.

1.1.2 Additional Non Clinical Recommendations

There are no additional nonclinical recommendations.

1.1.3 Labeling

There are no nonclinical changes to the label.

1.2 Brief Discussion of Nonclinical Findings

This supplement presented 3 nonclinical studies that provided support for the change in the route of administration from intravenous to subcutaneous administration. There are no changes to the indication or patient population in this supplement. There are no nonclinical changes to the label.

The potential for local irritation and tolerance of the SC formulation at pH 7.2 or 7.6 was studied in rats by single administration of a single dose, then followed for up to 5 days. Another study was conducted in rabbits to assess local tolerance for the possibility that it may be inadvertently injected into a blood vessel, paravenously or intramuscularly. The rat and rabbit were used in previous toxicological studies for abatacept approval and the rat also was used in the postmarketing commitment to conduct juvenile animal studies. However, binding kinetics to CTLA4 and subsequent Fc effector kinetics in these species for comparison to humans has not been evaluated.

BMS-188667 (abatacept) ready-to-use (RTU) clinical formulation (125 mg/mL, pH 7.2) or saline control was administered (1 mL/injection site) each to a group of 8 male rats as a single subcutaneous dose (125 mg/animal). [For comparison, the human proposed dose is also 125 mg/adult patient]. Abatacept slightly increased incidence and severity of histopathologic signs of acute inflammation on day 2 and subacute inflammation on day 5. None of the changes were judged to be toxicologically significant. There were also no changes in survival, clinical or dermal signs, body weight, or gross-pathology findings that could be attributed to abatacept.

To address accidental exposure of injection into a blood vessel or intramuscularly, rabbits received a single injection of abatacept subcutaneous formulation (125 mg/ml)

either intravenously (lateral marginal ear vein, 62.5 mg), intra-arterially (central ear artery, 62.5 mg), paravenously (medial marginal ear vein, 25 mg) or intramuscularly (quadriceps femoris muscle, 31.25 mg). Similar incidences and severities of gross (tissue discoloration: red, blue, or black) and histopathological findings occurred at both vehicle (saline) and abatacept-treated injection sites. Also there were no abatacept-related mortalities, changes in body weight, or clinical observations. The doses in this study were less than that to be administered subcutaneously in patients, which was not addressed by the Applicant. Doses were constrained by the feasible injection volume coupled with the use of the to-be-marketed formulation prepared as 125 mg/mL as the source of drug. Previous studies within the original BLA submission for the initial intravenous route of administration had satisfactorily addressed the potential for vascular toxicity.

In summary, the three nonclinical toxicological studies support the safety of the abatacept's subcutaneous formulation and this route of administration in patients.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number 332348-12-6

2.1.2 Generic Name Abatacept (Orencia, proprietary name)

2.1.3 Code Name BMS-188667

2.1.4 Chemical Name 1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin Gl (human)

2.1.5 Molecular Weight ~92300 Daltons

2.1.6 Structure Recombinant, fusion protein consisting of extracellular domain of human CTLA-4 and a fragment ("hinge"-CH2-CHJ domains) of the Fc domain of human IgG1

2.1.7 Pharmacologic class Fusion protein immunosuppressant

2.2 Relevant IND/s, NDA/s, and DMF/s

BLA 125118 (Orencia®, abatacept, approved Dec 2005)
IND 9391 (abatacept)

2.3 Clinical Formulation

Abatacept injection (125 mg/mL) is a single dose, ready-to-use (RTU) subcutaneous (SC) formulation to allow for self-administration. (b) (4)

(b) (4)

- Abatacept injection prefilled syringe with flange extender consisting of three components: the abatacept injection prefilled syringe, a plunger rod and a flange extender.

Table 1: Composition of Abatacept Injection, 125 mg/Syringe (125 mg/mL)

Component	Quality Standard	Function	Amount per Syringe (mg)[a]
Abatacept	BMS[b] Specification	Active Ingredient	(b) (4)
Sucrose	NF/Ph.Eur.	(b) (4)	
Poloxamer 188	NF/ Ph.Eur/BP		
(b) (4)	USP/BP		
Sodium Phosphate Dibasic, Anhydrous	USP/Ph.Eur.		
Water for Injection	USP/Ph.Eur./JP		
(b) (4)	NF/JP		
(b) (4)			

[b] BMS: Bristol-Myers Squibb

(b) (4)

The abatacept drug substance used for prefilled syringe is the same as approved for ORENCIA® (Abatacept for Injection, 250 mg/Vial). The abatacept drug substance consists of approximately 50 mg/mL abatacept in 25 mM phosphate buffer containing 50 mM sodium chloride at pH 7.5.

Table 2: Composition of Abatacept Injection, 125 mg/mL

Ingredient	Formulation A (mg/mL)	Formulation B (mg/mL)
Abatacept	125	125
Sucrose	170	170
Poloxamer 188	8.00	8.00
(b) (4)	(b) (4)	(b) (4)
Sodium phosphate Dibasic, Anhydrous	(b) (4)	0.838
Water for Injection	q.s to 1 mL	q.s to 1 mL
(b) (4)	--	--
(b) (4)		

(b) (4)

2.3.2 Comments on Novel Excipients

There are no novel excipients.

2.3.3 Comments on Impurities/Degradants of Concern

The presence and formation of high molecular weight (HMW) impurities were studied under various pHs and temperature conditions to minimize their levels. A drug product stability study found that the rates of HMW species formation and deamidation of abatacept increases as pH decreases; however, the rate of deamidation decreases as formulation pH decreases. At pH of about 7.2 (formulation B), the rate of deamidation is slower than at pH 7.65 (formulation A) with little impact on HMW formation. Therefore, a SC formulation at the target pH of 7.2 (formulation B) was selected for Phase IIb and Phase III clinical studies and is the final drug product intended for commercialization.

The nonclinical study DS07088 titled "Single-Dose Subcutaneous Local Tolerance Study in Rats" was conducted with formulation B abatacept, and the formulation of the other two studies could not be distinguished as being either formulation A or B from the available information. As there were no toxicologically significant effects in any of the three nonclinical subcutaneous administration studies and both formulations had been used in clinical studies, and High Molecular Weight (HMW) impurities are within acceptable product quality specifications, there are no concerns at this time with the HMW impurities in the formulation B intended for commercialization.

2.4 Proposed Clinical Population and Dosing Regimen

Clinical Population

- Adult Rheumatoid Arthritis (RA), patients with moderately to severely active RA in adults.
- Juvenile Idiopathic Arthritis, pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis.

Dosing Regimen

Adult RA, Intravenous Administration

Body Weight of Patient	Dose
<60 kg	500 mg
60 to100 kg	750 mg
>100 kg	1000 mg

- Administer as a 30-minute intravenous infusion.
- Following initial dose, give at 2 and 4 weeks, then every 4 weeks
- Prepare ORENCIA using only the silicone-free disposable syringe

Adult RA, Subcutaneous Administration

- **125 mg** administered by subcutaneous injection regardless of body weight at weekly intervals with or without initial IV loading dose

Juvenile Idiopathic Arthritis

Body Weight of Patient	Dose
< 75 kg	10 mg/kg based on the patient's body weight
> 75 kg	follow the adult dosing regimen, not to exceed a maximum dose of 1000 mg

Dosage Forms and Strengths

Intravenous infusion,

- 250 mg single-use vial

Subcutaneous injection

(b) (4)

- 125 mg/1 mL in a single-dose prefilled syringe with flange extenders

2.5 Regulatory Background

The BLA for abatacept (Orencia®) for the treatment of rheumatoid arthritis was approved in Dec 2005.

At the pre-sBLA meeting on June 3, 2010, the Applicant discussed the development program for the subcutaneous (SC) abatacept product to support use of SC abatacept for the following indication:

ORENCIA® 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. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

The following are key regulatory meetings or communications with the Applicant:

4/11/2006 Letter from FDA to BMS with Agency comments on SC abatacept clinical development plan.

3/28/2007 Letter from FDA to BMS with Agency comments on SC abatacept clinical development plan.

12/27/2007 EOP2 Meeting minutes from FDA to BMS on SC abatacept clinical development plan. The EOP2 meeting took place on 11/27/2007.

11/13/2008 EOP2 Meeting minutes from FDA to BMS on SC abatacept CMC development plan. The EOP2 meeting took place on 10/14/2008.

6/29/2010 Pre-sBLA Meeting minutes from FDA to BMS on SC abatacept planned sBLA. The pre-sBLA meeting took place on 6/3/2010.

Only the preBLA meeting covered the nondinical program. It was determined to be appropriate and those studies are reviewed here.

Other recent nonclinical information included a communication to the Applicant of Oct 20, 2010 acknowledging fulfillment and release of the following postmarketing commitments:

1. Final study report for juvenile animal study DN07013.
2. Final study report for the follow-up juvenile rat study assessing the effects of exposure at post-natal day 4 versus post-natal day 28 (DS07165).
3. Final study report for the follow-up juvenile animal study assessing the mechanism of T-regulatory cell depletion (DS07166).

Based upon the results of the above studies, the Applicant was released from the following postmarketing requirement:

4. Deferred pediatric trial under PREA for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients ages 2-5.

3 Studies Submitted

3.1 Studies Reviewed

Study number / Submission Location	Title
Study DS05129 m4\42-stud-rep\423-tox\4236-loc-tol\ds05129 Module 4.2.3.6	Single-Dose Subcutaneous Local Tolerance Study in Rats
Study DS07088 m4\42-stud-rep\423-tox\4236-loc-tol\ds07088 Module 4.2.3.6	Single-Dose Subcutaneous Local Tolerance Study in Rats
Study DS08084 m4\42-stud-rep\423-tox\4236-loc-tol\ds08084 Module 4.2.3.6	Single-Dose Intravenous, Intraarterial, Paravenous and Intramuscular Local Tolerance Study in Rabbits

3.2 Studies Not Reviewed

All studies were reviewed.

3.3 Previous Reviews Referenced

BLA 125118 S0000, Pharmacology-Toxicology Review of July 2005

4 Pharmacology

4.1 Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86 on antigen presenting cells, thereby blocking interaction with CD28 on T-cells. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and are found in the synovium of patients with RA. *In vitro*, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon-γ. The relationship of these biological response markers to the mechanisms by which abatacept exerts its effects in RA is unknown.

4.2 Pharmacodynamics

In clinical trials with Orencia at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNFα. The relationship of these biological response markers to the mechanisms by which Orencia exerts its effects in RA is unknown.

5 Pharmacokinetics/ADME/Toxicokinetics

There were no animal toxicokinetic data for the 3 studies included in this application.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: BMS-188667 (abatacept): Single dose subcutaneous local tolerance study in rats

Study no.:	DS05129
Study report location:	Module 4.2.3.6 m4\42-stud-rep\423-tox\4236-loc-tol\ds05129
Conducting laboratory and location:	Bristol-Myers Squibb Pharmaceutical Research Institute Departments of Toxicology and Pathology Syracuse, New York USA
Date of study initiation:	June 23, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BMS-188667, Lot 5E01928, Purity 98.8%

Key Study Findings

BMS-188667 (abatacept) ready-to-use (RTU) clinical formulation (125 mg/mL) or saline control was administered (1 mL/injection site) each to a group of 8 male rats as a single subcutaneous dose in the dorsal thorax to determine local tolerance. BMS-188667 (abatacept) slightly increased incidence and severity of histopathologic signs of acute inflammation on Day 2 (n=4/group) and subacute inflammation on Day 5 (n=4/group). There were no changes in survival, clinical or dermal signs, body weight, or gross-pathology findings that could be attributed to abatacept.

Methods	
Doses:	0 or 125 mg
Frequency of dosing:	single injection to the dorsal thorax ('back')
Route of administration:	subcutaneous
Dose volume:	1-mL
Formulation:	Each 1-mL of the BMS-188667 solution contained approximately 125 mg abatacept, 170 mg sucrose, and 8 mg Poloxamer 188 in (b) (4)
Control Vehicle:	0.9% sodium chloride
Species/Strain:	(b) (4) rats(Crl:CD [SD] IGS), males
Number/Sex/Group:	4/group
Age:	9 weeks old
Weight:	285.8 - 305.7 g
Satellite groups:	none
Unique study design:	Animals were sacrificed on day 2 (+24 hrs) or day 5 (+96 hrs)

Group Number	BMS-188667			Control Dose Volume (mL)[a]	Number and Sex of Animals[b]
	Dose (mg)	Volume (mL)	Concentration (mg/mL)		
1	-	-	-	1.0	8M
2	125	1.0	125	-	8M

[a] 0.9% Sodium Chloride for Injection, USP, was injected as a control.

[b] Four (4) rats per group were necropsied on Days 2 (approximately 24 hours postdose) and 5, respectively.

Deviation from study protocol:	There were no deviations that influenced the study interpretations and conclusions.

Observations and Results

Mortality: checked once daily

There were no mortalities.

Clinical Signs: checked once daily, injections sites examined 1-2 hrs and 4-6 hrs postinjection.

There were no abatacept related clinical signs.

Dermal observations consisted of pinpoint scabbing at the injection site of 1 animal on Day 2, thought to be due to the injection procedure and not drug-related irritation.

Body Weights: weighed preinjection and at sacrifice

There were no effects on body weight.

Feed Consumption; not assessed
Ophthalmoscopy: not assessed
ECG: not assessed
Hematology: not assessed
Clinical Chemistry: not assessed
Urinalysis: not assessed

Gross Pathology: collected cutaneous and subcutaneous tissues from the injection site

There were no abatacept -related gross findings. A scab was noted at the injection site of 1 animal examined on Day 2 considered to be due to the injection procedure as noted above.

Organ Weights: not assessed

Histopathology: only of the injection site and surrounding tissues

Adequate Battery	Yes
Peer Review	No

There was no difference in the incidence and severity of edema between groups, but the incidence and severity of acute or subacute inflammation were increased at the abatacept treated sites on both days 2 and 5. Mononuclear-cell infiltration occurred only at the saline injection sites on Days 2 (2 animals) and 5 (4 animals). Findings of acute/subacute inflammation and mononuclear cell infiltration were not observed at the same locations when they occurred in the same animal.

Changes related to the injection procedure in contrast to irritation included hemorrhages, necrosis of a venule (attributed to incidental needle traumatization) fibrosis of the injection canal, and a superficial scab.

Table 3: Summary of Histopathology Results

Text Table 1: Irritation-Related Changes on Days 2 and 5

	Day 2		Day 5	
Group	1	2	1	2
	Saline Control	BMS-188667 (125 mg)	Saline Control	BMS-188667 (125 mg)
Number Examined	4	4	4	4
Edema, Subcutis	3	4	4	3
Minimal	-	1	-	-
Slight	1	-	3	3
Mild	2	3	1	-
Infiltration, Mononuclear-Cell	2	1	4	2
Minimal	2	1	2	2
Slight	-	-	2	-
Inflammation, Acute, Subcutis	2	4	-	-
Minimal	1	-	-	-
Slight	1	1	-	-
Mild	-	2	-	-
Moderate	-	1	-	-
Inflammation, Subacute	-	-	1	4
Minimal	-	-	1	-
Slight	-	-	-	4

- indicates absence of finding

Table 4: Day 2 Histopathology Results (all findings)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX Necropsy Status: End-of-Dose Necropsy (KO) PATHOLOGY TABLE 2			
Sex	Males		
Dose Group No. Animals per Dose Group	01 4	02 4	
INJECTION SITE No. Examined	4	4	
- Edema	3	4	
Grade 1	-	1	
Grade 2	1	-	
Grade 3	2	3	
- Hemorrhage	1	1	
Grade 2	1	-	
Grade 3	-	1	
- Infiltration: mononuclear cell	2	1	
Grade 1	2	1	
- Inflammation: acute	2	4	
Grade 1	1	-	
Grade 2	1	1	
Grade 3	-	2	
Grade 4	-	1	
- Necrosis	1	-	
Grade 2	1	-	
- Scab	1	1	
Grade 1	1	1	

Group 01, Control, males: BMS-188667 (0 mg)
Group 02, Dose Group, males: BMS-188667 (125 mg)

Table 5: Day 5 Histopathology Results (all findings)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX Necropsy Status: Postdose Necropsy (R1) PATHOLOGY TABLE 2			
Sex	Males		
Dose Group No. Animals per Dose Group	01 4	02 4	
INJECTION SITE No. Examined	4	4	
- Edema	4	3	
Grade 2	3	3	
Grade 3	1	-	
- Fibroplasia/fibrosis	-	1	
Grade 2	-	1	
- Infiltration: mononuclear cell	4	2	
Grade 1	2	2	
Grade 2	2	-	
- Inflammation: subacute	1	4	
Grade 1	1	-	
Grade 2	-	4	

Group 01, Control, males: BMS-188667 (0 mg)
Group 02, Dose Group, males: BMS-188667 (125 mg)

Toxicokinetics not assessed

Stability and Homogeneity:
The concentration and stability of the BMS-188667 dosing formulation prepared for use on Day 1 were within 10% of theoretical values. Doses were stable during the dosing period and there was no abatacept detected in the vehicle control.

Study title: Single-Dose Subcutaneous Local Tolerance Study in Rats

Study no.:	DS07088
Study report location:	m4\42-stud-rep\423-tox\4236-loc-tol\ds07088 Module 4.2.3.6
Conducting laboratory and location:	Bristol-Myers Squibb Drug Safety Evaluation Syracuse, New York
Date of study initiation:	21-May-2007 (day of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Abatacept (BMS-188667) ready to use solution formulation) Batch 67559-016, Purity 98.2%

Key Study Findings

There were no toxicologically significant differences in macroscopic or microscopic changes between abatacept-treated and vehicle-treated injection sites at either 2 or 5 days postinjection of a single dose of abatacept or control saline into the right or left, respectively, of the dorsal thorax.

Methods	
Doses:	0 or 125 mg abatacept
Frequency of dosing:	single administration
Route of administration:	subcutaneously, in the dorsal thorax
Dose volume:	1.0 mL
Formulation:	Vial solution containing 125 mg/mL abatacept with 170 mg/mL sucrose, 8 mg/mL Poloxamer 188, in (b) (4)
Control Vehicle:	0.9% sodium chloride for injection
Species/Strain:	(b) (4) (Crl: CD [SD IGS BR]) rats
Number/Sex/Group:	Males only
Age:	9 weeks old
Weight:	278.9 to 310.4 g
Satellite groups:	none
Study design:	First 4 males were necropsied at ~24 hours postdose and the remaining 4 males were necropsied ~96 hours postdose

Group Number	Daily Dose Abatacept (mg)	Volume (mL)	Concentration Abatacept (125 mg/mL)	Number of Animals
1[a]	0[b]	1.0	0[b]	8 M
1[a]	125	1.0	125	8 M

[a] Each rat was administered a single subcutaneous injection of control on the left side of its dorsal thorax and a single subcutaneous injection of abatacept RTU formulation on the right side of its dorsal thorax.
[b] 0.9% sodium chloride for injection, USP (control)

Deviation from study protocol:	There were no deviations that influenced the study interpretations and conclusions.

Observations and Results

Mortality once daily

There was no mortality.

Clinical Signs in addition to clinical signs, the injection sites were examined for signs of irritation (erythema or edema) prior to dosing on Day 1, at approximately 1 hour and at 4 to 6 hours after injection, and then once daily until necropsy

Observations noted over the 5-day period, including focal or multifocal scabs and perianal soiling. Red discoloration of the injection site was also noted at both control and abatacept injection sites.

Feed Consumption; not assessed
Ophthalmoscopy: not assessed
ECG: not assessed
Hematology: not assessed
Clinical Chemistry: not assessed
Urinalysis: not assessed

Gross Pathology:

There were no toxicologically significant differences in macroscopic changes between abatacept-treated and saline-treated animals. At 24 hours postinjection, a dark or red discoloration, 1 to 5 mm in size, was observed in the subcutaneous tissue of 1 control injection site (#L101) and 2 drug-treatment injection sites (#R103 and R104). These had resolved by 96 hours.

Organ Weights: not assessed

Histopathology

Adequate Battery: yes
Peer Review: no

There were no toxicologically significant histopathological differences between abatacept-treated and saline injection sites at either 24 or 96 hours after injections. Observed findings included focal subcutaneous edema, subcutaneous hemorrhage, dermal and/or subcutaneous mononuclear cell infiltrations, and superficial scabs. There were differences between groups at 24 hours in the severity of mononuclear cell infiltration. A foreign-body granuloma was noted in 1 abatacept-treated injection site at 96 hours in which granulomatous tissue developed around a hair shaft or shafts. This may be related to the injection procedure rather than abatacept itself.

Table 6: Summary of Histopathology Findings

Time Point	24 hours		96 hours	
Dose (mg):	0	125	0	125
No. of Injection Sites	4	4	4	4
Sex:	M	M	M	M
Injection Site				
Edema	-	1	-	-
minimal	-	1	-	-
Foreign-Body Granuloma	-	-	-	1
minimal	-	-	-	1
Hemorrhage	4	4	1	-
minimal	3	3	1	-
slight	1	-	-	-
mild	-	1	-	-
Infiltration, mononuclear cell	3	4	4	4
minimal	2	1	3	4
slight	1	2	1	-
mild	-	1	-	-
Scab	1	-	2	-
minimal	1	-	2	-

A dash (-) indicates absence of finding in group.

Table 7: Histopathological Findings by Animal

Time Point	24 hours		96 hours	
Dose (mg):	0	125	0	125
No. of Injection Sites	4	4	4	4
Sex:	M	M	M	M
Injection Site				
Edema				
minimal	-	R102	-	-
Foreign-Body Granuloma				
minimal	-	-	-	R108
Hemorrhage				
minimal	L102	R101	L106	-
	L103	R102		
	L104	R104		
slight	L101	-	-	-
mild	-	R103	-	-
Infiltration, mononuclear cell				
minimal	L102	R101	L105	R105
	L103		L106	R106
			L107	R107
				R108
slight	L104	R102	L108	-
		R104		
mild	-	R103	-	-
Scab				
minimal	L102	-	L106	-
			L108	

A dash (-) indicates absence of finding in group.

Numbers in parentheses reflect the injection-site numbers affected.

Toxicokinetics not assessed

Stability and Homogeneity

The concentration and stability of abatacept dosing formulation were verified. The protein concentration was 123.5 mg/mL for the Batch 67559-016 and 124.8 mg/mL for the dosing solution used on the day of administration.

Study title: Single-Dose Intravenous, Intraarterial, Paravenous and Intramuscular Local Tolerance Study in Rabbits

Study no.:	DS08084
Study report location:	m4\42-stud-rep\423-tox\4236-loc-tol\ds08084
Conducting laboratory and location:	Bristol-Myers Squibb Drug Safety Evaluation Syracuse, New York USA
Date of study initiation:	June 26, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Abatacept, Batch #8C46123, Purity 97.4%

Key Study Findings

A single dose of abatacept ready to use (RTU) subcutaneous formulation (125 mg/ml) did not induce irritation or damage when administered to rabbits by the intravenous (lateral marginal ear vein, 62.5 mg), (central ear artery, 62.5 mg), paravenous (medial marginal ear vein, 25 mg) or intramuscular (quadriceps femoris muscle, 31.25 mg) routes. The noted gross and microscopic effects occurred at similar incidences and severities in both vehicle (saline) and abatacept-treated injection sites.

Methods	
Doses (mg/animal):	0, paravenous (25 mg), intramuscular (31.25 mg), intravenous (62.5 mg), intra-arterial (62.5 mg)
Frequency of dosing:	single injection
Route of administration:	intravenously (IV, bolus, lateral marginal ear vein) intra-arterially (IA, bolus, central ear artery), paravenously (PV, bolus, medial marginal ear vein intramuscularly (IM, bolus, quadriceps femoris muscle)
Dose volume:	0.2 to 0.5 mL (see table below for volume administered to specific sites)
Formulation:	Ready-to-use (RTU) abatacept solution contained approximately 125 mg abatacept, 171 mg sucrose, 8 mg Poloxamer 188, 0.14 mg monobasic sodium phosphate, monohydrate, and 0.98 mg dibasic sodium phosphate, anhydrous, in water for injection, pH 7.2
Control Vehicle:	0.9% sodium chloride for injection
Species/Strain:	New Zealand White Hra: (NZW) SPF rabbits, only females
Number/Sex/Group:	6 females/group

Age:	5 months of age
Weight:	2.6 and 2.9 kg
Satellite groups:	None
Unique study design:	refer to table below, 3 animals were sacrificed at 24 hours post-dosing and 3 at 5 days post-dosing

Group	Site	Number of Animals	Daily Dose Abatacept (mg)	Volume (mL)	Concentration Abatacept (mg/mL)
1	Right Ear Intravenous[b]	6 (F)	62.5	0.5	125
	Right Ear Intraarterial[b]		62.5	0.5	125
	Right Ear Paravenous		25	0.2	125
	Right Quadriceps Femoralis Intramuscular		31.25	0.25	125
	Left Ear Intravenous[b]		-	0.5[a]	-
	Left Ear Intraarterial[b]		-	0.5[a]	-
	Left Ear Paravenous		-	0.2[a]	-
	Left Quadriceps Femoralis Intramuscular		-	0.25[a]	-

a. Control dose: saline (0.9%, sterile USP)

b. Intravenous and intraarterial injections performed as a bolus injection (less than 3 mL/min)

Note: For the purposes of gross and microscopic pathology reporting, injection sites were assigned to separate groups: Intravenous Drug Treatment, Intravenous Control, Intraarterial Drug Treatment, Intraarterial Control, Paravenous Drug Treatment, Paravenous Control, Intramuscular Drug Treatment and Intramuscular Control.

Deviation from study protocol:	There were no deviations that influenced the study interpretations and conclusions.

Observations and Results

Mortality

There were no deaths.

Clinical Signs in addition to standard observations the injection sites were examined for signs of irritation (erythema and edema) after all injections were completed and at approximately 4, 24, 48, 72 and 96 hr postdose

There were no abatacept effects on clinical signs.

Body Weights Each rabbit was weighed pretest, on the day of dosing (Day 1), and prior to necropsy

There were no effects on body weight.

Feed Consumption; not assessed
Ophthalmoscopy: not assessed
ECG: not assessed
Hematology: not assessed
Clinical Chemistry: not assessed
Urinalysis: not assessed

Gross Pathology

There were no abatacept related gross findings. Gross findings were of similar incidence and severity in both vehicle control- and abatacept-injected animals and were attributed to minor trauma associated with the injection procedure. Gross lesions consisted of red, blue, or black discoloration of the ear at the injection site, and red or black and red discoloration of the quadriceps femoris injection site. Discoloration of the ear generally corresponded with the microscopic observation of subcutaneous hemorrhage, whereas discoloration at the quadriceps femoris site corresponded microscopically with hemorrhage in only 1 site.

Organ Weights not assessed

Histopathology
Adequate Battery: yes
Peer Review:yes

There were no abatacept-related histopathological findings. Both abatacept-injected and saline control injected sites had similar incidences and severities of findings at both the day 2 and day 5 assessments.

In intravenous, intraarterial, and paravenous injection sites of the ears, findings included vascular degeneration, most commonly in the absence of thrombosis; and perivascular and subcutaneous inflammation, hemorrhage, and/or edema. Inflammation was generally acute at Day 2 and subacute, chronic, or chronic-active at Day 5. There were no clear differences in the incidence or severity of vascular degeneration at abatacept- and vehicle control-injected sites, but these changes occurred at greater incidence and severity at day 5 compared to day 2. This was attributed to the time required for the development of these changes. Vascular degeneration consisted of endothelial changes (rounded and hyperchromatic nuclei) and, less commonly, fragmentation and/or separation of the vascular wall. Degeneration of cutaneous nerves in the ear, characterized by vacuolation and loss of axons and, less commonly, hemorrhage or

cellular infiltration, was attributed primarily to pressure atrophy secondary to subcutaneous hemorrhage. Nerve degeneration was most common at intra-arterial sites, and was attributed to the density of cutaneous nerves in the periarterial subcutis being damaged by arterial needle punctures themselves, as well as the induction of hemorrhage. There were no drug-related microscopic findings in either the Day 2 or Day 5 quadriceps femoris injection site.

Table 8: Histopathological Findings for the Intravenous Site of Administration on Day 2

	Injection site		Proximal		Distal	
Dose (mg/kg):	0	62.5	0	62.5	0	62.5
No. of sites:	3	3	3	3	3	3
Degeneration, vascular						
Minimal	-	-	-	-	-	-
Slight	1	-	-	1	1	1
Inflammation						
Minimal	1	-	1	-	1	-
Slight	-	-	-	-	-	1
Hemorrhage						
Minimal	1	2	2	1	2	-
Slight	-	-	-	-	-	1
Edema						
Minimal	-	1	1	-	2	2

A dash (-) indicates absence of finding in group

Table 9: Histopathological Findings for the Intravenous Site of Administration on Day 5

	Injection site		Proximal		Distal	
Dose (mg/kg):	0	62.5	0	62.5	0	62.5
No. of sites:	3	3	3	3	3	3
Degeneration, vascular						
Minimal	-	-	-	-	-	-
Slight	2	1	3	2	2	2
Mild	1	1	-	-	-	1
Thrombus						
Minimal	-	-	1	-	1	1
Edema						
Minimal	2	-	-	2	2	1
Slight	-	1	1	1	-	1

A dash (-) indicates absence of finding in group.

Table 10: Histopathological Findings for the Intraarterial Site of Administration on Day 2

	Injection site		Distal	
Dose (mg/kg):	0	62.5	0	62.5
No. of sites:	3	3	3	3
Thrombus				
Minimal	-	-	-	-
Slight	-	-	-	1
Inflammation				
Minimal	1	1	1	1
Slight	-	1	2	1
Mild	-	-	-	1
Hemorrhage				
Minimal	-	1	-	-
Slight	1	1	1	2
Mild	2	-	2	-
Moderate	-	1	-	1
Edema				
Minimal	-	-	-	-
Slight	1	1	1	-
Mild	1	1	2	3
Degeneration, nerve				
Minimal	1	-	-	1
Slight	1	-	1	1
Mild	-	-	1	1

A dash (-) indicates absence of finding in group

Table 11: Histopathological Findings for the Intraarterial Site of Administration on Day 5

	Injection site		Distal	
Dose (mg/kg):	0	62.5	0	62.5
No. of sites:	3	3	3	3
Degeneration, vascular				
Minimal	-	-	1	-
Slight	-	-	1	-
Inflammation				
Minimal	-	1	2	2
Slight	1	1	1	1
Hemorrhage				
Minimal	-	1	1	2
Slight	1	1	1	1
Edema				
Minimal	1	-	-	-
Slight	-	-	3	1
Degeneration, nerve				
Minimal	-	-	-	-
Slight	1	-	1	-

A dash (-) indicates absence of finding in group

Table 12: Histopathological Findings for the Paravenous Site of Administration on Day 2

	Injection site		Proximal		Distal	
Dose (mg/kg):	0	25	0	25	0	25
No. of sites:	3	3	3	3	3	3
Degeneration, vascular						
Minimal	-	-	-	-	-	-
Slight	-	1	-	1	-	1
Inflammation						
Minimal	1	-	-	-	1	-
Slight	1	-	1	-	-	-
Hemorrhage						
Minimal	1	1	1	-	-	-
Slight	-	-	-	-	-	-
Mild	-	-	-	1	-	1
Edema						
Minimal	1	1	2	-	-	-
Slight	-	-	-	-	1	1
Mild	1	1	1	-	-	-

A dash (-) indicates absence of finding in group

Table 13: Histopathological Findings for the Paravenous Site of Administration on Day 5

	Injection site		Proximal		Distal	
Dose (mg/kg):	0	25	0	25	0	25
No. of sites:	3	3	3	3	3	3
Degeneration, vascular						
Minimal	-	-	-	-	-	-
Slight	2	3	2	2	-	3
Mild	-	-	-	1	-	-
Inflammation						
Minimal	-	-	-	-	1	-
Hemorrhage						
Minimal	-	-	-	-	-	1
Slight	-	-	-	-	1	-
Mild	-	-	-	-	-	-
Edema						
Minimal	-	-	1	-	1	-
Slight	-	2	-	1	-	-
Degeneration, nerve						
Minimal	-	-	-	-	1	-
Slight	-	-	1	-	1	-

A dash (-) indicates absence of finding in group

Toxicokinetics	Not assessed.
Stability and Homogeneity within its appropriate shelf life.	Not assessed. The Applicant indicated it was used

11 Integrated Summary and Safety Evaluation

BMS submitted this supplemental BLA for Abatacept for an alternative route of administration (SC) to that of the originally approved route of administration (IV). In support of this new route, the Applicant conducted 3 nonclinical local tolerance studies using the subcutaneous route of administration to rats and rabbits. These species were used in previous toxicological studies for abatacept approval and the rat was also used in the postmarketing commitment to conduct juvenile animal studies. However, binding kinetics to CTLA4 and subsequent Fc effector kinetics in these species for comparison to humans has not been evaluated.

The potential for local irritation and tolerance of the SC formulation was studied in rats by single administration of a single dose, then followed for up to 5 days. Another study was conducted in rabbits to assess local tolerance for the possibility that it may be inadvertently injected into a blood vessel, paravenously or intramuscularly.

BMS-188667 (abatacept) ready-to-use (RTU) clinical formulation (125 mg/mL) or saline control was administered (1 mL/injection site) each to a group of 8 male rats as a single subcutaneous dose (125 mg/animal). [For comparison, the human proposed dose is also 125 mg/adult patient]. Abatacept slightly increased incidence and severity of histopathologic signs of acute inflammation on day 2 and subacute inflammation on day 5. None of the changes were judged to be toxicologically significant. There were also no changes in survival, clinical or dermal signs, body weight, or gross-pathology findings that could be attributed to abatacept.

To address accidental exposure of injection into a blood vessel or intramuscularly, rabbits received a single injection of abatacept subcutaneous formulation (125 mg/ml) either intravenously (lateral marginal ear vein, 62.5 mg), intra-arterially (central ear artery, 62.5 mg), paravenously (medial marginal ear vein, 25 mg) or intramuscularly (quadriceps femoris muscle, 31.25 mg). Similar incidences and severities of gross (tissue discoloration: red, blue, or black) and histopathological findings occurred at both vehicle (saline) and abatacept-treated injection sites. Also there were no abatacept-related mortalities, changes in body weight, or clinical observations. Although the doses in this study were less than that to be administered subcutaneously in patients, this was not addressed by the Applicant. Doses were probably constrained by the feasible injection volume coupled with the use of the to-be-marketed formulation prepared as 125 mg/mL as the source of drug. Previous studies within the original BLA submission for the initial intravenous route of administration had satisfactorily addressed the potential for vascular toxicity.

In summary, the three nonclinical toxicological studies support the safety of the abatacept's subcutaneous formulation and this route of administration in patients.

Reviewer Signature L Steven Leshin **Date** 5/5/2011

Supervisor Signature Mary E. Tapper **Date** 5/5/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125118 **Applicant: Bristol-Myers Squibb Co.** **Stamp Date: Oct 4 2010**

Drug Name: Orencia (abatacept) **BLA Type:**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Differences in the excipients between the currently approved IV formulation and the proposed SC formulation
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No new impurity issues
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES,

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues were identified for the 74 day letter.

Submitted studies: 3 additional nonclinical studies to support subcutaneous administration of abatacept

To evaluate the potential for local irritation of the SC formulation:
2 studies in rats were conducted with the clinical SC formulation at different pH levels to assess local tolerance following the intended SC route of administration

To assess local tolerance following accidental exposure via the IV, intraarterial, paravenous, or intramuscular route of administration:
1 study in rabbits

L Steven Leshin, DVM, PhD — Nov 20, 2010 — Nov 1, 2010
Reviewing Pharmacologist — Date

Molly Topper, PhD — Nov. 24, 2010
Team Leader/Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125118/122
Drug Name:	Orencia (Abatacept) Injection Solution
Indication(s):	Subcutaneous Injection Administration for Rheumatoid Arthritis
Applicant:	Bristol-Myers Squibb Company
Date(s):	Receipt date: October 4, 2010
	PDUFA date: August 4, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kiya Hamilton, Ph.D.
Concurring Reviewers:	Joan Buenconsejo, Ph.D., Team Leader
	Thomas Permutt, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy and Rheumatology Products
Clinical Team:	Keith Hull, M.D., Medical Reviewer
	Sarah Yim, M.D., Team Leader
	Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director
Project Manager:	Colette Jackson

Keywords: BLA review, clinical studies, non-inferiority trial design, sensitivity analyses

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1. EXECUTIVE SUMMARY

Bristol-Myers Squibb (BMS) proposes a new formulation of abatacept (Orencia®) to be administered subcutaneously (SC). The applicant conducted Study IM101174 to evaluate the efficacy and safety of SC abatacept compared to intravenous (IV) abatacept in subjects with rheumatoid arthritis (RA), who were receiving background methotrexate (MTX), and that were experiencing an inadequate response to MTX (MTX-IR). The non-inferiority (NI) margin for Study IM101174 was -7.5%, which preserved at least 70% of the treatment effect (benefit over placebo using ACR 20 response rate). The study met the success criteria: non-inferiority of SC abatacept to IV abatacept. The applicant provided rationale for the study design of non-inferiority.

I identified no statistical issues during the course of my review. In the primary and secondary analysis of ACR/HAQ response rates, subjects who received the study mediation but dropped out prior to study endpoint were included in the analysis and treated as non-responders in the analysis. For the secondary analysis for HAQ-DI, missing data was imputed with the last observation carried forward (LOCF) except for subjects with only baseline observations. There was a 6% dropout rate in each treatment group for Study IM101174. The most common reason for early dropout in both treatment groups was due to adverse events (AE); 17 (2%) patients in the SC abatacept group and 25 (4%) patients in the IV abatacept group. Given that the percentage of dropouts was low and the findings were consistent after applying different imputation strategies, the impact of missing data in this application is inconsequential. It is worthwhile to note that analyses for the secondary endpoints were not adjusted for multiplicity.

I conclude that the evidence of efficacy from Study IM101174 is substantial in terms of analysis populations such as intent-to-treat (ITT) and per-protocol (PP), in terms of missing data handling, subpopulations based on baseline demographics and disease characteristics, and statistical model with covariates of stratification.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Intravenous (IV) abatacept (Orencia®) was approved in the United Stated of America (US) in December 2005 for the treatment of adult rheumatoid arthritis (RA). Abatacept is also approved for the treatment of juvenile idiopathic arthritis (JIA) in the US. RA is an autoimmune disease that causes chronic inflammation of the tissues around the joints, as well as in other organs in the body. It is a chronic, symptomatic disease that can result in a variety of outcomes with different chronologies, severities, and overall patient effects. In this application a new formulation of abatacept is proposed, subcutaneous (SC) abatacept, to be used for the treatment of RA.

The new formulation will allow for self-administration by patients. SC abatacept is administered by subcutaneous injection once a week regardless of weight. Bristol-Myers Squibb (BMS) is

requesting approval for dosage strength of 125 mg, to include information on IV and SC formulations in the same label, that the currently approved IV abatacept claims are extended to SC abatacept, and that additional descriptions of the clinical experience, dosing regimens, and product information for SC are included in the label.

2.1.2 History of Drug Development

IND 9,391, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, for SC abatacept formulation was submitted on September 6, 2007. An end-of-phase 2 meeting was held on November 27, 2007 where the applicant suggested in study IM101174, that there should be a 12.5% non-inferiority margin between SC abatacept and IV abatacept groups to preserve approximately 55% of the IV abatacept treatment effect compared to MTX monotherapy (from the Phase 3 study of IV abatacept/MTX in RA patients with inadequate response to MTX, Study IM101102). The division recommended that the applicant decrease the margin to preserve a greater proportion of the treatment benefit, at least 70%; this lead to a non-inferiority margin of -7.5%. The applicant agreed.

On October 4, 2010, BMS submitted a supplemental Biologics Licensing Application (sBLA) for the reason described below.

> To describe the efficacy, safety, immunogenicity and product quality results from the studies comprising (BMS') development program for the subcutaneous (SC) abatacept product to support use of SC abatacept for the following indication:
>
> ORENCIA® 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. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists. ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy, such as anakinra.

2.1.3 Specific Studies Reviewed

Efficacy Study IM101174 is the focus of this review. This study is based on subjects with RA who are receiving background methotrexate (MTX), and experiencing an inadequate response to MTX (MTX-IR). Study IM101174 is a phase 3b, randomized, double-blind, double-dummy, placebo-controlled, multi-center non-inferiority trial. Approximately 1,464 subjects were randomized to SC abatacept or IV abatacept in a 1:1 ratio stratified by weight (< 60 kg, 60 to 100 kg, and > 100 kg). There were 242 study centers worldwide: 82 sites in the US, 64 sites in Europe (Austria, Belgium, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Turkey, and the United Kingdom), 13 sites in Canada, 6 sites in Australia, 14 sites in Brazil, 13 sites in Mexico, 7 sites in South Africa, 5 sites in the Republic of Korea, 6 sites in Taiwan, 5 sites in Russia, 7 sites in India, and 20 sites in South America (Argentina, Chile, and Peru).

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in (b) (4) transport format. The data and final study report for the electronic submission were archived under the network path location \\cber-fs3\m\eCTD_Submissions\STN125118\125118.enx. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoint analyses. I was able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study IM101174 used a non-inferiority (NI) trial design with IV abatacept as the active comparator. The NI margin of -7.5% was based on two prior IV abatacept registrational studies (IV abatacept versus placebo) conducted by BMS. The NI margin was justified as preserving 70% of the minimum expected benefit of 25% in ACR 20 at 6 months based on FDA guidance for Non-Inferiority Clinical Trials. Study IM101174 employed a phase 3b, randomized, double-blind, double-dummy, placebo-controlled 6-month treatment (short term [ST]) period followed by an open-label long term (LT) period that compared the efficacy, safety, pharmacokinetics (PK), and immunogenicity of abatacept administered SC and IV in subjects with RA, receiving background MTX, and experiencing an inadequate response to MTX-IR. During the double-blind ST period, all subjects were randomized in a 1:1 ratio with stratification by body weight (< 60 kg, 60 to 100 kg, > 100 kg) to receive abatacept through two different routes of administration. One group received 125 mg weekly SC abatacept injections (with an IV abatacept loading dose on Day 1, based on weight) and the other group received IV abatacept infusions on Days 1, 15, 29, and every 28 days, thereafter. A 'double-dummy' design was used to protect the blind. Thus, subjects receiving IV infusions of abatacept ("IV abatacept") also received SC injections of placebo ("SC Placebo"). Conversely, subjects receiving SC injections of abatacept ("SC abatacept") also received IV infusions of placebo ("IV Placebo") with the exception that on Day 1 a loading dose of IV abatacept replaced the IV Placebo treatment. Subjects continued taking their current dose of MTX from the day of randomization. Increases in doses of MTX were not permitted during the first 6 months (up to Day 169). Methotrexate dose could only be decreased for toxicity. Biologics or DMARDs other than MTX were not permitted. After 6 months, subjects entered the LT period during which all subjects received 125 mg weekly of SC abatacept. Subjects did not receive any IV infusions (active or placebo) in the LT period.

The primary efficacy endpoint was the proportion of subjects achieving an ACR 20 response at day 169, which was defined as the proportion of subjects meeting the ACR criteria of 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the remaining 5

core set measures (subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and one acute phase reactant value [CRP]). The secondary efficacy endpoints were as follows:

- Proportion of subjects with ACR 50 response at Day 169
- Proportion of subjects with ACR 70 response at Day 169
- Mean change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Day 169
- Proportion of subjects with HAQ response at Day 169.

ACR 50 and ACR 70 responses are defined similarly to ACR 20 with 50% and 70% improvement, respectively.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

The applicant's target population was defined as

> Subjects with RA who had been treated with MTX for at least 3 months and had experienced an inadequate response to MTX. This patient population did not include subjects who failed anti-tumor necrosis factor (TNF) therapy.

A total of 2,472 subjects were enrolled into study IM101174. Of this, 1,464 were randomized and 1,457 were treated in the study. According to the applicant

> The most frequent reason for not being randomized was subjects no longer meeting study criteria (N = 918, 37%). Seven (7) subjects were randomized but not treated (4 subjects no longer met study criteria, 2 subjects withdrew consent, and 1 subject was randomized in error [other]).

Of the 1,457 subjects in the ST period, there were 736 patients in the SC abatacept group and 721 patients in the IV abatacept group. In the ST period, 6% of patients in the SC abatacept group and in the IV abatacept group discontinued from the study; the most common reason for early termination in both treatment groups was adverse events (AE); 17 (2%) patients in the SC abatacept group and 25 (4%) in the IV abatacept group. Figure 1 summarizes the patient disposition in the ST and LT periods of the study. Table 9 in the appendix summarizes the reasons for discontinuation during the ST period for all randomized and treated patients.

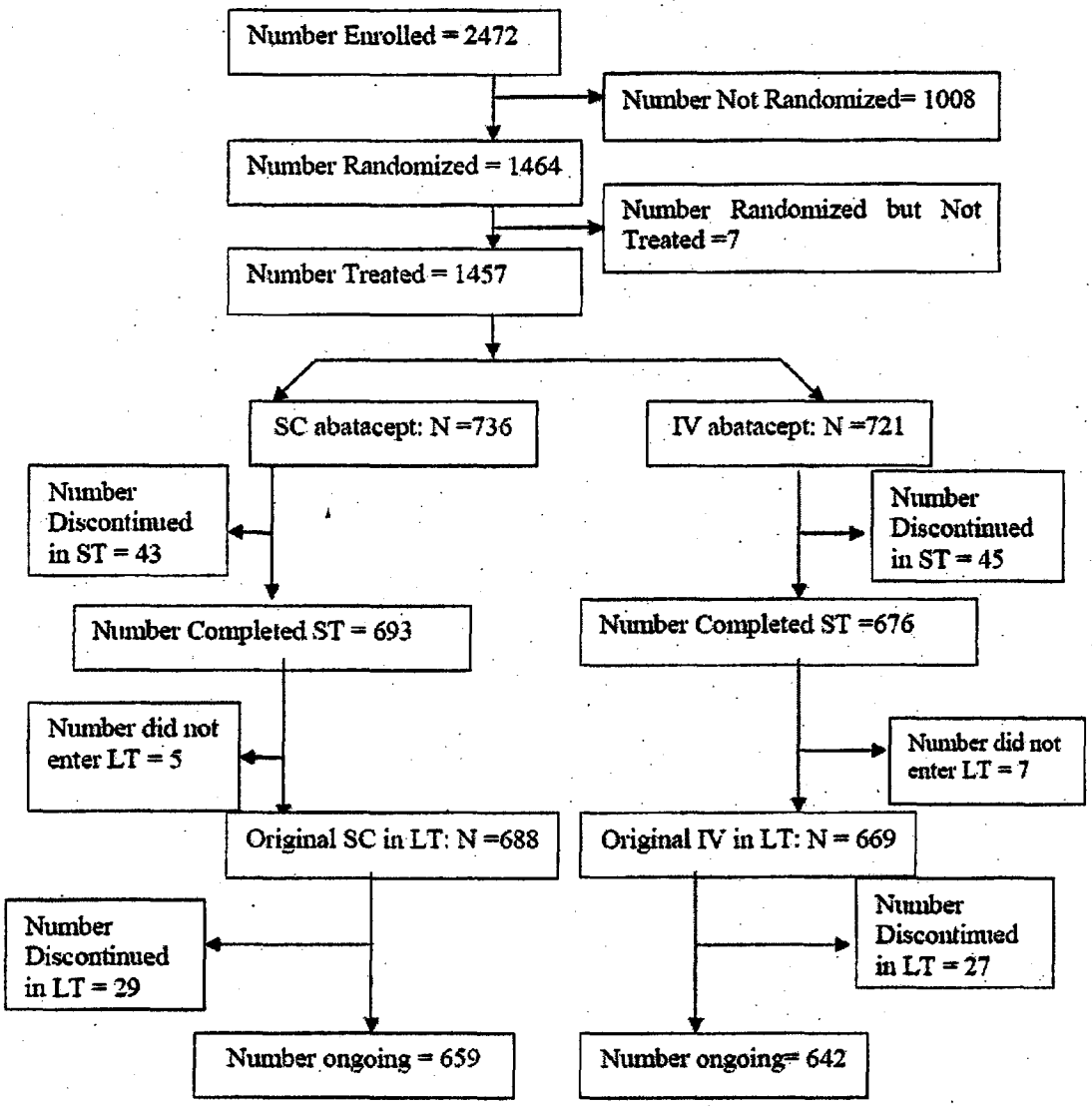


Figure 1 Patient Disposition in the ST and LT Periods
Source: Final Clinical Report Figure 5.1, page 135

The mean age was 50 years and the mean body weight was 72 kg. About 67% of the subjects were in the 60 to 100 kg category, 25% of the subjects were in the low weight group (<60% kg), and 8% of the subjects were in the high weight group (>100kg). Most subjects were women (82%) and Caucasian (74%). About 50% of the subjects were from South America. The mean MTX dose at baseline was about 16.4 mg/week. The disease characteristics at baseline were evenly matched between the two treatment groups. There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups. Detailed information on demographic and baseline characteristics based on the per protocol (PP) population for the ST period are summarized in Tables 10-11 in the appendix.

The primary and key secondary efficacy analyses were conducted on the PP population. The PP set was defined as all randomized patients with at least one dose of study medication without relevant protocol deviations that might affect the primary efficacy outcomes. The relevant protocol deviations are as follows:

1. Functional class IV RA.
2. Joint Count at randomization (< 10 swollen joints, <12 tender joints).
3. CRP < 0.5 mg/dL prior to or on Day 1.
4. Subject received ≤ 5 mg MTX per week for more than 1 week during the 4 weeks prior to Day 1.
   Note: If a subject has multiple records of MTX weekly dose at a particular time point, then an overall MTX weekly dose will be calculated and reported.
5. Subjects received inadequate washout for Biologic or leflunomide prior to Day 1; inadequate washout is defined as wash out was short in more than 7 days.
6. Subjects received 2 or more Anti-TNF therapy for anytime prior to Day 1.
7. Addition of prohibited DMARD: Sulfasalazine, chloroquine, hydroxychloroquine, azathioprine, gold and leflunomide during Day 1 to Day 169.
8. Use of Biologic during Day 1 to Day 169.
9. Prohibited medications: mycophenolate mofetil, cyclosporine, calcineurin inhibitors, D-Penicillamine during Day 1 to Day 169 if taken in route of IV, IM, SC or oral.
10. Prohibited Procedures: immunoadsorption column(s) such as Prosorba protein-A silica column during Day 1 to Day 169.
11. A n increase in MTX weekly dose at Day 169 in at least 5 mg/week more than the weekly dose at a baseline.
12. Received I A/IM/IV, or high dose steroid bursts < 28 days prior to Day 169.
13. Received more than 2 IA injection(s) during Day 1 to Day 169. A course of high dose steroid during Day 1 to Day 169 is counted toward to the limit of 2 IA injections.
14. Subject missed 5 or more consecutive SC doses during Day 1 to Day 169.
15. Subject missed 2 or more consecutive IV doses during Day 1 to Day 169.

The applicant also provided summaries of the ACR and HAQ responses which were conducted on the intent-to-treat (ITT) population. The ITT set was defined as all randomized patients with at least one dose of study medication. All other efficacy analyses were performed using the ITT population, unless otherwise specified.

3.2.3 Statistical Methodologies

The NI margin chosen was based on two prior studies from abatacept IV registrational studies (IV abatacept versus placebo) conducted by BMS. The minimum expected benefit of IV abatacept over placebo in ACR 20 at 6 months is 25%. According to the Applicant,

> A 20% change in ACR criteria and difference from placebo is considered clinically important and valid. Goldsmith et al, reported that an active drug needs to have at least 18% improvement in ACR 20 over placebo to be clinically important. Therefore, it would be reasonable to expect that any difference between the 2 active formulations that is within ±20% of the difference of IV from placebo would not be clinically meaningful.
>
> Based on regulatory guidelines and feedback from regulatory authorities, non-inferiority of abatacept SC to abatacept IV will be demonstrated by showing that the SC formulation preserves at least 70% treatment effect (benefit over placebo using the ACR 20 response rate) seen with the IV formulation. In this case, the non-inferiority margin that leads to 70% preservation of the minimum effect of abatacept IV is 7.5% determined from (1-0.7) x 25%. This proposed non-

inferiority margin of 7.5% is within ±20% of the difference of IV from placebo and, as described above, would not be considered clinically meaningful.

Therefore, the SC formulation was pre-specified to be non-inferior to the IV formulation, if the lower limit of a two-sided 95% confidence interval (CI) of the difference in ACR 20 response rates between SC abatacept and IV abatacept were greater than or equal to the non-inferiority margin of -7.5%.

Treatment difference of ACR 20 response rate at Day 169 between SC abatacept and IV abatacept were provided with the point estimate and the two-sided 95% CI using the minimum risk weights method to account for the randomization stratification. The ACR 20 response rate was summarized for each treatment group using the point estimate and 95% CI by visit and the proportion of subjects achieving ACR 20 were plotted over time.

The secondary analysis of ACR 50 and ACR 70 responses were summarized similarly to ACR 20 with 50% and 70% improvement, respectively. No NI margin was pre-specified for the ACR 50 and ACR 70 responses. Thus, the treatment difference in ACR 50 and ACR 70 were provided for descriptive purposes only.

Physical function was characterized by HAQ-DI. The proportion of subjects achieving HAQ response was summarized by the point estimate and 95% CI for each treatment group by visit. HAQ response rate over time was plotted by treatment group. The difference in the HAQ response rates between the treatment groups were provided by the point estimate and the 2-sided 95% CI using minimum risk weights methods to account for the randomization stratification. No NI margin was pre-specified for the HAQ response, thus, the treatment difference in HAQ response was provided for descriptive purposes only. A summary of the mean change from baseline in HAQ-DI and its subscales by an analysis of covariance (ANCOVA) model were provided by treatment group and visit. The ANCOVA model included treatment as the main factor, baseline values and weight stratification as covariates. Table 1 summarizes the planned efficacy analyses.

Table 1 Planned Efficacy Analyses

Measure of Interest	Analysis Method
ACR response	Point estimate of response rate, 95% CI, point estimates and 95% CI of treatment difference adjusted for stratification
Changes in HAQ disability index	ANCOVA*, adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups
HAQ response	Point estimate of response rate, 95% CI, point estimates and 95% CI of treatment difference adjusted for stratification
Changes in DAS28-CRP	ANCOVA*, adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups

* ANCOVA = Analysis of Covariance
Source: Final Clinical Study Report Table 7.1, page 3679

All subjects who prematurely discontinue the study after receiving study medication had missing data imputed as non-responder at all scheduled protocol visits subsequent to the point of discontinuation for ACR/HAQ response. For the summaries by an ANCOVA model in HAQ-DI and its subscales, missing values were imputed using the last observation carried forward (LOCF) except for subjects with only baseline observations.

The applicant conducted subgroup analyses for the primary and key secondary efficacy endpoints based on age, women's age, baseline weight, baseline weight quartile, gender, race, geographic region, duration of rheumatoid arthritis, anti-TNF historical use, baseline DAS28-CRP, and baseline rheumatoid factor status. Point estimates and 95% CI for each treatment group at day 169 were calculated for each subgroup. The subgroup analyses were performed using the PP analysis population.

3.2.4 Results and Conclusions

The applicant states that the primary objective of the study was met: non-inferiority of SC injections of abatacept to IV infusions of abatacept. I was able to confirm the applicant's results from the Final Clinical Study Report.

The applicant's overall efficacy summary in the ST period is stated below:

- SC abatacept was non-inferior to IV abatacept as measured by ACR 20 response at 6 months.
- Improvements in physical function as measured by HAQ response rates (reduction of at least 0.3 units from baseline) at 6 months were comparable between the SC abatacept group and the IV abatacept group.
- The trajectory of increasing proportion of subjects achieving HAQ response rate over the course of 6 months was similar between the SC abatacept group and the IV abatacept group.
- The ACR 50 and ACR 70 response rates at 6 months were comparable between the SC abatacept group and the IV abatacept group.
- The trajectories of increasing proportion of subjects achieving ACR 20, ACR 50, and ACR 70 response rates over the course of 6 months were similar between the SC abatacept group and the IV abatacept group.
- Efficacy as measured by ACR 20 and HAQ responses at 6 months was similar between the SC abatacept group and the IV abatacept group within each of the subgroups analyzed, including all weight-based subgroups.

The applicant's table below, Table 2 (excerpted from the final clinical study report, Table 6.3.2) shows the primary analysis results for ACR 20 response at Day 169 for the PP population. The lower bound of the 95% CI for the difference, 0.3%, is greater than the NI margin, -7.5%. Thus, the study met the non-inferiority criterion. Figure 2 summarizes the primary efficacy endpoint in the ST period.

Table 2 Proportion of Subjects with ACR 20 Response at Day 169: PP Population in ST Period

Study Day			SC Abatacept N=693	IV Abatacept N=678
Day 169	ACR 20	Number of subjects (%)	527 (76.0%)	514 (75.8%)
		95% CI	(72.9, 79.2)	(72.6, 79.0)
		Estimate of Difference (95% CI)	0.3 (-4.2, 4.8)	N/A

Estimate and 95% CI for difference is based on minimum risk weights method with stratification of baseline weight. Subjects from site 229 were excluded from the efficacy analyses.
Source: Final Clinical Study Report Table 63.2, page 158

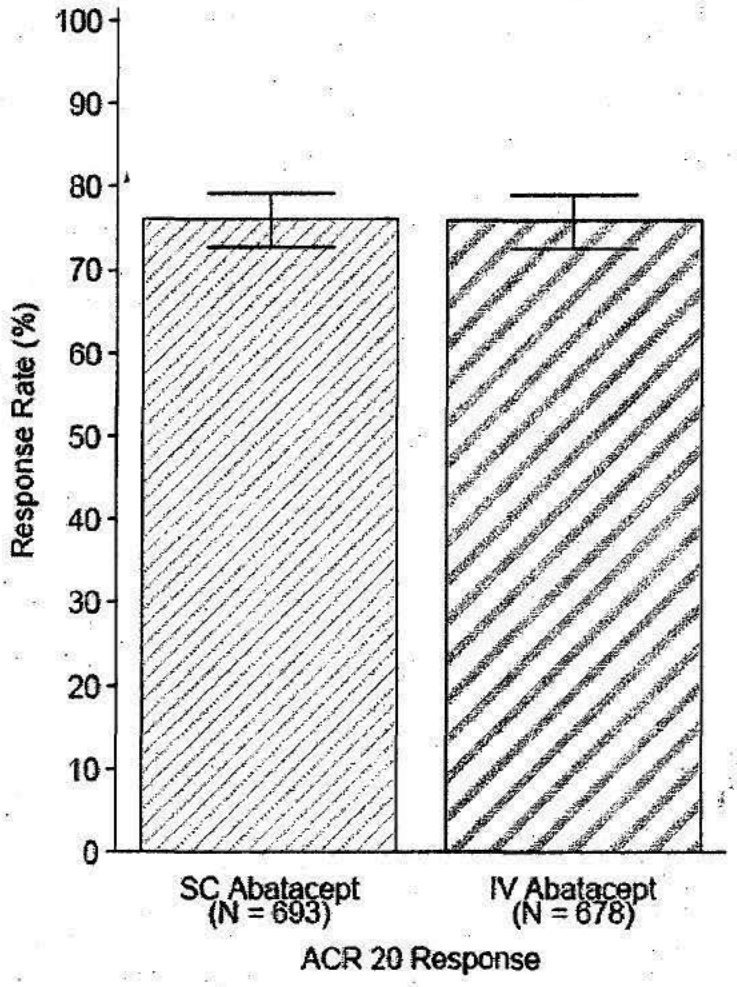


Figure 2 ACR 20 Response at Day 169 (PP Analysis): PP Population in ST Period
Source: Final Clinical Study Report Figure 63.2A, page 159

The applicant also conducted the above analysis using the ITT population. The same conclusion was drawn from the ITT analysis as was from the PP analysis; the estimated difference between the SC abatacept group and the IV abatacept group in the proportion of ACR 20 responders at Day 169 was 0.5% (95% CI: -4.0%, 4.9%). The proportion of subjects the SC abatacept group

and the IV abatacept group with an ACR 20 response at Day 169 was 74.8% and 74.3%, respectively. The lower bound of the 95% CI for the difference, 0.5%, is greater than the NI margin, -7.5%.

For ACR 20 response over time

> At the first assessment in the ST period (Day 15), the ACR 20 response rate was 25.0% in the SC abatacept and 25.2% in the IV abatacept group. The ACR 20 response rates in both treatment groups continued to increase comparably over the 6-month ST period.

Figure 3 show the trajectories of the increasing proportion of subjects achieving ACR 20 response rates over 6 months.

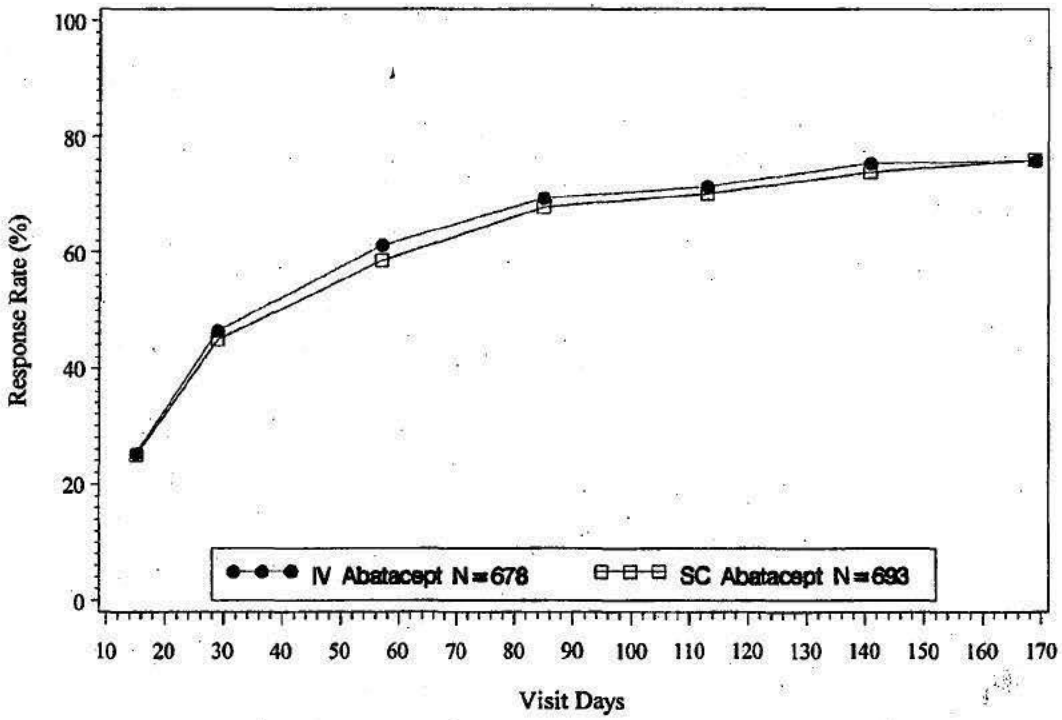


Figure 3 ACR 20 Response Over Time during ST Period (PP analysis)
Source: Final Clinical Study Report Figure 6.3.2B, page 160

The results of the secondary efficacy endpoints for ACR 50 and ACR 70 are as follows

> The ACR 50 response rates in both treatment groups were similar at the first assessment on Day 15, and continued to increase comparably over the 6-month ST period. The ACR 50 response rates at Day 169 were similar between the SC abatacept group and the IV abatacept group (50.2% and 48.6%, respectively).
>
> The ACR 70 response rates in both treatment groups were similar at the first assessment on Day 15, and continued to increase comparably over the 6-month ST period. The ACR 70 response rates at Day 169 were similar between the SC abatacept group and the IV abatacept group (25.8% and 24.2%, respectively).

Table 3 summarizes the applicant's results for ACR 50 and ACR 70 at Day 169 for the ITT population.

Table 3 Proportion of Subjects with ACR Response at Day 169: ITT Population in ST Period

Study Day			SC Abatacept N=733	IV Abatacept N=716
Day 169	ACR 50	Number of subjects (%)	368 (50.2%)	348 (48.6%)
		95% CI	(46.6, 53.8)	(44.9, 52.3)
		Estimate of Difference (95% CI)	1.6 (-3.5, 6.8)	N/A
	ACR 70	Number of subjects (%)	189 (25.8%)	173 (24.2%)
		95% CI	(22.6, 29.0)	(21.0, 27.3)
		Estimate of Difference (95% CI)	1.6 (-2.9, 6.1)	N/A

Estimate and 95% CI for difference is based on minimum risk weights method with stratification of baseline weight. Subjects from site 229 were excluded from the efficacy analyses.
Source: Final Clinical Study Report page 864

Figure 4 shows the trajectories of the increasing proportion of subjects achieving ACR 50 response rates over 6 months.

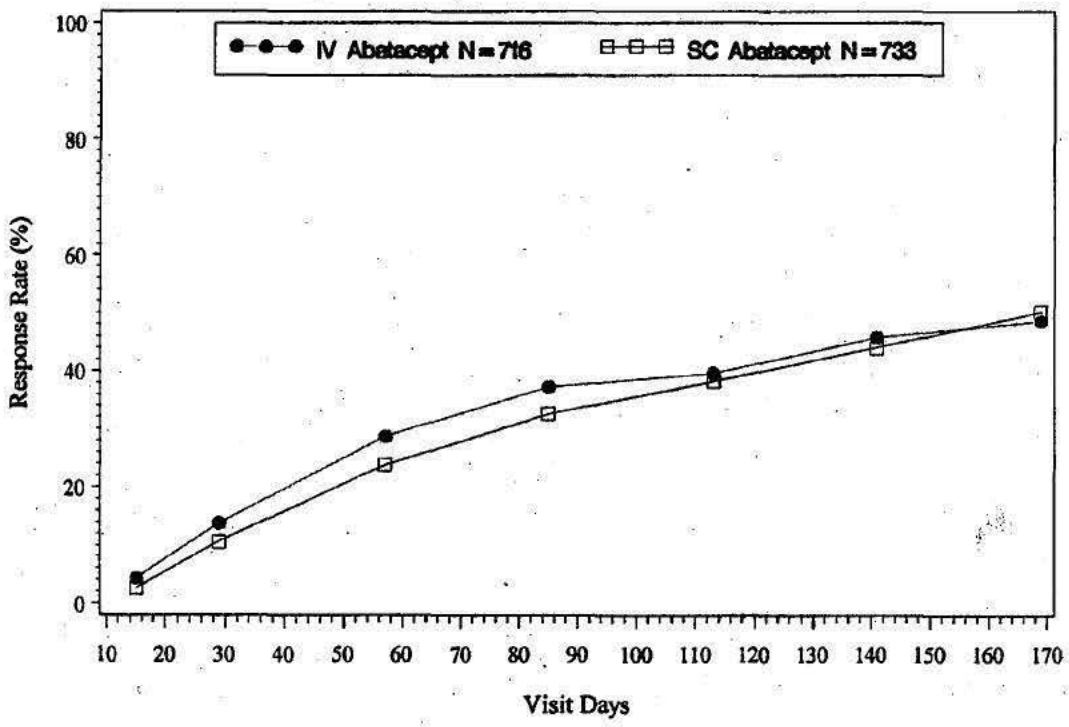


Figure 4 ACR 50 Response Over Time during ST Period (ITT Analysis)
Source: Final Clinical Study Report Figure 6.3.3.1A, page 161

Figure 5 shows the trajectories of the increasing proportion of subjects achieving ACR 70 response rates over 6 months.

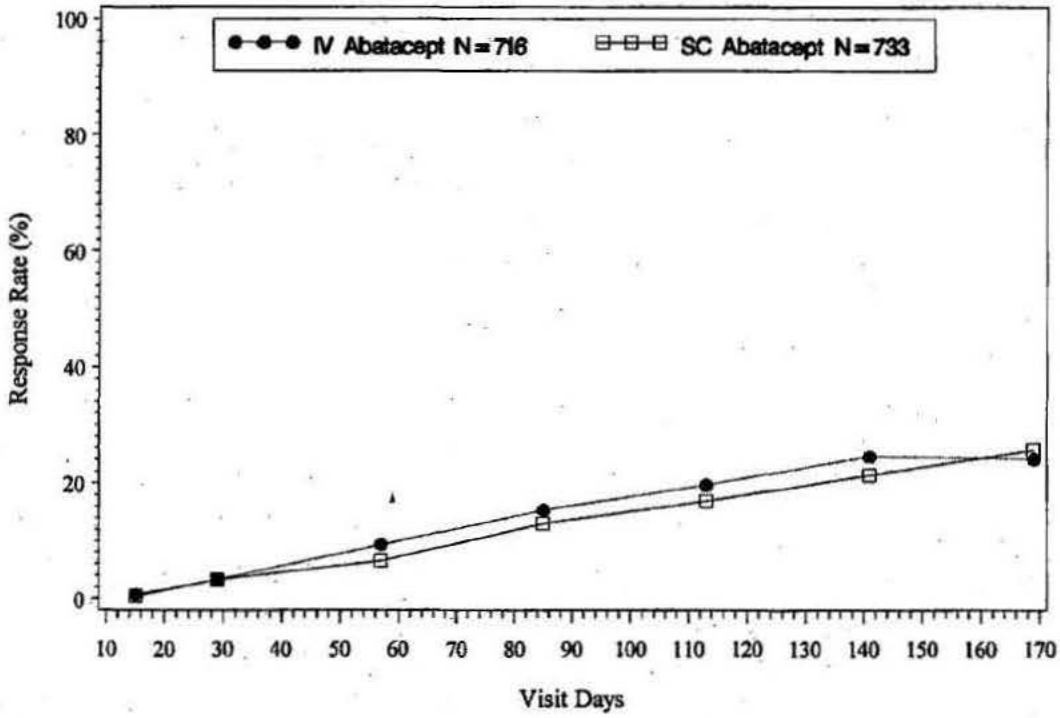


Figure 5 ACR 70 Response Over Time during ST Period (ITT Analysis)
Source: Final Clinical Study Report Figure 6.3.3.1B, page 162

The results of the secondary efficacy endpoint for HAQ response rates using the PP population are as follows

> The HAQ response rate (reduction of at least 0.30 units in HAQ score from baseline) in both treatment groups continued to increase comparably over the 6-month ST period. The HAQ response rates at Day 169 were similar between the SC abatacept group and the IV abatacept group (69.7% and 65.2%, respectively). A considerable proportion of subjects achieved HAQ response as early as the first assessment (Day 15) in both the SC abatacept group and the IV abatacept group (32.2 % and 30.8%, respectively).

Table 4 summarizes the applicant's results for HAQ response at Day 169 for the PP population.

Table 4 Proportion of Subjects with HAQ Response at Day 169: PP Analysis in the ST Period

Study Day			SC Abatacept N=693	IV Abatacept N=678
Day 169	HAQ	Number of subjects (%)	483 (69.7%)	442 (65.2%)
		95% CI	(66.3, 73.1)	(61.6, 68.8)
		Estimate of Difference (95% CI)	4.7 (-0.3, 9.7)	N/A

HAQ response is defined as an improvement of at least 0.3 units from baseline in the HAQ Disability Index. Estimate and 95% CI for difference is based on minimum risk weights method with stratification of baseline weight. Subjects from site 229 were excluded from the efficacy analyses.
Source: Final Clinical Study Report page 1026

The applicant conducted the above analysis for HAQ response rates using the ITT population. The same conclusion was drawn from the ITT analysis as was from the PP analysis.

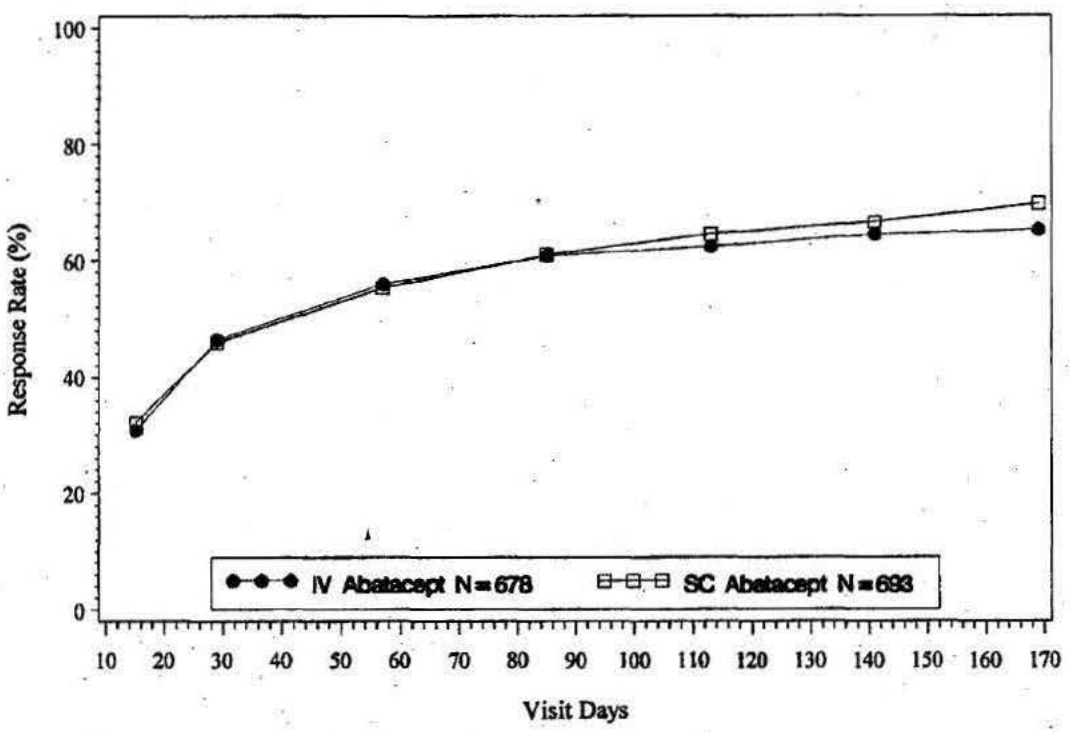


Figure 6 HAQ Response Over Time during ST Period (PP Analysis)
Source: Final Clinical Study Report Figure 6.3.3.2, page 164

The results of the secondary efficacy endpoint for HAQ-DI using the ITT population are as follows (Table 5)

> The mean reductions in disability, as assessed by adjusted mean change from baseline in the HAQ-DI score continued to decrease comparably over the 6-month ST period in both treatment groups. At Day 169, the adjusted mean reductions from baseline in HAQ-DI were the same between the SC abatacept group and the IV abatacept group; -0.69 (95% CI: -0.73, -0.64) and -0.70 (95% CI: -0.74, -0.65), respectively.
>
> Adjusted mean change from baseline in each of the HAQ-DI subscales was also similar between the two treatment groups. The reduction in the HAQ-DI subscales as observed in adjusted mean change from baseline across all subscales was consistent within each treatment group.

Table 5 HAQ-DI Adjusted Mean Change from Baseline Over Time- LOCF Analysis, ITT Population in ST Period

Study Day			SC Abatacept N=733	IV Abatacept N=716
Day 169	HAQ-DI	n	729	711
		Baseline Mean (SD)	1.72 (0.68)	1.67 (0.67)
		Post-Baseline Mean (SD)	1.02 (0.72)	0.99 (0.71)
		Adjusted Mean Change from Baseline (SE)	-0.69 (0.02)	-0.70 (0.02)
		95% CI	(-0.73, -0.64)	(-0.74, -0.65)
		Adjusted mean difference from IV (95% CI)	0.01 (-0.05, 0.07)	N/A

n is the number of subjects with both baseline and post-baseline measurements.
HAQ-DI = HAQ Disability Index
Adjustment based on ANCOVA model with treatment as factor and baseline value, baseline weight as2 covariates.
Change from Baseline = Post-baseline – Baseline value.
LOCF Analysis: the last observed values are carriedforward for missing data after discontinuation.
Subjects from site 229 were excluded from the efficacy analyses.
Source: Final Clinical Study Report page 1032

The applicant observed that there was a randomization system and dataset error. The error was discovered when BMS compared a (b) (4) dataset received for the original sBLA filing in January 2010 to another (b) (4) dataset from October 2010 in preparation for the 120-day safety update. The error consisted of the stratification (strata) information based on baseline body weight for 73 (5%) subjects. The applicant stated that the derivation of the stratification variable had been inadvertently linked to the most recently reported weight values instead of the baseline body weight values at the time of enrollment. The applicant acknowledged that the most recently reported weights could be different from the baseline body weight, thus the strata values for some of the subjects were changed from those provided in the original (b) (4) dataset used for the sBLA. By checking the vial the subject actually received, the applicant claims that the actual treatment assignment and dosing schedule for all subjects were correct. The applicant also states that the second (b) (4) file received for the 120-day safety update contains the correct strata information. They claim that based on the primary analysis results, the correction of the dataset error does not affect the overall conclusions of Study IM101174. The applicant's table with the uncorrected and corrected results is below.

Table 6 Corrected Results of the Primary Efficacy Endpoint: PP Analysis

	ACR 20 Responses at 6 Months		SC-IV Estimate & 95% CI
	SC abatacept	IV abatacept	
Data as currently reported	76.1% (530/696)	75.7% (517/683)	0.3 (-4.2, 4.8)
Data upon correction	76.0% (527/693)	75.8% (514/678)	0.3 (-4.2, 4.8)

Source: General Correspondence, date December 2, 2010

I found that out of the 73 subjects with the dataset error that there were 71 subjects included in the ITT population. There were 68 subjects included in the PP population.

The applicant also identified non-compliance with GCP regulations at Site 229 in (b) (4) As a result Site 229 was excluded from all the efficacy analyses. There were 8 subjects affected by this exclusion. I conducted an analysis including site 229 on ACR 20 response at Day 169 for both the PP and ITT populations. The conclusion was the same as the analysis excluding site 229.

I conducted a sensitivity analysis where I imputed missing values due to subjects who prematurely discontinued the study after receiving medication using LOCF for ACR20/HAQ response in the PP and ITT populations. The same conclusion was drawn from this analysis as was the analysis imputing missing data as non-responders.

I conducted an analysis on the PP and ITT populations for ACR 20 response that included the anti-TNF failure study subjects. The anti-TNF failure sub-study was to assess the immunogenicity, safety, and efficacy of the SC abatacept versus IV abatacept in a separate cohort of subjects who failed one anti-TNF therapy. There were 18 subjects randomized into this study at selected sites in Belgium, France and the US. Since there was difficulty enrolling eligible subjects, the recruitment for this sub-study was closed with Study IM101174 enrollment closure before reaching target enrollment. My analysis resulted in the same conclusion as drawn from the analysis where the anti-TNF failure sub-study subjects were excluded.

3.3 Evaluation of Safety

The evaluation of safety was conducted by Dr. Keith Hull. Reader is referred to Dr. Keith Hull's review for this section.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on the primary (ACR 20) and key secondary (HAQ response) efficacy endpoints at DAY 169 were performed by age, gender, race, weight, baseline weight quartiles, geographic location, duration of RA, anti-TNF historical use, baseline DAS28-CRP, and baseline RF status. The subgroup analyses were performed using the PP population.

4.1 Gender, Race, Age, and Geographic Region

The applicant states that

> Efficacy as measured by ACR 20 and HAQ responses at Day 169 was similar between the SC abatacept group and the IV abatacept group across all subgroups analyzed.

The summaries of subgroup analysis on age, woman and age, gender, race, and geographic region are given in Table 7 for the ST period. The subjects randomized in the study were mainly Caucasians, African Americans, and Asians, the rest of the subgroups are grouped into the "Other" category.

Table 7 Subgroup Analysis of ACR 20 and HAQ Reponses at Day 169: PP Analysis- All Randomized and Treated Subjects in ST Period

	ACR 20 Response Number of Subjects n/N (%) (95% CI)		HAQ Response Number of Subjects n/N (%) (95% CI)	
Subgroup	**SC Abatacept N=693**	**IV Abatacept N=678**	**SC Abatacept N=693**	**IV Abatacept N=678**
Age				
< 65 years	472/603 (78.3%) (75.0, 81.6)	456/600 (76.0%) (72.6, 79.4)	434/603 (72.0%) (68.4, 75.6)	396/600 (66.0%) (62.2, 69.8)
≥ 65 years	55/90 (61.1%) (51.0, 71.2)	58/78 (74.4%) (64.7, 84.0)	49/90 (54.4%) (44.2, 64.7)	46/78 (59.0%) (48.1, 69.9)
≥ 75	6/13 (46.2%) (19.1, 73.3)	7/14 (50.0%) (23.8, 76.2)	4/13 (30.8%) (5.7, 55.9)	7/14 (50.0%) (23.8, 76.2)
Women and Age				
< 50 years	237/285 (83.2%) (78.8, 87.5)	206/254 (81.1%) (76.3, 85.9)	217/285 (76.1%) (71.2, 81.1)	182/254 (71.7%) (66.1, 77.2)
≥ 50 years	213/298 (71.5%) (66.3, 76.6)	211/291 (72.5%) (67.4, 77.6)	196/298 (65.8%) (60.4, 71.2)	182/291 (62.5%) (57.0, 68.1)
Gender				
Male	77/110 (70.0%) (61.4, 78.6)	97/133 (72.9%) (65.4, 80.5)	70/110 (63.6%) (54.6, 72.6)	78/133 (58.6%) (50.3, 67.0)
Female	450/583 (77.2%) (73.8, 80.6)	417/545 (76.5%) (73.0, 80.1)	413583 (70.8%) (67.2, 74.5)	364/545 (66.8%) (62.8, 70.7)
Race				
White	383/516 (74.2%) (70.5, 78.0)	372/505 (73.7%) (69.8, 77.5)	359/516 (69.6%) (65.6, 73.5)	316/505 (62.6%) (58.4, 66.8)
Black	20/26 (76.9%) (60.7, 93.1)	16/24 (66.7%) (47.8, 85.5)	16/26 (61.5%) (42.8, 80.2)	14/24 (58.3%) (38.6, 78.1)
Asian	45/60 (75.0%) (64.0, 86.0)	54/67 (80.6%) (71.1, 90.1)	39/60 (65.0%) (52.9, 77.1)	45/67 (67.2%) (55.9, 78.4)
Other	79/91 (86.8%) (79.9, 93.8)	72/82 (87.8%) (80.7, 94.9)	69/91 (75.8%) (67.0, 84.6)	67/82 (81.7%) (73.3, 90.1)
Geographic Region				
North America	82/129 (63.6%) (55.3, 71.9)	72/111 (64.9%) (56.0, 73.7)	73/129 (56.6%) (48.0, 65.1)	61/111 (55.0%) (45.7, 64.2)
South America	294/338 (87.0%) (83.4, 90.6)	278/340 (81.8%) (77.7, 85.9)	275/338 (81.4%) (77.2, 85.5)	252/340 (74.1%) (69.5, 78.8)
Europe	80/123 (65.0%) (56.6, 73.5)	86/123 (69.9%) (61.8, 78.0)	72/123 (58.5%) (49.8, 67.2)	64/123 (52.0%) (43.2, 60.9)
Rest Of the World	71/103 (68.9%) (60.0, 77.9)	78/104 (75.0%) (66.7, 83.3)	63/103 (61.2%) (51.8, 70.6)	65/104 (62.5%) (53.2, 71.8)

Source: Final Clinical Study Report Table 63.5, page 170 and 171

4.2 Other Special/Subgroup Populations

Since IV abatacept is based on weight and SC abatacept is a fixed-dose regimen, efficacy in the different weight subgroups was of interest.

Across each of the weight subgroups, the ACR 20 and HAQ response rates were similar between the SC abatacept and IV abatacept treatment groups. In both the IV abatacept group (weight-tiered

dose regimen) and the SC abatacept group, the ACR 20 and HAQ response rates were numerically lower for the highest weight group of > 100 kg compared to the 2 other weight groups of < 60 kg and 60 to 100 kg. Similar observations were made in the analyses by weight quartiles.

Table 8 summarizes the subgroup analysis of ACR 20 and HAQ Responses at day 169 for the PP analysis.

Table 8 Subgroup Analysis of ACR 20 and HAQ Responses at Day 169: PP Analysis- All Randomized and Treated Subjects in ST Period

	ACR 20 Response Number of Subjects n/N (%) (95% CI)		HAQ Response Number of Subjects n/N (%) (95% CI)	
Subgroup	**SC Abatacept N=693**	**IV Abatacept N=678**	**SC Abatacept N=693**	**IV Abatacept N=678**
Baseline Weight				
< 60 kg	141/173 (81.5%) (75.7, 87.3)	138/168 (82.1%) (76.4, 87.9)	119/173 (68.8%) (61.9, 75.7)	113/168 (67.3%) (60.2, 74.4)
60 to 100 kg	349/463 (75.4%) (71.5, 79.3)	347/463 (74.9%) (71.0, 78.9)	334/463 (72.1%) (68.1, 76.2)	302/463 (65.2%) (60.9, 69.6)
> 100 kg	37/57 (64.9%) (52.5, 77.3)	29/47 (61.7%) (47.8, 75.6)	30/57 (52.6%) (39.7, 65.6)	27/47 (57.4%) (43.3, 71.6)
Baseline Weight by Quartiles				
1st Quartile (≤ 59.4 kg)	143/175 (81.7%) (76.0, 87.4)	139/169 (82.2%) (76.5, 88.0)	122/175 (69.7%) (62.9, 76.5)	114/169 (67.5%) (60.4, 74.5)
2nd Quartile (> 59.4 kg - ≤ 69 kg)	135/169 (79.9%) (73.8, 85.9)	150/183 (82.0%) (76.4, 87.5)	130/169 (76.9%) (70.6, 83.3)	131/183 (71.6%) (65.1, 78.1)
3rd Quartile (> 69 kg - ≤ 81.9 kg)	123/172 (71.5%) (64.8, 78.3)	116/167 (69.5%) (62.5, 76.4)	120/172 (69.8%) (62.9, 76.6)	98/167 (58.7%) (51.2, 66.2)
4th Quartile (> 81.9 kg)	126/177 (71.2%) (64.5, 77.9)	109/159 (68.6%) (61.3, 75.8)	111/177 (62.7%) (55.6, 69.8)	99/159 (62.3%) (54.7, 69.8)
Duration of RA				
≤ 2 years	178/229 (77.7%) (72.3, 83.1)	158/206 (76.7%) (70.9, 82.5)	169/229 (73.8%) (68.1, 79.5)	145/206 (70.4%) (64.2, 76.6)
2 to ≤ 5 years	115/144 (79.9%) (73.3, 86.4)	111/144 (77.1%) (70.2, 83.9)	114/144 (79.2%) (72.5, 85.8)	100/144 (69.4%) (61.9, 77.0)
5 to ≤ 10 years	100/134 (74.6%) (67.3, 82.0)	117/152 (77.0%) (70.3, 83.7)	88/134 (65.7%) (57.6, 73.7)	92/152 (60.5%) (52.8, 68.3)
> 10 years	134/186 (72.0%) (65.6, 78.5)	128/176 (72.7%) (66.1, 79.3)	112/186 (60.2%) (53.2, 67.2)	105/176 (59.7%) (52.4, 66.9)
Anti-TNF Historical Use				
Prior Users	13/23 (56.5%) (36.3, 76.8)	24/31 (77.4%) (62.7, 92.1)	12/23 (52.2%) (31.8, 72.6)	20/31 (64.5%) (47.7, 81.4)
Non-Prior Users	514/670 (76.7%) (73.5, 79.9)	490/647 (75.7%) (72.4, 79.0)	471/670 (70.3%) (66.8, 73.8)	422/647 (65.2%) (61.6, 68.9)
Baseline DAS-CRP				
> 5.1	483/630 (76.7%) (73.4, 80.0)	470/620 (75.8%) (72.4, 79.2)	449/630 (71.3%) (67.7, 74.8)	412/620 (66.5%) (62.7, 70.2)
≤ 5.1	43/60 (71.7%) (60.3, 83.1)	44/58 (75.9%) (64.8, 86.9)	33/60 (55.0%) (42.4, 67.6)	30/58 (51.7%) (38.9, 64.6)
Baseline RF Status				
Negative	61/102 (59.8%) (50.3, 69.3)	56/91 (61.5%) (51.5, 71.5)	58/102 (56.9%) (47.3, 66.5)	44/91 (48.4%) (38.1, 58.6)
Positive	456/579 (78.8%) (75.4, 82.1)	450/578 (77.9%) (74.5, 81.2)	419/579 (72.4%) (68.7, 76.0)	393/578 (68.0%) (64.2, 71.8)

Source: Final Clinical Study Report Table 63.5, page 169, 171-172

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

There were no statistical issues identified during the course of my review. In the ACR and HAQ analyses, subjects who received the study medication but dropped out prior to Day 169 were included in the analysis and missing data was imputed as non-responder. In the analysis of HAQ-DI, the LOCF strategy was used for missing values. Of the 1457 randomized patients in Study IM101174, only 6% dropped out in each treatment group. AEs were the most common reason for early termination in both treatment groups; 17 (2%) patients in the SC abatacept group and 25 (4%) patients in the IV abatacept group. Given that the percentage of dropouts was low and the findings were consistent after applying different imputation strategies and sensitivity analyses, the impact of missing data in this application is inconsequential. In addition, I was able to replicate the applicant's subgroup analysis. I conducted sensitivity analyses including the patients from Site 229 (b) (4) for ACR 20 at Day 169, as well as including the patients from the anti-TNF failure sub-study. Both results were consistent with the applicant's primary efficacy analysis for both the PP and ITT population.

5.2. Comments on the Proposed Label

Applicant's changes to the Clinical Studies section of the label include:

- Clinical response section: added SC abatacept, stating that SC abatacept infusions are non-inferior to IV abatacept infusions with respect to ACR 20 responses up to 6 months of treatment. Patients treated with SC abatacept achieved similar ACR 50 and 70 responses as those treated with IV abatacept at 6 months. There was no difference in clinical response across the 3 weight groups.

- Physical Function Response and Health-Related Outcomes section: added SC abatacept, stating that improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between SC and IV administration.

- Table 4: Clinical Responses in Controlled Trials: added results for SC abatacept study, Study IM101174, for ACR 20, ACR 50 and ACR 70 at month 3 and month 6.

Comments to the proposed label:

Several suggestions were made to the description of the study design and how the results are presented to make it more understandable and clear. P-values are removed in Table 5 given these are secondary endpoints and the results are based on the per-protocol population.

5.3. Conclusions and Recommendations

Study IM101174 is a non-inferiority study comparing SC abatacept to IV abatacept conducted in patients with RA, receiving background MTX, and experiencing an inadequate response to

MTX-IR. The study employed a non-inferiority margin of -7.5%. Based on my statistical review of the non-inferiority study, there is substantial evidence to support the claim that SC abatacept is non-inferior to IV abatacept.

6. APPENDICES

Table 9 Patient Disposition-Reasons for Discontinuation during ST Period: All Randomized and Treated Patients

	Number (%) of Subjects		
	SC Abatacept N=736	IV Abatacept N=721	Total N=1457
Number Discontinued	43 (5.8)	45 (6.2)	88 (6.0)
Reason:			
Adverse Event	17 (2.3)	25 (3.5)	42 (2.9)
Subject Withdrew Consent	11 (1.5)	5 (0.7)	16 (1.1)
Pregnancy	0	0	0
Lost To Follow-Up	0	6 (0.8)	6 (0.4)
Administrative Reason By Sponsor	1 (0.1)	0	1 (<0.1)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Subject No Longer Meets Study Criteria	2 (0.3)	1 (0.1)	3 (0.2)
Lack Of Efficacy	6 (0.8)	1 (0.1)	7 (0.5)
Poor/Non-Compliance	3 (0.4)	0	3 (0.2)
Other	2 (0.3)	6 (0.8)	8 (0.5)
Number Ongoing	0	0	0
Number Completed Period	693 (94.2)	676 (93.8)	1369 (94.0)

(b) (4)

28JAN2010 16:18

Source: Final Clinical Study Report Table 5.1A, page 136

Table 10 Baseline Demographics Characteristics - Per-protocol Analysis: Per protocol Population in ST Period

		SC Abatacept N=696	IV Abatacept N=683	Total N=1379
Age (years)	N	696	683	1379
	Mean	49.9	49.9	49.9
	SD	13.0	12.7	12.8
	Median	51.0	51.0	51.0
	Min	18.0	18.0	18.0
	Max	85.0	83.0	85.0
Weight (kg)	N	696	683	1379
	Mean	72.1	71.5	71.8
	SD	18.1	17.5	17.8
	Median	69.1	68.8	69.0
	Min	37.0	36.5	36.5
	Max	169.8	146.5	169.8
Weight category, n (%)	<60 kg	175 (25.1)	171 (25.0)	346 (25.1)
	60-100 kg	464 (66.7)	465 (68.1)	929 (67.4)
	>100 kg	57 (8.2)	47 (6.9)	104 (7.5)
Gender, n (%)	MALE	110 (15.8)	134 (19.6)	244 (17.7)
	FEMALE	586 (84.2)	549 (80.4)	1135 (82.3)

Abbreviations: ROW = Rest of World.
Baseline is Day 1 of the study.

(b) (4)

19NOV2010 11:02

Source: Final Clinical Study Report Table 6.1.1, page 140

Table 11 continued Baseline Demographics Characteristics- PP Analysis in ST Period

		SC Abatacept N=696	IV Abatacept N=683	Total N=1379
Race, n (%)	WHITE	516 (74.1)	505 (73.9)	1021 (74.0)
	BLACK/AFRICAN AMERICAN	26 (3.7)	24 (3.5)	50 (3.6)
	AMERICAN INDIAN/ALASKA NATIVE	5 (0.7)	1 (0.1)	6 (0.4)
	ASIAN	63 (9.1)	72 (10.5)	135 (9.8)
	NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	0	0	0
	OTHER	86 (12.4)	81 (11.9)	167 (12.1)
Region, n (%)	NORTH AMERICA	129 (18.5)	111 (16.3)	240 (17.4)
	SOUTH AMERICA	338 (48.6)	340 (49.8)	678 (49.2)
	EUROPE	123 (17.7)	123 (18.0)	246 (17.8)
	ROW	106 (15.2)	109 (16.0)	215 (15.6)

Abbreviations: ROW = Rest of World.
Baseline is Day 1 of the study.

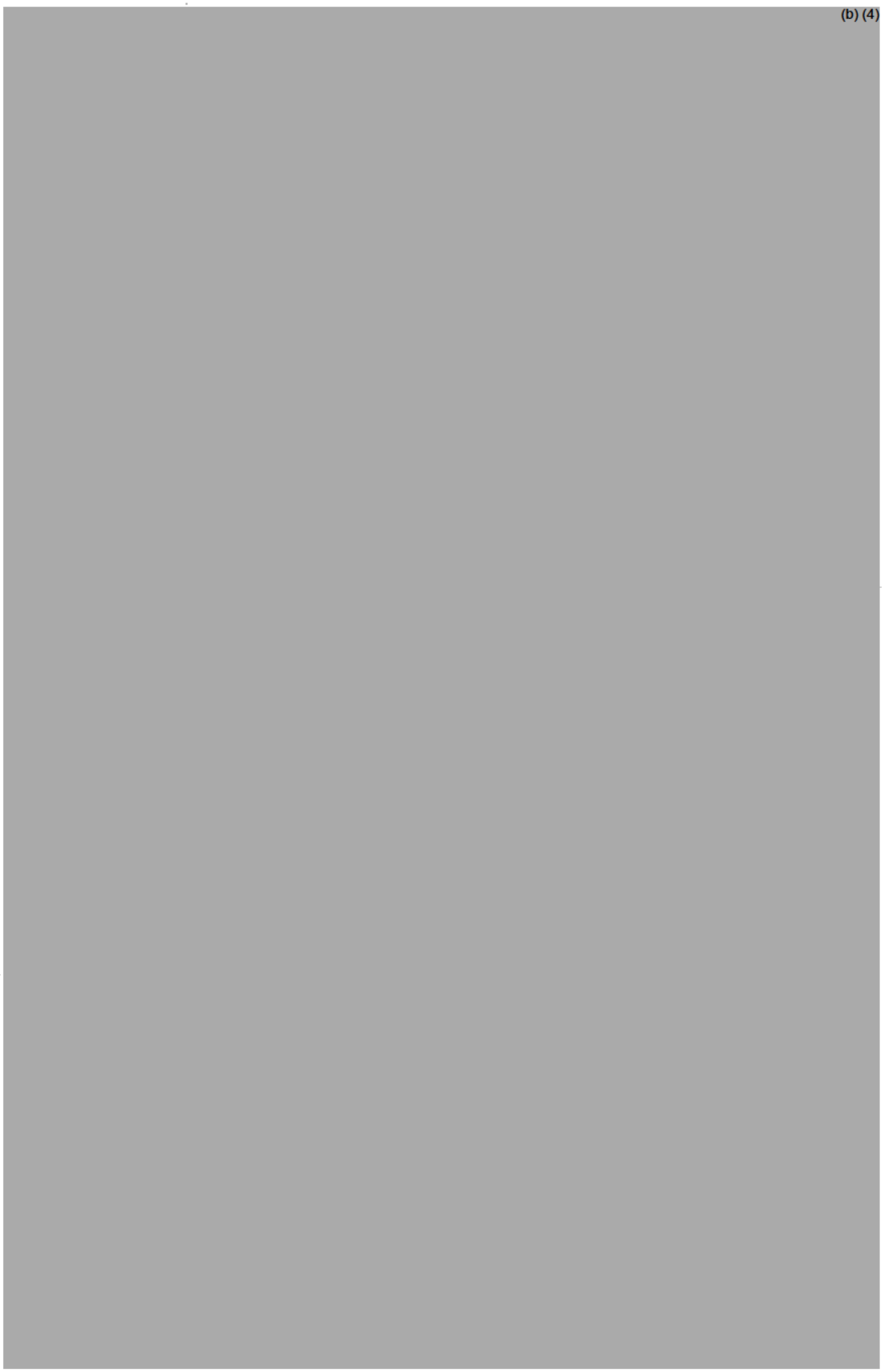
(b) (4) 18NOV2010 11:02

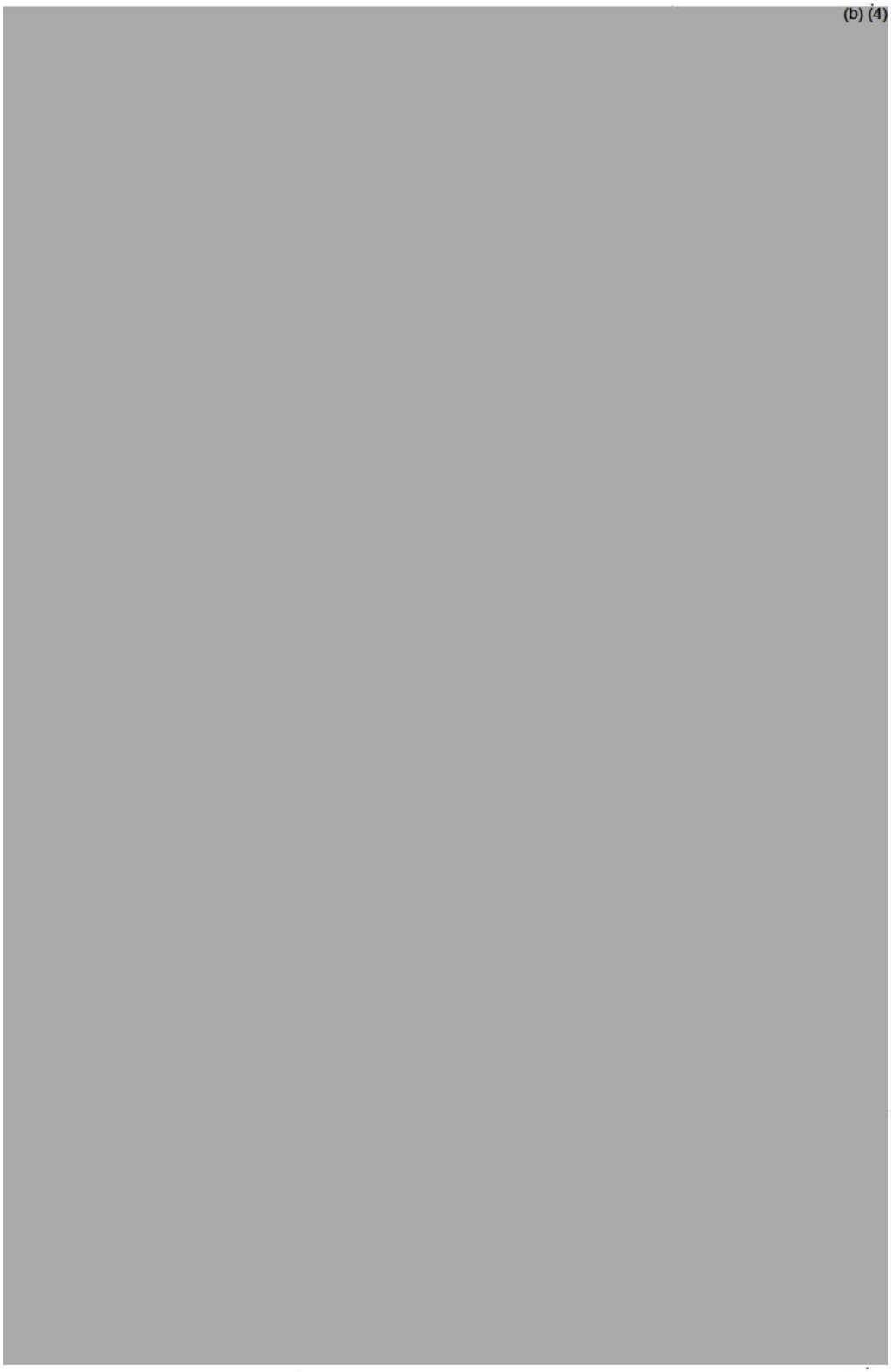
Source: Final Clinical Study Report Table 6.1.1, page 141

Applicant's Minimum Risk Weights macro:

The statistical methods used in the analysis can be found in the paper titled "Minimum risk weights for comparing treatments in stratified binomial trials" by Mehrotra and Railkar (Statistics in Medicine, 2000; 19: 811-825). (b) (4) macro code for the method is as follows:

(b) (4)


(b) (4)


(b) (4)

7. SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Kiya Hamilton, Ph.D.

Date: June 29, 2011

Statistical Team Leader: Joan Buenconsejo, Ph.D.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 125118 **Applicant: Bristol-Myers Squibb** **Stamp Date: June 29, 2010**

Drug Name: Orencia (abatacept) **NDA/BLA Type: BLA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No comments to the Sponsor for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician — Date 11/22/10

Supervisor/Team Leader — Date 11/22/10

File name: 5_Statistics Filing Checklist for a New NDA_BLA125118

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: June 30, 2011
To: Administrative File, STN 125118/122
From: Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Review memo: Efficacy Supplement: Abatacept Subcutaneous Efficacy Supplement
US License: # 1713
Applicant: Bristol-Myers Squibb Company
Mfg Facility: Bristol-Myers Squibb Holdings Pharma, LTD., P.O. Box 301000, Road 686, KM. 2.3, Manati, Puerto Rico 00674-3000 (FEI: 2650089).
Product: Orencia® (Abatacept, BMS-188667, CTLA4IG, Human CTLA4Ig)
Dosage: Solution for injection for subcutaneous administration (125 mg/1mL pre-filled syringe with (b) (4) flange extenders)
Indication: Treatment of rheumatoid arthritis: reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists; Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
Due Date: August 4, 2011

Recommendation for Approvability: This submission was reviewed from a sterility assurance and microbiology product quality perspective and is recommended for approval with the following post-marketing commitments:

1) To re-assess the bioburden action limits for the formulated drug product step (b) (4) based on the manufacturing scale data from 30 lots and submit the final report by December 31, 2014.
2) To collect bioburden data at the concentrated protein solution step and set appropriate bioburden limits for this step. The final study report should be submitted by December 31, 2014.
3) To develop a container closure integrity test for use in lieu of sterility in the stability program. The final study report should be submitted by December 31, 2012.

SUMMARY: This efficacy supplement provides for a subcutaneous route of administration for Orencia® (pre-filled syringe presentation) for the treatment of rheumatoid arthritis. The drug substance used for the pre-filled syringe presentation is the same as that used for the approved lyophilized presentation of ORENCIA® (abatacept). Drug substance information is included in

this sBLA via reference to the original BLA STN 125118. The submission includes drug product manufacturing information at the BMS Manati, Puerto Rico facility. The facility was inspected February 23-March 28, 2011 and classified VAI. The drug product QC and stability testing will be performed at the BMS East Syracuse, New York facility. The facility was inspected August 16-20, 2010 and classified NAI.

(b) (4)

abatacept injection prefilled syringe with flange extender. The prefilled syringe (the drug product formulation and primary packaging components) (b) (4). (b) (4)®

The supplement was submitted in electronic format. The supplement and amendments eCTD sequence 122 dated 12/7/2010 (drug substance hold error correction); 123 dated 12/14/2010 (container closure integrity test and microbial control information); 133 dated 3/10/2011 (proposal for supplemental validation of filling process); 135 dated 3/16/2011 (CDRH response and additional information on container closure integrity); 137 dated 4/8/2011 (stability update); 139 dated 5/31/2011 (submission of supplemental validation of filing process post-approval); and 141 dated 6/22/2011 (response to microbial control information request) are reviewed here.

ASSESSMENT:

Abatacept, an inhibitor of T-cell activation, is indicated for the treatment for rheumatoid arthritis (RA). The intravenous (IV) formulation (Orencia®) is currently marketed by Bristol-Myers Squibb (BMS) as a lyophilized powder for intravenous infusion (250 mg/vial). Abatacept injection (125 mg/mL) is a single dose, subcutaneous (SC) formulation that would allow for self-administration by RA patients. (b) (4)

abatacept injection prefilled syringe with flange extender. (b) (4)

Abatacept bulk drug substance for the SC formulation is the same as that used for approved Orencia®. The drug substance information is included in this sBLA via cross reference to the original BLA STN 125118. Abatacept injection is manufactured by Bristol-Myers Squibb Holdings Pharma, LTD in Manati, Puerto Rico (BMS-MAN). The secondary packaging in a paperboard carton, labeling, and final release also occur at BMS-MAN. The proposed shelf-life for abatacept injection stored at 2-8°C and protected from light is (b) (4) month.

3.2.S. DRUG SUBSTANCE:

The drug substance information is included in this sBLA via cross reference to the original BLA STN 125118. A new (b) (4) is used for manufacture of Abatacept. The drug substance batch 9A305 was manufactured from the process using the new (b) (4) (STN BL 125118/107). The accelerated and long-term stability data for one abatacept injection drug product batch (Batch 9G47899; one of the process validation batches) manufactured from drug substance batch 9A305 were included in the submission. The PV and stability data for this batch are reviewed under the Section 2.3.P.3, "Process Validation and/or Evaluation", and Section 2.3.P.8, "Stability," respectively.

3.2.P. DRUG PRODUCT:

3.2.P.1. Description and Composition of the Drug Product:

Abatacept injection (125 mg/syringe) is a single dose SC solution packaged in a 1-mL long glass syringe barrel with fill line markings, and stoppered with a (b) (4) coated (b) (4) plunger stopper. (b) (4)

(b) (4)

(b) Abatacept injection prefilled syringe with flange extender.

The composition of the drug product is shown in Table 1.

Table 1: Composition of Abatacept Injection, 125 mg/Syringe (125 mg/mL).

Component	Quality Standard	Function	Amount per Syringe (mg)[a]
Abatacept	BMS[b] Specification	Active Ingredient	(b) (4)
Sucrose	NF/Ph.Eur.	(b) (4)	
Poloxamer 188	NF/ Ph.Eur/BP		
(b) (4)	USP/BP		
Sodium Phosphate Dibasic, Anhydrous	USP/Ph.Eur.		
Water for Injection	USP/Ph.Eur./JP		
(b) (4)	NF/JP		
(b) (4)			

[b] BMS: Bristol-Myers Squibb

(b) (4)

(b) (4) for Abatacept Injection Prefilled Syringe

The needle and syringe hold up volume of abatacept injection in the prefilled syringe with a 29 gauge needle for 1.0 mL fill volume was determined. An (b) (4) of abatacept injection is included in each syringe to account for losses during use of the product. The overfill also accounts for the variability and the recommended tolerance level of the filling machine.

Secondary packaging consists of a paperboard carton. The assembled products are placed inside a tray prior to placing in the carton. The secondary packaging provides for functional protection during shipping and protection from light.

3.2.P.2.5. Microbiological Attributes:

Container Closure Integrity Testing (CCIT) Evaluation:
A container closure integrity evaluation was conducted on the primary packaging components for abatacept injection prefilled syringe (b) (4)

Review comment: There was no information on the correlation of the (b) (4)

In an amendment eCTD sequence 123 dated 12/14/2010, the applicant provided additional information on CCIT. (b) (4)

The sensitivity of the (b) (4)

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A set of 330 WFI filled syringes, processed using the same manufacturing equipment and procedures as for the drug product at the BMS-Manati facility and assembled with flange extender and plunger rods, were tested for CCIT (b) (4)

SATISFACTORY

3.2.P.3. MANUFACTURER:

3.2.P.3.1. Manufacturer(s):

Abatacept injection prefilled syringe with (b) (4) flange extender are manufactured, assembled, packaged, quality control tested, released, and stability tested at the facilities listed in Table 3.

Table 3: Manufacturing and testing sites information.

Facility	Responsibility
Bristol-Myers Squibb Holdings Pharma, LTD. P.O.Box 30100 Road 686, KM. 2.3 Manati, Puerto Rico 00674	Drug product manufacture Drug product quality control testing Drug product release Labeling and Assembly Secondary packaging Market-life stability testing
Bristol-Myers Squibb Company 600 Thompson Road East Syracuse, New York, 13057, USA	Drug product quality control testing Market-life stability testing

Review comment: Please see section CGMP status for the compliance status of the facilities.

3.2.P.3.3. Description of Manufacturing Process and Process Controls:

(b) (4)

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(b) (4)

2.3.P.8. STABILITY

In the original sBLA, the stability data provided to support a proposed 24-month shelf life for the abatacept injection prefilled syringe with (b) (4) flange extender included:

- 18 months of long-term data (5°C) and 6 months of accelerated data (25°C/60%RH) on three primary batches (8A44629, 8C42809 and 8C42810) of abatacept injection prefilled syringe (125 mg/mL Syringe). Data from stability samples stored at stress conditions are also provided.

- Data (through 21 and 27 months) on two supporting clinical batches (7F25817 and 7K24254) and accelerated data through 6 months on each supporting batch.

In addition, 3 months of data on one batch (9G47899) of abatacept injection prefilled syringe manufactured from drug substance using the new (b) (4) was provided in this submission. The batch is one of the abatacept injection process validation batches. Nine months of data are currently available for the other process validation batches.

The testing included stability indicating assays, (b) (4) for batches in the stability protocol. The 2 supporting clinical batches did not have data collected on (b) (4). The stability testing was performed only on the pre-filled syringes and considered by the applicant to be supportive of the shelf life of the prefilled syringe with (b) (4) flange extender (b) (4)

Manufacturing Batch Number	8A44629	8C42809	8C42810
Drug Substance Batch Number	7Z070	7Z102	7Z031
Drug Substance Manufacturing Date	July 2007	August 2007	October 2006
Drug Substance Process	F	F	F
Drug Substance Manufacturing Site	Lonza Biologics, Inc., Portsmouth, New Hampshire		
Date of Drug Product Manufacture	March 2008	April 2008	April 2008
Batch Size (liters)	20	20	20
Batch Size (syringes)	12,643	11,004	11,509
Date on Stability	April 2008	May 2008	May 2008
Manufacturing Site	Bristol-Myers Squibb, Manati, Puerto Rico		
Stability Storage Site	Bristol-Myers Squibb, New Brunswick, New Jersey		
Stability Testing Sites	Bristol-Myers Squibb, Manati, Puerto Rico Bristol-Myers Squibb, East Syracuse, New York (b) (4) (b) (4)		
Packaging Components[1]			
Syringe	(b) (4) 1-mL long, Type I glass syringe barrel (b) (4) with 29G stainless steel needle with rigid needle shield		
Stopper	(b) (4) coating on product contact side		

[1] Packaging components are described in Section 3.2.P.7 "Container Closure System". Unmarked syringe barrels were used for the stability batches.

The stability data demonstrate that abatacept injection (125 mg/Syringe) is stable for at least 18 months, when stored at 5°C protected from light. Both horizontal and upright (needle downward) orientations were studied. (b) (4) tests are performed initially and at 12, 24, and 36 month time-points. (b) (4) data for the initial and 12 months time-point for batches stored at 5°C H were included. All results met the proposed acceptance criteria. (b) (4) testing data for the initial and 12 months time-point for batches stored at 5°C H were included. All results were <0.04 EU/mg and met the proposed acceptance criteria. The 24 month proposed shelf-life is based on 21 and 27 month data from two supporting batches manufactured using the same commercial process. (b) (4) testing was not performed on these batches.

The applicant submitted updates to the stability data in an amendment (eCTD sequence number 137 dated 4/8/2011). Based on the updated data from the three primary stability batches, a (b) (4) month shelf life is now being proposed for the drug product as compared to the 24-month proposal included in the initial sBLA. (b) (4) testing was performed at initial, and at the 12 and 24 months time-points of storage at 5°C H. All (b) (4) results met the proposed acceptance criterion. (b) (4) testing was performed at initial, and after 12 and 24 months of

storage at 5°C H. All results were <0.25 EU/mg and met the proposed acceptance criteria. (b) (4) data was not collected at the 30-month time-point but will be performed at the 36 month time-point.

Review comment: Product quality data other than (b) (4) *from the stability studies should be reviewed by OBP/DMA. The* (b) (4) *test is performed at release, and annually thereafter until expiry. The current guidance to industry is to perform container closure integrity testing in lieu of the sterility test on stability samples at 12 and 24 months. It is recommended that the applicant develop the container closure integrity test method for their stability program. This will be requested as a post-marketing commitment.*

SATISFACTORY

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Bristol-Myers Squibb commits to the completion of all on-going stability studies for the Abatacept injection prefilled syringe in the long-term stability study program and to monitoring on-going stability studies in accordance with the assigned stability protocols. (b) (4) will be monitored initially, annually thereafter, and at expiry. There are no changes to the acceptance criteria for these tests.

SATISFACTORY

3.2.A. APPENDICES

3.2.A.1. Facilities and Equipment

Abatacept injection is manufactured at the Parenteral Syringe Area (PSA) facility at Bristol-Myers Squibb Holdings Pharma, LTD in Manati, Puerto Rico (BMS-Manati). Drug product release and stability testing are also performed at BMS-Manati. The BMS-Manati facility operates as a multi-product facility. This facility is used to manufacture abatacept injection, 125 mg/Syringe (b) (4). The (b) (4) is manufactured for clinical studies of (b) (4) Product contact equipment were listed. Floor diagrams (area room classifications and pressure differentials, personnel flow, equipment flow, material flow, process flow and waste flow) for areas used for manufacturing and storage were included. A description of measures that have been established to prevent cross-contamination of materials, products and equipment were provided.

Reviewer comments: The appendix provides background information for the inspection of the facility. The facility was inspected by team of investigators led by Mr. Cruz from February 23rd through March 28, 2011. There were 483 observations with respect to environmental monitoring excursions during filling of Orencia lyophilized powder for IV infusion, inadequate smoke studies, visual inspection procedures, and documentation to support release testing activities during assembly of Orencia SC presentation. The inspection was classified as VAI.

Environmental Assessment

This sBLA is for a change in presentation to support subcutaneous rather than intravenous route of administration. The proposed change will not significantly change the distribution of the active compound or degradation products in the environment. Therefore, Bristol-Myers Squibb Company requests a categorical exclusion from the requirements of an environmental assessment, as provided in 21 CFR 25.31(c). This drug is manufactured using a synthetic process and is not known to be derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b).

cGMP Status

There are no pending or ongoing compliance actions to prevent approval of STN 125118/122 at this time. The status of the drug product manufacturing sites is shown below:

Establishment	FEI	Inspection date	Classification	Profile
Bristol-Myers Squibb Holdings Pharma, LTD. P.O.Box 30100 Road 686, KM. 2.3 Manati, Puerto Rico 00674	2650089	February 23-March 28, 2011	VAI	CTL, SVS, SVL, and TRP
Bristol-Myers Squibb Company 600 Thompson Road East Syracuse, New York, 13057, USA	1317461	August 16-20, 2010	NAI	CTL

Conclusion

I. Sections 3.2.P of the PAS pertaining to [redacted] (b) (4) assurance of the drug product manufacturing process were reviewed and found to be acceptable. The sBLA is recommended for approval with the following post marketing commitment:

1) To re-assess the bioburden action limits for the formulated drug product step [redacted] (b) (4) based on the manufacturing scale data from 30 lots and submit the final report by December 31, 2014.
2) To collect bioburden data at the [redacted] (b) (4) step and set appropriate bioburden limits for this step. The final study report should be submitted by December 31, 2014.
3) To develop a container closure integrity test for use in lieu of sterility in your stability program. The final study report should be submitted by December 31, 2012.

II. CMC drug product specific information and data should be reviewed by OBP/DMA reviewer.

III. The Bristol-Myers Squibb Holdings Pharma, LTD. facility located in Manati, Puerto Rico, was inspected by SJN-DO on February 23 through March 28, 2011. The inspection was classified as VAI.

SIGNATURES/DISTRIBUTION LIST

Primary BMT Reviewer: Kalavati Suvarna, Ph.D. Date: 6/27/2011
Concurring BMT Team Leader: Patricia. F. Hughes, Ph.D. Date: 6/27/11

Cc: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes
OND/ODEII/DPARP, Jackson, Colette
DMPQ/BMT/Building 51, eCTD Files (STN:125118)

Archived File: S:\archive\BLA\125118\125118.122.rev.mem.sBLA.06-30-2011.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	125118/122
Submission Date:	10/04/2010
Brand Name	Orencia®
Submission Type	Efficacy Supplement
Generic Name	Abatacept (BMS188667)
OCP Reviewer	Liang Zhao, Ph.D.
Team Leader (Acting)	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Liang Zhao, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Bristol Myers Squibb
Formulation; Strength(s); Administration Route	250 mg single-use vial; 30-minute intravenous infusion for approved product for the approved product
Approved Indication	Moderately to severely active RA in adults; Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older
Proposed Indication	Same as above
Purpose of this Efficacy Supplement	Approval for the subcutaneous route of administration
Approved Dosage Regimen	**Adult RA (2.1)** **Body Weight of Patient / Dose / Number of Vials** <60 kg / 500 mg / 2 60 to 100 kg / 750 mg / 3 >100 kg / 1000 mg / 4 **Juvenile Idiopathic Arthritis (2.2)** • Pediatric patients weighing less than 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg (2.2). Following initial dose, give at 2 and 4 weeks, then every 4 weeks
Proposed Dosage Regimen	125 mg administered by subcutaneous injection once a week regardless of weight

Table of Contents

1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

General findings

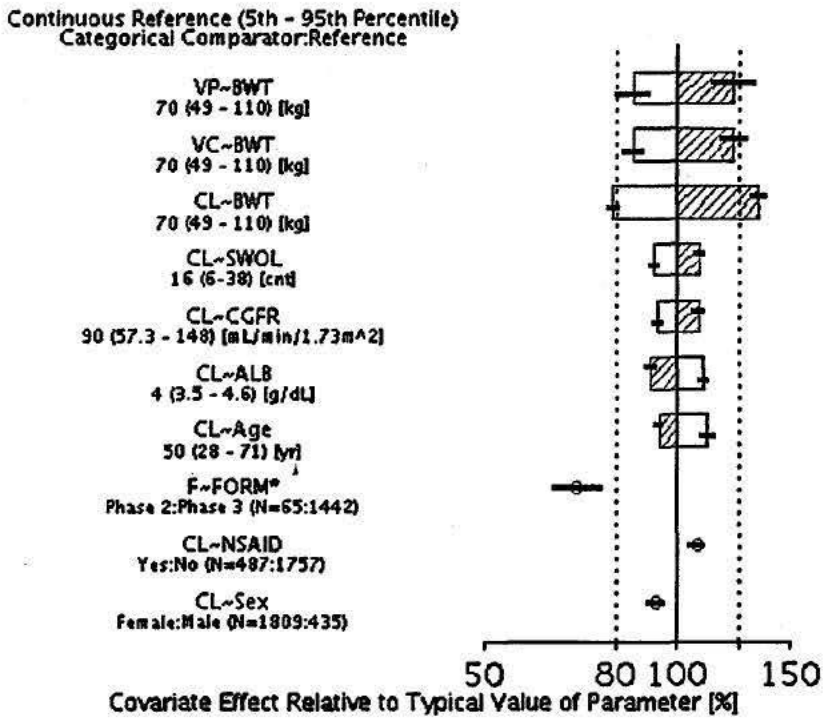
The studies including a PK component were IM101013, IM101063, IM101174, IM101167, IM101063, and IM101185. The half lives (T1/2) based on non-compartmental analyses were found to be approximately 16.7 and 13.1 days for healthy subjects and RA patients, respectively. Comparison of the non-compartmental PK results suggests that there was no clinically relevant impact on atabacept PK by concomitantly administering methotrexate or etanercept. The bioavailability of abatacept was identified to be 78.6% from trial IM101174.

Population PK and exposure-response analysis

Population PK

The patient level parameters in the final report were coded by their relationship with identified covariates with/without inter-individual variability in a two-compartment structural model. As indicated by Figure 1, the magnitude of all covariate effects (except for body weight) on PK parameters, as measured by the 95% confidence intervals, were within 80%-125% of reference values, suggesting that none of those effects could be concluded as clinically relevant. It also has been found that the trough concentrations at steady state (Cminss) following subcutaneous (SC) injection were comparable or higher than the Cminss's following intravenous (IV) administration at low, medium, and high weight groups (i.e., <60 kg, 60-100 kg, and >100 kg).

Figure 1. Final population PK model covariate effects plot



Source: /global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/plot.cov.eff.ssc

* For the formulation, if subject had both Phase 2 and 3 formulation, the subject is counted once for the Phase 2 and once for the Phase 3

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, body weight= 70 kg, age= 50 yr, CGFR = 90 mL/min/1.73m2, albumin = 4.0 mg/dL, swollen joint count = 16, not taking NSAIDs and using Phase 3 formulation. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

Exposure-response analyses

A positive relationship between the Cminss's and the magnitude of the DAS28 reduction at Month 6 has been identified (Figure 2). The relationship has been characterized by an Emax-Tmax exposure-efficacy response model. It has also been identified that DAS reduction reaches to a plateau phase when Cminss exceeds approximately10 µg/mL.

Figure 2. Observed Change from Baseline DAS28 at Month 6 versus Cminss

Events of infection and serious infection were used as safety response in the model. All of the analyses did not reveal significant exposure-safety response correlation post both IV and SC doses.

Immunogenicity:
Immunogenicity rates were low following SC treatment. SC abatacept did not increase immunogenicity rates as compared to IV abatacept based on Phase III study IM101174. The immunogenicity profiles post IV and SC treatments were comparable. The titers of antibodies against abatacept were low, non-persistent, comparable post either IV or SC treatment. The presence of antibodies against abatacept had no identified impact on safety, efficacy, or PK. The immunogenicity response did not appear to correlate with baseline body weight following either SC or IV abatacept treatment.

When SC abatacept was used as monotherapy or when SC abatacept was used following IV abatacept treatment, no significant increase in immunogenicity rates or antibody titers were observed.

Long-term continuous treatment with SC abatacept had no identified impact on immunogenicity rates. However, increase in immunogenicity rates was observed upon withdrawal of SC abatacept therapy. The immunogenicity associated with withdrawal was not persistent upon

reintroduction of SC abatacept therapy. Reintroduction of SC abatacept did not have identified impact on safety, efficacy, or PK, with or without IV abatacept loading dose.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Abatacept (ORENCIATM, BMS-188667, CTLA4Ig) is a recombinant, soluble, fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge– CH2–CH3 domains) of the Fc domain of human IgG1. The molecular weight obtained by MALDI-TOF is 92,300 Daltons. It is a biological inhibitor of T-cell activation and was developed as the first generation of biological antirheumatics that have significantly improved the therapy for rheumatoid arthritis (RA). Abatacept drug substance is produced as a secreted protein in large-scale cell culture using a Chinese Hamster Ovary (CHO) cell line and purified using a series of chromatographic and filtration steps.

Formulation: The intravenous (IV) formulation (ORENCIA®) is currently marketed by Bristol-Myers Squibb (BMS) as a lyophilized powder for intravenous infusion (250mg/vial). Abatacept injection (125 mg/mL) is a single dose, ready-to-use (RTU) subcutaneous (SC) formulation to allow for self-administration by RA patients in order to provide greater convenience in obtaining therapy.

2.1.2. What is the approved therapeutic indication, dosage and route of administration?

Indication:

Moderately to severely active RA in adults; Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older; intravenous route of administration.

Dosage and Route of Administration:

Adult RA (2.1)

Body Weight of Patient	Dose	Number of Vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1000 mg	4

Juvenile Idiopathic Arthritis (2.2)

- **Pediatric patients weighing less than 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).**

Following initial dose, give at 2 and 4 weeks, then every 4 weeks.

In this supplement, sponsor is seeking approval of 125 mg administered by subcutaneous injection once a week regardless of weight.

2.2 General Clinical Pharmacology

2.2.1. What are the clinical pharmacology and clinical trials used to support the proposed claims?

The trials were summarized in Table 1.

Table 1. Tabular Listing of Clinical Studies

Study Type	Study ID	Report Location in CTD	Study Objective	Study Design Type of Control	Formulation Dosage Regimen Route	Number of Treated Subjects	Subject Type	Duration of Treatment	Study Status Type of Report
PK	IM101013 DCN: 930015830	5.3.3.1	Single dose PK of subcutaneous abatacept in healthy subjects	Double-blind, randomized (within dose), placebo-controlled, parallel-group	SC ABA (50, 75, 100, or 150 mg), single dose	48 (40 abatacept, 8 PBO)	Healthy subjects ≤ 100 kg	1 day (single dose)	Completed Full
PK	IM101063 ST DCN: 930025069	5.3.3.2	To assess the steady-state trough serum concentrations of abatacept following weekly SC dosing in subjects with active RA who were receiving DMARDs.	Double-blind, randomized, placebo-controlled, parallel-group, multiple-dose	IV ABA: 500, 750, and 1000 mg based on body weight SC ABA: 75 mg, 125 mg, or 200 mg weekly IV ABA load followed by weekly SC doses	68 subjects (51 ABA 17 PBO)	Subjects with active RA receiving MTX and no more than 1 additional DMARD	ST: 12 weeks	ST -Completed Full LT- Ongoing
Safety	IM101128 DCN: 930022181	5.3.4.1	To assess immunogenicity of single dose of subcutaneous ABA (given approx. 3 years previously during IM101013)	Follow up uncontrolled	SC ABA (50, 75, 100, or 150 mg), single dose	26 subjects treated with ABA and 5 subjects treated with PBO in IM101013	Healthy subjects ≤ 100 kg	1 day (during IM101013)	Completed Full
Efficacy/ Safety	IM101174 DCN: 930043284	5.3.5.1	To demonstrate that SC injections of abatacept plus a loading IV infusion of abatacept are non-inferior to IV infusions of abatacept in ACR 20 response after 6 months of treatment	Randomized, double-blind, double dummy, placebo-controlled	ST: SC ABA, 125 mg, weekly (single IV ABA loading dose, weight-tiered on Day 1) plus IV PBO on Days 1, 15, 29, 57, and every 28 days thereafter. IV ABA, weight-tiered dosing, on Days 1, 15, 29, and every 28 days thereafter plus SC PBO, given weekly LT: SC ABA, 125 mg, weekly	ST: SC ABA = 736 IV aba = 721 LT: SC ABA = 1357	Subjects who had active RA, were receiving MTX and experiencing an inadequate response to MTX	6 months ST, Up to 18 months in LT	ST -Completed Full LT- Ongoing
Safety / Immunogenicity	IM101167 DCN 930039208	5.3.5.1	To assess safety and immunogenicity in subjects with RA where, after clinical response, SC abatacept was withdrawn for 12 weeks or maintained for 12 weeks	Randomized, double-blind, placebo-controlled	ST: Period I: SC ABA, 125 mg/week (IV ABA loading dose, weight-tiered on Day 1) Period II: SC ABA, 125 mg weekly OR SC PBO weekly Period III: Period II SC ABA to:SC ABA 125 mg weekly (IV PBO loading dose) AND Period II SC PBO to: SC ABA 125 mg weekly (IV ABA loading dose weight-tiered) OR SC ABA 125 mg weekly (IV PBO loading dose) LT: SC ABA, 125 mg, weekly	ST: Period I N = 167 Period II: N = 120 Period III: N = 119 LT: N = 150	Subjects with active RA (DAS28-CRP ≥ 3.1 to ≤ 5.2), Inadequate response to MTX, Concomitant background MTX therapy	9 months ST, Up to 15 months LT	ST -Completed Full LT- Ongoing

Study Type	Study ID	Report Location in CTD	Study Objective	Study Design Type of Control	Formulation Dosage Regimen Route	Number of Treated Subjects	Subject Type	Duration of Treatment	Study Status Type of Report
PK/Safety	IM101063 LT DCN: 930041843	5.3.5.2	To assess the safety, immunogenicity, and long-term tolerability of SC administration of abatacept in subjects who had completed the initial 12-week treatment (initial IV loading dose followed by weekly SC doses) with abatacept.	Double-blind, randomized, placebo-controlled, parallel-group, multiple-dose	Variable Dose Phase SC ABA: 75, 125, or 200 mg weekly based on body weight) Fixed Dose Phase SC ABA: 125 mg weekly Route: IV load followed by SC	Variable dose phase SC ABA N = 63 Fixed dose Phase: SC ABA N =48	Subjects with active RA receiving MTX and no more than 1 additional DMARD	LT extension: up to 47.3 months	Ongoing Addendum
Safety / Immunogenicity	IM101173 ST DCN: 930038658 LT DCN: 930042879	5.3.5.2	ST: to evaluate the immunogenicity of abatacept when used with or without MTX, in the absence of an IV loading dose of abatacept. LT: to assess the safety and LT tolerability as well as maintenance of responses in subjects who completed the initial 4-month treatment period	Open-label, uncontrolled	ST: SC ABA, 125 mg administered weekly (no IV ABA loading dose) given either as: monotherapy (i.e., no background DMARD) or with Concomitant MTX LT: SC ABA, 125 mg, weekly	ST: 100 subjects (monotherapy, N = 49) or SC abatacept + MTX, N = 51) LT: SC ABA N = 90	Active RA (> 20 mm on the Subject Global Assessment of Disease Activity visual analog scale MTX naive or discontinued MTX > 4 weeks prior to first dose of study drug) or were receiving stable MTX therapy	4 months ST, Up to 20 months LT	ST -Completed Full LT- Ongoing LT addendum
Safety	IM101185 DCN: 930042875	5.3.5.2	To describe the safety of abatacept in subjects who switched from IV to SC abatacept therapy at 3 months (Day 85).	Open-label, uncontrolled	ST: SC ABA, 125 mg, weekly (no IV ABA loading dose) LT: SC ABA, 125 mg, weekly	123 subjects	Subjects with active RA who participated in LT extension period of Studies IM101102 or IM101029 with IV ABA and who reached had ≥ 5 y of IV ABA treatment	ST: 12 months	ST -Completed Full LT- Ongoing

RA = rheumatoid arthritis; ST = short-term; LT = long-term; ABA = abatacept; DMARDs = disease modifying anti-rheumatic drugs; m = months; MTX = methotrexate; MTX-IR = Methotrexate-inadequate-responders; PBO = placebo; PK = pharmacokinetics; RA = rheumatoid arthritis; SC = subcutaneous; IV = intravenous; TNF = tumor necrosis factor; TNF-IR = TNF-antagonist-inadequate-responders;; y = year(s); DCN = document control number; PK = pharmacokinetics; ACR 20 = 20% improvement in American College of Rheumatology criteria; DAS = Disease Activity Score; CRP = C-reactive protein

Studies IM101013, IM101063, IM101174, IM101167, IM101185, and IM101173 had a PK component.

2.2.2. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Abatacept serum concentrations were determined by a validated method by enzyme linked immunosorbent assay (ELISA). A monoclonal antibody against CTLA4Ig was used to capture abatacept. Abatacept was then detected with a (b) (4) antibody against

CTLA4Ig, followed by detection with streptavidin [redacted]

Assay sections were separately reviewed for each study. For the Phase III study IM101174, The results for the standard curves (well-fitted to the regression model) and analytical QCs (after [redacted]) indicate that the human serum assay method was precise and accurate (Table 2).

Table 2. Summary of assay and performance for abatacept in human serum

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV*	Within-run %CV*	Mean % Deviation from Nominal Concentration*
BMS-188667	1.0	30.0	≤ 6.7	≤ 5.3	± 4.5

* Maximum value from Accuracy and Precision table with data exclusions α=0.01 for the analysis of analytical QCs (Source: Appendix 1)

A method summary for a study IM101174 is shown by Table 3.

Table 3. Assay method description

Method Parameter	Description
Bioanalytical Methodology	ELISA
[redacted]	(b) (4)

2.2.3. What are the PK characteristics of abatacept in patients?

The pharmacokinetics characteristics of abatacept in both healthy volunteers and RA patients following IV administration have been reviewed by Dr. Anil Rajpal in the original BLA submission. The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. The half lives (T1/2) based on non-compartmental analyses were found to be approximately 16.7 and 13.1 days for healthy subjects and RA patients, respectively. Comparison of the non-compartmental PK results suggests that there was no clinically relevant impact on atabacept PK by concomitantly administering methotrexate or etanercept. Table 4 was the summary of the PK parameters in submission. The bioavailability of abatacept was identified to be 78.6% from trial IM101174.

Table 4. Mean (range) pharmacokinetic parameter estimates for abatacept following SC or IV multiple dose administration in RA subjects

PK Parameter	SC	IV
CL (mL/h/kg) [a]	0.28 (0.03, 0.58)	0.29 (0.11, 0.71)
Vss (L/kg) [a]	0.11 (0.02, 0.17)	0.11 (0.03, 0.36)
T-HALF (days) [a]	14.3 (9.19, 24.5)	14.2 (4.69, 79.1)
AUC (TAU) (µg•h/mL) [b,c]	5875.5 (1261.0, 13068.4)	41981.5 (18315.6, 88991.5)
Observed Cmax (µg/mL) [b]	48.1 (9.8, 132.4)	231.6 (123.1, 458.9) [d]
Observed Cmin (µg/mL) [b,e]	32.5 (6.6, 113.8)	22.3 (1.2, 80.6)

[a] Population PK model estimate from IM101174 [12]

[b] Observed Mean (range) from the IM101174 study [8]

[c] TAU = 7 days for SC and TAU = 28 days for IV

[d] The PK sample for Cmax was taken 30 minutes after the end of infusion and represents an approximation

[e] Observed Mean (range) Cmin on Day 85 from the IM101174 study [8]

2.2.4. What are the PD characteristics of Atabacept in patients?

Immunogenicity results are summarized in its dedicated section. PD markers such as high sensitivity C-reactive protein (hsCRP) and rheumatoid factor (RF) were not monitored in all trials. The PD characteristics in trials are summarized.

IM101174

At Day 169, 33 (5.6%) of the 586 baseline RF-positive subjects in the SC abatacept group and 40 (6.9%) of 582 baseline RF-positive subjects in the IV abatacept group had a negative RF seroconversion (i.e., positive baseline, negative Day 169 value). Two (1.9%) of the baseline RF-positive 106 subjects in the SC abatacept group and 3 (3.2%) of the baseline RF-positive 93 subjects in the IV abatacept group who were RF negative at baseline had a positive RF seroconversion (i.e., negative baseline, positive Day 169) (Table 5).

Table 5. Cross classification of rheumatoid factor with baseline: all randomized and treated subjects in short-term period.

		POST BASELINE STATUS					
		SC Abatacept			IV Abatacept		
STUDY DAY	STATUS AT BASELINE	Total N	Negative n (%)	Positive n (%)	Total N	Negative n (%)	Positive n (%)
Day 169	Negative	106	104 (98.1)	2 (1.9)	93	90 (96.8)	3 (3.2)
	Positive	586	33 (5.6)	553 (94.4)	582	40 (6.9)	542 (93.1)

IM101173

Summary statistics for observed and change from baseline values for hsCRP levels over time are summarized in Table 6. The change from baseline in hsCRP appeared to be comparable between the SC abatacept and the MTX + SC abatacept monotherapy cohorts.

Table 6. hsCRP(mg/dL) - Mean Change from Baseline Over Time: All Treated Subjects (IM101173)

		SC Aba + MTX N = 51	SC Aba Only N = 49
Day 15	n	49	47
	Baseline Mean (SD)	1.18 (1.65)	3.02 (3.66)
	Post-Baseline Mean (SD)	1.32 (2.70)	2.56 (3.27)
	Mean Change from Baseline (SE)	0.14 (0.37)	-0.46 (0.24)
	95% CI	(-0.59, 0.88)	(-0.95, 0.03)
Day 29	n	49	47
	Baseline Mean (SD)	1.18 (1.65)	3.01 (3.66)
	Post-Baseline Mean (SD)	0.98 (1.36)	2.84 (3.91)
	Mean Change from Baseline (SE)	-0.19 (0.16)	-0.17 (0.35)
	95% CI	(-0.50, 0.12)	(-0.87, 0.53)
Day 43	n	49	45
	Baseline Mean (SD)	1.18 (1.65)	2.61 (3.27)
	Post-Baseline Mean (SD)	0.75 (1.14)	1.94 (2.69)
	Mean Change from Baseline (SE)	-0.42 (0.19)	-0.67 (0.28)
	95% CI	(-0.81, -0.04)	(-1.24, -0.09)
Day 57	n	49	47
	Baseline Mean (SD)	1.18 (1.65)	2.87 (3.63)
	Post-Baseline Mean (SD)	0.85 (1.05)	2.17 (3.02)
	Mean Change from Baseline (SE)	-0.33 (0.18)	-0.70 (0.42)
	95% CI	(-0.70, 0.04)	(-1.54, 0.14)
Day 85	n	49	45
	Baseline Mean (SD)	1.18 (1.65)	2.76 (3.50)

n is the number of subjects with baseline and post-baseline values.
Change from Baseline = Post-baseline - Baseline value.

A total of 92 subjects (47 in SC abatacept + MTX cohort, 45 in SC abatacept monotherapy cohort) had RF data at baseline (Day 1) and Day 113. At Day 113, one subject in each cohort had a negative RF seroconversion (ie, positive baseline, negative Day 113 value), and 2 subjects (both in SC abatacept + MTX cohort) had a positive RF seroconversion (ie, negative baseline, positive Day 113) (Table 7).

Table 7. Cross Classification of Rheumatoid Factor Category at Day 113 with Baseline: All Treated Subjects

		POST BASELINE STATUS					
			SC Aba + MTX			SC Aba Only	
STUDY DAY	STATUS AT BASELINE	TOTAL N	NEGATIVE n (%)	POSITIVE n (%)	TOTAL N	NEGATIVE n (%)	POSITIVE n (%)
Day 113	NEGATIVE	14	12 (85.7)	2 (14.3)	15	15 (100.0)	0 (0.0)
	POSITIVE	33	1 (3.0)	32 (97.0)	30	1 (3.3)	29 (96.7)

Overall, positive RF seroconversion rate was low and negative RF seroconversion was high after abatacept treatment with and without MTX. The change from baseline in hsCRP appeared to be comparable between the SC abatacept and the MTX + SC abatacept monotherapy treatments.

2.2.5. What are the key results from the population PK analysis?

The objective for the population PK analysis was to characterize the population pharmacokinetics of SC abatacept, and to investigate and quantify potential relationships between covariates and SC abatacept pharmacokinetic parameters in patients with RA. Characterization of the exposure-efficacy response relationship between abatacept exposure and DAS28 in patients with RA for both IV and SC administered abatacept, and exploration of the exposure-safety response relationships between abatacept exposure and infections, and serious infections for both IV and SC administered abatacept was also undertaken.

Dataset composition

There were a total of 2244 RA subjects who received IV infusion and/or SC injection of abatacept from 3 Phase 2 IV studies, IM103002, IM101100, and IM101101; 1 Phase 2 SC study, IM101063; 3 Phase 3 IV studies, IM101102, IM101029, and IM101031; and 4 Phase 3 SC studies, IM101167, IM101173, IM101174 (IM101174 PK substudy is also included), and IM101185 in RA subjects. Based on PK data from these patients, there were a total of 11628 serum concentrations used in the population PK analysis.

There were 1958 subjects from trials IM101100, IM101102, and IM101174 used for the Exposure-Response analysis, for whom measures of abatacept exposure were available or who were randomized to receive placebo. DAS28, calculated using C-reactive protein up to 6 months after first abatacept or placebo dose, was used as the clinical endpoint for response.

There were 1408 subjects, who had PK exposure measures available, from trial IM101174 were used for Exposure-Safety analysis. Infections and serious infections were used as the safety endpoints.

Final population PK model:
The patient level parameters in the final report were coded by their relationship with identified covariates with/without inter-individual variability in a two-compartment structural model. In the final model, abatacept clearance was described by

$$CL = CL_{TV,ref}(\frac{BWT_b}{BWT_{ref}})^{CL_{BWT}}(\frac{AGE_b}{AGE_{ref}})^{CL_{AGE}}(\frac{ALB_b}{ALB_{ref}})^{CL_{ALB}}(\frac{CGFR_b}{CGFR_{ref}})^{CL_{CGFR}}(\frac{SWOL_b+1}{SWOL_{ref}+1})^{CL_{SWOL}}$$
$$\exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID}) \times \exp(\eta_1)$$

$$VC = VC_{TV,ref}(\frac{BWT_b}{BWT_{ref}})^{VC_{BWT}} \times \exp(\eta_2)$$

$$Q = Q_{TV,ref} \times \exp(\eta_3)$$

$$VP = VP_{TV,ref}(\frac{BWT_b}{BWT_{ref}})^{VP_{BWT}} \times \exp(\eta_4)$$

$$F = VP_{TV,ref}(\frac{BWT_b}{BWT_{ref}})^{VP_{BWT}} \times \exp(\eta_5)$$

$$F_{TV} = F_{TV,ref} + FORM \times F_{FORM}$$

Where CL_T represents the total drug clearance; VC is the central volume of distribution; Q is the inter-compartmental flow; VP is the peripheral volume of distribution; F is the bioavailability; BWT_b is the baseline body weight; ALB_b is the baseline albumin level [g/dl]; AGE_b is the baseline age; $CGFR_b$ is the baseline calculated GFR [ml/min/1.73m^2]; $SWOL_b$ is the baseline swollen joint count; NSAID indicates comedication status with NSAID (1=yes; 0=no;-9999=missing information); SEX indicates gender (1=female; 0=male); FORM is the SC formulation (1 = Phase 3 Formulation; 0 = Phase 2 Formulation; -9999=Missing Information); $P_{TV,ref}$ is the typical value of a PK parameter (P) for a reference (ref) subject (BWT_{ref} = 70 kg, AGE_{ref} = 50 yr, ALB_{ref} = 4.0 mg/dL, $CGFR_{ref}$ = 90 mL/min/1.73m2, $SWOL_{ref}$ = 16, SEX_{ref} = Male, $NSAID_{ref}$ = No, $FORM_{ref}$ = Phase 3 formulation). The inter-individual variability is indicated by $\exp(\eta)$. The reference values of continuous covariates were selected to be approximately median values in the population PK dataset, and the reference values for the categorical covariates are the mode in the population PK dataset, except for sex where male is used as the reference.

The final population PK model was validated internally at FDA. Both visual and quantitative predictive performance checks were conducted to compare statistics of observed concentration with corresponding statistics calculated from simulated data using the final model for the steady state abatacept dosing of ~10 mg/kg IV Q4W and 125 mg SC QW. The final model reasonably captures the major PK characteristics of abatacept.

Population PK modeling results

The PK parameters in RA patient population, based on the NONMEM output by re-running sponsor's final model, are shown in Table 8.

Table 8. Final estimates of model parameters for RA patients

	Fixed-Effects Parameters	Estimate	RSE(%)	CI95
1	CL[L/h]	0.0204	2.225	(0.01951-0.02129)
2	VC[L]	3.27	1.697	(3.161-3.379)
3	Q[L/h]	0.0265	9.283	(0.02168-0.03132)
4	VP[L]	4.26	4.484	(3.886-4.634)
5	KA[1/h]	0.00305	27.11	(0.001429-0.004671)
6	F[-]	1.42	7.817	(1.202-1.638)
7	Proportional ERR[-]	0.215	3.344	(0.2009-0.2291)
8	Additive ERR[ug/ml]	0.341	34.02	(0.1136-0.5684)
9	BWT~CL[-]	0.65	4.969	(0.5867-0.7133)
10	BWT~VC[-]	0.451	12.79	(0.3379-0.5641)
11	BWT~VP[-]	0.453	20.42	(0.2717-0.6343)
12	Form~F1[-]	-1.17	-13.16	(-1.472--0.8682)
13	CGFR~CL[-]	0.157	16.31	(0.1068-0.2072)
14	SEX~CL	-0.075	-22.53	(-0.1081--0.04188)
15	ALB~CL	-0.691	-12.46	(-0.8598--0.5222)
16	NSAID~CL	0.071	22.39	(0.03984-0.1022)
17	SWOL~CL	0.0953	12.17	(0.07256-0.118)
18	AGE~CL	-0.189	-14.34	(-0.2421--0.1359)
19				
20	Inter-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
21	CL	31.48	3.471	18.36
22	Corr(CL-V2)	0.5206	13.11	-
23	V2	25.14	7.421	51.87
24	Corr(CL-Q)	0.4617	14.29	-
25	Corr(V2-Q)	0.2472	43	-
26	Q	65.5	12.12	61.72
27	Corr(CL-V3)	0.4708	10.82	-
28	Corr(V2-V3)	0.4373	16.15	-
29	Corr(Q-V3)	0.6962	13.43	-
30	V3	61.4	8.501	50.55
31	KA	127.7	16.6	83.68
32	F1	84.26	8.099	56.42
33				
34	Intra-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
35	ERR[-]	1	-	14.71

Given all the continuous covariates identified, a forest plot was used to indicate their impact on drug PK parameters based on reviewer's independent analysis (Figure 3).

Figure 3. Final population PK model covariate effects (reviewer's analyses)

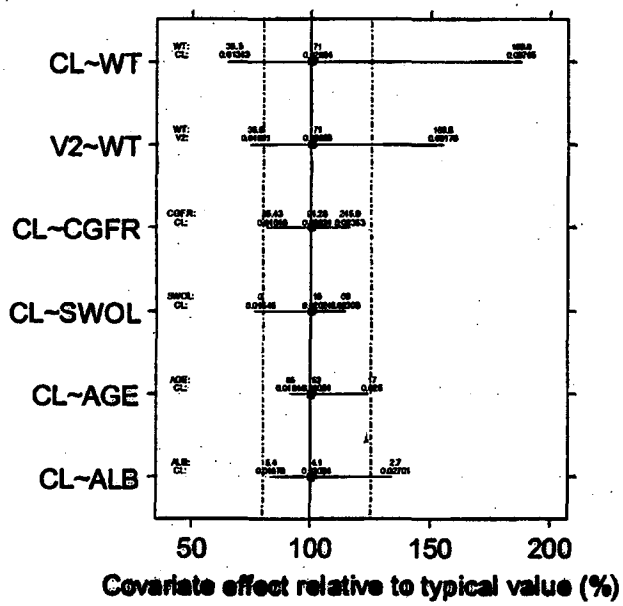
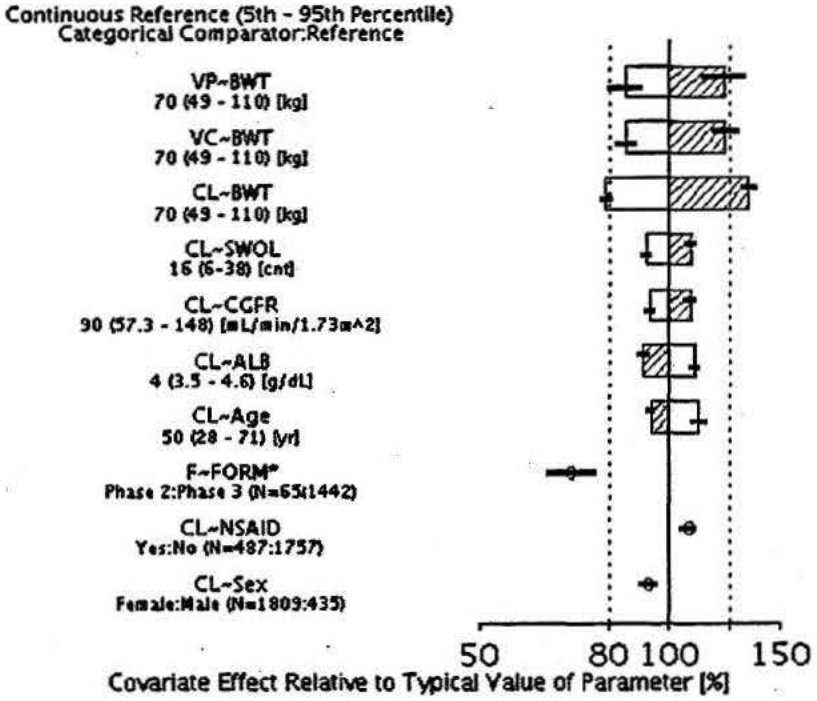


Figure 3 indicates that the full covariate effect on PK parameters by showing the corresponding PK parameter variation over the full covariate range. The most significant covariate to impact CL was body weight, where drug exposure decrease as body weight increases. The median trough concentration in the highest body weight group (>100 kg) is comparable to that achieved with the approved IV dosing regimen. Age was identified as a covariate for efficacy response where DAS28 response decreases with age post active abatacept treatment. For categorical covariates (i.e., SEX and NSAID), female patient would have slight drug clearance (-7.5%) and use of NSAID will slightly increase drug clearance by 7.1%. Figure 4 shows the sponsor supplied evaluation of covariate effects in a range of 5^{th}-95^{th} percentiles on PK parameters.

Figure 4. Final population PK model covariate effects plot



Source: /global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/plot.cov.eff.ssc

* For the formulation, if subject had both Phase 2 and 3 formulation, the subject is counted once for the Phase 2 and once for the Phase 3

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, body weight= 70 kg, age= 50 yr, CGFR = 90 mL/min/1.73m2, albumin = 4.0 mg/dL, swollen joint count = 16, not taking NSAIDs and using Phase 3 formulation. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

As indicated by Figure 4, the magnitude of all covariate effects (except for body weight) on PK parameters, as measured by the 95% confidence intervals, were within 80%-125% of reference values, suggesting that none of those effects could be concluded as clinically relevant. Due to fewer patients in Phase II, the formulation effect on bioavailability should be interpreted with caution.

Body weight effect on Cminss was further evaluated for SC and IV treatments. As shown by Table 9, the Cminss's following SC injection were comparable or higher than the Cminss's following intravenous (IV) administration at low, medium, and high weight groups (i.e., <60 kg, 60-100 kg, and >100 kg).

Table 9. Predicted steady state Cmin by body weight groups for IM101174.

Body Weight Groups	IV [µg/mL] Median (5th - 95th percentile)	SC [µg/mL] [a] Median (5th - 95th percentile)
<60 kg	16.0 (7.15 - 35.3)	34.7 (19.1 - 59.4)
60-100 kg	18.7 (7.73 - 42.0)	26.7 (13.9 - 51.5)
>100 kg	20.1 (9.99 - 29.2)	19.8 (11.2 - 33.0)
Total	18.1 (7.76 - 39.1)	27.5 (13.6 - 54.9)

[a] SC abatacept treatment associated with IV loading dose

Final exposure-efficacy response model: DAS28

After evaluating drug exposure metrics such as Cminss, Cmax at steady state (Cmaxss), and average concentration, Cminss was identified as the best predictor of response. A significant relationship between Cminss and efficacy response as measured by DAS28 was established with an Emax-Tmax model. The model was parameterized in terms of maximum placebo effect (EMX0), maximum drug effect (EMX1), abatacept concentration needed to achieve 50% maximum drug effect (EC50), and time to achieving half of maximum response (T50). The covariate analysis showed that the placebo response (EMX0) increased with baseline DAS28 (E0) and drug response (EMX1) decreased with AGE. Route of administration (IV vs. SC) was not found to be a significant covariate on any of the Exposure-Response parameters. Implying that for a given Cminss, the DAS28 response is expected to be the same regardless of route of administration achieving that Cminss. Table below shows the final parameter estimates of the final exposure-response Model.

$$DAS28(t) = E0 - EMX\frac{t}{T50+t}$$

$$EMX = EMX0 + \frac{EMX1 \times C_{min,ss}}{EC50 + C_{min,ss}}$$

$$EMX0_{TV} = EMX0_{TV,ref} \times \exp(E0_{IIV} EMX0_{E0})$$

$$EMX1_{TV} = EMX1_{TV,ref} \times (\frac{AGE_b}{AGE_{ref}})^{EMX1_{AGE}}$$

Subscript TV indicates population typical value. Inter-individual variabilities (IIV) were assigned to E0, EMX (EMX=EMX0+EMX1), and T50, which were modeled by a reduced band matrix with correlation between E0 and T50, with normal distributions for E0 and EMX and lognormal distribution for T50. Intra-individual variability was modeled by an additive error model.

The final model was validated by evaluating population/individual predictions against observed DAS28 scores, conditional weighted residual (CWRES) against time, CWRES against predicted population means, for IV, SC, and placebo groups, separately. Both visual and quantitative predictive performance checks were conducted to compare statistics of observed DAS28 scores with corresponding statistics calculated from simulated data using the final model. The

developed model reasonably captured the characteristics of the relationship between Cminss and the observed DAS28 score.

Exposure-efficacy response results: DAS28

Different steady state drug exposures (i.e., trough concentration, peak, and average concentration) for both IV and SC administrations had been compared to predict the efficacy response of DAS28 at 6 months post treatment. It had been stated that efficacy response as measured by DAS28 reaches to its pseudo-maximum at a steady–state concentration of 10 µg/mL. However, the associated models for exposure-efficacy responses using peak and average concentration as drug exposure were not reported. Table 10 summarizes the NONMEM generated parameter sets for exposure-efficacy response analyses.

Table 10. Final exposure-response parameter estimates for RA patients

Name [Units][a]	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects			
E0 [-]	6.22	0.0201 (0.323)	6.18 - 6.26
EMX0 [-]	1.97	0.165 (8.38)	1.62 - 2.27
T50 [day]	63.2	5.50 (8.70)	50.6 - 72.9
EMX1 [-]	2.15	0.159 (7.39)	1.84 - 2.45
EC50 [µg/mL]	6.82	1.69 (24.8)	3.76 - 10.4
EMX0 ~ *E0*	1.00	0.125 (12.5)	0.668 - 1.17
EMX1 ~ *AGE*	-0.381	0.0871 (22.9)	-0.540 - -0.212
Random Effects			
ZEMX [-]	1.44 (1.20)	0.192 (13.3)	1.19 - 1.97
ZE0 [-]	0.423 (0.650)	0.0228 (5.39)	0.385 - 0.477
ZT50 [-]	1.34 (1.16)	0.264 (19.7)	0.588 - 1.64
ZE0:ZT50	0.571 (0.758)	0.0616 (10.8)	0.395 - 0.647
Residual Error			
θ_{ADD} [-]	0.360 (0.600)	0.00869 (2.41)	0.344 - 0.377

Figure 5 presents the relationship between Cminss and the change of DAS28 score from baseline at 6 months after first dose. Based on either observed DAS28 values or predicted values by the final exposure-efficacy response model, the above figure shows the positive relationship between trough concentration at steady state (Cminss) and the magnitude of the DAS28 reduction at Month 6. It also shows that DAS reduction reaches to a plateau phase when Cminss exceeds approximately10 µg/mL.

Figure 5. Observed Change from Baseline DAS28 at Month 6 versus Cminss

Final exposure-safety response model: infections and serious infections

Graphical approach was used to evaluate the relationship between exposures (Cminss , Cmaxss, and Cavgss) and infections and serious infections. First, drug exposures were plotted against the binary safety outcomes to examine potential differences. Second, patients were subset into four groups based on their ranks of drug exposure. Kaplan meier plots were used to show time to first safety event for each subset group in order to spot any difference in time to event pattern among the four groups with different drug exposures.

Exposure-safety response outcomes: infections and serious infections

Events of infection and serious infection were used as safety response in the model. All of the analyses did not reveal significant exposure-safety response correlation post both IV and SC doses.

2.3 Intrinsic Factors

2.3.1. What was the impact of demographic covariates on abatacept exposure?

Only body weight has been identified as a covariate that results in clinical relevant exposure variation. The impact of all other covariates such as age, gender, race, renal function (measured

by CGFR), hepatic function (measured by albumin and total bilirubin), and concomitant medication of methotrexate, corticosteroid, or NSAIDs, were all considered as clinically non-relevant.

2.3.2. What were the immunogenicity findings for abatacept? What was the impact of immunogenicity on exposure and/or safety?

As summarized by Table 11, there are five studies that evaluated immunogenic response to abatacept if administered subcutaneously.

Table 11. Clinical studies of subcutaneous abatacept treatment of RA with immunogenicity.

Study / Number of Study Centers/ Locations	Study Start Date/ Study status/ Total enrollment / Enrollment goal	Design/ Control type	Study and Control Drugs Dose, Route, Regimen	# Subjects by group entered/ completed / Mean (SD) Exposure (d/m)	Gender (Male/Female) Median Age (Range)	Diagnosis/ Inclusion Criteria
IM101174 (Phase 3b) Non-inferiority Study ST: 242 sites worldwide LT: 242 sites worldwide Substudy: 42 sites worldwide	ST: 17-Jan-2008 to 14-Oct-2009 Completed 2472/~2400 LT: 20-Aug-2008 to 21-Jan-2010 (Database lock date) Ongoing NA Substudy: 20-Aug-2008 to 21-Jan-2010 (Database lock date) Ongoing NA	ST: Multi-center, DB, double-dummy, comparison of IV and SC ABA in RA subjects with inadequate response to MTX LT: Multi-center, OL extension Substudy: Multi-center, DB, comparison of IV and SC ABA in RA subjects with inadequate response to anti-TNF	ST: SC ABA, 125 mg, administered weekly (IV ABA loading dose, weight-tiered on Day 1) plus IV PBO on Days 1, 15, 29, 57, and every 28 days thereafter IV ABA, weight-tiered dosing, on Days 1, 15, 29, and every 28 days thereafter plus SC PBO, given weekly LT: SC ABA, 125 mg, weekly Substudy: Same as above	ST: SC ABA, N = 736/693 166.5 (15.7) d IV ABA, N = 721/676 165.6 (18.5) d LT: 1357/ongoing 1301at DBL From original SC ABA: 682/ 659 ongoing 8.1 (3.0) m From original IV ABA: 669/ 642 ongoing 8.0 (2.9) m Substudy: SC ABA, N = 8/18 169.3 (3.3) d IV ABA, N = 10/18 163.9 (13.0) d	ST: 256/1201 51.0 y (18 - 85) LT: 241/1116 51.0 y (18 - 85) Substudy: 1/17 44.5 y (20 - 70)	-Moderate to severe active RA for > 1 y -Inadequate response to MTX after at least 3 m of treatment -Subjects must have had at least 10 SJC and 12 TJC at Day 1, as well as hsCRP ≥ 0.8 mg/dL Substudy: -Moderate to severe active RA for > 1 y -Inadequate response to anti-TNF after at least 3 m of treatment -Subjects must have had at least 10 SJC and 12 TJC at Day 1, as well as hsCRP ≥ 0.8 mg/dL
IM101173 (Phase 3b) Monotherapy, Immunogenicity, and Safety Study ST: 22 sites worldwide LT: 22 sites worldwide	ST: 14-Dec-2007 to 19-Dec-2008 Completed 119/~100 LT: 12-Apr-2008 to 21-Dec-2009 (Database lock date) Ongoing NA	ST: Multi-center, 16 week, open label study. LT: Multi-center, OL extension	ST: SC ABA, 125 mg administered weekly (no IV ABA loading dose) given either as: Monotherapy (i.e., no background DMARD) or Concomitant with MTX LT: SC ABA, 125 mg, weekly	ST: SC ABA + MTX = 51/50 114.4 (14.41) d SC ABA Only = 49/46 115.0 (12.73) d LT: SC ABA = 90/75 ongoing 15.7 (3.22) m	ST: 25/75 54.0 y (26.0 - 84.0) LT: 23/67 54.0 y (26.0 - 84.0)	-Active RA -MTX-naive or discontinued MTX >4 weeks prior to first dose of study drug) or were receiving stable MTX therapy -Subjects had a score of > 20 mm on the Subject Global Assessment of Disease Activity visual analog scale (VAS), indicating requirement for a new therapeutic intervention for RA
IM101167 (Phase 3b) Withdrawal-Restart, Immunogenicity, and Safety Study ST: 32 sites worldwide LT: 32 sites worldwide	ST: 14-Nov-07 to 29-Jul-09 Period I: 22-Jan-08 to 16-Dec-08 Completed 167/180 Period II: 15-Apr-08 to 10-Mar-09 Completed 120/105 Period III: 04-Jun-08 to 05-May-09 Completed 119/105 LT: 23-Apr-2008 to 04-Feb-2010 (Database cut-off date) Ongoing NA	ST: Multi-center, randomized, DB, withdrawal study consisting of 3 periods: 12-week, OL induction (Period I) followed by 12-week DB, randomized, PBO-controlled withdrawal period (Period II) in responders, and 12-week, OL reintroduction period (Period III). LT: Multi-center, OL extension in Period III completers and Period I non-responders	ST: Period I: SC ABA, 125 mg/week (IV ABA loading dose, weight-tiered on Day 1) Period II: SC ABA, 125 mg/week SC PBO weekly Period III: Period II SC ABA to: SC ABA 125 mg/week (IV PBO loading dose, weight-tiered) Period II SC PBO to: SC ABA 125 mg/week (IV ABA loading dose) SC ABA 125 mg/week (IV PBO loading dose) LT: SC ABA, 125 mg, weekly	ST: Period I: SC ABA = 167/157 87.7 (10.9) d Period II: SC ABA = 40/40 82.1 (7.5) d SC PBO = 80/79 82.5 (8.5) d Period III: IV PBO loading dose + SC ABA, weekly = 40/40 84.8 (8.6) d Reintroduction: IV ABA loading dose + SC ABA, weekly = 35/35 86.1 (12.2) d IV PBO loading dose + SC ABA, weekly = 44/42 85.5 (7.9) d LT: ABA = 150/138 ongoing (37 Period I non-responders and 113 ST completers) 10.2 (1.7) m	ST: Period I: 27/140 50.0 y (21.0 - 84.0) Period II: 19/101 50.0 (21.0 - 73.0) Period III: 25/125 50.0 (21.0 - 84.0) LT: 25/125 50.0 (21.0 - 79.0)	-Active RA -Inadequate response to MTX -Concomitant background MTX therapy - DAS28-CRP ≥ 3.1 to ≤ 5.2

Study / Number of Study Centers/ Locations	Study Start Date/ Study status/ Total enrollment / Enrollment goal	Design/ Control type	Study and Control Drugs Dose, Route, Regimen	# Subjects by group entered/ completed / Mean (SD) Exposure (d/m)	Gender (Male/Female) Median Age (Range)	Diagnosis/ Inclusion Criteria
IM101126 (Phase 3b) IV to SC Switch Safety Study ST: 32 sites worldwide LT: 32 sites worldwide	ST: 06-May-2008 to 08-Dec-2009 Completed 123/~ 200 LT: 04-Jun-2009 to 29-Jan-2010 (Database lock date) Ongoing NA	ST: Multi-center, OL, single treatment arm study. ST period was 12 months in duration, with primary and secondary objectives analyzed for first 3 months (Day 85) LT: Multi-center, OL extension	ST: SC ABA, 125 mg, weekly (no IV ABA loading dose) LT: SC ABA, 125 mg, weekly	Up to Day 85: IM101029 = 52/49 85.0 (8.6) d IM101102 = 71/71 84.4 (1.3) d Cumulative: IM101029 = 52/43 ongoing 14.6 (4.0) m IM101102 = 71/69 ongoing 16.0 (2.2) m	IM101029: 10/42 56.0 y (28.0 - 77.0) IM101102: 12/59 55.0 y (27.0 - 80.0)	-Active RA -Participated in LT periods of Studies IM101102 or IM101029 with IV ABA and who reached the Day 1821/ Day 1989 visits of IV ABA studies (i.e., had ≥ 5 y of IV ABA trt)
IM101063 (Phase 2) ST: 13 sites, USA only LT: 13 sites, USA only	ST: 11-Jan-2006 to 16-May-2007 Completed 68/up to 72 LT: 13-Apr-2006 to 30-Dec-2009 (Clinical database cut-off date) Ongoing NA	ST: 12-week, Multi-center, DB, randomized, PBO-controlled, parallel-group study LT: OL extension; blinded IV loading dose (PBO or ABA) on Day 85 only	ST: IV loading dose (ABA or PBO) given on Day 1, followed 1 h later by SC ABA or SC PBO, administered weekly for 12 weeks. IV Dosing (ABA or PBO) was weight-tiered: - 500 mg for subjects weighing < 60 kg - 750 mg for subjects weighing 60 to 100 kg - 1 g for subjects weighing > 100 kg SC Dosing (ABA or PBO) was weight-tiered: Trt 1 and 2: < 60 kg: 500 mg IV, 75 or 125 mg SC Trt 3: 60 - 100 kg: 750 mg IV, 125 mg SC Trt 4 and 5: > 100 kg: 1000 mg IV, 125 or 200 mg SC LT: Variable-dose phase: On Day 85, IV dose of ABA (for subjects who received PBO in ST) or PBO (for subjects who received ABA in ST) followed by weekly SC ABA at 75, 125, and 200 mg/kg. IV Dosing (ABA or PBO) was weight-tiered: - 500 mg for subjects weighing < 60 kg - 750 mg for subjects weighing 60 to 100 kg - 1 g for subjects weighing > 100 kg SC Dosing (ABA or PBO) was weight-tiered: - < 60 kg: 75 mg SC - 60-100 kg: 125 mg SC - > 100 kg: 200 mg SC Fixed-dose phase: SC ABA125 mg, weekly	ST: Trt 1: ABA = 7/7, 133 d PBO = 2/2,133 d Trt 2: ABA = 4/3, 130 d PBO = 2/2, 133 d Trt 3: ABA = 29/26, 129 d PBO = 9/9, 133 d Trt 4: ABA = 6/5, 120 d PBO = 2/2, 133 d Trt 5: ABA = 5/5, 134 d PBO = 2/2, 133 d LT: Variable-dose phase: ABA 75 mg/kg = 11/8 15.6 (6.84) m ABA 125 mg/kg = 42/32 19.4 (6.77) m ABA 200 mg/kg = 10/8 17.2 (4.34) m Fixed-dose phase: ABA = 48/ 45 ongoing 16.0 (2.49) m	ST: 11/57 NA (40 - 81) LT: 11/52 60.0 y (40.0 - 82.0)	- Active RA - Receiving MTX and no more than 1 additional DMARD

Study / Number of Study Centers/ Locations	Study Start Date/ Study status/ Total enrollment / Enrollment goal	Design/ Control type	Study and Control Drugs Dose, Route, Regimen	# Subjects by group entered/ completed / Mean (SD) Exposure (d/m)	Gender (Male/Female) Median Age (Range)	Diagnosis/ Inclusion Criteria
IM101013 (Phase I) 1 site worldwide	25-Nov-2003 to 23-Jun-2006 Completed 48/48	Single-dose, single-center (US), DB, randomized (within dose), PBO-controlled, parallel-group.	Single SC ABA dose 50, 75, 100 or 150 mg (100 mg/vial) and matching PBO Single IV ABA dose 50 or 75 mg (250 mg/vial) or and matching PBO (200 mg/vial)	SC ABA: Trt A: 50 mg, 5/5 Trt B: 75 mg, 5/5 Trt C: 100 mg, 5/5 Trt D: 150 mg, 5/5 Trt E: 50 mg/0.5 mL, 5/5 Trt F: 75 mg/0.75 mL, 5/5 IV ABA: Trt G: 50mg, 5/5 Trt H: 75 mg, 5/5 PBO: 8/8 1 d	~ 83% male (20 - 79 y)	- Healthy subjects weighing ≤100 kg

Study IM101174

The primary assay used for immunogenicity detection in the ST period was the ELISA assay. The presence of neutralizing antibodies to abatacept was evaluated in all subjects who had a positive on-treatment or post-treatment sample for anti-CTLA4-T antibody by ELISA during the ST period.

On-treatment, 3 (3/671, 0.4%) developed anti-abatacept antibodies and 2 (2/681, 0.3%) subjects developed anti-CTLA4-T antibodies in the SC abatacept group. In comparison, 5 (5/691, 0.7%) subjects developed anti-abatacept antibodies and 4 (4/658, 0.6%) subjects developed anti-CTLA4-T antibodies in the IV abatacept group. Post-treatment, no anti-abatacept antibodies were detected and 3 (3/28, 10.7%) subjects developed anti-CTLA4-T antibodies in the SC abatacept group. In comparison, no anti-abatacept antibodies were detected and 7 (7/31, 22.6%) subjects had anti-CTLA4-T antibodies in the IV abatacept group.

Approximately first 10% randomized and treated subjects (SC abatacept, N = 82 and IV abatacept N = 71) were tested for immunogenicity via the ECL assay. Only 1 subject (IV abatacept group) had developed CTLA4 and possibly Ig at Day 169.

The immunogenicity response were noted to be body-weight independent, consistent with what was previously demonstrated in the IV abatacept development program, immunogenicity was not associated with any effect on efficacy, safety, or PK profile.

Study IM101167

During the withdrawal period (Period II), all of the 120 subjects who were treated had immunogenicity data. During the reintroduction period (Period III), 119 subjects, all subjects treated in the period except for 1 subject in the SC placebo group who withdrew based on patient consent on Day 197) had data available.

Primary Immunogenicity Endpoints were evaluated at day 169. At Day 169 (end of the withdrawal period), 0/38 for subjects who received continuous SC abatacept (SC abatacept group) and 7/73 (9.6%) for subjects who had SC abatacept withdrawn in Period II (SC placebo group) were tested as immunogenicity positive. The point estimate (95% CI) of the treatment difference was 9.59% (0.83, 18.34). This observed difference was not statistically significant, p-value = 0.119.

In Period III after reintroduction of treatment with SC abatacept in the SC placebo group and continuation of treatment in the SC abatacept group, immunogenicity rates on Day 253 (end of the drug reintroduction period) were 1/38 (2.6%) in the SC abatacept group and 2/73 (2.7%) in

the SC placebo group. The point estimate (95% CI) of the treatment difference was 0.11% (-8.21, 8.43).

It seemed that the presence of anti-abatacept or anti-CTLA4-T antibodies had no impact on the efficacy or safety of SC abatacept therapy after treatment reintroduction on Day 169. In subjects who received SC abatacept throughout the ST period, Cmin concentrations of abatacept were comparable at the presence or absence of a seropositive response. No consistent differences were found in Cmin values between seropositive and seronegative subjects who received SC placebo in Period II. In subjects who received SC abatacept throughout the ST period, Cmin concentrations of abatacept were comparable at the presence or absence of a seropositive response. There was no consistent difference in Cmin concentrations between seropositive and seronegative subjects who received SC placebo in Period II. Table 12 summarizes the findings.

Table 12. Immunogenicity results of trial IM101167

	Period II SC Aba N = 40	Period II SC Pbo N = 80	Estimate of difference[a] (95% CI)
	Number of Subjects n/m (%) (95%) CI		
Day 169 (end of withdrawal period)			
Anti-abatacept	0/37 N/A	1/71 (1.4) (0.0,4.1)	1.41 (-3.39,6.21)
Anti-CTLA4-T	0/38 N/A	6/73 (8.2) (1.9,14.5)	8.22 (-0.08,16.52)
Total with antibody response	0/38 N/A	7/73 (9.6) (2.8,16.3)	9.59 (0.83,18.34) p = 0.119
Day 253 (end of reintroduction period)			
Anti-abatacept	0/38 N/A	0/73 N/A	N/A
Anti-CTLA4-T	1/38 (2.6) (0.0,7.7)	2/73 (2.7) (0.0,6.5)	0.11 (-8.21,8.43)
Total with antibody response	1/38 (2.6) (0.0,7.7)	2/73 (2.7) (0.0,6.5)	0.11 (-8.21,8.43)

[a] Treatment difference for SC placebo vs. SC abatacept.
n = Number of subjects who are positive, m = Number of subjects in the analysis.
N/A = not applicable
P-value is based on the continuity corrected Chi-square test.

Study 101173

At the end of the short-term treatment period (Day 113), none of the 95 subjects with immunogenicity data (50 in SC abatacept + MTX cohort; 45 in SC abatacept monotherapy cohort) were seropositive for anti-abatacept or anti-CTLA4-T antibodies (ELISA assay). Positive antibody responses (based on ELISA) were observed infrequently at earlier time points during the short-term treatment period or during the follow-up for subjects who did not enter the long-term period. These positive antibody responses were transient, generally occurred before Day 85, and were associated with low titers.

During the short-term treatment period, the overall immunogenicity rate at any time in the SC abatacept monotherapy and SC abatacept + MTX cohorts was 4.1% (2/49) and 3.9% (2/51), respectively, based on the ELISA assay. Only 1 seropositive response was observed following treatment discontinuation. One subject in the SC abatacept monotherapy cohort was seropositive

for anti-CTLA4-T antibodies at post-treatment Day 85 but did not develop neutralizing antibodies. Due to lack of efficacy, this subject was withdrawn after receiving 12 SC injections. There did not appear to be any correlation of the development of antibodies with clinical safety or efficacy.

The overall abatacept-induced immunogenicity rate based on the ECL assay for the LTE period was 1.1% (1/90) for subjects receiving SC abatacept. No subject on treatment had an abatacept-induced seropositive response during the LTE period. One subject in the original SC abatacept + MTX cohort, who was discontinued from the LTE period for lack of efficacy and was seronegative to CTLA4g and possibly Ig at all preceding evaluations, had positive titer values for CTLA4g and possibly Ig on days 56 and 85 after the last SC injection of abatacept. There did not seem to be correlation of the development of antibodies with clinical safety findings. Abatacept Cmin concentrations were consistent at the absence and presence of seropositivity in the ST or LTE periods.

Overall, no positive immunogenicity response (based on ELISA assay) was seen at 4 months of treatment with abatacept, injected SC at a weekly dose of 125 mg, either as monotherapy or on a background of MTX and in the absence of an initial IV loading dose, in subjects with RA.

Study IM101185

During the first 3 months (Day 85), a single subject had positive anti-CTLA4-T antibody (based on the ELISA assay); this subject did not exhibit a positive titer value for anti-CTLA4-T during the previous IV abatacept study. During the first 3 months, 1 subject without evidence of a prior antibody response on IV abatacept (based on ELISA) had a positive result for anti-abatacept antibodies after switching to SC abatacept treatment; this positive response was associated with very low titers. Six other subjects who had positive anti-abatacept results during the first 3 months on SC abatacept also had positive anti-abatacept antibody findings prior to receipt of SC abatacept. Thus, the overall immunogenicity rate based on the ELISA assay was 6.6% (8/122 subjects) (all on-treatment). There was no apparent relationship between the occurrence of a positive immunogenic response during the first 3 months of SC abatacept treatment, based on the ELISA assay, and efficacy or safety results during this period. The single subject who had positive antibody titers for anti-CTLA4 on Days 57 and 85 of SC abatacept treatment developed an autoimmune disorder (sarcoidosis) on Day 131 that was serious and resulted in treatment discontinuation.

Abatacept-induced immunogenicity based on the ECL assay was not observed in any subject during the first 3 months (Day 85) and for 1 subject (0.8%) during the cumulative treatment period. The latter abatacept-induced immunogenic response based on the ECL assay consisted of titer values at the lowest quantifiable level (10) on Days 253 and 365, and this abatacept-induced seropositive finding was not associated with any SAE or autoimmune disorders or changes in efficacy responses.

In summary, among all subjects with a positive immunogenicity finding (based on ELISA or ECL) during the cumulative treatment period, abatacept Cmin concentrations were consistent before and after demonstration of a seropositive response. The rate for a positive anti- TLA4-T antibody result (0.8%), based on the ELISA method, during the first 3 months was low and consistent with historical ELISA assay results for IV abatacept.

Study IM101013

Immunogenicity to the SC formulation (osmolality 386 mOsm/kg) was not greater than that of the IV formulation (osmolality 900 mOsm/kg) given SC. Overall, 11 of the 40 subjects (27.5%) developed antibodies to the CTLA4 binding portion of the abatacept molecule: 8 of the 30 abatacept-treated subjects (26.7%) who received the SC formulation and 3 of the 10 abatacept-treated subjects (30.0%) who received the IV formulation given SC developed antibodies to the CTLA4 portion of the molecule. The earliest onset of seroconversion was at Day 43. No dose-dependent increases in immunogenicity were observed. Only 1 subject had a serum sample that possessed neutralization activity. The development of immunogenicity did not appear to be correlated with adverse safety outcomes.

Summary

Immunogenicity rates were low following SC treatment. SC abatacept did not increase immunogenicity rates as compared to IV abatacept based on Phase III study IM101174. The immunogenicity profiles post IV and SC treatments were comparable. The titers of antibodies against abatacept were low, non-persistent, comparable post either IV or SC treatment. The presence of antibodies against abatacept had no identified impact on safety, efficacy, or PK. The immunogenicity response did not appear to correlate with baseline body weight following either SC or IV abatacept treatment.

When SC abatacept was used as monotherapy or when SC abatacept was used following IV abatacept treatment, no significant increase in immunogenicity rates or antibody titers were observed.

Long-term continuous treatment with SC abatacept had no identified impact on immunogenicity rates. However, increase in immunogenicity rates was observed upon withdrawal of SC abatacept therapy. The immunogenicity associated with withdrawal was not persistent upon reintroduction of SC abatacept therapy. Reintroduction of SC abatacept did not have identified impact on safety, efficacy, or PK, with or without IV abatacept loading dose.

3 Labeling Recommendation

At the time of writing this review, the following are the suggested changes (denoted by strikethrough (for deletions) and underline (for additions)). Exact language will be finalized upon further discussion within the review team. Refer to the sBLA action letter for the full text of the final labeling.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for Cmin and Cmax at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between SC and IV administration.

(b) (4) was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an IV load. When the IV loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved

after 2 weeks of dosing. [redacted]

Consistent with the [redacted] data, population pharmacokinetic analyses for [redacted] abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant [redacted], corticosteroids, and NSAIDs [redacted] did not [redacted] influence abatacept apparent clearance.

Signatures

Liang Zhao
Clinical Pharmacology Reviewer_____

Yaning Wang
Pharmacometrics Team Leader_____

Suresh Doddapaneni
Clinical Pharmacology Team Leader_____ 6/28/11

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-796-1672

Memorandum

PROJECT MANAGER'S REVIEW-Amendment

Application Number:	STN 125188/122
Name of Drug:	Orencia® (abatacept)
Sponsor:	Bristol-Meyers Squibb Company
Material Reviewed:	ORENCIA® (abatacept) Carton and Container Labels and Prescribing Information sections: Highlights and Full Prescribing-Title line, Dosage forms and strengths, Description and How Supplied
Submission Date:	August 6, 2010, July 25, 2011

Executive Summary

The carton, container and prescribing information for ORENCIA® (abatacept) were reviewed and conformed to the regulations under 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 and 21 CFR 200.100; and The United States Pharmacopeia, USP 34/NF 29 (5/1/11-7/31/11). Label deficiencies were identified and mitigated. The revised carton and container labels are acceptable. Please see the comments in the conclusions section.

Background:

Bristol-Meyers Squibb Company has submitted a supplement to the Biologic License Application (BLA) for ORENCIA® (abatacept) to introduce a solution in a prefilled syringe configuration for subcutaneous administration. The marketed product is a lyophilized powder administered by intravenous infusion after reconstitution. (b) (4) glass syringe (b) (4) containing a clear, colorless to pale yellow solution at a concentration of 125 mg/mL (b) (4) proposed.

Labels Reviewed:

ORENCIA® (abatacept) Container Label
PFS label
ORENCIA® (abatacept) Carton Labels
(b) (4)
Four Count
Physician sample

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

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBP/IO

Comment/Concurrence:

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Barry Cherney, Ph. D.
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-796-1672

Memorandum

PROJECT MANAGER'S REVIEW

Application Number:	STN 125188/122
Name of Drug:	Orencia® (abatacept)
Sponsor:	Bristol-Meyers Squibb Company
Material Reviewed:	ORENCIA® (abatacept) Carton and Container Labels and Prescribing Information sections: Highlights and Full Prescribing-Title line, Dosage forms and strengths, Description and How Supplied
Submission Date:	August 6, 2010

Executive Summary

The carton, container and prescribing information for ORENCIA® (abatacept) were reviewed and conformed to most of the regulations under 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 and 21 CFR 200.100; and The United States Pharmacopeia, USP 34/NF 29 (5/1/11-7/31/11). Label deficiencies will be provided to the applicant for mitigation. Please see the comments in the conclusions section.

Background:

Bristol-Meyers Squibb Company has submitted a supplement to the Biologic License Application (BLA) for ORENCIA® (abatacept) to introduce a solution in a prefilled syringe configuration for subcutaneous administration. The marketed product is a lyophilized powder administered by intravenous infusion after reconstitution. (b) (4) glass syringe (b) (4) containing a clear, colorless to pale yellow solution at a concentration of 125 mg/mL (b) (4) proposed.

Labels Reviewed:

ORENCIA® (abatacept) Container Label
PFS label
ORENCIA® (abatacept) Carton Labels
(b) (4)
Four Count
Physician sample

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

(b) (4)

[redacted]

7/21/11

Kimberly Rains, Pharm.D
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date:	June 22, 2011
To:	Badrul Chowdhury, MD, Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN 6/22/11 Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)** Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Shawna Hutchins 6/22/11 Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert and Instructions for Use)
Drug Name(s):	• ORENCIA (abatacept) Lyophilized Powder for Intravenous Infusion • ORENCIA (abatacept) Injection, Solution for Subcutaneous Administration
Application Type/Number:	BLA 125118
Supplement Number:	122
Applicant/sponsor:	Bristol-Myers Squibb
OSE RCM #:	2010-2241

1 INTRODUCTION

On August 25, 2009 a Biologics Licensing Application (BLA) was approved for Orencia (abatacept) Lyophilized Powder for Intravenous Infusion indicated for the treatment of moderately to severely rheumatoid arthritis (RA) in adult patients as well as moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. On October 4, 2010, the Applicant submitted an supplemental Biologics Licensing Application (sBLA) for the purpose of describing the efficacy and safety of the use of Orencia (abatacept) Injection, Solution for Subcutaneous Administration indicated for the treatment of moderately to severely rheumatoid arthritis (RA) in adult patients as well as moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older.

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to provide a review of the Applicant's Patient Package Insert (PPI) and Instructions for Use (IFU) of Orencia (abatacept) Injection, Solution for Subcutaneous Administration.

DRISK conferred with DMEPA and a separate DMEPA review of the IFU's will be forthcoming.

2 MATERIAL REVIEWED

- Draft ORENCIA (abatacept) Injection, Solution for Subcutaneous Administration Prescribing Information (PI) received on October 4, 2010, revised by the reviewing division throughout the reviewing cycle, and received by DRISK on June 8, 2011.
- Draft ORENCIA (abatacept) Injection, Solution for Subcutaneous Administration PPI and IFU's received on October 4, 2010 and received by DRISK on June 8, 2011.

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 PPI and IFU's the target reading level is at or below an 8th grade level.

In addition, 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.

In our review of the PPI and IFU's we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU's are consistent with the prescribing information (PI)
- removed unnecessary or redundant information within the PPI and IFU's

- ensured that the PPI and IFU's meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU's are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI and IFU's are appended to this memo.

Please let us know if you have any questions.

Orencia (abatacept)
BLA# 125118 S-122
CC list

1. Chowdhury, Badrul
2. Karwoski, Claudia
3. Willy, Mary
4. Griffiths, LaShawn
5. Hulett, Melissa
6. Hutchins, Shawna
7. Jackson, Colette
8. Rashid, Nichelle
9. Duer, Robin
10. Oleszcuk, Zachary
11. Miller, Cathy
12. Dempsey, Mary

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******Pre-decisional Agency Information******

Memorandum

Date: June 20, 2011

To: Colette Jackson, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer RSzydlo 6/20/11
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Karen Munoz, Regulatory Review Officer
L. Shenee' Toombs, Regulatory Review Officer
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: BLA 125118/122
DDMAC draft labeling comments for Orencia (abatacept)
Lyophilized Powder for Intravenous Administration and Injection,
Solution for Subcutaneous Administration (Orencia)

Per your November 30, 2010, consult request, DDMAC has reviewed the proposed product package insert (PI) and proposed carton and container labeling for Orencia. Reference is also made to DDMAC's consult response dated June 17, 2011, regarding the proposed Patient Information, Patient/Caregiver Instructions for Use, and Frequently Asked Questions sections of the labeling.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "subc-abata-sponsor amended draft with FDA edits 6-16-11.doc" that was sent via email from Dr. Sarah Yim of DPARP to DDMAC on June 16, 2011. While this is an efficacy supplement, DDMAC has reviewed the entire label and thus may be commenting on sections of the label that are already approved. Our comments on the PI are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the proposed carton and container labels submitted by the applicant on October 1, 2010, available in the EDR at:

- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mg4ct-ssi-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mg1ct-ssi-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mgsmpl-ssi-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mg4ct-clin-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mg1ct-clin-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mgsmpl-clin-abata-car.pdf
- \\cbsap58\M\eCTD_Submissions\STN125118\\0115\m1\us\subc-125mg-label-abata-con.pdf

We offer the following comments on the proposed carton and container labeling:

1. We note that the packaging for (b) (4) If this text is not considered essential, we recommend that it be deleted.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI or carton/container labeling please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: June 17, 2011

To: Colette Jackson, Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research

From: Karen Munoz, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Shefali Doshi, DTC Group Leader, DDMAC
L. Shenee' Toombs, Regulatory Review Officer, DDMAC
Roberta Szydlo, Regulatory Review Officer, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC
Michael Wade, Regulatory Health Project Manager, DDMAC
Becki Vogt, Regulatory Health Project Manager, DDMAC

Subject: **BLA 125118**
DDMAC Labeling Comments for Orencia (abatacept)
***Patient Information, Patient/Caregiver Instructions for Use, and Frequently Asked Questions* sections**

Per your November 30, 2010 consult request, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the draft Orencia (abatacept) Patient Information, Patient/Caregiver Instructions for Use, and Frequently Asked Questions sections and offers the following comments. Specifically, this label revision includes a new route of administration – subcutaneous injection.

DDMAC's comments on the Patient Information, Patient/Caregiver Instructions for Use, and Frequently Asked Questions sections for Orencia (abatacept) are based on the proposed draft marked-up labeling titled, "subc-abata-sponsor amended draft with FDA edits 6-16-11.doc" e-mailed by Sarah Yim on June 16, 2011. DDMAC's comments are provided directly on the document attached below.

In this attachment, we offer comments on the *Patient Information, Patient/Caregiver Instructions for Use, and Frequently Asked Questions* sections only. DDMAC's comments on the PI will follow under separate cover.

Thank you for the opportunity to comment on these proposed materials.
If you have any questions, please contact LCDR Karen Munoz at (301) 796-3274 or karen.munoz@fda.hhs.gov.

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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 Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	June 1, 2011
Application Type/Number:	BLA 125118/S-122
To:	Badrul Chowdhury, MD, PhD, Director Division of Pulmonary, Allergy, and Rheumatology
Through:	Zachary Oleszczuk, Pharm.D., Team Leader 6/1/11 Kellie Taylor, PharmD., MPH, Associate Director 6/1/11 Todd Bridges, R.Ph., Acting Deputy Director 6/1/11 Carol Holquist, R.Ph., Director 6/1/11 Division of Medication Error Prevention and Analysis
From:	Manizheh Siahpoushan, Pharm.D., Safety Evaluator MS 6/1/11 Division of Medication Error Prevention and Analysis
Drug Name(s):	Orencia (Abatacept) Injection, 125 mg
Applicant/sponsor:	Bristol-Myers Squibb
OSE RCM #:	2010-2240

***** This document contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

1 INTRODUCTION

This review evaluates the container closure, container labels, carton and insert labeling as well as Patient Instructions for Use of Orencia for any potential to contribute to medication errors. The applicant is proposing a fixed dose subcutaneous injection for Rheumatoid Arthritis and (b) (4) containing 125 mg of Orencia. This review is in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products, dated October 21, 2010.

1.1 REGULATORY HISTORY

Orencia powder (250 mg per vial) for intravenous infusion (BLA 125118) was approved on December 23, 2005. On October 1, 2010, the applicant submitted a supplement (sBLA 125118/122) requesting approval for the use of subcutaneous Orencia injection 125 mg per syringe, in rheumatoid arthritis patients. Additionally, the Applicant submitted container labels, carton and insert labeling as well as Patient Instructions for Use on October 4, 2010.

1.2 PRODUCT INFORMATION

Orencia (abatacept) injection, 125 mg per syringe, is a single dose, disposable, ready-to-use subcutaneous solution. Orencia injection is packaged in a 1 mL long glass syringe with fill line markings and a coated (b) (4) stopper, and is present in (b) (4) as listed below:

(b) (4)

- Abatacept injection prefilled syringe with flange extender consisting of the abatacept injection prefilled syringe, plunger rod, and flange extender.

Subcutaneous Orencia is administered weekly at a dose of 125 mg by subcutaneous injection regardless of weight, and may be initiated with or without an intravenous loading dose. The currently approved Orencia is delivered by intravenous infusion at a dose of 500 mg to 1000 mg every four weeks following an initial dose given at 2 and 4 weeks, and is calculated based on weight. Orencia for subcutaneous administration does not contain maltose (Orencia for intravenous administration contains maltose); therefore, patients do not need to alter their glucose monitoring.

2 METHODS

Since Orencia for intravenous infusion is currently marketed, DMEPA conducted a search of the FDA's Adverse Events Reporting System (AERS) database to identify medication error reports involving Orencia labels and labeling.

Additionally, DMEPA evaluated the container closure, container label, carton, package insert labeling, and patient information leaflet for Orencia injection 125 mg for

subcutaneous administration, using Failure Mode and Effects Analysis[1] (FMEA), principles of human factors, and lessons learned from the postmarketing experience to identify areas that can contribute to medication errors. DMEPA also evaluated the currently marketed labels for Orencia 250 mg powder for intravenous infusion for their ability to cause confusion that could lead to medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION CRITERIA

Search of the FDA Adverse Event Reporting System (AERS) database was conducted on January 20, 2011, using the following criteria: MedDRA reaction terms "Medication Errors" (HGLT), "Product Label Issues" (HLT), and "Product Quality Issue" (PT). No date limits were set in order to capture the maximum number of cases. We conducted the search using the active ingredient "abatacept", the trade name "Orencia", and the verbatim terms "abatac%" and "Orenc%".

Duplicate reports were combined into cases. Those cases, not pertaining to medication errors (e.g., adverse drug reactions, allergic reactions, injection site reactions, vomiting, headache) or pertaining to medication errors due to concomitantly administered drugs were excluded from further analysis. All cases of medication error were evaluated and grouped by the type of error. Each case was evaluated for the root cause.

2.2 PACKAGING, LABEL, AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) to evaluate the container closure, container label, carton and insert labeling as well as the patient instructions for use, submitted on October 4, 2010 (see Appendix B). Additionally, DMEPA evaluated the currently marketed labels submitted in Annual Report dated February 18, 2011 (see Appendix A).

3 RESULTS AND DISCUSSIONS

The following sections describe the results of DMEPA's medication error searches and labels and labeling evaluation.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION

The AERS search identified 73 reports. After eliminating cases as described in section 2.1, sixty-two (n = 62) medication error cases remained and are categorized below into 7 broad types . For a complete list of ISR numbers for the AERS cases, refer to Appendix D.

Wrong Technique (n = 37)

Thirty-seven cases reported the wrong technique during administration. Seven cases reported administration of the final product without the use of a filter. There were eight cases of failure to use a silicone-free disposable syringe when preparing Orencia. Four cases reported the use of a wrong diluent (e.g. lidocaine, 0.9% sodium chloride, or not identified). There were three cases of either wrong size bags (250 mL instead of 100 mL)

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

used for the final product dilution, or bag of dextrose used instead of 0.9% saline bag. The remaining fifteen cases describe incorrect mixing techniques, presence of clumps in the vials; needle not inserted completely into the vein, infiltration, and storage issues. Although these cases did not provide enough details to determine exact causality, all of these errors with the exception of storage issues, will not be present with the prefilled syringes because these preparation steps are not necessary with prefilled syringes and also because prefilled syringes are stored the same as Orencia vials (in the refrigerator). It is possible that patients and healthcare practitioners may forget to store this product in the refrigerator since people have forgotten to refrigerate the vial. However, clear labeling that this product needs to be refrigerated, should help minimize the risk of this error.

Wrong Duration (n = 9)

Nine cases reported an administration time that was different than the recommended 30 minutes.

Three of the nine cases reported infusion times longer than 30 minutes. In one of these cases, the physician had ordered the infusion time to be 1 to 2 hours.

Six of the nine cases reported infusion times of shorter than 30 minutes. In one of these cases, it was reported that the patient suffered hypertension, and in another case the patient experienced pain.

Although the cases did not provide enough information to determine an exact root cause, we note that the insert labeling clearly states the infusion time of 30 minutes.

The errors of wrong duration should not be a problem with the prefilled syringes since the injection is given as subcutaneous injection and not as an infusion.

Wrong Frequency (n = 4)

Four cases described Orencia being administered at incorrect frequencies.

In one case, a nurse reported that patient received her second infusion at week one instead of week two. A physician reported in another case that patient was accidentally infused at two weeks versus four weeks. Patient did not experience any adverse events. Another case reported that patient's dose was missed by 48 hours with no further details provided. The last case reported a patient who received abatacept at 6 weeks instead of 4 weeks.

The contributing factors of these errors could not be determined due to the lack of sufficient information provided in the case narrative.. We note that the proposed label clearly states the frequency of intravenous infusions, thus, we do not think that these errors are due to labels and labeling.

However, the introduction of the prefilled syringes will also include a different frequency of administration (i.e. weekly) than the currently marketed product (i.e. administered at 2 weeks, 4 weeks, then every 4 weeks). This difference in frequency may cause some confusion. Additionally, our postmarketing experience with products that are

administered once weekly shows that this frequency of administration has lead to confusion[2] that resulted in medication errors.

Two products, Methotrexate and Risedronate, have lead to patients administering the intended weekly dose as a once daily because of confusion with the frequency of administration. Both of these products are oral products and both have once daily regimens that are listed in the prescribing information. These characteristics may have contributed to the confusion with these dosing regimens because most oral tablets are not available for once weekly administration and daily dosing regimens are listed in the prescribing information.

However, Orencia is not an oral product and does not have a frequency of administration listed in the prescribing information that is once daily. Additionally, the errors that were reported with the current frequency of administration did not report that the product was administered more frequently than once a week. Thus, we do not anticipate that this product will be administered more frequently than once weekly because there is no mention of a once daily frequency of administration in the prescribing information.

It is possible that the current frequency of administration and the proposed frequency of administration will be confused, however, we can include the frequency of administration as a labeling comment on the container labels and carton labeling for Orencia to remind patients of the correct frequency of administration and minimize the risk of this error. Additionally, the more simplistic frequency of every week may help patients remember to administer this product at the correct interval.

Wrong Dose (n = 4

Of the four cases of wrong dose, two cases reported under doses and two cases reported overdoses. One case reported a patient receiving 750 mg of abatacept instead of the newly changed dose of 1000 mg by the physician. However, the error was caught and patient was scheduled to receive another vial. Another case reported that patient was administered the wrong dose after the rheumatologist increased the dose from 500 mg to 1000 mg. These cases did not provide sufficient detail to determine contributing factors to the error. The other two cases are case of overdosae. One patient received five vials of abatacept instead of four vials with no adverse events reported. Due to lack of sufficient information, the causality could not be determined. In another case, patient received three vials of abatacept instead of two vials. The cause of this error was reported to be the incorrect number of vials taken out of the refrigerator by students in an externship which was caught by the physician's assistant. The patient did not experience any adverse events. The prefilled syringes may help minimize the risk of error of wrong dose for patients, since all patients using the prefilled syringes will receive the same dose of 125 mg per week.

Dose Omission (n = 3)

Three cases reported that patients missed a dose of Orencia. One case reported that a patient missed the dose of abatcept and took the dose two months later. Another case reported that a patient a missed a dose of abatacept and the next dose will be administered

[2] Choen, Michael; Drugs given once a week may be prone to deadly dosage errors; www.philly.com, March 14, 2011.

16 days late. The third case reported that a patient missed a dose with no other information provided. None of these cases provided enough details to determine the causality.

Wrong Drug (n = 3)

Three wrong drug cases were identified from AERS.

One case involved a reporter expressing concern over name confusion between Orencia and Oracea due to orthographic and phonetic similarities. However, there have been no medication errors reported involving Orencia and Oracea. We considered the similarities of these names prior to approval in OSE Review # 03-0236 dated April 1, 2005. DMEPA did not find potential for confusion between the two names due to differentiating product characteristics such as route of administration (intravenous vs. oral), dosage form (lyophilized powder for injection vs. capsule), dosing frequency (monthly vs. daily), storage (refrigerated vs. room temperature), and indication of use (rheumatoid arthritis vs. rosacea). Furthermore,

The other two wrong drug errors involved confusion between infliximab and abatacept. One case described accidental administration of infliximab instead of abatacept to a patient during her second infusion. The patient felt sick. It was reported in another case that the patient accidentally received two vials of abatacept instead of infliximab. No adverse events were reported. In both cases, there was insufficient details provided to determine the causality. To ensure that infliximab and abatacept are differentiated during product selection by healthcare professionals, we evaluated and compared the carton labels for both products. We concluded that the carton labels for infliximab and abatacept are differentiated when selecting products (see Appendix C). Additionally, the proprietary names and established names are orthographically and phonetically differentiated from one another, thus, DMEPA could not identify the root cause of theses errors, but they do not appear to be related to labels or labeling.

Wrong Route (n = 2)

There were two cases of the intravenous product administered subcutaneously. It will be important to clearly identify the appropriate route of administration on the container labels and carton labeling as well as in the package insert and instructions for use since the applicant is introducing subcutaneous administration into their product line retaining the name Orencia.

3.2 PACKAGING, LABELS, AND LABELING

Our evaluation finds that the proposed prefilled syringe (b) (4) is appropriate for this product because the subcutaneous dose is a fixed 125 mg dose and (b) (4) syringe contains 125 mg. However, we have two concerns regarding the presentation of the (b) (4) First, since this product is packaged in a syringe with a needle, it is possible that this product will be administered intravenously or by another parenteral route. Our postmarketing experience shows that injectable products can be administered by the wrong route of administration. This is also supported by our AERS finding where two cases reported that the intravenous product was administered subcutaneously.

We evaluated the appropriateness of managing this product under the name Orencia as well as pursuing a unique proprietary name, or Orencia with a modifier. None of the options are without some risk of medication errors. However, pursing a unique proprietary name could lead to concomitant therapy between this product and the currently marketed Orencia if healthcare practitioners and patients do not realize they are the same product. Additionally, using a modifier in conjunction with the proprietary name Orencia is difficult because it is unclear what type of modifier could be used to distinguish this product form the currently marketed Orencia product. Using a modifier that focuses on the difference in frequency of administration for this product such as "Orencia Weekly" may be misinterpreted as a frequency for the currently marketed product. Similarly using a modifier that focuses on the difference of administration such as "Orencia Subq" may be misinterpreted as a route of administration for the currently marketed Orencia product. Thus, these name could lead to medication errors.

Marketing this product under the name Orencia and using warning statements on the labels and labeling to remind healthcare practitioners and patients of the correct route of administration and frequency of administration is the most appropriate approach from a medication error perspective.

Our second concern regarding the (b) (4) contain different features. (b) (4) (b) (4) Additionally, the marketing of (b) (4) containing the (b) (4) (b) (4) is uncommon. Regardless of how well the (b) (4) Although, the patient would still receive the right drug and dose, this error could be problematic if patients are unable to adjust to operating the (b) (4) and incorrectly administer the drug. For this reason, it would be ideal if the (b) (4) were combined into (b)

Additionally, our evaluation of the container label, carton and insert labeling, and the Patient Instructions for Use, identified areas of improvement that will help minimize the risk of medication errors associated with the proposed label and labeling for the subcutaneous Orencia as well as the currently marketed container labels for the intravenous Orencia. We identified the following deficiencies:

- (b) (4)
- (b) (4)
- (b) (4)
- Subcutaneous and intravenous instructions in the package insert are not clearly delineated
- Lack of presentation of important information such as (b) (4)

(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container closure, container label, carton, and insert labeling as well as the Patient Instructions for Use has noted areas where information can be further improved to minimize medication errors with the proposed product and currently marketed product. Additionally, improvements can be made on the currently marketed container labels for the intravenous Orencia, to help minimize medication errors. Section 4.1 *Comments to the Division*, contains our recommendations for the insert labeling and the Patient Instructions for Use. Section 4.2 *Comments to the Applicant*, contains our recommendations for the proposed container label, carton labeling as well as the currently marketed container labels for the intravenous Orencia.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any further questions or need clarifications on this review, please contact Nishelle Rashid, OSE Project Manager, at 301-796-3904.

4.1 COMMENTS TO THE DIVISION

We have the following recommendations for the proposed prefilled syringe design, insert labeling and currently marketed container labels and carton labeling:

A. Prefilled Syringe Design

(b) (4)

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5 REFERENCES

1. ***Adverse Events Reporting System (AERS)***

   AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. ***Previous OSE Review***

   Culley, Kimberly. ODS Consult # 03-0236, Orencia (abatacept) Lyophilized Powder for Injection 250 mg per vial Proprietary Name Review.

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Appendix D: ISR Listings from AERS database

5040327	5794989	6024601	6593520	6593626
5118213	5682640	6407444	6593511	6593636
5040342	6342950	6424458	6593509	6593669
5118255	5795055	7042992	6593536	6593679
5118304	5795073	6593296	6593555	6593706
5118305	5901196	6593308	6593568	6593707
5119373	5853017	6593331	6593570	6593711
5277014	5901215	6593342	6593573	6593718
5368664	5901230	6593348	6593574	6593729
5368685	5901244	6593366	6593582	6601753
5368720	5901267	6593401	6593584	6601768
5468226	6024504	6593405	6593587	6601772
5570459	6024546	6593420	6593603	7116740
5570511	6024551	6593451	6593613	
5765057	6024596	6593486	6593616	

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: May 18, 2011
From: Jacqueline Ryan Medical Officer WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Collette Jackson, Senior Regulatory Project Manager, WO Bldg 22, 3322
CDER
Subject: CDRH Consult, GEN 1100466, sBLA 125118/122, (b) (4) to deliver Bristol-Myers Squibb's Orencia (abatacept)

1. Issue

The Center for Drug Evaluation and Research (CDER)] has requested a follow up consult from the Center for Devices and Radiological Health (CDRH), regarding sBLA 125118/122. (b) (4) The device component was reviewed in CDRH on December 20, 2010 by LCDR Nikhil Thakur.

2. Device Description

Orencia is supplied in a prefilled (b) (4)

3. Documents Reviewed

sBLA 125118/122

4. CDRH Review and Comments

5.

The sponsor was asked to address the deficiencies below from the December 20, 2010 review.

CDRH Question 1
According to Drawing No DMC6506550503 (Created February 14, 2003, Revision 2), the thickness of the (b) (4) atop the glass syringe barrel is (b) (4) millimeters. ISO 11040 states that the minimum thickness for this collar should be 1.9 millimeters. In your submission, you state that the Orencia pre-filled syringe will be equipped with a "flange extender" that (b) (4) Please clarify whether the "flange extender" will be attached to all new Orencia pre-filled syringes.

Sponsor's Response:
The proposed abatacept injection prefilled syringe with flange extender product presentation proposed in the sBLA is comprised of a prefilled syringe with flange

extender which will be fully assembled prior to release to the market.
In addition, as stated in ISO 11040-4:2007 Table 1 – "Barrel dimensions", the glass finger flange thickness for a 1 mL long syringe barrel has a nominal specification of 1.9 mm with a tolerance of +/- 0.5 mm. The vendor drawing DMC6506550503 states a minimum glass finger flange thickness of (b) (4) mm, thus the syringe meets the minimum requirement as stated in the ISO standard.

CDRH response:
This is acceptable.

CDRH Question 2
Additionally, regarding the flange extender, you have provided human factors simulated use testing to demonstrate that the user can successfully manipulate the Orencia prefilled syringe with the flange extender attached. However, it was unclear whether the testing assessed whether the user (b) (4) Please demonstrate that the (b) (4) please demonstrate that the glass barrel syringe meets collar thickness requirement under ISO 11040.

Sponsor's response:
The abatacept injection prefilled syringe with flange extender presentation will be fully assembled at the manufacturing site prior to release to the market. (b) (4) *under normal handling and shipping this does not happen. Since the product is provided fully assembled and the Instructions for Use indicate the flange extender in the diagrams, it is expected that users will use the product* (b) (4) *as intended.*
As described in the response to Question 1, the glass finger flange thickness of the syringe which is minimally (b) (4) mm meets the minimum requirement as stated in ISO 11040-4. Every syringe batch BMS has tested has passed the minimum flange thickness of 1.4 mm.

CDRH response:
This is acceptable.

CDRH Question 3
There was no description on whether the Hydrolytic Resistance and Annealing Quality testing was performed on the glass barrel of the prefilled syringe. CDRH notes that the syringe is manufactured by (b) (4) However, since the pre-filled syringe will be approved under the sBLA 125118, it is your responsibility to ensure that the syringe is safe and effective for its intended use. Please demonstrate that the (b) (4) pre-filled syringe has been subjected to the Hydrolytic Resistance and Annealing Quality testing.

Sponsor Response:
Per USP <660> and Ph. Eur.3.2.1, hydrolytic resistance testing is performed as one of the physicochemical tests listed in the BMS syringe specifications (please refer to Table 3.2.P.7.1.1.T01 of Section 3.2.P.7.1.1 Packaging Components Specifications-Abatacept Injection Prefilled Syringe in the initial sBLA). Every batch BMS has tested for hydrolytic resistance has passed. The results from one representative batch of syringes, 9M39750 are presented in Table Q3.T01.

BMS has been informed by (b) (4) that the syringe barrels go through the annealing step (b) (4) during manufacturing I. After the annealing step, a (b) (4) Every syringe batch BMS has tested has passed this (b) (4) inspection.

CDRH response:
This is acceptable

CDRH Question 4
Within sBLA 125118, it appears that you have made a promissory note to assess container closure integrity during manufacturing. Whereas it relevant to ensure that devices that are manufactured meet the leak testing performance criteria as part of the validation of the manufacturing process, it is more critical to demonstrate that the syringe that is selected for the delivery of Orencia is free of leaks and prevents any ingress of foreign matter within the pre-filled syringe barrel. Please demonstrate that leak testing has been performed on the prefilled Orencia syringe.

Sponsor response:
To mitigate the possibility of the prefilled syringe leaking, the primary components are subjected to a leak test as part of the incoming inspection. Every batch tested by BMS to date has passed the leak test.
In addition, during the development of the primary container system, CCIT testing was performed and the results were provided in section 3.2.P.2.5, "Pharmaceutical Development - Microbiological Attributes" of the initial sBLA. Also as part of the assembly validation and shipping qualification activities CCIT testing was performed. CCIT summaries are being provided in response to questions 1 and 3 received from FDA on March 8, 2011.

CDRH response:
This is acceptable

CDRH Recommendation

The sponsor has adequately addressed the deficiencies.

Sincerely,

Jacqueline Ryan
Medical Officer

Concurred By:

5/18/2011
LCDR Nikhil Thakur
Combination Products Team Leader

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: DEC 2 7 2010

TO: Colette Jackson, OND/ODEII/DPARP, CDER, WO-22, Room 3322

Cc: Sandy Barnes, OND/ODEII/DPARP, CDER, WO-22, Room 3306;
Office of combination products at combination@fda.gov

THRU: Valerie Flournoy, Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66 Room 3526 VF, 12/22/10

FROM: M. Isabel Tejero, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66 Room G254

SUBJECT: Inter-Center consult requested by DPARP/CDER, of sBLA 125118/122, submitted by Bristol-Myers Squibb Company. This is a supplement to expand the use of Orencia (abatacept) to subcutaneous administration for the treatment of rheumatoid arthritis.

INSTRUCTIONS: Evaluate the need for inspection of the combination product manufacturer.

Objective

The Office of Compliance at CDRH received a consult request from CDER regarding the BLA supplement 125118/122 on November 13, 2010. The consult requested CDRH's consultative involvement with the (b) (4) pre-filled syringe with flange extender.

CDER's request to CDRH Office of Compliance was to evaluate the need of a FDA inspection of the combination product manufacturer.

Product Description

This BLA supplement (b) (4) the abatacept prefilled syringe with a flange extender. The prefilled syringe (125

mg/mL), including drug product and primary packaging, [redacted] is the manufacturer of the [redacted] syringe used.

Abatacept is the active ingredient of Orencia. The approved use of Orencia is 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. Orencia may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs other than tumor necrosis factor (TNF) antagonists.

The abatacept injection prefilled syringe [redacted]

[redacted]

The abatacept prefilled syringe with a flange extender is comprised of three device components (**Figure 2**) that will be assembled [redacted] the prefilled syringe, a plunger, and the flange extender. [redacted] manufactures the plunger

rod and flange extender; [redacted] (b) (4) manufactures the plunger stopper. The extended flange is designed to facilitate patient auto-injection by providing better support for the fingers.

Secondary packaging for [redacted] (b) (4) of the combination product will be a tray that will then be placed inside a paperboard carton. This product is light and temperature sensitive, and must be stored and shipped refrigerated in opaque containers. The firm included in the application under review their proposed shipping validation studies.

Consult Evaluation

Upon review of the records provided, CDRH Office of Compliance has established that Bristol-Myers Squibb Company, located in Princeton, New Jersey, is responsible for the finished abatacept prefilled syringe with [redacted] (b) (4) flange extender combination [redacted] (b) (4). Bristol-Myers Squibb Holdings Pharma, Ltd. in Manati, Puerto Rico, is where drug manufacturing, finished combination product assembly, labeling, and packaging will take place.

CDRH recommends a Level II QSIT inspection of Bristol-Myers Squibb Holdings Pharma, Ltd., focusing on Design Controls, Purchasing Controls, Product and Process Controls, Acceptance Activities, MDRs, Complaint Handling, Corrective and Preventive Actions, and Corrections and Removals for the abatacept prefilled syringe [redacted] (b) (4), or a substantially equivalent product such as other Orencia presentations. The complete address of this firm is as follows:

Bristol-Myers Squibb Holding Pharma, Ltd
P.O. Box 30100
Manati, Puerto Rico 00674-3000
FEI: 2650089

CDRH does not recommend at this time the inspection of Bristol-Myers Squibb Company headquarters. However, CDRH will revise this opinion if, during the inspection of the Manati plant, the compliance with any of the applicable regulations, as they relate to the abatacept prefilled syringe with [redacted] (b) (4) nd flange extender [redacted] (b) (4), cannot be determined.

CDRH Recommendation

CDRH recommends that the approval of sBLA125118/122 is deferred until the time when satisfactory pre-approval inspection has been conducted at the site recommended for inspection above. Attached to this review is an inspection guidance document with inspectional suggestions for the site CDRH recommends to be inspected.

M. Isabel Tejero, MD PhD

Prepared/typed: MITejero: 12/21/2010.
Reviewed/approved: VAFlournoy: VAF-12/22/10
Finalized: GK 12/25/10

cc:
WO66-3515 (DOE-A Firm File)
WO66-3515 (Division Chron File)
WO66-XXX (MI Tejero)

CTS No.: GEN1001394

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: December 20, 2010

From: Nikhil Thakur, Combination Products Team Leader WO66, RM2562
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Collette Jackson, Senior Regulatory Health Project Manager WO 22 RM3322
Division Pulmonary, Allergy and Rheumatology Products, ODEII, OND, CDER

Subject: sBLA 125118 (Pre-Filled Syringe for Orencia (Abatacept))

1. **Issue**

Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health, regarding Bristol-Myers Squibb's combination drug / device product for delivering Orencia (Abatacept). The product is delivered to the patient via a pre-filled syringe.

2. **Documents Reviewed**

sBLA 125118

3. **Device Description**

Orencia is pre-filled into the (b) (4) glass barrel syringe. The syringe is

(b) (4)

4. **CDRH Review and Comments**

In the current submission, the Sponsor has performed bench testing and human factors testing on the device constituent of this combination product. CDRH has assessed the performance of the pre-filled syringe and the human factors testing that the Sponsor has performed. We have not assessed biocompatibility, sterilization, or product labeling as these elements are being reviewed by the CDER review team (as appropriate).

Device Performance

(b) (4)

(b) (4)

Based on comparing the dimensional aspects and performance characteristics of the syringe to ISO 11040, it appears that this pre-filled syringe is consistent with the requirements within the standard, with the exception of the following:

1. There was no description on whether the Hydrolytic Resistance and Annealing Quality testing was performed on the glass barrel of their prefilled syringe. CDRH notes that the syringe is manufactured by (b) (4) However, since the pre-filled syringe will be approved under the sBLA 125118, it is Bristol-Myers Squibb's responsibility to ensure that the syringe is safe and effective for its intended use. The Sponsor should provide the testing results that demonstrate that the (b) (4) pre-filled syringe meets these requirements.
2. Within sBLA 125118, it appears that the Sponsor has made a promissory note to assess container closure integrity during manufacturing. Whereas it relevant to ensure that devices that are manufactured meet the leak testing performance criteria, as part of the validation of the manufacturing process, it is more critical to demonstrate that the syringe that is selected for the delivery of Orencia (abatacept) is free of leaks and prevents any ingress of foreign matter within the pre-filled syringe barrel.
3. Regarding the thickness of the glass barrel syringe (b) (4) according to Drawing No DMC6506550503 (Created February 14, 2003, Revision 2), the thickness of the (b) (4) atop the glass syringe barrel is (b) (4) millimeters. The Standard states that the minimum thickness for this (b) (4) should be 1.9 millimeters. However, Bristol-Myers Squibb has designed a "Flange Extender" that is placed around the (b) (4) which (b) (4) to a point where the requirements within the ISO Standard have been satisfied. However it is unclear whether all Orencia pre-filled syringes will have this "flange extender" component, thus the Sponsor should be asked to clarify whether the flange extender will be placed on each Orencia Syringe, and demonstrate that the flange extender (b) (4) to impact the safety and effectiveness of the syringe.

(b) (4)

Human Factors

The Sponsor has performed device user testing on the pre-filled syringe. CDRH has assessed this user testing and the detailed comments regarding our assessment can be found in Attachment 1 of this review memorandum. To summarize the review in Attachment 1, it appears that the user testing is acceptable, and we do not have any further concerns regarding human factors / simulated use testing that the Sponsor has performed for this product.

5. Deficiencies:

The following deficiencies should be issued to the Sponsor:

1. According to Drawing No DMC6506550503 (Created February 14, 2003, Revision 2), the thickness of the (b) (4) atop the glass syringe barrel is (b) (4) millimeters. ISO 11040 states that the minimum thickness for this collar should be 1.9 millimeters. In your submission, you state that the Orencia pre-filled syringe will be equipped with a "flange extender" that (b) (4)

(b) (4). Please clarify whether the "flange extender" will be attached to all new Orencia pre-filled syringes.

2. Additionally, regarding the flange extender, you have provided human factors / simulated use testing to demonstrate that the user can successfully manipulate the Orencia prefilled syringe with the flange extender attached. However, it was unclear whether the testing assessed whether the user (b) (4). Please demonstrate that the (b) (4) please demonstrate that the glass barrel syringe meets collar thickness requirement under ISO 11040.
3. There was no description on whether the Hydrolytic Resistance and Annealing Quality testing was performed on the glass barrel of the prefilled syringe. CDRH notes that the syringe is manufactured by (b) (4) However, since the pre-filled syringe will be approved under the sBLA 125118, it is your responsibility to ensure that the syringe is safe and effective for its intended use. Please demonstrate that the (b) (4) pre-filled syringe has been subjected to the Hydrolytic Resistance and Annealing Quality testing.
4. Within sBLA 125118, it appears that you have made a promissory note to assess container closure integrity during manufacturing. Whereas it relevant to ensure that devices that are manufactured meet the leak testing performance criteria as part of the validation of the manufacturing process, it is more critical to demonstrate that the syringe that is selected for the delivery of Orencia is free of leaks and prevents any ingress of foreign matter within the pre-filled syringe barrel. Please demonstrate that leak testing has been performed on the prefilled Orencia syringe.

Please contact Nikhil Thakur at (301) 796 – 5536, if you have any questions.

Sincerely,

Nikhil Thakur
Combination Products Team Leader
General Hospital Devices Branch
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment A

Date:	December 10, 2010
From:	Molly Follette Story, Consultant, CDRH/ODE/DAGID/GHDB
To:	Nikhil Thakur, Requestor, CDRH/ODE/DAGID/GHDB
Consult:	CON1018298, Human Factors
Parent Document:	BLA125118
Device:	Abatacept Injection Prefilled Syringe (b) (4) (b) (4)
Applicant:	Bristol-Myers Squibb Company

Review Scope

This review addresses but is limited to the human factors considerations associated with the information provided by the Sponsor, listed below.

Materials Reviewed

(b) (4)

Device Description

Abatacept injection prefilled syringe (b) (4) consists of the biologic drug product and device components physically combined into a single entity; therefore it is considered a combination product according to 21 CFR 3.2(e)(1). The product is intended to deliver the entire contents of abatacept injection using a manual injection stroke. This drug product presentation consists of (b) (4) (Right image shows assembled system.)

(b) (4)

Discussion and Deficiencies

1. *Study Population*

The design validation study involved 31 participants with RA, ages 28 to 63, of whom 91% had a moderate to severe form of the disease, 61% were presently self-injecting a medication, and 80% were female (3.2.P.2.7.4, Design Verification and Validation, page 3).

- The study population is acceptable.

2. *Study Tasks*

The Sponsor conducted a user failure mode and effects analysis (UFMEA) to identify the critical tasks for device operation, listed in their Table 3.2.P.2.7.4.T01 (3.2.P.2.7.4, Design Verification and Validation, pages 3 and 4).

- It is unclear why [redacted] (b) (4)
- The method of critical task identification is acceptable.

3. *Data Collection*

"If a study subject was unsuccessful at prioritizing and performing critical steps as defined by the complete product use sequence, then additional training, including passive and/or active learning, was provided by the moderator" (3.2.P.2.7.4, Design Verification and Validation, page 5).

- In validation testing, we would prefer that participant failure be followed by exploration with the participant of the root cause of the problem to identify and understand any hazards that might require mitigation. Generally this would take the form of an interview with open-ended questions.
- However, given that the study participants failed to complete the critical tasks in only 1 of 62 trials, it appears that moderator actions after a failure caused little valuable data to be lost.
- The results are acceptable.

Conclusion

The human factors testing is acceptable.

Signed

12/10/2010

Dated

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125118	NDA Supplement #:S- BLA STN # 125118/122	Efficacy Supplement Type SE-
Proprietary Name: Orencia Established/Proper Name: abatacept Dosage Form: Injection Strengths: 250 mg single use vial		
Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable):		
Date of Application: October 4, 2010 Date of Receipt: October 4, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: August 4, 2011	Action Goal Date (if different): N/A	
Filing Date: December 3, 2010	Date of Filing Meeting: November 4, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): Subcutaneous administration		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☒ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): IND 9391, (b) (4) and (b) (4)

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***			X	

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: *Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not**, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #		X		
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff:*			X	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			X	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	Applicant wishes to use currently approved proprietary name
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			Applicant submitted a waiver request for the one-half page limitation for the Highlights section of the label

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			OCP and CDRH consults sent on 11/13/2010
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**		X		

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, distribute minutes before filing meeting				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 3, 2010 ***If yes, distribute minutes before filing meeting***	**X**			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		**X**		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 4, 2010

BLA/NDA/Supp #: 125118/122

PROPRIETARY NAME: Orencia

ESTABLISHED/PROPER NAME: abatacept

DOSAGE FORM/STRENGTH: 250 mg/vial

APPLICANT: Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Subcutaneous Administration

BACKGROUND: Biological product already approved and this efficacy supplement proposes a new subcutaneous route of administration.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Colette Jackson	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Keith Hull	Y
	TL:	Sarah Okada	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Liang Zhao	N
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Kiya Hamilton	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Steve Leshin	Y
	TL:	Molly Topper	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Jack Ragheb	Y
	TL:	Susan Kirshner	Y
Product Quality (CMC)	Reviewer:	Jack Ragheb	Y
	TL:	Susan Kirshner	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	N
	TL:		
Facility Review/Inspection	Reviewer:	Kalavati Suvarna	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Carolyn Volpe	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: **If no, for an original NME or BLA application, include the reason. For example:** o **this drug/biologic is not the first in its class** o **the clinical study design was acceptable** o **the application did not raise significant safety**	☐ YES Date if known: ☒ NO ☐ To be determined Reason: this biologic is not the first in its class.

or efficacy issues ○ **the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease**	
• Abuse Liability/Potential **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)** **Comments:**	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments:**	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Badrul A. Chowdhury, M.D., Ph.D., Division Director

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Filing Meeting: November 4, 2010
Filing Reviews Due: November 26, 2010
60th Day Letter Due: December 3, 2010
Mid-Cycle Meeting: March 1, 2011
Labeling Meeting: June 7, 2011
Wrap-Up: June 14, 2011
Labeling Tcon with Applicant: July 12, 2011
Primary Reviews: June 30, 2011
Secondary Reviews: July 7, 2011
CDTL Memo Due: July 14, 2011

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☒	Conduct labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Colette Jackson, Sr RPM 11/29/10

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: BLA STN 125118/122

Name of Drug: Orencia (abatacept)

Applicant: Bristol-Myers Squibb

Material Reviewed:

Submission Date(s): October 4, 2010

Receipt Date(s): October 4, 2010

Submission Date of Structure Product Labeling (SPL): October 4, 2010

Type of Labeling Reviewed: WORD

Background and Summary

On October 4, 2010, Bristol-Myers Squibb submitted a supplemental Biologic Licensing Application for Orencia (abatacept) for a new subcutaneous route of administration for the treatment of Rheumatoid Arthritis.

The proposed labeling text for Orencia was provided in SPL. Draft labeling text was provided in WORD (.doc) format as a review aid, submitted by Bristol-Myers Squibb also on October 4, 2010.

Review

Primary reviewer: Colette Jackson, Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
OND, ODE II, CDER

The .xml version of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD. There were no deficiencies identified in the formatting of the proposed labeling.

Colette Jackson 11/29/10
Senior Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: CCJ/ November 13, 2010
Revised/Initialed: Barnes/ November 19, 2010
Finalized: CCJ/ November 29, 2010
Filename: BLA STN 125118 S122 PLR Labeling Review

CSO LABELING REVIEW OF PLR FORMAT

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: __BL125118 Product: __Orencia_____ Applicant: Bristol Myers Squibb

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date ___11/4/2010 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - __x_ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☐ Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers ❑ If foreign applicant, US Agent signature.	Y N Y N Y N	
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y N	
User Fee payment received	Y N	
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Pediatric rule: study, waiver, or deferral	Y N	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
records □ protocols for clinical trials present □ all electronic submission components usable (e.g. conforms to published guidance)	Y N Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement: □ description and results of studies performed to evaluate the change □ relevant validation protocols □ list of relevant SOPs	Y N Y N Y N	
if clinical supplement: □ changes in labeling clearly highlighted □ data to support all label changes □ all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	
if electronic submission: □ required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC?_____

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:_____
- Dates: _____

Recommendation (circle one): File RTF

RPM Signature: _____ Branch Chief concurrence: _____

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Quality overall summary [2.3]	Y	N	
❑ Drug Substance	Y	N	
❑ Drug Product	Y	N	
❑ Facilities and Equipment	Y	N	
❑ Adventitious Agents Safety Evaluation	Y	N	
❑ Novel Excipients	Y	N	
❑ Executed Batch Records	Y	N	
❑ Method Validation Package	Y	N	
❑ Comparability Protocols	Y	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y	N	
❑ process validation (prospective	Y	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y N	
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N	
Drug Product [3.2.P]		
❑ description and composition	Y N	
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
❑ control of excipients (justification of specifications; analytical method	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation; excipients of human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation) ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N Y N Y N	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N Y N Y N Y N Y N Y N Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	Y N	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	Y N	
❑ novel excipients	Y N	
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package	Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ comparability protocols	Y N	
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	Y N Y N Y N Y N Y N Y N Y N Y N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y N	
includes data demonstrating consistency of manufacture	Y N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	 Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

_____

_____

_____

_____

_____

_____

_____

_____

Recommendation (circle one): File RTF

Reviewer: _____ Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Non-clinical overview [2.4]	Y N	
Non-clinical summary [2.6]	Y N	
❑ Pharmacology	Y N	
❑ Pharmacokinetics	Y N	
❑ Toxicology	Y N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	Y N	
Study Reports and related info. [4.2]	Y N	
❑ Pharmacology	Y N	
❑ Pharmacokinetics	Y N	
❑ Toxicology	Y N	
Literature references and copies [4.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	Y N	
❑ all electronic submission components usable	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
animal reproduction studies included, if the biological product is to be administered to people with reproductive potential, unless an explanation of why such studies are not applicable	Y N	
includes carcinogenicity and/or reproductive and developmental toxicology studies deemed necessary by well established agency interpretation or communication during the IND review process	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): File RTF

Pharm/Tox reviewer: _____
(signature/ date)

Branch Chief concurrence: _____
(signature/ date)

Division. Director concurrence: _____
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	No Section 2.1 in module II
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
❑ Biopharmaceutics and associated analytical methods	Y	N	
❑ Clinical pharmacology [includes immunogenicity]	Y	N	
❑ Clinical Efficacy [for each indication]	Y	N	
❑ Clinical Safety	Y	N	
❑ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	No such section has been found.
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
❑ Biopharmaceutic	Y	N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
❑ Pharmacokinetics (PK)	Y	N	
❑ Pharmacodynamic (PD)	Y	N	
❑ Efficacy and Safety	Y	N	
❑ Postmarketing experience	Y	N	
❑ Case report forms	Y	N	
❑ Individual patient listings (indexed by study)	Y	N	
o electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
❑ legible	Y	N	
❑ English (or certified translation into English)	Y	N	
❑ compatible file formats	Y	N	
❑ navigable hyper-links	Y	N	
❑ interpretable data tabulations (line	Y	N	

Examples of Filing Issues	Yes?	If not, action & status
listings) & graphical displays ❑ summary reports reference the location of individual data and records	Y N	
❑ protocols for clinical trials present	Y N	Can not locate protocols
❑ all electronic submission components usable	Y N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	Y N	
❑ conducted in compliance with requirements for informed consent	Y N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y N	
drug interaction studies communicated as during IND review as necessary are included	Y N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	
comprehensive analysis of safety data	Y N	

Examples of Filing Issues	Yes?	If not, action & status
from all current world-wide knowledge of product		
data supporting the proposed dose and dose interval	Y N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
(b) (4) (IV)	Y	N	Y	N	NR	Y	N	Y	N	NR
im101033 (IV)	Y	N	Y	N	NR	Y	N	Y	N	NR
im101033 (IM)	Y	N	Y	N	NR	Y	N	Y	N	NR
im101063 (IM)	Y	N	Y	N	NR	Y	N	Y	N	NR
im101174 (IM)	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File ~~RTF~~

Reviewer: _____ 11/22/2010 Type (circle one): Clinical (Clin/Pharm) Statistical
(signature/ date)

Concurrence: Yun Xu (acting team leader) 11/22/2010

Branch Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

BLA/~~NDA~~ Number:	**Applicant:**	**Stamp Date:**
125118\122	Bristol-Myers Squibb	October 4, 2010
Established/Proper Name:	**BLA/~~NDA~~ Type:**	
Orencia (abatacept)	Efficacy supplement	

Brief description of the change:	A new subcutaneous (SC) formulation of abatacept (Orencia®) 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. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.
Reviewer:	Kalavati Suvarna
Office/Division:	OC/DMPQ/BMT

On **initial** overview of the BLA/~~NDA~~ **supplement** for filing:

The following was submitted in support of the change (check all that apply):

X	A detailed description of the proposed change
X	Identification of the product(s) involved
X	A description of the manufacturing site(s) or area(s) affected
X	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
X	The data derived from such studies
X	Relevant validation protocols and data
	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? **Yes**

If the supplement is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide bioburden and endotoxin limits at the drug product formulation step and the (b) (4) *step prior to final fill of abatacept drug product.*

2. Please provide data on the microbial challenge test for container closure integrity and the correlation to the dye-ingress test. Also, provide the acceptance criteria established for the methylene blue dye intrusion spectrophotometric test along with information on the limit of detection and limit of quantitation of the test method.

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

Kala Suvarna 10/23/2010

Product Quality Microbiology Reviewer KALAVATI SUVARNA Date

10/23/2010

Team Leader Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125118/S-122

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125118 Supplement Number: 122 NDA Supplement Type (e.g. SE5): _____

Division Name: DPARP PDUFA Goal Date: August 4, 2011 Stamp Date: 10/4/2010

Proprietary Name: Orencia

Established/Generic Name: abatacept

Dosage Form: subcutaneous injection

Applicant/Sponsor: Bristol-Myers Squibb

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Adult Rheumatoid Arthritis
(2) Juvenile Idiopathic Arthritis
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Adult Rheumatoid Arthritis

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	5 yr. __ mo.	☐	☐	☒	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	6 yr. __ mo.	17 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

ediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is ppropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the roduct are sufficiently similar between the reference population and the pediatric subpopulation for which formation will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page} 6/29/11

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

BLA NO. 125118

ABATACEPT (BMS-188667) - SUBCUTANEOUS sBLA

21 CFR § 601.27 Request for Deferred Submission of Pediatric Assessments

Under the provisions of 21 CFR § 601.27(b), Bristol-Myers Squibb Company is requesting deferral of the requirement for inclusion of pediatric data in this sBLA.

Consistent with FDA's guidance on complying with the Pediatric Research Equity Act, BMS acknowledges the need to complete a pediatric assessment of SC abatacept in RA patients. BMS considers that data from Study IM101174 and the approval of IV abatacept (for juvenile idiopathic arthritis) provide the information required to assess the use of SC abatacept in a pediatric population.

BMS is requesting a deferral for pediatric assessment at the time of sBLA submission for SC abatacept in adults. We plan to submit the pediatric assessment for SC abatacept separately. This approach was also discussed at the pre-sBLA meeting of 3 June, 2010. FDA stated that while our proposal to request a deferral for JIA patients is reasonable, a final determination of the acceptability of our proposal will be made during the sBLA review.

We are currently also planning to request a Type C meeting with FDA to discuss the proposed pediatric development plan prior to its implementation. A separate sBLA will be planned upon completion of the pediatric investigations with SC abatacept.

Anand S. Achanta

Anand S. Achanta, Ph.D.
Director
Global Regulatory Sciences
Bristol-Myers Squibb, D32-08
Princeton, NJ 08543-4000

Date: 17 Sep 2010

BLA NO. 125118

ABATACEPT (BMS-188667) - SUBCUTANEOUS sBLA

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

Anand J Achanta

Anand S. Achanta, Ph.D.
Director, Global Regulatory Sciences
Bristol-Myers Squibb Company
P.O. Box 4000 (Mail Stop D32-07)
Princeton, NJ 08543
609-252-6595

22 Jul 10

Certification Date

Jackson, Colette

From:	Pohlhaus, Timothy
nt:	Friday, July 15, 2011 1:13 PM
:	Jackson, Colette
Cc:	CDER-TB-EER; Pohlhaus, Timothy
Subject:	Final TB-EER response - STN 125118/122
Attachments:	Final TB-EER response - STN 125118-122.doc

The Division of Good Manufacturing Practice Assessment has completed its review and evaluation of the TB-EER for STN 125118/122. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.

Final TB-EER
esponse - STN 12...

Timothy J. Pohlhaus, Ph.D.
Interdisciplinary Scientist, Chemist
Food and Drug Administration
CDER/OC/OMPQ
0903 New Hampshire Avenue
ilding 51, Room 1333
ilver Spring, MD 20993
Phone - (301) 796-5224

From:	Jackson, Colette
Sent:	Saturday, July 09, 2011 4:48 PM
To:	Pohlhaus, Timothy
Cc:	CDER-TB-EER
Subject:	RE: TB-EER response - STN 125118/122

Dear Timothy,

Attached is the required TBP-EER Request form for sBLA 125118/122 Orencia that is due 15 to 30 days before action. The PDUFA date for this supplement is Thursday, August 4, 2011, but Dr. Chowdhury would like to sign the action letter on July 29, 2011, due to work travel on the PDUFA date.

Please contact me if you have any questions.

Thank you,

<< File: 125118 s122 TBP EER.pdf >>

Colette Jackson
Senior Regulatory Health Project Manager
ivision of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
Center for Drug Evaluation and Research

10903 New Hampshire Avenue, Bld 22 Room 3322
Silver Spring, MD 20993-0002
Phone: 301-796-1230
FAX: 301-796-9718/9728
E-mail: Colette.Jackson@fda.hhs.gov

From: Pohlhaus, Timothy
Sent: Tuesday, May 24, 2011 4:51 PM
To: Jackson, Colette
Cc: Pohlhaus, Timothy; CDER-TB-EER
Subject: TB-EER response - STN 125118/122

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 125118/122. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.

<< File: TB-EER response - STN 125118-122.doc >>

Timothy J. Pohlhaus, Ph.D.
Interdisciplinary Scientist, Chemist
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 1333
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Jackson, Colette
Sent: Friday, April 29, 2011 1:35 PM
To: CDER-TB-EER
Subject: sBLA 125118 s122 TBP EER

To TBP EER,

Attached is the TBP EER for sBLA 125118 s122. This is a prior approval supplement which proposes the use of abatacept for subcutaneous administration. The PDUFA date is August 4, 2011.

I will make sure that I send another request 15 to 30 days prior to the action date (@ July 5, 2011).

Thank you for your assistance with this application. Please let me know if you need additional information.

<< File: 125118 s122 TBP EER.pdf >>

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue, Bld 22 Room 3322
Silver Spring, MD 20993-0002
Phone: 301-796-1230

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: August 4, 2011

Applicant Name: Bristol-Myers Squibb
U.S. License #: 1713
STN(s): 125118/122
Product(s): Orencia (abatacept)
Short summary of application: This is a prior approval supplement to allow the use of subcutaneous administration of abatacept.

FACILITY INFORMATION

(b) (4)

Short summary of manufacturing activities performed: *Drug Substance Manufacturing and Release*

Inspected (b) (4) by (b) (4)-DO and classified VAI. The CBI profile was updated and is acceptable. This site was also inspected (b) (4) to cover issues related to equipment maintenance. That inspection was also classified VAI.

Bristol-Myers Squibb Company

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

6000 Thompson Road
East Syracuse, New York 13057
Establishment number: 1317461
Short summary of manufacturing activities performed: *Drug Substance Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by NYK-DO August 16-20, 2010 and classified NAI. The inspection covered the Quality, Production, Laboratory Control, Facilities & Equipment and Materials systems. The CTL profile was updated and is acceptable.

(b) (4)

Inspected by (b) (4)-DO (b) (4) and classified VAI. This was a surveillance inspection of a biologic product testing site. The CTL profile was covered and is acceptable.

(b) (4)

Inspected by (b) (4)DO (b) (4) and classified NAI. The CTX profile was updated and is acceptable.

(b) (4)

Inspected (b) (4) by (b) (4)DO and classified VAI. Mycoplasma testing was covered. The CTL profile was covered and is acceptable.

(b) (4)

(b) (4)

No evaluation of this site is required for this site based on the responsibility listed.

(b) (4)

No evaluation of this site is required for this site based on the responsibility listed.

Bristol-Myers Squibb Holdings Pharma, LTD.
P.O. Box 301000
Road 686, KM. 2.3
Manati, Puerto Rico 00674-3000
Establishment Number: 2650089
Short summary of manufacturing activities performed: *Manufacturing, Microbiological Control Testing, Packaging, Labeling, Release, and Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by SJN-DO February 23-March 28, 2011 and classified VAI. This was a GMP inspection to verify corrective actions following the Warning Letter issued on August 30, 2010. The CTL, SVS, SVL, and TRP profiles were updated and are acceptable.

Bristol-Myers Squibb Company
6000 Thompson Road
East Syracuse, New York 13057
Establishment number: 1317461
Short summary of manufacturing activities performed: *Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by NYK-DO August 16-20, 2010 and classified NAI. The CTL profile was updated and is acceptable.

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

/s/

MARY GRACE LUBAO
08/01/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 25, 2011

To: Ashley Pereiera	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

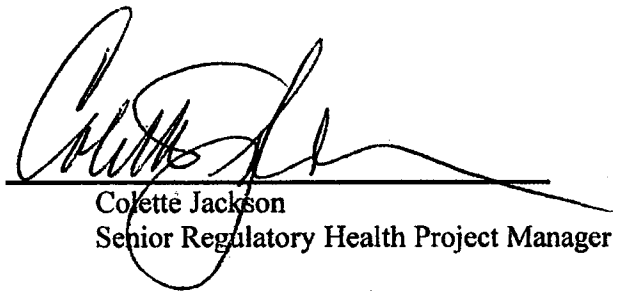
Document to be mailed: **YES** **xNO**

STN: BLA 125118/122 July 25, 2011
Orencia® (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We also refer to your July 22, 2011, submission which included revised package insert and patient package insert. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert, and Patient Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and we may have additional comments. We request that you provide your response by the close of business on July 27, 2011.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Enclosure: FDA Proposed Labeling for Orencia



Colette Jackson
Senior Regulatory Health Project Manager

Drafted: July 25, 2011
Initialed by: Barnes/ July 25, 2011
Yim/ July 22, 2011

Finalized: CCJ/ July 25, 2011

Filename: 125118 s122 July 25 2011 Label Fax.doc

File path: Data/My Documents/BLA/125118

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 20, 2011

To: Ashley Pereiera	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 July 20, 2011
Orencia® (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We also refer to your July 14, 2011, submission which included revised package insert and patient package insert. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert, and Patient Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and we may have additional comments. We request that you provide your response by the close of business on July 22, 2011.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: FDA Proposed Labeling for Orencia

Drafted: July 20, 2011
Initialed by: Barnes/ July 20, 2011
Yim/ July 20, 2011

Finalized: CCJ/ July 20, 2011

Filename: 125118 s122 July 20 2011 Label Fax.doc

File path: Data/My Documents/BLA/125118

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2011

To: Ashley Pereiera	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122 FDA Proposed Carton and Container Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 July 19, 2011
Orencia® (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following FDA recommendations and comments for the proposed Carton and Container Labeling for the Single-Dose Pre-filled Syringe with flange extender. Our comments and recommendations are not all-inclusive and we may have additional comments. We request that you provide your response by the close of business on July 22, 2011.

1. The following comments pertain to the carton label.

   a. To comply with the USPC Official 5/1/11-7/31/11, USP 34/NF 29, <1091> Labeling of Inactive Ingredients, list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount)

   b. Revise the order of the storage information for clarity. (b) (4) [redacted]

2. The following comments pertain to the Container and Carton labels.

   a. Revise the strength presentation, (b) (4) [redacted] and comply with the Institute for Safe Medication Practices, *List of Error-Prone Abbreviations, Symbols, and Dose Designations.*

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: July 19, 2011
Initialed by: Barnes/ July 19, 2011
Yim/ July 19, 2011

Finalized: CCJ/ July 19, 2011

Filename: 125118 s122 July 2011 Carton Container Label Fax.doc

File path: Data/My Documents/BLA/125118

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2011

To: Ashley Pereira	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230
Subject: BLA STN 125118/122	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 July 15, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following comments. Please respond by COB July 19, 2011, in order to facilitate our review.

We ask that you conduct the following as a PREA post marketing requirement.

1. Conduct a PK/safety study of SC abatacept in polyarticular JIA patients ages 6 to 17.

We ask that you conduct the following as post marketing commitments for Orencia

1. Re-evaluate the acceptance criteria for drug product release specifications based on data from at least 30 commercial lots and submit a PMC final report. The specifications established for DP release testing are based on a limited data set and in some instances are broader than the limits for the abatacept injection intravenous presentation. The submission should include the proposed specifications and a justification that includes manufacturing data and data from lots used in the clinical trials.

2. Establish separate release and shelf-life limits and/or acceptance criteria for product attributes that are stability indicating and submit a PMC final report.

3. Develop and validate a quantitative IEF specification using a method such as CE-IEF and submit a PMC final report.

4. Develop and validate a quantitative B7 binding specification that includes measurements of Keq and/or kd using a method such SPR and submit a PMC final report.

5. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product based on the risks to product quality when stored under the approved conditions.

6. Perform real time and accelerated stability studies on 2 additional batches of DP produced from DS manufactured with (b) (4).

7. Conduct extractables and leachables studies. Extractables analysis should be performed under the appropriate exaggerated conditions using the prefilled syringe components that come into contact with the drug (b) (4) Extractables studies should include a spectrum of (b) (4) Supplier data can

be used as a starting point, or in place, of the extractables study when sufficiently representative.

Leachables analysis should be conducted on the assembled prefilled syringe unit under the real-time conditions and should include multiple stability time- points throughout the dating period of the product using the Drug Product Vehicle with (b) (4) the Active Pharmaceutical Ingredient, as extraction media.

Where studies of leachables have not been performed under the conditions encountered during the licensed manufacturing process, repeat the studies under the relevant conditions or provide a justification why it is not necessary to do so. In addition to metals, studies should test for the presence of (b) (4) Studies should employ methods (e.g. ICP-DRC-MS) that permit chemical identification and quantitation (e.g., ppb, ppm) of each compound and report the same. A justification of the sample size used (i.e., number of lots and units within each lot) should be provided.

Submit a PMC final report(s) with the results of these studies.

For each listed post marketing requirement/commitment, please provide in the following format:

PMC#: (State postmarketing committment)
Submission of Final Protocol: (proposed date)
Completion of Study: (proposed date)
Submission For Final Report: (proposed date)

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: July 15, 2011

Initialed by: Barnes/ July 15, 2011
Yim/ July 15, 2011

Finalized: CCJ/ July 15, 2011

Filename: 125118 s122 July 2011 PMC/PMR Fax

File path: Data/My Documents/BLA/125118/s122

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 5, 2011

To: Ashley Pereiera	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 July 5, 2011
Orencia® (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert, and Patient Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and we may have additional comments. We request that you provide your response by the close of business on July 13, 2011.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Enclosure: FDA Proposed Labeling for Orencia

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

Drafted: July 4, 2011
Initialed by: Barnes/ July 5, 2011
Yim/ July 1, 2011

Finalized: CCJ/ July 5, 2011

Filename: 125118 s122 July 2011 Label Fax.doc

File path: Data/My Documents/BLA/125118

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2011

To: Ashley Pereira	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 June 30, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following comments. Please respond by COB July 6, 2011, in order to facilitate our review.

We ask that you conduct the following as post marketing commitments for Orencia

1. To re-assess the bioburden action limits for the formulated drug product step [redacted] (b) (4) based on the manufacturing scale data from 30 lots.

2. To collect bioburden data at the [redacted] (b) (4) step and set appropriate bioburden limits for this step.

3. To develop a container closure integrity test for use in lieu of sterility in the stability program.

For each listed post marketing commitment, please provide in the following format:

PMC#: (State postmarketing committment)
Submission of Final Protocol: (proposed date)
Completion of Study: (proposed date)
Submission For Final Report: (proposed date)

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: June 29, 2011

Initialed by: Barnes/ June 30, 2011
Suvarna/ June 29, 2011
Hughes/ June 29, 2011

Finalized: CCJ/ June 30, 2011

Filename: 125118 s122 June 2011 PMC Fax

File path: Data/My Documents/BLA/125118/s122

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 17, 2011

To: Ashley Pereira	**From:** Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	**Fax number:** 301-796-9718
Phone number: 609-897-2825	**Phone number:** 301-796-1230

Subject: BLA STN 125118/122 Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 June 17, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following requests for information. Please submit this information by COB June 20, 2011, in order to facilitate our review.

1. Poloxamer 188 is used as a (b) (4) in the abatacept SC (b) (4) formulation (b) (4) (Poloxamer 188 (b) (4) Poloxamer 188 (b) (4)

2. Re-adjust the (b) (4) for the formulated drug product (b) (4) step to reflect process capability and available data from commercial manufacturing. Please also provide the bioburden limits for the (b) (4) step.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: June 15, 2011

Initialed by: Barnes/ June 16, 2011
Ragheb/ June 16, 2011
Suvarna/ June 16, 2011

Finalized: CCJ/ June 17, 2011

Filename: 125118 s122 Product and Facilities June 2011 Fax

File path: Data/My Documents/BLA/125118/s122

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 8, 2011

To: Ashley Pereira	From: Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 609-897-2825	Phone number: 301-796-1230

Subject: BLA STN 125118/122 Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 June 8, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following requests for information. Please submit this information by COB June 13, 2011, in order to facilitate our review.

We have concerns that the [redacted] has flange extenders for ease of use [redacted] The marketing of [redacted] is uncommon. Regardless of how well the [redacted] called Orencia, have the same drug concentration, drug volume, and [redacted]. Although, the patient would still receive the right drug and dose, this error could be problematic if patients are unable to adjust to operating the [redacted] they normally use. It is also not clear [redacted] would be dispensed if prescribers [redacted] Please provide the following information:

1. Provide your rationale for having [redacted]

2. Clarify how you propose to ensure that patients [redacted]

3. Clarify what the [redacted]

4. Clarify how you propose to ensure that the [redacted] at the dispensing level.

5. Provide your pharmacovigilance plans for the [redacted]. If [redacted] approved and marketed, and reports were being submitted regarding device failures, medication errors, or other product quality issues with the prefilled [redacted] it may be difficult to conduct a root cause analysis unless the report happened to contain very detailed information about [redacted]

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: June 6, 2011

Initialed by: Barnes/ June 7, 2011
Yim/ June 8, 2011

Finalized: CCJ/ June 8, 2011

Filename: 125118 s122 OSE June Fax

File path: Data/My Documents/BLA/125118/s122

Jackson, Colette

From: Ryan, Jaqueline
nt: Thursday, May 19, 2011 10:46 AM
: Jackson, Colette
Cc: Thakur, Nikhil
Subject: GEN 1100466 sBLA 12511/122

Attachments: GEN 1100466.pdf; GEN 1100466 sBLA 12511 Orencia.doc

Dear Colette,
Here is the CDRH consult. Please call if you have any questions.
Thanks.
Jackie


GEN 1100466.pdf
(209 KB)


GEN 1100466 sBLA
12511 Orencia...

Jacqueline Ryan, MD
Office of Device Evaluation
Center for Devices & Radiological Health
US Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD, 20993-0002

SBlan BC
3/18/11

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: 5/18/11
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

Team Leader
Com B. BLOD
5/18/2011

To (Consulting Center):
Center: **CDRH**
Division: **ODE/DAGID/GHDB**
Mail Code:
Consulting Reviewer Name: **Nikhil Thakur**
Building/Room #: **WO 66 Room 2562**
Phone #: **301-796-5536**
Fax #:
Email Address: **Nikhil.Thakur@fda.hhs.gov**
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: **CDER**
Division: **DPARP**
Mail Code:
Requesting Reviewer Name: **Colette Jackson**
Building/Room #: **WO Bldg 22/Room 3322**
Phone#: **301-796-1230**
Fax #:
Email Address: **Colette.Jackson@fda.hhs.gov**
RPM/CSO Name and Mail Code: **Colette Jackson**
Requesting Reviewer's Concurring Supervisor's Name: **Sandy Barnes**
DPARP Medical Officer: **Keith Hull, MD at 6-1227**
OBP Product Reviewer: **Jack Ragheb at 301-435-4566**
OC/DMPQ/BMT: **Kalavati Suvarna at 6-0821**

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: **3/18/11**

Requested Completion Date: 5/18/2011

Submission/Application Number: **125118/122**
(Not Barcode Number)

Submission Type: **sBLA**
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: __Drug-device combination __Drug-biologic combination x Device-biologic combination __Drug-device-biologic combination __Not a combination product

Submission Receipt Date: **March 10, and 17, 2011**

Official Submission Due Date: **8/4/2011**

Name of Product: **Orencia (abatacept)**

Name of Firm: **Bristol-Myers Squibb**

Intended Use: **Subcutaneous administration for the treatment of rheumatoid arthritis**

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Response to the CDRH comments listed in the 12/20/2010 review.

Documents to be returned to Requesting Reviewer? __Yes x No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

We are requesting CDRH's consultative involvement with the (b) (4) pre-filled syringe with flange extender. We would also like to know if the device constituent of the combination product needs to be inspected.

Type of Request: x Consultative Review __ Collaborative Review
(940 characters max -- use additional sheet if necessary)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 8, 2011

To: Ashley Pereira	From: Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 609-897-2825	Phone number: 301-796-1230

Subject: BLA STN 125118/122 Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 March 8, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following request for information. Please submit this information by COB March 16, 2011, in order to facilitate our review.

1. Submit the Container Closure Integrity Testing (CCIT) summary data performed on assembled pre-filled syringes [redacted] (b) (4)

2. Provide shipping validation summary data for Orencia® pre-filled syringe [redacted] (b) (4) including data on plunger movement during shipping.

3. Provide summary data from the container closure integrity testing performed on syringes subjected to shipping conditions.

4. Provide summary data from the [redacted] (b) (4) shipping system from the BMS manufacturing site in Manatí, PR to the BMS distribution center in Mt Vernon, IN.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: March 7, 2011
Initialed by: Barnes/ March 7, 2011
Suvarna and Hughes/ FDA Reviewer initiated fax March 7, 2011

Finalized: CCJ/ March 8, 2011

Filename: 125118 s122 Product March Fax

File path: Data/My Documents/BLA/125118/s122

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2011

To: Ashley Pereira	From: Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 609-897-2825	Phone number: 301-796-1230

Subject: BLA STN 125118/122 Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 March 4, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following request for information. Please submit this information by COB March 16, 2011, in order to facilitate our review.

1. In your sBLA submission dated October 4, 2010, you provided the study report, data listing datasets, and the analysis datasets for Study IM101174. In the study report, you reported that 1464 subjects were randomized, and 1457 were treated (Figure 5.1. page 135). In your datasets (i.e. (b) (4) the number from variables (b) (4) is 1475. Removing site 229 patients, we got 1467. Please clarify this difference in order for us to proceed with our analyses of the primary and secondary endpoints. This discrepancy not only affected the patient disposition, the protocol violations, but it affected all the efficacy datasets.

2. In dataset (b) (4)', explain why you have duplicate baseline visit information for 6 subjects (b) (4) *'IM101174-* (b) (4) *'IM101174-* (b) (4) *'IM101174-* (b) (4) *'IM101174-* (b) (4) *' or usubjid='IM101174-* (b) (4) *'IM101174-* (b) (4). In addition, explain why you have duplicate Day 169 information for (b) (4) *IM101174-* (b) (4). Of note, the total sample size at visit 1 (or baseline) is 1481 and at visit 169 is 1476.

Please send your response or the new datasets with the appropriate flags for ITT, PP, and As-treated populations.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: March 2, 2011
Initialed by: Barnes/ March 3, 2011
Hamilton/ March 3, 2011
Buenconsejo/ March , 2011

Finalized: CCJ/ March 4, 2011

Filename: 125118 s122 March 2011 Stats Fax

File path: Data/My Documents/BLA/125118

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2011

To: Ashley Pereira	From: Colette Jackson
Company: BMS	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 609-897-2825	Phone number: 301-796-1230

Subject: BLA STN 125118/122 Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/122 March 4, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following request for information. Please submit this information as soon as possible in order to facilitate our review.

1. According to Drawing No DMC6506550503 (Created February 14, 2003, Revision 2), the thickness of the (b) (4) atop the glass syringe barrel is (b) (4) millimeters. ISO 11040 states that the minimum thickness for this collar should be 1.9 millimeters. In your submission, you state that the Orencia pre-filled syringe will be equipped with a "flange extender" that (b) (4) Please clarify whether the "flange extender" will be attached to all new Orencia pre-filled syringes.

2. Additionally, regarding the flange extender, you have provided human factors / simulated use testing to demonstrate that the user can successfully manipulate the Orencia prefilled syringe with the flange extender attached. However, it was unclear if the testing assessed whether or not the user (b) (4) Please demonstrate that the (b) (4) , please demonstrate that the glass barrel syringe meets collar thickness requirement under ISO 11040.

3. There was no description on whether the Hydrolytic Resistance and Annealing Quality testing was performed on the glass barrel of the prefilled syringe. CDRH notes that the syringe is manufactured by (b) (4) However, since the pre-filled syringe will be approved under the sBLA 125118, it is your responsibility to ensure that the syringe is safe and effective for its intended use. Please demonstrate that the (b) (4) pre-filled syringe has been subjected to the Hydrolytic Resistance and Annealing Quality testing.

4. Within sBLA 125118, it appears that you have made a promissory note to assess container closure integrity during manufacturing. Whereas it is relevant to ensure that devices that are manufactured meet the leak testing performance criteria as part of the validation of the manufacturing process, it is more critical to demonstrate that the syringe that is selected for the delivery of Orencia is free of leaks and prevents any ingress of foreign matter within the pre-filled syringe barrel. Please demonstrate that leak testing has been performed on the prefilled Orencia syringe.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: March 2, 2011
Initialed by: Barnes/ March 3, 2011

Finalized: CCJ/ March 4, 2011

Filename: 125118 s122 March 2011 CDRH Fax

File path: Data/My Documents/BLA/125118

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2011

To: Anand S. Achanta, Ph.D.	From: Colette Jackson
Company (b) (4)	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 609-252-6595	Phone number: 301-796-1230

Subject: (b) (4) Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

STN: BLA 125118/22 January 11, 2011
Orencia (abatacept)

Please refer to your supplemental biologics application submission dated October 4, 2010. We have the following request for information. Please submit this information by COB January 28, 2011, in order to facilitate our review.

In your recent submission, you informed the Division of two recent observations made by you related to study conduct and data quality of Study IM101174. One of these observations is related to the randomization system and dataset error. Submit a new dataset for the 73 subjects who were part of the randomization system and dataset error. This should include the ID numbers of the 73 subjects, the actual baseline body weight, the subject's annual weight, the body weight used for randomization, ACR 20, and the treatment group the subjects were in.

Include in your submission the (b) (4) programs used to generate the efficacy results (i.e., the primary and secondary endpoints) in your Clinical Study Report as well as the results generated in the December 2, 2010 correspondence.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Colette Jackson
Senior Regulatory Health Project Manager

Drafted: January 4, 2011
Initialed by: Barnes/ January 5, 2011
Hamilton/ January 11, 2011
Buenconsejo/ January 11, 2011

Finalized: CCJ/ January 11, 2011

Filename: 125118 s122 Stats Fax

File path: Data/My Documents/BLA/125118

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: **CDRH**
Division: **ODE/DAGID/GHDB**
Mail Code:
Consulting Reviewer Name: **Nikhil Thakur**
Building/Room #: **WO 66 Room 2562**
Phone #: **301-796-5536**
Fax #:
Email Address: **Nikhil.Thakur@fda.hhs.gov**
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: **CDER**
Division: **DPARP**
Mail Code:
Requesting Reviewer Name: **Colette Jackson**
Building/Room #: **WO Bldg 22/Room 3322**
Phone#: **301-796-1230**
Fax #:
Email Address: **Colette.Jackson@fda.hhs.gov**
RPM/CSO Name and Mail Code: **Colette Jackson**
Requesting Reviewer's Concurring Supervisor's Name: **Sandy Barnes**
DPARP Medical Officer: **Keith Hull, MD at 6-1227**
OBP Product Reviewer: **Jack Ragheb at 301-435-4566**
OC/DMPQ/BMT: **Kalavati Suvarna at 6-0821**

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: **11/12/10**

Requested Completion Date: 12/10/2010

Submission/Application Number: **125118/122**
(Not Barcode Number)

Submission Type: **sBLA**
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: __Drug-device combination __Drug-biologic combination x Device-biologic combination __Drug-device-biologic combination __Not a combination product

Submission Receipt Date: **10/4/2010**

Official Submission Due Date: **8/4/2011**

Name of Product: **Orencia (abatacept)**

Name of Firm: **Bristol-Myers Squibb**

Intended Use: **Subcutaneous administration for the treatment of rheumatoid arthritis**

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Description and Composition of the Drug Product, Pharmaceutical Development, Manufacture, Container Closure system, and human factor related studies.

Documents to be returned to Requesting Reviewer? __Yes **x** No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

We are requesting CDRH's consultative involvement with the (b) (4) in this sBLA, the pre-filled syringe with (b) (4) flange extender. We would also like to know if the device constituent of the combination product needs to be inspected.

Type of Request: **x** Consultative Review __ Collaborative Review
(940 characters max -- use additional sheet if necessary)

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: **CDRH**
Division: **OC/DOEA/GHDB**
Mail Code:
Consulting Reviewer Name: **Valerie Flournoy**
Building/Room #: **WO 66 Room 3526**
Phone #: **301-796-5495**
Fax #:
Email Address: **Valerie.Flournoy@fda.hhs.gov**
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: **CDER**
Division: **DPARP**
Mail Code:
Requesting Reviewer Name: **Colette Jackson**
Building/Room #: **WO Bldg 22/Room 3322**
Phone#: **301-796-1230**
Fax #:
Email Address: **Colette.Jackson@fda.hhs.gov**
RPM/CSO Name and Mail Code: **Colette Jackson**
Requesting Reviewer's Concurring Supervisor's Name: **Sandy Barnes**
DPARP Medical Officer: **Keith Hull, MD at 6-1227**
OBP Product Reviewer: **Jack Ragheb at 301-435-4566**
OC/DMPQ/BMT: **Kalavati Suvarna at 6-0821**

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: **11/12/10**

Requested Completion Date: 12/10/2010

Submission/Application Number: **125118/122**
(Not Barcode Number)

Submission Type: **sBLA**
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: __Drug-device combination __Drug-biologic combination x Device-biologic combination __Drug-device-biologic combination __Not a combination product

Submission Receipt Date: **10/4/2010**

Official Submission Due Date: **8/4/2011**

Name of Product: **Orencia (abatacept)**

Name of Firm: **Bristol-Myers Squibb**

Intended Use: **Subcutaneous administration for the treatment of rheumatoid arthritis**

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Description and Composition of the Drug Product, Pharmaceutical Development, Manufacture, Container Closure system, and human factor related studies

Documents to be returned to Requesting Reviewer? __Yes x No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

We are requesting CDRH's consultative involvement with the (b) (4) in this sBLA, the pre-filled syringe with (b) (4) flange extender. We would also like to know if the device constituent of the combination product needs to be inspected.

Type of Request: x Consultative Review __ Collaborative Review
(940 characters max -- use additional sheet if necessary)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 125118/122

December 3, 2010

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Anand S. Achanta, Ph.D.
Director, Global Regulatory Sciences

Dear Dr. Achanta:

This letter is in regard to the supplement to your biologics license application (BLA), dated October 4, 2010, received October 4, 2010 submitted under section 351 of the Public Health Service Act, Orencia (abatacept).

We have completed an initial review of your supplement to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your supplement today. The review classification for this supplement is **Standard**. Therefore, the user fee goal date is August 4, 2011. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 14, 2011.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

We have the following requests for information.

1. Provide bioburden and endotoxin limits at the drug product formulation step and the (b) (4) step prior to final fill of the abatacept drug product.

2. Provide data on the microbial challenge test for container closure integrity and the correlation to the dye-ingress test. Also, provide the acceptance criteria established for the methylene blue dye intrusion spectrophotometric test along with information on the limit of detection and limit of quantitation of the test method.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a (b) (4) We will consider your request during labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients zero to 16 years of age.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

Badrul A. Chowdhury

/Badrul A. Chowdhury/
Badrul A. Chowdhury
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SB for BC 12/1/10

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

R-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Colette Jackson, Senior RPM
Division of Pulmonary, Allergy, and Rheumatology Products, HFD-570

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
November 30, 2010		125118/122	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Orencia (abatacept)	Standard	T-cell costimulation modulator	**May 26, 2011**

NAME OF FIRM:
Bristol-Myers Squibb

PDUFA Date: August 4, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: Submission dated October 4, 2010

\\cber-fs3\m\eCTD Submissions\STN125118\125118.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:
Mid-Cycle Meeting: March 1, 2011
Labeling Meetings: June 7, and July 12, 2011
Wrap-Up Meeting: June 14, 2011

SIGNATURE OF REQUESTER 12/2/10

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☒ eMAIL ☐ HAND

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM: Colette Jackson, Senior RPM Division of Pulmonary, Allergy, and Rheumatology Products, HFD-570
il: OSE	

DATE	IND NO.	BLA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 20, 2010		125118/122	S122	October 4, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Abatacept	Standard	T-cell costimulation modulator	May 26, 2011

NAME OF FIRM: Bristol Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a consult request on the labeling for supplemental BLA 125118/s122. This submission proposes the use of ORENCIA (abatacept) for subcutaneous administration.
The submission is electronic and can be found in the CBER EDR (sequence 0115) with the following link:

<\\cber-fs3\m\eCTD_Submissions\STN125118\125118.enx>

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125118/122

PRIOR APPROVAL SUPPLEMENT
ACKNOWLEDGEMENT
October 18, 2010

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Anand S. Achanta, Ph.D.
Director, Global Regulatory Sciences

Dear Dr. Achanta:

Please refer to your Supplemental Biologics License Application (sBLA) dated October 4, 2010, received October 4, 2010, submitted under section 351 of the Public Health Service Act for the following:

BL NUMBER: 125118

SUPPLEMENT NUMBER: 122

PRODUCT NAME: Abatacept

DATE OF SUBMISSION: October 4, 2010

DATE OF RECEIPT: October 4, 2010

This supplemental application proposes the subcutaneous use of Abatacept.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 3, 2010, in accordance with 21 CFR 601.2(a). If the application is filed, the user fee goal date will be August 4, 2011.

If you have not already done so, promptly submit 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1230.

Sincerely,

/ Colette Jackson /
Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Jackson, Colette

From: Benjamin, Jessica
Sent: Friday, October 15, 2010 5:15 PM
To: Jackson, Colette
Subject: Abatacept - pre-sBLA meeting minutes

Attachments: abatacept_presBLA.PDF

Hi Colette,

I was going through my folders and found the pre-sBLA meeting minutes for the supplement you just received for abatacept. The meeting was held June 3, 2010 - the date stamp on the meeting minutes is incorrect, the minutes were issued on July 1st (instead of June 1st).

abatacept_presBLA .PDF (470 KB)...

Jessica

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125118

Bristol-Myers Squibb
P.O. Box 4000 (Mail Stop: D32-07)
Princeton, NJ 08543-4000

JUN 0 1 2010

Attention: Anand S. Achanta, PhD
Director, Global Regulatory Sciences

Dear Dr. Achanta:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Orencia (abatacept).

Attached are the Division's responses to the questions from your meeting package for our upcoming Pre-sBLA meeting scheduled for June 3, 2010, to discuss a new formulation for Orencia. Your questions are in italics and the Division's responses are in bold.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-3924.

Sincerely,

Jessica Benja

Jessica Benjamin
Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE: April 28, 2010

TIME: 3:00 PM – 4:00 PM (EST)

LOCATION: Food and Drug Administration, White Oak, Bldg. 22, Room 1315

APPLICATION: BLA 125118

PRODUCT: abatacept

INDICATION: rheumatoid arthritis (RA)

SPONSOR: Bristol-Myers Squibb

TYPE OF MEETING: Pre-sBLA, Type B

MEETING CHAIR: Sarah Okada, MD, clinical team leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

MEETING RECORDER: Jessica Benjamin, Regulatory Project Manager

FDA Attendees	Title
Badrul A. Chowdhury, MD, PhD	Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Okada, MD	Clinical Team Leader
Keith Hull, MD	Clinical Reviewer
Molly Shea, PhD	Pharmacology/Toxicology Supervisor
Virgil Whitehurst, PhD	Pharmacology/Toxicology Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader
Zhihong Li, PhD	Clinical Pharmacology Reviewer
Susan Kirshner, PhD	Product Team Leader
Jack Ragheb, Ph.D.	Product Reviewer
Joan Buenconsejo, PhD	Biostatistics Team Leader
Ruthanna Davi, PhD	Biostatistics Reviewer
Jessica Benjamin	Regulatory Health Project Manager
Bristol-Myers Squibb	**Title**
Bindu Murthy, Pharm.D.	Associate Director, Clinical Discovery
Kalyan Ghosh, PhD	Executive Director, Global Biometric Sciences
Keqin Qi, PhD	Director, Global Biometric Sciences
Richard Aranda, MD	Group Director, Global Clinical Research
Ingrid Delaet, PhD	Director, Global Clinical Research

Shiela Gujrathi, MD	Vice President, Global Clinical Research
Michael Corbo, PhD	Vice President, Global Development Champion
Anthony Waclawski, PhD	Vice President, Global Regulatory Sciences
Anand Achanta, PhD	Director, Global Regulatory Sciences
Mitali Aon, MS	Director, Device Operations
Erbel Colon, BS	Principal Engineer, Packaging Engineering
Thomas Damratoski, BS	Director, Manufacturing Operations
Michael Grace, PhD	Executive Director, Analytical Development and Testing
Tony Mazzeo, PhD	Principal Scientist, Stability
Amol Mungikar, PhD	Principal Scientist, Biopharmaceutics R&D
Denise Perniciaro, MS	Director, Global Regulatory Sciences – CMC
Xuhong Cheng, PhD	Manager, Global Regulatory Sciences - CMC

Question 1. *Does the FDA have any comments on our efficacy or safety conclusions related to SC abatacept based on Study IM101174?*

FDA Response:
In general, your conclusions appear to be supported by the data presented in the briefing package. We cannot determine whether our conclusions will be similar until the full data are reviewed in the BLA submission.

Question 2. *Does the FDA have any comments based on our conclusions concerning the immunogenicity of SC abatacept and its impact on clinical efficacy, safety, and PK based on the results of Studies IM101174, IM101173, IM101167, and IM101185?*

FDA Response:
The bridging data from the ECL assays for these studies is essential to assess the immunogenicity of SC abatacept and its impact on clinical efficacy, safety, and PK. The information provided in Section 4.5.3 of the meeting submission is insufficient to make such an assessment. In your BLA submission, provide the ECL immunogenicity results for each individual in each study, as well as summary tables, and indicate when the serum sample was obtained relative to the dose. In addition, include data on anti-drug antibody neutralizing activity, epitope specificity, and cross-reactivity with endogenous CTLA4. For those samples displaying cross-reactivity with endogenous CTLA4, assess whether the anti-drug antibody has agonist or antagonist activity. If there is data from single dose PK/immunogenicity studies in healthy subjects, please provide this as well.

Question 3. *Does the FDA have any comments on the subgroup analysis (weight groups) based on Study IM101174?*

FDA Response:
We note that weekly fixed-dose abatacept 125 mg SC regimen is not intended to be bioequivalent to the IV regimen, but rather was selected to ensure that the heaviest patients receiving the dose would achieve target trough levels of abatacept. As noted at the EOP2, this appeared to be reasonable based on available data suggesting higher exposures were not obviously associated with increased risks of serious toxicities. Nonetheless, the magnitude of the increase in trough levels of abatacept in patients weighing less than 100 kg is large (1.5 to 2 fold higher than that observed with the IV abatacept weigh-tiered doses). Although the safety and immunogenicity data from the above studies appear to be comparable in the IV and SC clinical experience, the numbers of patients in the lowest weight (highest exposure) category are limited. Therefore, in your BLA submission you will need to provide strong justification of the safety of this higher exposure with all pertinent clinical data from your IV and SC clinical programs.

Question 4. *Does the FDA have any concerns on our proposals related to the proposed revisions of the USPI based on results from the SC abatacept program?*

FDA Response:
You are proposing: 1) to include information on IV and SC presentations in the same USPI, 2) that currently approved IV abatacept claims be extended to SC abatacept, and 3) that additional descriptions of the clinical experience, dosing regimen, and product presentations for SC be included in the USPI. We note that the two presentations were not intended to be bioequivalent. Relative efficacy of SC vs. IV appears to be adequately addressed via the non-inferiority trial, pending full review of the data in the BLA; however relative safety of SC vs. IV abatacept, and the adequacy of the data to support conclusions in this regard, will be key review issues when the BLA is submitted. We do not have additional comments on your proposals for the USPI at this time, pending full review of the BLA submission.

Question 5. *Does the FDA have any comments on our proposed post-marketing pharmacovigilance program?*

FDA Response:
We do not currently have additional comments on your proposed post-marketing pharmacovigilance program. However the Office of Surveillance and Epidemiology will be consulted regarding these plans when your BLA is submitted, and additional comments may arise from their review.

Question 6. *Does the FDA have any comments on the content/structure of our sBLA filing proposal and the subsequent 120-day safety update?*

FDA Response:
Your proposal to provide a Summary of Clinical Efficacy without pooled efficacy data across studies and to provide a Summary of Clinical Safety with pooled analysis of safety data from the short-term and long-term periods is acceptable to the Division.

The initial BLA application should contain sufficient safety data such that the Division can make a regulatory decision based on that data. Additional safety data from the 120-day safety update as described is acceptable, but if a safety signal is identified, additional data submission and delay in a regulatory decision may result.

Question 7. *Does the FDA agree with the approach to investigate SC abatacept in pediatric subjects with RA?*

FDA Response:
Your proposal to request a deferral for JIA patients at the time of submission for the adult BLA is reasonable. However, the final determination of the acceptability of your proposal will be made during the BLA review.

Question 8. *Does the Agency agree that the previously performed non-clinical user study by BMS and the design verification and validation by* (b) (4)

FDA Response:
We will provide a response either at the meeting or in a post-meeting note when we have received a final consult from the Center for Devices and Radiological Health (CDRH).

Question 9. *Does the Agency agree with BMS' proposal to* (b) (4) (b) (4) *at least 3 months prior to the PDUFA Action Date, without considering it a Major Amendment?*

FDA Response:
We will provide a response either at the meeting or in a post-meeting note when we have received a final consult from CDRH.

Question 10. *Does the Agency agree with the design validation strategy to support the proposed* (b) (4) *for the abatacept prefilled syringe? Does the Agency agree with the proposal of filing a change to the* (b) (4) *of the abatacept prefilled syringe via the Annual Report?*

FDA Response:
The briefing package does not have sufficient information for the Agency to make a determination, but we would note that the proposed studies should be sufficiently comprehensive to assure comparability of DP critical quality attributes, including accelerated stability studies.

Question 11. *Does the Agency agree that the assembly process validation program for abatacept injection with* (b) (4) *flange extender is acceptable?*

FDA Response:
We will provide a response either at the meeting or in a post-meeting note when we have received a final consult from CDRH.

Question 12. *Considering the product presentation planned for submission at this time, does the Agency agree that assembly PV results could be maintained on-site, available for inspection rather than included in the sBLA?*

FDA Response:
We will provide a response either at the meeting or in a post-meeting note when we have received a final consult from CDRH.

Question 13. *Does the Agency agree with the proposal for release of the abatacept prefilled syringe with* (b) (4) *the flange extender?*

FDA Response:
Evaluation of the proposed release specifications is a review issue. Release specifications must assure the safety and efficacy of the product and be supported by data obtained during clinical and commercial manufacturing.

Question 14. *Does the Agency agree with the stability plan or have any comments on the stability information to be included in the sBLA to support the* (b) (4)

FDA Response:
The proposed plan appears suitable at this time.

Question 15. *Does the Agency agree that the* (b) (4) *to the PDUFA Action Date without considering it a Major Amendment?*

FDA Response:
In general, the (b) (4) during the review process will not delay the completion of the review, but the Agency can provide (b) (4) to that affect.

Question 16. *Does the Agency agree that the abatacept injection shelf life* (b) (4)

FDA Response:
Provided that there is adequate bridging data submitted to support the method change, the Agency concurs with the (b) (4)

Question 17. *Does the Agency have any comments on the proposed structure/content of the sBLA CMC sections?*

FDA Response:
Not at this time.

Question 18. *Will CDRH be involved in the review of the CMC device-related sections of the abatacept injection sBLA? If yes, please advise if CDRH will play a consultative or collaborative review role?*

FDA Response:
CDRH will be involved in the review of your BLA. However, a determination of their specific role will not be determined until the BLA review.