CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125433Orig1s14

Trade Name: Simponi Aria

Generic Name: Golimumab

Sponsor: Janssen Biotech, Inc.

Approval Date: 08/05/2015

Indication: Simponi Aria is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) in combination with methotrexate.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125433/S-014

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Attention: Paul Imm, Pharm.D.
Associate Director, Global Regulatory Affairs

Dear Dr. Imm:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received October 6, 2014, submitted under section 351(a) of the Public Health Service Act for Simponi Aria (golimumab) injection, for intravenous use.

We acknowledge receipt of your amendments dated December 23, 2014, and January 12, March 3, and July 15, 2015.

This Prior Approval supplemental biologics application provides the inclusion of language in the package insert regarding the improvement in general health status, assessed by the Short Form health survey (SF-36).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

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, except with the revisions indicated, the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

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

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

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

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

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

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

/s/

BADRUL A CHOWDHURY
08/05/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SIMPONI ARIA
(golimumab) injection, for intravenous use
Initial U.S. Approval: 2009

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

- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI ARIA (5.1).**
- **Discontinue SIMPONI ARIA if a patient develops a serious infection or sepsis (5.1).**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI ARIA (5.1).**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1).**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member (5.2).**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.1, 5.2, 5.9) 12/2014

----------INDICATIONS AND USAGE----------
SIMPONI ARIA is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) in combination with methotrexate (1 1)

----------DOSAGE AND ADMINISTRATION----------
- 2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks (2.1)
- Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 50 mg/4 mL (12.5 mg/mL) in a single use vial (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious infections – Do not start SIMPONI ARIA during an active infection. If an infection develops, monitor carefully, and stop SIMPONI ARIA if infection becomes serious (5.1).
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI ARIA, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1).
- Hepatitis B reactivation – Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI ARIA and begin anti-viral therapy (5.1).
- Malignancies – More cases of lymphoma have been observed among patients receiving TNF-blockers compared with patients in the control groups. Cases of other malignancies have been observed among patients receiving TNF-blockers (5.2).
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI ARIA if new or worsening symptoms occur (5.3).
- Demyelinating disease, exacerbation or new onset, may occur (5.4).
- Hypersensitivity reactions: Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.10).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥3%) are: upper respiratory tract infection, viral infection, bronchitis, hypertension, and rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Biologics, including abatacept and anakinra: Increased risk of serious infection (5.1, 5.5, 5.6, 5.7, 7.2)
- Live vaccines should not be given with SIMPONI ARIA (5.9, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

Discontinue SIMPONI ARIA if a patient develops a serious infection.

Reported infections with TNF-blockers, of which SIMPONI ARIA is a member, include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMPONI ARIA use and during therapy. Initiate treatment for latent tuberculosis prior to SIMPONI ARIA use.**

- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**

- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Consider the risks and benefits of treatment with SIMPONI ARIA prior to initiating therapy in patients with chronic or recurrent infection.

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

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

SIMPONI ARIA, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

The SIMPONI ARIA dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

SIMPONI ARIA should be given in combination with methotrexate. Other non-biologic DMARDs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with SIMPONI ARIA.

The efficacy and safety of switching between intravenous and subcutaneous formulations and routes of administration have not been established.

2.2 Evaluation for Tuberculosis and Hepatitis B Prior to Dosage

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

2.3 Important Administration Instructions

SIMPONI ARIA solution for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

1. Calculate the dosage and the number of SIMPONI ARIA vials needed based on the recommended dosage of 2 mg/kg and the patient's weight. Each 4 mL vial of SIMPONI ARIA contains 50 mg of golimumab.
2. Check that the solution in each vial is colorless to light yellow. The solution may develop a few fine translucent particles, as golimumab is a protein. Do not use if opaque particles, discoloration or other foreign particles are present.
3. Dilute the total volume of the SIMPONI ARIA solution with 0.9% w/v sodium chloride for infusion to a final volume of 100 mL. For example, this can be accomplished by withdrawing a volume of the 0.9% w/v sodium chloride solution from the 100-mL infusion bag or bottle equal to the total volume of SIMPONI ARIA. Slowly add the total volume of SIMPONI ARIA solution to the 100-mL infusion bag or bottle. Gently mix. Discard any unused solution remaining in the vials.
4. Prior to infusion, visually inspect the diluted SIMPONI ARIA solution for particulate matter or discoloration. Do not use if these exist.
5. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.22 micrometer or less).

6. Do not infuse SIMPONI ARIA concomitantly in the same intravenous line with other agents. No physical biochemical compatibility studies have been conducted to evaluate the use of SIMPONI ARIA with other intravenous agents in the same intravenous line.
7. Infuse the diluted solution over 30 minutes.
8. Once diluted, the infusion solution can be stored for 4 hours at room temperature.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg of golimumab per 4 mL of solution (12.5 mg of golimumab per mL) in each single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with SIMPONI ARIA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI ARIA and these biologic products is not recommended *[see Warnings and Precautions (5.5, 5.6) and Drug Interactions (7.2)]*.

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

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA. Discontinue SIMPONI ARIA if a patient develops a serious infection, an opportunistic infection, or sepsis. For patients who develop a new infection during treatment with SIMPONI ARIA, perform a prompt and complete diagnostic workup

appropriate for an immunocompromised patient and initiate appropriate antimicrobial therapy and closely monitor them.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI ARIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI ARIA, assess if treatment for latent tuberculosis is needed; An induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

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

Cases of active tuberculosis have occurred in patients treated with the subcutaneous formulation of golimumab during and after treatment for latent tuberculosis. Monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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

Invasive Fungal Infections

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

Hepatitis B Virus Reactivation

The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI ARIA, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

5.2 Malignancies

Malignancies in Pediatric Patients

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI ARIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports. Use of SIMPONI ARIA in patients under 18 years of age has not been established.

Malignancies in Adult Patients

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

In the controlled portions of clinical trials of TNF-blockers including the subcutaneous formulation of golimumab more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of the reported TNF-blocker associated cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF-blocker at or prior to diagnosis. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Melanoma has been reported in patients treated with TNF-blocking agents, including the subcutaneous formulation of golimumab. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener’s granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory clinical trial evaluating the use of the subcutaneous formulation of golimumab in patients with severe persistent asthma, more patients treated with golimumab reported malignancies compared with control patients. The significance of this finding is unknown.

During the controlled portion of the Phase 3 trial in RA for SIMPONI ARIA, the incidence of malignancies other than lymphoma and NMSC per 100-patient-years of follow-up was 0.56 (95% CI: 0.01, 3.11) in the SIMPONI ARIA group compared with an incidence of 0 (95% CI: 0.00, 3.79) in the placebo group.

5.3 Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers, including SIMPONI ARIA. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI ARIA has not

been studied in patients with a history of CHF and SIMPONI ARIA should be used with caution in patients with CHF. If a decision is made to administer SIMPONI ARIA to RA patients with CHF, these patients should be closely monitored during therapy, and SIMPONI ARIA should be discontinued if new or worsening symptoms of CHF appear.

5.4 Demyelinating Disorders

Use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with rare cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. Cases of central demyelination, MS, optic neuritis, and peripheral demyelinating polyneuropathy have rarely been reported in patients treated with the subcutaneous formulation of golimumab. Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI ARIA, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI ARIA should be considered if these disorders develop.

5.5 Use with Abatacept

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

5.6 Use with Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI ARIA, is not recommended *[see Drug Interactions (7.2)]*.

5.7 Switching Between Biological Disease Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic product to another biologic product since overlapping biological activity may further increase the risk of infection.

5.8 Hematologic Cytopenias

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical studies, cases of pancytopenia, leukopenia, neutropenia, and thrombocytopenia have also occurred in SIMPONI ARIA-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI ARIA, in patients who have or have had significant cytopenias.

5.9 Vaccinations/Therapeutic Infectious Agents

Live Vaccines

Patients treated with SIMPONI ARIA may receive vaccinations, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to live vaccination, or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Therapeutic Infectious Agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with SIMPONI ARIA.

5.10 Hypersensitivity Reactions

In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following administration of the subcutaneous formulation of golimumab. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI ARIA should be discontinued immediately and appropriate therapy instituted.

6 ADVERSE REACTIONS

The most serious adverse reactions were:

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

6.1 Clinical Trials Experience

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

The safety data described below are based on one, randomized, double-blind, controlled Phase 3 trial in patients with RA receiving SIMPONI ARIA by intravenous infusion (Trial 1). The protocol included provisions for patients taking placebo to receive treatment with SIMPONI ARIA at Week 16 or Week 24 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Comparisons between placebo and SIMPONI ARIA were based on the first 24 weeks of exposure.

Trial 1 included 197 control-treated patients and 463 SIMPONI ARIA-treated patients (which includes control-treated patients who switched to SIMPONI ARIA at Week 16). The proportion

of patients who discontinued treatment due to adverse reactions in the controlled phase of Trial 1 through Week 24 was 3.5% for SIMPONI ARIA-treated patients and 0.5% for placebo-treated patients. Upper respiratory tract infection was the most common adverse reaction reported in the trial through Week 24 occurring in 6.5% of SIMPONI ARIA-treated patients as compared with 7.6% of control-treated patients, respectively.

Infections

Serious infections observed in SIMPONI ARIA-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections, tuberculosis (TB), and invasive fungal infections. Cases of TB included pulmonary and extrapulmonary TB. The majority of the TB cases occurred in countries with a high incidence rate of TB *[see Warnings and Precautions (5.1)]*.

In the controlled phase of Trial 1 through Week 24, infections were observed in 27% of SIMPONI ARIA-treated patients compared with 24% of control-treated patients, and serious infections were observed in 0.9% of SIMPONI ARIA-treated patients and 0.0% of control-treated patients. Through Week 24, the incidence of serious infections per 100 patient-years of follow-up was 2.2 (95% CI 0.61, 5.71) for the SIMPONI ARIA group, and 0 (0.00, 3.79) for the placebo group. In the controlled and uncontrolled portions of Trial 1, 958 total patient-years of follow-up with a median follow-up of approximately 92 weeks, the incidence per 100 patient-years of all serious infections was 4.07 (CI: 2.90, 5.57) in patients receiving SIMPONI ARIA *[see Warnings and Precautions (5.1)]*. In the controlled and uncontrolled portions of Trial 1, in SIMPONI ARIA treated patients, the incidence of active TB per 100 patient-years was 0.31 (95% CI: 0.06; 0.92) and the incidence of other opportunistic infections per 100 patient-years was 0.42 (95% CI: 0.11, 1.07).

Malignancies

One case of malignancy other than lymphoma and NMSC with SIMPONI ARIA was reported through Week 24 during the controlled phase of Trial 1. In the controlled and uncontrolled portions through approximately 92 weeks, the incidence of malignancies per 100 patient-years, other than lymphoma and NMSC, in SIMPONI ARIA-treated patients was 0.31 (CI: 0.06, 0.92) and the incidence of NMSC was 0.1 (95% CI: 0.00, 0.58).

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers.

In the controlled phase of Trial 1, through Week 24, ALT elevations $\geq$ 5 x ULN occurred in 0.8% of SIMPONI ARIA-treated patients and 0% of control-treated patients and ALT elevations $\geq$ 3 x ULN occurred in 2.3% of SIMPONI ARIA-treated patients and 2.5% of control-treated patients.

Since many of the patients in the Phase 3 trial were also taking medications that cause liver enzyme elevations (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], methotrexate [MTX],

or isoniazid prophylaxis), the relationship between SIMPONI ARIA and liver enzyme elevation is not clear.

Autoimmune Disorders and Autoantibodies
The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome.

At Week 20 in Trial 1, 17% of SIMPONI ARIA-treated patients and 13% of control patients were newly ANA-positive (at titers of 1:160 or greater). Of these patients, one SIMPONI ARIA-treated patient and no control-treated patients had newly positive anti-dsDNA antibodies.

Administration Reactions
In the controlled phase of Trial 1 through Week 24, 1.1% of SIMPONI ARIA infusions were associated with an infusion reaction compared with 0.2% of infusions in the control group. The most common infusion reaction in SIMPONI ARIA treated patients was rash. No serious infusion reactions were reported.

Immunogenicity
Antibodies to SIMPONI ARIA were detected in 13 (3%) golimumab-treated patients following IV administration of SIMPONI ARIA in combination with MTX through Week 24 of Trial 1.

All patients who were positive for antibodies to golimumab had neutralizing antibodies based on an *in vitro* cell-based assay. The small number of patients positive for antibodies to SIMPONI ARIA limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI ARIA in an ELISA assay. The ELISA assay is subject to interference by co-present golimumab and thus the results are an underestimate of the rate of product immunogenicity and are in addition highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI ARIA with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions
Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI ARIA + MTX group with a higher incidence than in the placebo + MTX group during the controlled period of Trial 1 through Week 24.

Table 1: Adverse Drug Reactions Reported by ≥1% of SIMPONI ARIA-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in Trial 1 through Week 24

	Placebo + MTX	SIMPONI ARIA + MTX

Table 1: Adverse Drug Reactions Reported by ≥1% of SIMPONI ARIA-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in Trial 1 through Week 24

	Placebo + MTX	SIMPONI ARIA + MTX
Patients treated	197	463
Adverse Reaction		
Infections and Infestations		
Upper respiratory tract infection (such as upper respiratory tract infection, nasopharyngitis, pharyngitis, laryngitis, and rhinitis)	12%	13%
Viral infections (such as influenza and herpes)	3%	4%
Bacterial infections	0%	1%
Bronchitis	1%	3%
Vascular disorders		
Hypertension	2%	3%
Skin and subcutaneous disorders		
Rash	1%	3%
General disorders and administration site conditions		
Pyrexia	1%	2%
Blood and lymphatic disorders		
Leukopenia	0%	1%

Other and less common clinical trial adverse drug reactions

Adverse drug reactions that do not appear in Table 1 or that occurred <1% in SIMPONI ARIA - treated patients during Trial 1 through Week 24 that do not appear in the Warnings and Precautions section included the following events listed by system organ class:

Infections and Infestations: Superficial fungal infection, sinusitis, abscess, lower respiratory tract infection (pneumonia), pyelonephritis

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, neutrophil count decreased

Nervous system disorders: Dizziness, paresthesia

Gastrointestinal disorders: Constipation

6.2 Post-marketing Experience

There is no post-marketing experience available for SIMPONI ARIA. The following adverse reactions have been identified during post-approval use of the subcutaneous formulation of golimumab. 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 golimumab exposure.

Neoplasm Benign and Malignant: Melanoma *[see Warnings and Precautions (5.2)]*

Immune System Disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) *[see Warnings and Precautions (5.10)]*, sarcoidosis

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Skin exfoliation, bullous skin reactions

7 DRUG INTERACTIONS

7.1 Methotrexate

SIMPONI ARIA should be used with methotrexate (MTX) *[see Clinical Studies (14)]*. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies.

7.2 Biologic Products for RA

An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI ARIA with other biologic products, including abatacept or anakinra is not recommended *[see Warnings and Precautions (5.5 and 5.6)]*. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. The concomitant use of SIMPONI ARIA with biologics approved to treat RA is not recommended because of the possibility of an increased risk of infection.

7.3 Live Vaccines/Therapeutic Infectious Agents

Live vaccines should not be given concurrently with SIMPONI ARIA *[see Warnings and Precautions (5.9)]*.

Therapeutic infectious agents should not be given concurrently with SIMPONI ARIA *[see Warnings and Precautions (5.9)]*.

Infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy *[see Use in Specific Populations (8.1)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI ARIA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI ARIA in pregnant women. Because animal reproduction and developmental studies are not always

predictive of human response, it is not known whether SIMPONI ARIA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI ARIA should be used during pregnancy only if clearly needed.

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (200 times greater than the maximum recommended human dose-MRHD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (33 times and 12 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since SIMPONI ARIA is an IgG antibody, infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy *[see Warnings and Precautions (5.10)]*.

8.3 Nursing Mothers

It is not known whether SIMPONI ARIA is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI ARIA, 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.

In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of SIMPONI ARIA in pediatric patients less than 18 years of age have not been established. Malignancies, some fatal, have been reported among children, adolescents,

and young adults who received treatment with other TNF-blocking agents *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

In Trial 1 in RA, the number of patients ages 65 or older was too small to make comparisons with younger SIMPONI ARIA -treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI ARIA.

10 OVERDOSAGE

In a clinical study, 5 patients received single infusions of up to 1000 mg of SIMPONI ARIA without serious adverse reactions or other significant reactions.

11 DESCRIPTION

SIMPONI ARIA (golimumab) is a human IgG1κ monoclonal antibody specific for human tumor necrosis factor alpha (TNFα) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. SIMPONI ARIA was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. SIMPONI ARIA is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

The SIMPONI ARIA drug product is a sterile concentrated solution of the golimumab antibody supplied in a 4 mL glass vial for intravenous infusion.

SIMPONI ARIA does not contain preservatives, natural rubber or latex. The solution is colorless to light yellow with a pH of approximately 5.5. Each 4 mL vial of SIMPONI ARIA contains 50 mg golimumab, 9.5 mM L-histidine, 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of rheumatoid arthritis. TNFα is an important mediator of the articular inflammation that is characteristic of RA. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible

for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF). The clinical relevance of these findings is unknown.

12.2 Pharmacodynamics

Following treatment with SIMPONI ARIA in patients with RA, decreases from baseline were observed in tissue inhibitor of metalloproteinases 1 (TIMP-1), matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-3 (MMP-3), resistin, interleukin-6 (IL-6), macrophage inflammatory protein-1 (MIP-1b), vascular endothelial growth factor (VEGF), serum amyloid A (SAA), S100A12, and high sensitivity C-Reactive protein (hsCRP). Conversely, increases from baseline were observed in tartrate-resistant acid phosphatase (TRAP-5b). The clinical relevance of this information is not known.

12.3 Pharmacokinetics

Absorption

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, a mean C_{max} of 44.4 ±11.3 μg/mL was observed in patients with RA. Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.

Distribution

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA. The volume of distribution of golimumab may indicate that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Elimination

The elimination pathways for golimumab have not been characterized.

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg in healthy subjects and 7.6 ± 2.0 mL/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days.

When 2 mg/kg SIMPONI ARIA was administered intravenously to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 μg/mL in patients with active RA despite MTX therapy.

Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI following SC administration.

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose.

Effect of weight on pharmacokinetics
Following intravenous administration, patients with higher body weight tended to have higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on a mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following intravenous administration of 2 mg/kg SIMPONI ARIA in patients across a range of different body weights.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study conducted in mice using an analogous anti-mouse TNFα antibody administered by the intravenous route at doses up to 40 mg/kg once per week showed no impairment of fertility.

14 CLINICAL STUDIES

The efficacy and safety of SIMPONI ARIA were evaluated in one multicenter, randomized, double-blind, controlled trial (Trial 1) in 592 patients ≥ 18 years of age with moderately to severely active RA despite concurrent MTX therapy and had not previously been treated with a biologic TNF-blocker. Patients were diagnosed according to the American College of Rheumatology (ACR) criteria, at least 3 months prior to administration of study agent and were required to have at least 6 swollen and 6 tender joints. Patients were randomized to receive either SIMPONI ARIA 2 mg/kg (n=395) or placebo (n=197) over a 30 minute intravenous infusion at Weeks 0, 4 and every 8 weeks thereafter in addition to their weekly maintenance MTX dose (15-25 mg). All patients receiving placebo + MTX received SIMPONI ARIA + MTX after Week 24, but the trial remained blinded until all patients had completed 108 weeks of treatment. Efficacy data were collected and analyzed through Week 52. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint in Trial 1 was the percentage of patients achieving an ACR 20 response at Week 14. In Trial 1, the majority of subjects were women (82%) and were Caucasian (80%) with a median age of 52 years and a median weight of 70 kg. Median disease duration was 4.7 years, and 50% of the patients used at least one DMARD other than MTX in the past. At baseline, 81% of patients received concomitant NSAIDs and 81% of patients received low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day). The median baseline DAS28-CRP was 5.9 and the median van der Heijde-Sharp score at baseline was 28.5.

Clinical Response

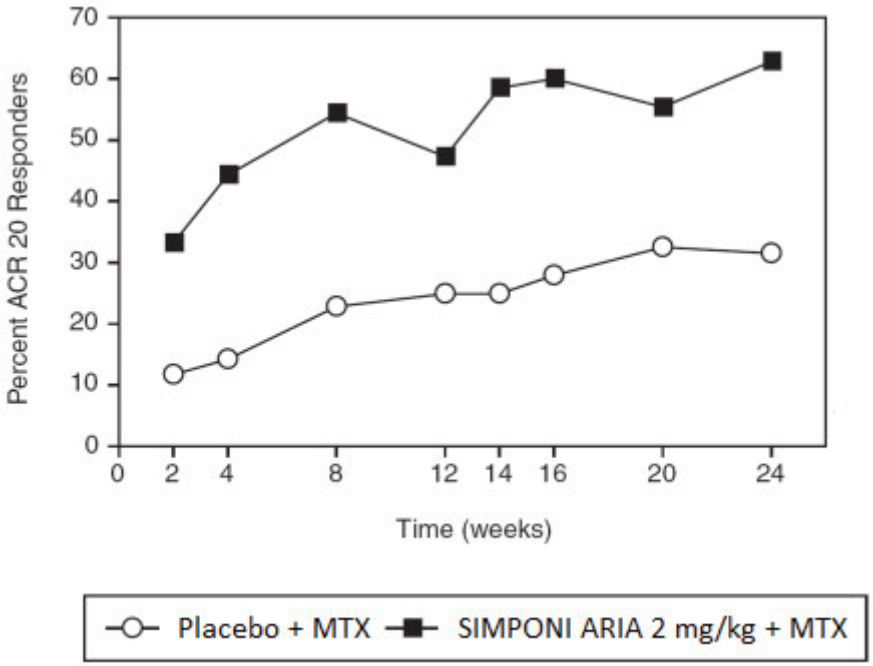
A greater percentage of patients treated with the combination of SIMPONI ARIA + MTX achieved ACR 20 at Week 14 and ACR50 at Week 24 versus patients treated with the placebo + MTX as shown in Table 2. The percent of patients achieving ACR 20 responses by visit for Trial 1 is shown in Figure 1.

Table 2: Trial 1 – Proportion of Patients with an ACR Response

Trial 1 Active RA, despite MTX			
	Placebo + MTX	**SIMPONI ARIA + MTX**	**95% CI[a]**
N[b]	197	395	
ACR 20			
Week 14	25%	59%	25.9, 41.4
Week 24	32%	63%	23.3, 39.4
ACR 50			
Week 14	9%	30%	15.3, 27.2
Week 24	13%	35%	15.1, 28.4
ACR 70			
Week 14	3%	12%	5.3, 13.4
Week 24	4%	18%	8.8, 18.1

[a] For difference in proportions
[b] N reflects randomized patients.

Figure 1: Trial 1 – Percent of Patients Achieving ACR 20 Response Over Time: Randomized Patients



The analysis is based on the intent-to-treat population. Last observation carried forward was performed for missing data. Patients who discontinued treatment due to lack of efficacy were counted as non-responders, as were patients who started prohibited medication or failed to achieve at least a 10% improvement in joint counts at Week 16.

The improvement in all components of the ACR response criteria for the SIMPONI ARIA + MTX group was greater compared to the placebo + MTX group in Trial 1 as shown in Table 3.

Table 3: Trial 1 ─ Components of ACR Response at Week 14

	Trial 1 Active RA, despite MTX	
	Placebo + MTX	**SIMPONI ARIA + MTX**
N[a]	197	395
Number of swollen joints (0-66)		
Baseline	15	15
Week 14	11	6
Number of tender joints (0-68)		
Baseline	26	26
Week 14	20	13
Patient's assessment of pain (0-10)		
Baseline	6.5	6.5
Week 14	5.6	3.9
Patient's global assessment of disease activity (0-10)		
Baseline	6.5	6.5
Week 14	5.5	4.0
Physician's global assessment of disease activity (0-10)		
Baseline	6.3	6.2

Week 14	4.9	3.1
HAQ score (0-3)		
Baseline	1.6	1.6
Week 14	1.4	1.1
CRP (mg/dL) (0-1)		
Baseline	2.2	2.8
Week 14	1.8	0.9
Note: All values are means. [a] N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.		

At Week 14, a greater proportion of patients treated with SIMPONI ARIA + MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 compared with the placebo + MTX group (15% compared to 5%; 95% confidence interval for difference [6.3%, 15.5%]).

Radiographic Response

In Trial 1, structural joint damage was assessed radiographically and expressed as a change in van der Heijde-Modified Sharp Score (vdH-S) and its components, the erosion score and Joint Space Narrowing (JSN) score, at Week 24 compared to baseline. The SIMPONI ARIA + MTX treatment group inhibited the progression of structural damage compared with placebo + MTX, as assessed by total vdH-S score as shown in Table 4.

Table 4: Trial 1 – Radiographic Change From Baseline at Week 24

	Placebo + MTX (N=197)[a]	**SIMPONI ARIA + MTX (N=395)[a,b]**
	Mean	**Mean**
Change Total vdH-S Score	1.1	0.03*
Change Erosion Score	0.5	-0.1
Change JSN Score	0.6	0.1
[a] N reflects randomized patients [b] p-value is displayed only for the major secondary endpoint * $p \leq 0.001$		

At Week 24, a greater proportion of patients in the SIMPONI ARIA + MTX group (71%) had no progression of structural damage (change in the total vdH-S score ≤ 0), compared to 57% of patients in the placebo + MTX group. At Week 52, the mean change from baseline in total vdH-S score was 1.2 in patients originally randomized to placebo + MTX who crossed over to SIMPONI ARIA + MTX at Week 16 or 24, and 0.1 in patients originally randomized to SIMPONI ARIA + MTX who remained on active treatment.

Physical Function Response in Patients with RA

Physical function was assessed by the disability index of the Health Assessment Questionnaire (HAQ-DI). At Week 14, the SIMPONI ARIA + MTX group showed greater mean improvement in the HAQ-DI compared with placebo + MTX (0.5 compared to 0.2; 95% confidence interval for difference [0.2, 0.4]).

Other Health-Related Outcomes

General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36.

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMPONI ARIA is available in packs of 1 vial NDC 57894-350-01

Vial

Each single-use vial contains 50 mg of SIMPONI ARIA per 4 mL of solution.

Storage and Stability

SIMPONI ARIA must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI ARIA beyond the expiration date (EXP) on the vial label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients of the potential benefits and risks of SIMPONI ARIA. Instruct patients to read the Medication Guide before starting SIMPONI ARIA therapy and to read it each time the prescription is renewed.

Infections

Inform patients that SIMPONI ARIA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation.

Malignancies

Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI ARIA.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864 at
Cilag AG
Schaffhausen, Switzerland

MEDICATION GUIDE

SIMPONI ARIA®
(SIM-puh-nee AHR-ee-uh**)**
(golimumab)
For Infusion

Read the Medication Guide for SIMPONI ARIA before each infusion. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. It is important to remain under your doctor's care while receiving SIMPONI ARIA.

What is the most important information I should know about SIMPONI ARIA?

SIMPONI ARIA is a medicine that affects your immune system. SIMPONI ARIA can lower the ability of your immune system to fight infections. Some people have serious infections while taking SIMPONI ARIA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that spread throughout their body. Some people have died from these serious infections.

- Your doctor should test you for TB and hepatitis B before starting SIMPONI ARIA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with SIMPONI ARIA.

You should not receive SIMPONI ARIA if you have any kind of infection unless your doctor says it is okay.

Before receiving SIMPONI ARIA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become

more severe if you receive SIMPONI ARIA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.
- use the medicine ORENCIA (abatacept), KINERET (anakinra), ACTEMRA (tocilizumab) or RITUXAN (rituximab).

After receiving SIMPONI ARIA, call your doctor right away if you have any symptoms of an infection. SIMPONI ARIA can make you more likely to get infections or make worse any infection that you have.

Cancer
- For children and adults receiving TNF-blocker medicines, including SIMPONI ARIA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children and teenage patients taking TNF-blocking agents.
- People with inflammatory diseases including rheumatoid arthritis especially those with very active disease, may be more likely to get lymphoma.
- Some people receiving medicines that are like SIMPONI ARIA, called TNF-blockers developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and another medicine called azathioprine or 6-mercaptopurine.
- Some people treated with SIMPONI ARIA developed skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with SIMPONI ARIA, tell your doctor.
- You should see your doctor periodically for skin examinations, especially if you have a history of skin cancer.

What is SIMPONI ARIA?

SIMPONI ARIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI ARIA is used with the medicine methotrexate to treat adults with moderately to severely active rheumatoid arthritis (RA).

SIMPONI ARIA is not for children under 18 years of age.

What should I tell my doctor before starting treatment with SIMPONI ARIA?

SIMPONI ARIA may not be right for you. Before receiving SIMPONI ARIA, tell your doctor about all your medical conditions, including if you:

- have an infection (see "What is the most important information I should know about SIMPONI ARIA?")
- have or have had lymphoma or any other type of cancer.
- have or had heart failure
- have or have had a condition that affects your nervous system, such as multiple sclerosis or Guillain-Barré syndrome

- have a skin problem called psoriasis
- have recently received or are scheduled to receive a vaccine. People receiving SIMPONI ARIA should not receive live vaccines or treatment with a weakened bacteria (such as BCG for bladder cancer). People receiving SIMPONI ARIA can receive non-live vaccines.
- have a baby and you received SIMPONI ARIA during your pregnancy. Tell your baby's doctor before your baby receives any vaccine. Your baby may have an increased chance of getting an infection for up to 6 months after birth.
- are pregnant or planning to become pregnant. It is not known if SIMPONI ARIA will harm your unborn baby.
- are breastfeeding. It is not known if SIMPONI ARIA passes into your breast milk. You and your doctor should decide if you will receive SIMPONI ARIA or breastfeed. You should not do both without talking to your doctor first.

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

Especially tell your doctor if you:

- use ORENCIA (abatacept) or KINERET (anakinra). You should not receive SIMPONI ARIA while you are also taking ORENCIA (abatacept) or KINERET (anakinra).
- use other TNF-blocker medicines, including REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA (certolizumab pegol).
- receive RITUXAN (rituximab) or ACTEMRA (tocilizumab).

Ask your doctor if you are not sure if your medicine is one listed above.

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

How should I receive SIMPONI ARIA?

- SIMPONI ARIA is prepared and given by a healthcare provider through a needle placed in your vein (infusion). The infusion is usually given in your arm and should take 30 minutes.
- Your doctor will decide how much SIMPONI ARIA you will receive based on your weight. Your usual schedule for receiving SIMPONI ARIA after your first treatment should be:
    - 4 weeks after your first treatment
    - every 8 weeks after that
- If you forget or miss an appointment to receive SIMPONI ARIA, make another appointment as soon as possible.
- You may continue to use other medicines for your treatment while taking SIMPONI ARIA, such as non-steroidal anti-inflammatory drugs (NSAIDs), prescription steroids, and pain relief medicines.

What are the possible side effects of SIMPONI ARIA?

SIMPONI ARIA can cause serious side effects, including:

- See "**What is the most important information I should know about SIMPONI ARIA?"**

- **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 receive SIMPONI ARIA. Your doctor should do blood tests before you start treatment with SIMPONI ARIA and while you are receiving SIMPONI ARIA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

  - o feel very tired
  - o clay-colored bowel movements
  - o dark urine
  - o fevers
  - o skin or eyes look yellow
  - o little or no appetite
  - o vomiting
  - o muscle aches
  - o chills
  - o stomach discomfort
  - o skin rash

- **Heart failure, including new heart failure or worsening of heart failure that you already have.** New or worse heart failure can happen in people who use TNF-blocker medicines including SIMPONI ARIA.
  - o If you have heart failure, your condition should be watched closely while you receive SIMPONI ARIA.
  - o Call your doctor right away if you get new or worsening symptoms of heart failure while receiving SIMPONI ARIA (such as shortness of breath, swelling of your lower legs or feet, or sudden weight gain).

- **Nervous System Problems**
  Rarely, people using TNF-blocker medicines, including SIMPONI ARIA, have nervous system problems such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor right away if you get any of these symptoms:
  - o vision changes
  - o weakness in your arms or legs
  - o numbness or tingling in any part of your body

- **Liver Problems**
  Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI ARIA. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
  - o feel very tired
  - o skin or eyes look yellow
  - o poor appetite or vomiting
  - o pain on the right side of your stomach (abdomen)

- **Blood Problems**
  Low blood counts have been seen with TNF-blockers, including SIMPONI ARIA. Your body may not make enough blood cells that help fight infections or help

stop bleeding. Symptoms include fever, bruising or bleeding easily, or looking pale. Your doctor will check your blood counts before and during treatment with SIMPONI ARIA.

- **Allergic Reactions**
  Allergic reactions can happen in people who use TNF-blocker medicines including SIMPONI ARIA. Some reactions may be serious and can be life threatening. Some of these reactions can happen after receiving your first dose of SIMPONI ARIA. Call your doctor right away if you have any of these symptoms of an allergic reaction:
    - hives
    - swollen face
    - breathing trouble
    - chest pain

The most common side effects of SIMPONI ARIA include:

- upper respiratory infection (runny nose, sore throat, and hoarseness or laryngitis)
- viral infections such as flu and cold sores in the mouth
- bronchitis
- high blood pressure
- rash

Other side effects with SIMPONI ARIA include:

- **Immune System Problems.** Rarely, people using TNF-blocker medicines have developed symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these symptoms:
    - a rash on your cheeks or other parts of the body
    - sensitivity to the sun
    - new joint or muscle pains
    - becoming very tired
    - chest pain or shortness of breath
    - swelling of the feet, ankles, or legs

These are not all of the side effects with SIMPONI ARIA. Tell your doctor about any side effect that bothers you or does not go away.

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

General Information about SIMPONI ARIA

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use SIMPONI ARIA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about SIMPONI ARIA. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SIMPONI ARIA that is written for health professionals.

For more information go to www.SimponiAria.com or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in SIMPONI ARIA?

Active ingredient: golimumab

Inactive ingredients: L-histidine, polysorbate 80, and sorbitol. SIMPONI ARIA does not contain preservatives, natural rubber or latex.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864 at
Cilag AG
Schaffhausen, Switzerland

Approved: August 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	August 6, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125433, Supplement 0014
Applicant Name:	Janssen Biotech, Inc.
Date of Submission:	October 6, 2014
PDUFA Goal Date:	August 6, 2015
Proprietary Name:	Simponi Aria
Established Name:	Golimumab
Dosage form:	Injection, 50 mg/4 mL (12.5 mg/mL), in each single-use vial
Strength:	2 mg/kg for intravenous infusion
Proposed Indications:	Inclusion of SF-36 improvement information in the Clinical Studies section of the product labeling. Simponi Aria is approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis in combination with methotrexate.
Action:	Approval

1. Introduction

Janssen submitted this BLA supplement for re-consideration to include SF-36 findings in the Clinical Studies section of the product label for Simponi Aria. The original BLA for Simponi Aria was approved in July 2013 for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX). At the time of original approval, SF-36 findings were not included in the product label. This summary review will provide an overview of the application, and reasoning and rationale for inclusion of SF-36 results in the Clinical Studies section of the product label. The scientific considerations for inclusion of SF-36 findings in the Simponi Aria labeling is similar to that for Xeljanz (tofacitinib) where the SF-36 data was not included in the product labeling during original approval of Xeljanz in November 2012, but was later included in the labeling in November 2013 with approval of supplemental NDA 203214/S-002..

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 and slow

disease progression or produce a disease-modifying effect on 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. Tumor necrosis factor (TNF)-blockers are commonly used DMARDs because of their proven efficacy and safety profile and relatively long-term use experience (Table 2). Treatment of RA is typically initiated with NSAIDs or low-dose corticosteroids, with introduction of non-biologic DMARDs early in the course of the disease to prevent joint damage and bony erosions. Methotrexate is often the initial DMARD used as a single agent in patients with low disease activity or without features of poor prognosis, and then combined with other DMARDs, commonly biologics such as TNF blockers, in patients with high disease activity or with features of poor prognosis.[1]

Table 1. Non-biologic 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
Tofacitinib (XELJANZ) [Pfizer]	JAK inhibitor	2012

Table 2. Biologic large molecule 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-α 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-α 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	Human IgG1 k mAb *TNF-α inhibitor*	Clinical response Major clinical response Physical function response

[1] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care and Res 2012; 64:625-39.

Product Name (Trade Name) [Sponsor] {year} *	**Presentation and *ROA* †**	**Description and *MOA* ‡**	**Claims for adult RA §**
	SC injection		Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor through B7-1 and B7-2*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	Clinical response Physical function response 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-α inhibitor*	Clinical response Physical function response
Golimumab (SIMPONI ARIA) [Centocor] {2009}	Single use vial 50 mg per 4 mL *IV infusion*	Humanized IgG1 k mAb *TNF-α inhibitor*	Clinical response Physical function response Radiographic response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL *SC injection*	Humanized Fab fragment *TNF-α 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 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-month 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 6 or 12 months

Efficacy finding descriptions in RA product labeling:

For marketing approval of product for the treatment of RA, sponsors are required to demonstrate evidence of efficacy in two key RA domains – "clinical response" by American College of Rheumatology (ACR) criteria using ACR-20 threshold,[2] and "physical function response" by Health Assessment Questionnaire-Disability Index (HAQ-DI).[3] Demonstration of efficacy in other domains that are important to patients health are often assessed, and these include prevention of structural damage progression, clinical remission, and other aspects of RA. The Clinical Studies section of product label describes the efficacy findings from the key RA domains, and some other secondary and other efficacy findings. The Agency's prior precedence for inclusion or exclusion of some secondary and other efficacy findings for some products approved for RA is shown

[2] ACR 20 response is calculated as at least 20% reduction in tender joint count of 68 joints, and at least 20% reduction in swollen joint count of 66 joints, and at least a 20% reduction in at least 3 of the following 5 measures: patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP).

[3] HAQ-DI assesses a patient's level of functional ability and includes questions regarding fine movements of the upper extremities, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning intended to represent a comprehensive set of functional activities, including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients are asked to grade their status on a scale from 0 (no difficulty) to 3 (unable to do) for each question. The 8 category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled).

in Appendix 1.

The SF-36 information in the RA product labeling has not been consistent. The SF-36 results were described in some older product labeling, but not in recent DMARD product labeling (Appendix 1). As mentioned in Section 1 above, SF-36 results were not included in Xeljanz (tofacitinib) labeling during original approval of Xeljanz in November 2012, but was later included in the labeling in November 2013. In the following section the SF-36 instrument is briefly described, followed by the background that resulted in the inconsistency in describing SF-36 findings in RA product labels.

Short Form (SF-36) instrument:
The SF-36 is a multi-purpose, short-form health survey. It was originally developed in 1980s and 90s to satisfy minimum psychometric standards for group comparisons, and has been used in health planning and policy, and health services evaluation in an era of cost containment, and has subsequently been validated in many diseases, including RA and other rheumatic conditions. The developers of SF-36 states that it is the most widely used health status questionnaire in the world, translated in over 130 languages, and that it has been validated across countries and cultures. The developers of SF-36 also state that it has content, concurrent, criterion, construct, and predictive evidence of validity.[4]

The SF-36 consists of questions grouped into eight domains: four for physical health and four for mental health. The eight domains are reported as two psychometrically-based summary measures: physical component summary (PCS) and mental component summary (MCS). The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

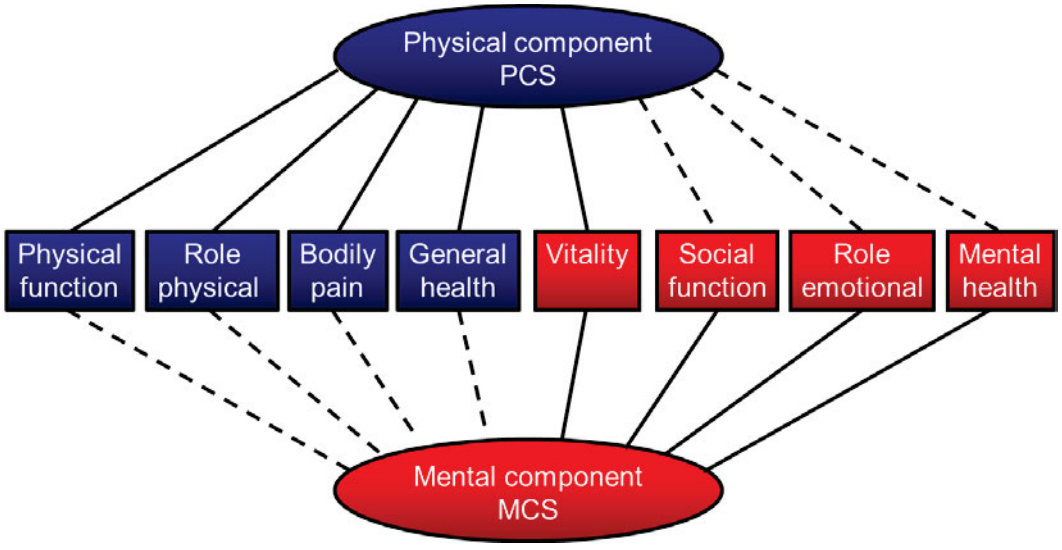


Figure 1. Conceptual model for deriving the PCS and the MCS from individual domains

[4] SF-36 Health Survey Update, John E, Ware; at http://www.sf-36.org/tools/sf36.shtml

Status of SF-36 in RA product labeling:

The use of SF-36 in RA drug development and the description of SF-36 findings in the RA product labels have evolved over time. In the past, SF-36, and more specifically the PCS, has been used as supportive evidence of efficacy for the "prevention of disability" claim assessed by HAQ-DI. The 1999 RA Guidance, which has been removed and updated with draft RA guidance published in 2013, mentioned use of SF-36 as a support of "prevention of disability" claim assessed by HAQ-DI. The intent at that time was to obtain data from long-term trials, such as 2 or 5 years, in RA. With approval of effective products for RA, it is no longer ethical to conduct long-term trials to assess "prevention of disability." The claim has morphed into "physical function response" that is assessed by HAQ-DI in short-term trials, such as 12 or 24 weeks.

In 2007-2008, the Study Endpoints and Labeling Development (SEALD) staff in the immediate Office of the New Drugs (OND) raised concerns and asked that SF-36 not be included in RA product labeling. The major concerns of the SEALD staff were that the SF-36 is a generic health survey that has not been shown to represent a health related quality of life in RA, and that PCS and MCS are composite measures of weighted scores from 8 sub-concepts or domains that are not independent and do not measure pure physical or mental functioning and therefore cannot be described in a way that is meaningful. Multiple internal discussions between the SEALD team and the then review division (Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP) occurred. Ultimately, due to the level of concern expressed by SEALD, DAARP reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function response claim because of the extensive accrued experience with HAQ-DI, and the observation that SF-36 results in RA studies were consistent with HAQ-DI results. As a result, SF-36 information from later products approved for RA did not mention SF-36 in the product labeling (Appendix 1).

This decision to discontinue inclusion of SF-36 in RA product labels has not been uniformly accepted by industry, academia, and research community. In a sNDA for Xeljanz (tofacitinib), Pfizer provided justification and rationale for inclusion of SF-36 findings in the tofacitinib label. As a result of the community's concerns, and because of that submission from Pfizer, the SEALD staff and DPARP have had multiple additional discussions about SF-36 to consider the best approach for moving forward. To address the community's concerns, and to be consistent with the way SF-36 has been used as a general health status instrument in RA trials, the Division decided to re-implement inclusion of SF-36 findings in RA product labeling as a measure of general health status rather than its previous use as a supportive measure for improvement in "prevention of disability" or "physical function response." To mitigate the risk of inappropriate conclusions and potential loss of information, and to be in line with the recommendations by the SF-36 researchers, the Division decided that results of PCS and MCS along with the relevant 8 domains will be described in the labeling in qualitative general language. The Division discussed that decision, as it would apply to Xeljanz (tofacitinib) submission, at a Center level Regulatory briefing held on September 20, 2013. At the Regulatory Briefing, the science behind development of SF-36, data and applicability of

SF-36 in RA clinical studies, the Agency's internal regulatory history of SF-36, the tofacitinib SF-36 data, and the Division's decision to re-implement inclusion of SF-36 findings in RA product labeling were presented by DPARP and Office of Biostatistics review teams, and discussed by senior level management participants. The SEALD staff expressed dissenting views at the Regulatory Briefing. The Division's decision to re-implement including SF-36 results in RA product labeling was supported for implementation by CDER senior management. At that time it was understood that other pharmaceutical companies who were previously denied inclusion of SF-36 results in their RA product labeling would likely apply for inclusion of SF-36 results in their product labeling and the Division would reconsider those applications. This supplement from Janssen for inclusion of SF-36 results in Simponi Aria label is such an application.

3. Chemistry, Manufacturing, and Controls

Simponi Aria is an approved and marketed product, and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this supplement. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

No new clinical pharmacology studies were required or performed for this supplement. The clinical pharmacology data were reviewed with the original application.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Janssen submitted two studies in support of this submission – a 52-week confirmatory study (Study CNT0148-ART3001) and a 48-week dose-ranging study (Study C0524T12). Both of these studies were submitted with the original BLA and previously reviewed.

b. Design and conduct of the studies

Studies CNTO148ART3001 and C0524T12 were multicenter, randomized, double-blind, placebo-controlled, and enrolled a similar population of patients with active, moderate-to-severe RA despite MTX therapy. Study C0524T12 utilized two intravenous golimumab dosing regimens 2 mg/kg and 4 mg/kg (with or without concomitant MTX) every 12 weeks. Study CNTO148ART3001 used intravenous golimumab 2 mg/kg at Weeks 0, 4, and then every 8 weeks, which is the currently approved dosing regimen. The protocol provided for early escape option at Week 16 for placebo-treated patients who had less

than 10% improvement in tender or swollen joint counts. Therefore, the assessment of continuous efficacy endpoints from later time points, i.e., Week 24, may be confounded by patients who have crossed-over from placebo to active treatment at Week 16. SF-36 was one of many endpoints assessed in these studies.

c. Efficacy findings and conclusions

The primary evidence of efficacy supporting the proposed claim of improvement in general health status was based on SF-36 data from a single confirmatory clinical study CNTO148ART3001. The same study provided the primary evidence of efficacy for approval of Simponi Aria demonstrating statistical and clinically meaningful superiority of intravenous golimumab plus MTX over placebo plus MTX for improvement in clinical response (ACR20), improvement in physical function (HAQ-DI), and inhibition of radiographic joint damage (van der Heijde-Sharp score) which were discussed in the original BLA. Additional supportive evidence of efficacy for the proposed claim of improvement in general health status is also provided by the SF-36 data from the dose-ranging study C0524T12 and the SF-36 data from the subcutaneous golimumab clinical development.

The change from baseline in PCS, MCS, and each of the 8 domain scores at Weeks 12, 16, and Week 24 were summarized by treatment group. To test for a treatment difference an analysis of variance on the van der Waerden normal scores was used with treatment group and C-reactive protein level at screening (<1.5 mg/dL or ≥ 1.5mg/dL) as covariates in the model. Significance was tested using a 2-sided alpha of 0.05. The primary analysis population was the intent-to-treat (ITT) population defined as all randomized patients regardless of whether or not they received the assigned treatment. Although SF-36 was not defined as a primary or major secondary endpoint to be controlled for the overall type I error, statistical significance was assessed after a Bonferroni adjustment was applied.

At all tested times in study CNTO148ART3001, Weeks 12, 16, and 24, patients who received intravenous golimumab + MTX showed significantly greater improvement in SF-36 PCS and MCS as compared to subjects who received placebo + MTX (Table 3). Sensitivity analysis, conducted by the FDA statistical review team, examined the continuous responder functions between placebo and treatment and showed results consistent with the analyses of the mean change from baseline. Clear separation between the intravenous golimumab + MTX and placebo + MTX groups was demonstrated as representative of SF-36 PCS data and SF-36 MCS data from study CNTO148ART3001 (Figure 2).

Janssen also submitted analyses of SF-36 data from Study C0524T06 from the subcutaneous golimumab program in RA (BLA 125,289), as supportive evidence of efficacy for the proposed labeling changes. In study C0524T06, RA patients were randomized to receive subcutaneous golimumab 50 mg plus MTX, subcutaneous golimumab 100 mg plus MTX, subcutaneous golimumab 100 mg plus placebo, or placebo plus MTX. SF-36 was collected and analyzed at baseline, Weeks 14, 24, and 48. Nominally statistically significant differences were observed between subcutaneous golimumab plus MTX groups as compared to subjects receiving placebo plus MTX in

PCS score at Weeks 14 and 24, and in MCS score in subjects receiving subcutaneous golimumab 100 mg, both with and without MTX, at Week 24.

The submitted data show consistent benefit on SF-36, and are adequate to support inclusion of SF-36 findings in the Clinical Studies section of the product labeling.

Table 3. Primary analysis (ITT LOCF imputation) of SF-36 composite scores, Mean ± SD, Study CNTO148ART3001

	Placebo + MTX (N=197)	IV Golimumab + MTX (N=395)
PCS change from baseline, Week 12		
Mean ± SD	3.2 ± 7.4	5.9 ± 7.7
p-value vs. Placebo		<0.001
PCS change from baseline, Week 16		
Mean ± SD	3.8 ± 7.5	7.4 ± 8.1
p-value vs. Placebo		<0.001
PCS change from baseline, Week 24		
Mean ± SD	3.8 ± 7.3	8.3 ± 8.3
p-value vs. Placebo		<0.001
MCS change from baseline, Week 12		
Mean ± SD	1.5 ± 9.9	4.9 ± 10.3
p-value vs. Placebo		<0.001
MCS change from baseline, Week 16		
Mean ± SD	1.3 ± 9.7	7.2 ± 10.3
p-value vs. Placebo		<0.001
MCS change from baseline, Week 24		
Mean ± SD	1.2 ± 10.1	6.9 ± 10.3
p-value vs. Placebo		<0.001

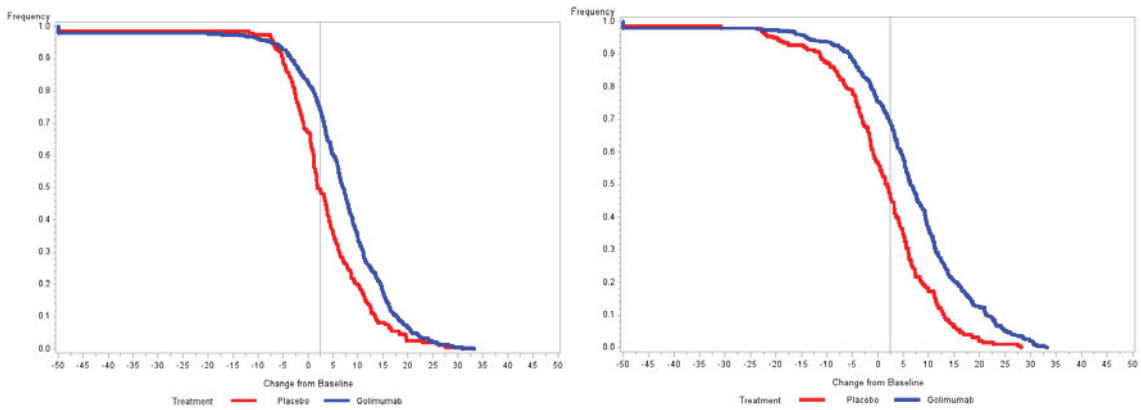


Figure 2. Change from baseline to week 16 in SF-36 PCS Score (left panel) and MCS Score (right panel), continuous responder analysis, Study CNTO148ART3001 (FDA statistical analysis)

8. Safety

a. Safety database

No new safety information was submitted with this supplement.

b. Safety findings and conclusion

The safety analysis of Simponi Aria was conducted during review of the original BLA. The major safety risks with Simponi Aria treatment in patients with RA include serious infections, and malignancy.

c. REMS/RiskMAP

The REMS for Simponi Aria will remain unchanged as no new safety information was submitted with this supplement.

9. Advisory Committee Meeting

This supplement is for an ancillary claim for the already approved RA indication; thus no AAC meeting was warranted. The regulatory history of SF-36 for RA was discussed at an internal Center level Regulatory Briefing on September 20, 2013, for Xeljanz (tofacitinib) as discussed in section 2 above.

10. Pediatric

The pediatric issues for Simponi Aria were discussed at a Pediatric Review Committee (PeRC) during review of the original BLA. This supplement did not trigger PREA requirements, and no new pediatric issues were identified.

11. Other Relevant Regulatory Issues

a. DSI Audits

During review of the original Simponi Aria application, DSI audit was conducted for representative clinical study sites based on high enrollment. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. During review of this 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 Office of Prescription Drug Promotion (OPDP), Division of Medication Error, Prevention, and Analysis (DMEPA), or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Simponi Aria was previously reviewed and found to be acceptable.

b. Physician Labeling

The labeling of Simponi Aira was reviewed previously with the original approval in July 2013. With this application the existing label will be updated to include new information regarding SF-36 in the Clinical Studies section. The SF-36 findings will be described under a separate subsection titled "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument, and not as supportive evidence of improvement of "physical function response." The findings will be described in qualitative terms stating improvement in PCS, MCS, and all 8 domains.

c. Carton and Immediate Container Labels

Simponi Aria is a marketed product, and there were no changes to the carton and immediate container labels with this application.

d. Patient Labeling and Medication Guide

Simponi Aria has a Medication Guide that will remain unchanged.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Janssen has submitted adequate data to support inclusion of SF-36 findings in the Clinical Studies section of the product labeling. The regulatory action for this application is Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of Simponi Aria remains favorable, as determined at the time of the original approval in July 2013. The current submission does not alter risk-benefit assessment of Simponi Aria for use in patients with RA.

c. Post-marketing Risk Management Activities

There are no new post-marketing risk management activities that will be required on the basis of this submission.

d. Post-marketing Study Commitments

There are no new post-marketing requirements or commitments based on review of this submission.

Appendix 4. Secondary and other claims for recently approved biologic DMARDs in their respective product labels

Proposed to be included in the Rayos product label	Etanercept (**ENBREL**) {1998} * †	Infliximab (**REMICADE**) {1999}	Anakinra (**KINERET**) {2001}	Adalimumab (**HUMIRA**) {2002}	Abatacept (**ORENCIA**) {2005}	Rituximab (**RITUXAN**) {2006}	Golimumab (**SIMPONI**) {2009}	Certolizumab (**CIMZIA**) {2009}	Tocilizumab (**ACTEMRA**) {2010}
ACR 50	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ACR 70	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ACR components	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12 wk ACR 20 response figure	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Morning stiffness ‡	Yes – 2 trials	No	No	No	Yes – 1 trial	No	No	No	No
DAS 28	No	No	No	No	Yes – 1 trial	No	No	No	Yes – 1 trial
SF 36 health survey §	Yes – 1 trial	Yes – 2 trials	Yes – 1 trial	Yes – 4 trials	Yes – 3 trials	(b) (4)	No	(b) (4)	(b) (4)
Fatigue by FACIT ¶	No	No	No	No	No		No		

* Year = Year of first approval for RA

† Of the small molecule DMARDs, **Arava** (leflumide), approved for RA in 1998, has the following secondary and other claims: ACR 50, ACR 70, ACR components, 12 wk ACR 20 response figure, morning stiffness (based on 3 trials), Health related QOL (based on 1 trial), and SF 36 health survey (based on 1 trial). **Arava** does not have DAS 28 and Fatigue claims.

Of the NSAIDs approved for signs and symptoms of RA, **EC-Naprosyn** and **Naprosyn** have the following secondary and other claims: reduction in joint swelling, reduction in duration of morning stiffness, reduction in disease activity, and increased mobility. **Indocin** has the following secondary and other claims: reduction in joint swelling, average number of joints involved, and morning stiffness; increased mobility, and improved functional capability.

‡ Label languages: "**Enbrel** was significantly better than placebo in all components of ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness. " "**Orencia** treated patients experienced greater improvement than placebo treated patients in morning stiffness." "**Arava** was significantly superior to placebo in improving morning stiffness, a measure of RA disease activity, not included in the ACR response criteria." **EC-Naprosyn** and **Naprosyn**: "Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time." "Improvement in patients treated with **Indocin** for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength."

§ Reasons for denial: The agency denied SF-36 claims due to concerns regarding multiplicity in the absence of strategies to address Type 1 error and concerns regarding the validity of SF-36 in RA. Specifically, the SF-36 instrument was not developed for RA patients and has features that are suboptimal for a patient reported outcome, such as lack of separation of mental and physical components in summary scores. Thus, there were reservations about including SF-36 in the label and the Agency denied SF-36 label claims. (Further summary available at the clinical reviews of BLA 125276/0, review date December 12, 2009, sBLA 125271, review date August 11, 2008, and sBLA 103705/5211, review date March 12, 2006.)

¶ (b) (4)

(b) (4)

(b) (4)

(b) (4) SF 36 is widely used as a generic measure of overall health status and produced two summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Using a domain of the multi-dimensional SF 36 was not considered to be valid. (Further summary available at the clinical review of sBLA 125271, review date August 11, 2008).

(b) (4)

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/s/

BADRUL A CHOWDHURY
08/05/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 16, 2015
From	Nikolay Nikolov, M.D. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review Update
NDA/BLA # **Supplement#**	BLA 125,433 0014
Applicant	Janssen Biotech, Inc.
Date of Submission	October 06, 2014
PDUFA Goal Date	August 06, 2015
Proprietary Name / **Established (USAN) names**	Simponi Aria/ golimumab
Dosage forms / Strength	2 mg/kg intravenous infusion
Proposed Claim	"Other Health-Related Outcomes: General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + methotrexate (MTX) demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4) ."
Recommended:	*Approval, with revisions to proposed labeling*

1. Introduction

Biologic Licensing Application (BLA) 125,433 from Janssen for intravenous (IV) golimumab, Simponi Aria, an injectable humanized anti-tumor necrosis factor (TNF)-alpha monoclonal antibody, was approved on July 18, 2013 for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX). The product is administered as an intravenous infusion of 2 mg per kg over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

This submission is a request for re-consideration for inclusion of SF-36 data in the product labeling for data submitted in the original BLA application. It is being reviewed as a labeling supplement with clinical data (BLA 125,433/supplement 0014) and Janssen proposes the following labeling changes in Section 14:

> *"Other Health-Related Outcomes:*
> *General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + methotrexate (MTX) demonstrated greater improvement from baseline compared with placebo + MTX in physical*

component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 [redacted] (b) (4) *."*

The overall intravenous golimumab development program was discussed in detail in the primary review of the original BLA dated, June 14, 2013. This document will focus on:

- Regulatory history of SF-36 in RA product labeling
- General discussion on SF-36 instrument
- Analyses on the SF-36 data from the golimumab clinical development program

The overall clinical efficacy and risk-benefit analysis of intravenous golimumab plus methotrexate remain consistent with the original BLA. Further, the Agency's analyses of the SF-36 data are in general agreement with the sponsor's analyses. The SF-36 data from the subcutaneous golimumab program are supportive of the SF-36 data in the IV golimumab application. Thus the SF-36 data submitted are adequate to support inclusion in product labeling.

2. Background

Rheumatoid arthritis (RA) is a chronic symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population worldwide. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.[i] Thanks to the advances in our understanding of the disease and the established drug development pathway, many effective treatments have been developed and approved for RA. The approval of most of these products was supported by establishing efficacy in the key domains of the disease, namely clinical response and physical function based on internationally agreed upon endpoints. The clinical response has been assessed by ACR response rates[1] and measures of low disease activity, such as DAS28[2] less than 2.6, have been used as supportive evidence of efficacy in this domain. For physical function, HAQ-DI[3] is usually used to demonstrate an improvement in physical function, and the SF-36, and more specifically the Physical Component Summary (PCS) has been historically used as supportive evidence of efficacy in this domain. Other outcomes that have important implications for patients and health care providers, such as radiographic endpoints, have been used to provide further characterization of the efficacy of a drug product and its utility in clinical practice.

There has been a recent emphasis on studying the effects of treatments on aspects of the disease that are important to patients and are not captured by other outcomes.[ii] These measures

1 ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.
2 DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.
3 HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

include patient-reported outcomes (PROs) such as the generic SF-36 health survey as an instrument to assess general health status.

Prior to 2008, SF-36 was included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. Between 2008 and 2013, the Agency denied proposed labeling for SF-36 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument and in particular the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. At the time, the Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP, (the review Division then) determined that SF-36 was no longer needed to supplement the data from the HAQ-DI in supporting the improvement in physical function claim. As a result, SF-36 information from four RA products, golimumab/Simponi, certolizumab/Cimzia, tocilizumab/Actemra, and tofacitinib/Xeljanz, was not included in the product labeling. Since then, based on continued pushback from the rheumatology academic community, the Agency's thinking on the utility of SF-36 in RA product development and labeling has evolved. The pertinent regulatory history of SF-36, as captured in Dr. Glaser's clinical review, was extensively discussed at an internal Regulatory Briefing on September 20, 2013 and the decision of the current review Division (DPARP) to re-implement SF-36 in RA product labeling to support a claim of improvement in general health status was supported by CDER senior management. Subsequently, information on SF-36, including on PCS, MCS, and the 8 domains, was included in the tofacitinib labeling (NDA 203,214) to support a general health status claim in November 2013. Following this precedent, Janssen submitted this request for re-consideration for inclusion of the SF-36 data, submitted in the original BLA on September 18, 2012, in the intravenous golimumab product labeling.

The SF-36 was not specifically discussed with the sponsor during pre-submission interactions. However, SF-36 was collected as a patient-reported outcome of interest in the protocols of phase 3 confirmatory clinical studies in both the subcutaneous and intravenous golimumab clinical programs and submitted to the respective applications.

3. CMC/Device

No new CMC information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Clinical Primary Reviewer: Rachel Glaser, M.D.
Statistical Primary Reviewer: Yongman Kim, Ph.D.
Statistical Team Leader: David Petullo, M.S.

Overview of the Clinical Program

The applicant conducted two randomized controlled studies, C0524T12 and CNTO148ART3001, in support of efficacy for the original BLA for intravenous golimumab. Study C0524T12 used a dose-finding regimen, different from that of the confirmatory efficacy study CNTO148ART3001 and the recommended dosing regimen; thus the data from that study are considered supportive. The key design features of the two studies are summarized in Table 1.

Table 1: Key Design Features of the Core Studies in RA Submitted in the Original BLA

Study	Design	Dose Regimen	Endpoints
Dose-Ranging Study			
C0524T12	48 wk, Phase 3, MC, R, DB, PC parallel group study in 643 subjects with RA, followed by a 24 wk extension with 50 mg SC q 4 wks	Dose cohorts: Group 1 (n=129): 2 mg/kg q 12 wks + MTX Group 2 (n=128): 2 mg/kg q 12 wks + PBO Group 3 (n=128): 4 mg/kg q 12 wks + MTX Group 4 (n=129): 4 mg/kg q 12 wks + PBO Group 5 (n=129): PBO IV q 12 wks + MTX Early escape at Wk 16 and dose regimen adjustment at Wk 24 if <20% improvement in both T/S JC	1°: ACR50 at Wk 14 2°: ACR20, DAS28 (CRP), SF-36 (PCS) at Wk 14; ACR50 at Wk 24
Confirmatory Clinical Study			
CNT0148-ART3001	52 wk, Phase 3, MC, R, DB, PC, parallel group, adaptive design study in 592 subjects with RA on 15-25 mg/wk MTX, followed by a 48 wk extension with 2 mg/kg IV q 8 wks	Dose cohorts: Group 1 (n=395): 2 mg/kg IV at Wks 0, 4, and then q 8 wks. PBO infusion at Wks 16 and 24. Group 2 (n=197): PBO IV infusion at Wks 0, 4, 12, 16, and 20. Cross over to GOL 2 mg/kg IV at Wks 24, 28, q 8 wks thereafter Early escape for PBO subjects at Wk 16 if < 10% improvement in both T/S JC	1°: ACR20 at Wk 14 2°: DAS28 (CRP) at Wk 14, Wk 14 HAQ, Wk 14 ACR 50; and change in total vDH-S score
Source: Dr. Glaser's Clinical Review, Adapted from Table 2.			

Briefly, both studies were multicenter, randomized, double-blind, placebo-controlled, and enrolled similar patient population of patients with active, moderate-to-severe rheumatoid

arthritis (RA) despite methotrexate (MTX) therapy. Study C0524T12 utilized two intravenous golimumab dosing regimens 2 mg/kg and 4 mg/kg (with or without concomitant MTX) every 12 weeks. In contrast, study CNTO148ART3001 used intravenous golimumab 2 mg/kg at Weeks 0, 4, and then every 8 weeks, which is the currently approved dosing regimen. Of note, the protocol provided for early escape option at Week 16 for placebo-treated patients who had less than 10% improvement in tender or swollen joint counts. Therefore, the assessment of continuous efficacy endpoints from later time points, i.e. Week 24, may be confounded by patients who have crossed-over from placebo to active treatment at Week 16.

Detailed protocol design, study conduct and results of endpoints such as ACR responses, HAQ-DI, and radiographic endpoints are discussed in the original BLA review and will not be discussed in this memorandum.

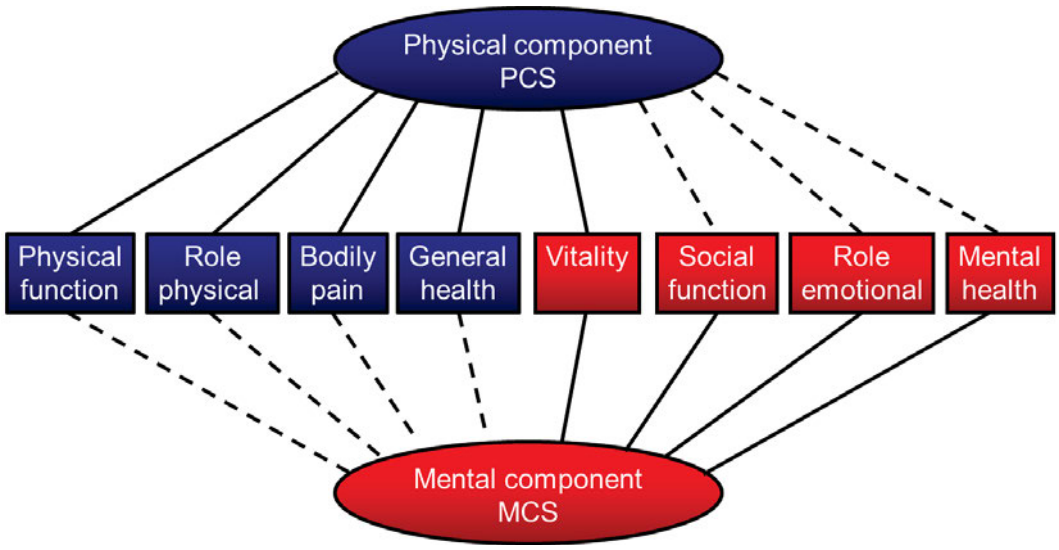
Brief Description of Short Form 36 (SF-36) Instrument

The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

The SF-36 consists of 36 questions relating to either physical or mental health. One question asks respondents to rate the amount of change experienced in their health in general and the remaining 35 questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitation). The eight domains are age, and gender adjusted and scored 0 (severe impairment) – 100 (no impairment).

Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality of life. The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

Figure 1. Conceptual Model for Deriving PCS and MCS from the Individual Domains



Based on considerations regarding the limitations of the SF-36 instrument and because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or only the summary scores, the SF-36 researchers have consistently emphasized the need to interpret the results of the domains, and PCS and MCS in parallel.

SF-36 in Golimumab Development Program

This review summarizes the analyses of SF-36 from the intravenous golimumab development program. The primary evidence of efficacy supporting the proposed claim of improvement in general health status is based on the data from SF-36 from a single confirmatory clinical study CNTO148ART3001. The same study provided the primary evidence of efficacy for approval of BLA 125,433 demonstrating statistical and clinically meaningful superiority of intravenous golimumab plus MTX over placebo plus MTX for improvement in clinical response (ACR20), improvement in physical function (HAQ-DI), and inhibition of radiographic joint damage (van der Heijde-Sharp score) which were discussed in the original BLA and will not be discussed in this review in further detail. Additional supportive evidence of efficacy for the proposed claim of improvement in general health status is also provided by the SF-36 data from the dose-ranging study C0524T12 and the SF-36 data from the subcutaneous golimumab clinical development.

Statistical Analysis of SF-36 Data

The change from baseline in PCS, MCS, and each of the 8 domain scores at Weeks 12, 16 and Week 24 were summarized by treatment group. To test for a treatment difference an analysis of variance on the van der Waerden normal scores was used with treatment group and C-reactive protein level at screening (<1.5 mg/dL or ≥1.5mg/dL) as covariates in the model. Significance was tested using a 2-sided alpha of 0.05.

The primary analysis population was the intent-to-treat (ITT) population defined as all randomized patients regardless of whether or not they received the assigned treatment.

Although SF-36 was not defined as a primary or major secondary endpoint to be controlled for the overall type I error, statistical significance was assessed after Bonferroni adjustment was applied.

Handling of SF-36 Missing Data

Missing data for an SF-36 item on completed questionnaires was imputed as suggested by the developer of the SF-36 instrument, using the mean from the all other items within the same domain, provided at least 50% of the items in that domain were completed. Since these rules do not account for when the total score is non-calculable or missing, the applicant applied additional rules for the total score for treatment comparisons as described in detail in Dr. Yongman's statistical review. For subjects that escaped at Week 16, each endpoint or component value after Week 16 was replaced with the corresponding value observed at the time of escape.

Patient Disposition

The population in the IV golimumab RA development program consisted of adult subjects with moderate to severely active RA who had an inadequate response to MTX.

For further discussion on the patients' disease and demographic characteristics and disposition the reader is referred to the review of the original BLA application.

The overall proportion of missing SF-36 questionnaires was low and similar in the two groups (2.1% in the golimumab group and 1.7% in the placebo group) and therefore not expected to substantially influence the analysis and conclusions.

Results of SF-36 Data

At all tested times in study CNTO148ART3001, Weeks 12, 16, and 24, subjects who received intravenous golimumab + MTX showed significantly greater improvement in SF-36 physical component and mental component scores (PCS and MCS) as compared to subjects who received placebo + MTX at as seen in Table 2. Both, the primary analysis using the last observation carried forward (LOCF), and the sensitivity analysis using data obtained after discontinuation of study drug or escape at Week 16, showed consistent results.

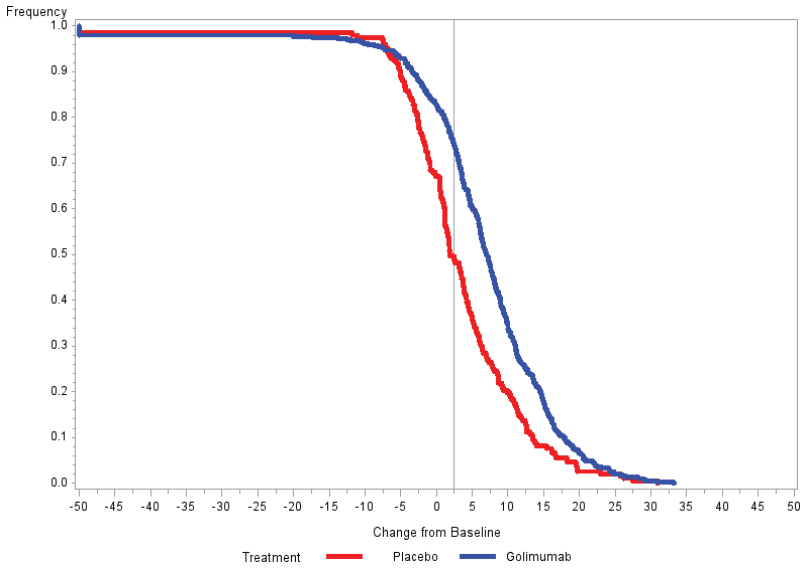
Table 2. Analyses on SF-36 Composite Scores – Study CNTO148ART3001

Analyses on SF-36 Composite Scores – Study CNTO148ART3001				
	Primary Analysis (ITT LOCF Imputation)		Sensitivity Analysis (ITT Retrieved-Dropouts)	
	Placebo + MTX (N=197)	IV Golimumab + MTX (N=395)	Placebo + MTX (N=197)	IV Golimumab + MTX (N=395)
PCS Change from Baseline				
Week 12 Mean ± SD p-value vs. Placebo	3.2 ± 7.4	5.9 ± 7.7 <0.001	3.2 ± 7.4	5.9 ± 7.7 <0.001
Week 16 Mean ± SD p-value vs. Placebo	3.8 ± 7.5	7.4 ± 8.1 <0.001	3.8 ± 7.5	7.4 ± 8.1 <0.001
Week 24 Mean ± SD p-value vs. Placebo	3.8 ± 7.3	8.3 ± 8.3 <0.001	5.5 ± 7.3	8.3 ± 8.3 <0.001
MCS Change from Baseline				
Week 12 Mean ± SD p-value vs. Placebo	1.5 ± 9.9	4.9 ± 10.3 <0.001	1.5 ± 9.9	4.9 ± 10.3 <0.001
Week 16 Mean ± SD p-value vs. Placebo	1.3 ± 9.7	7.2 ± 10.3 <0.001	1.3 ± 9.7	7.2 ± 10.3 <0.001
Week 24 Mean ± SD p-value vs. Placebo	1.2 ± 10.1	6.9 ± 10.3 <0.001	3.1 ± 10.0	7.0 ± 10.2 <0.001
Source: Adapted from Dr. Yongman Kim's Statistical Review, Tables 4 and 6				

Patients receiving intravenous golimumab + MTX had a greater mean change from baseline (improvement) in each of 8 domain scores at all time points (data not shown), consistent with the results for the summary scores.

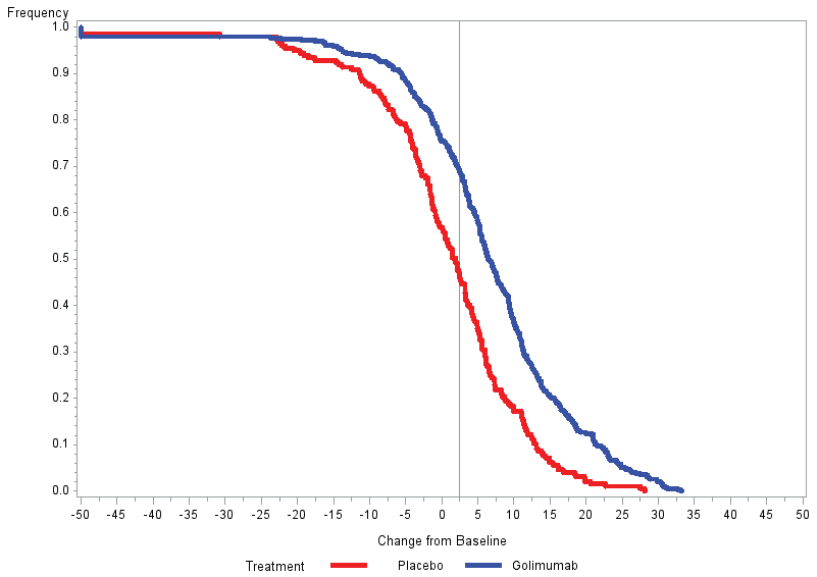
Sensitivity analysis, conducted by the FDA statistical reviewer Dr. Yongman Kim, examined the continuous responder functions between placebo and treatment and showed results consistent with the analyses of the mean change from baseline. Clear separation between the intravenous golimumab + MTX and placebo + MTX groups is demonstrated in Figure 2 as representative of SF-36 PCS data and in Figure 3 as representative of SF-36 MCS data from study CNTO148ART3001.

Figure 2. Change from Baseline SF-36 Physical Component Score, Week 16, Study CNTO148ART3001, Continuous Responder Analysis



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

Figure 3. Change from Baseline SF-36 Mental Component Score, Week 16, Study CNTO148ART3001, Continuous Responder Analysis



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

To further characterize the clinical meaningfulness of the SF-36 data from study CNTO148ART3001, Dr. Kim conducted responder analysis based on cut-off points of 2.5 units for the PCS and MCS, and 5 units for the 8 domains as suggested in the literature to be representative of a minimal clinically important change. The responder analyses were also consistent with the primary analysis with a higher proportion of patients in the golimumab +

MTX group achieving the response for PCS, MCS, as shown in Table 3 and the 8 domains (data not shown).

Table 3. Responder Analyses on SF-36 Composite Scores – Study CNTO148ART3001

Responder Analyses on SF-36 Composite Scores – Study CNTO148ART3001		
	Placebo + MTX (N=197)	IV Golimumab + MTX (N=395)
PCS Responders (proportion achieving at least 2.5 units of improvement from baseline)		
Week 12 n (%) p-value vs. Placebo	99 (50%)	263 (67%) <0.001
Week 16 n (%) p-value vs. Placebo	96 (49%)	291 (74%) <0.001
Week 24 n (%) p-value vs. Placebo	122 (62%)	288 (73%) 0.006
MCS Responders (proportion achieving at least 2.5 units of improvement from baseline)		
Week 12 n (%) p-value vs. Placebo	87 (44%)	225 (57%) 0.003
Week 16 n (%) p-value vs. Placebo	90 (46%)	271 (69%) <0.001
Week 24 n (%) p-value vs. Placebo	99 (50%)	248 (63%) 0.004
Source: Adapted from Dr. Yongman Kim's Statistical Review, Tables 8		

Timing of SF-36 Assessment

Supportive Evidence of Efficacy for SF-36

SF-36 Data from Study C0524T12

Study C0524T12 used an unapproved lower-exposure dosing regimen (every 12 weeks vs. the approved every 8 weeks), and while it did not meet the primary objective of achieving statistical superiority of intravenous golimumab versus placebo plus MTX for ACR50, the

observed trend to improvement was consistent with that expected with golimumab treatment. Thus the SF-36 data from this study was considered as only supportive. Greater mean changes from baseline were seen in the PCS, MCS, and all subscale scores at Weeks 14 and 24 in subjects randomized to receive IV golimumab in combination with MTX as compared to MTX or intravenous golimumab alone with nominally statistical significance at Week 14 for physical functioning, vitality, and social functioning domains, and physical functioning domain at Week 24. These results support the SF-36 efficacy seen in study CNTO148ART3001.

SF-36 Data from the Subcutaneous Golimumab Program

The applicant also submitted analyses of SF-36 data from the subcutaneous golimumab program in RA (BLA 125,289) as supportive evidence of efficacy for the proposed labeling changes. Of the phase 3 clinical studies in the subcutaneous golimumab program, SF-36 data were reviewed from study C0524T06 as this was the only study that enrolled a population similar to the population in Study CNTO148ART3001 allowing for a more appropriate comparison of efficacy, including SF-36, across the studies from the subcutaneous and intravenous golimumab programs.

In study C0524T06, RA patients were randomized to receive subcutaneous golimumab 50 mg plus MTX, subcutaneous golimumab 100 mg plus MTX, subcutaneous golimumab 100 mg plus placebo, or placebo plus MTX. SF-36 was collected and analyzed at baseline, Weeks 14, 24, and 48.

Nominally statistically significant differences were seen between subcutaneous golimumab plus MTX groups as compared to subjects receiving placebo plus MTX in PCS score at Weeks 14 and 24, and in MCS score in subjects receiving subcutaneous golimumab 100 mg, both with and without MTX, at Week 24 (data not shown). Numerical improvement was seen in all eight domain scores in the subcutaneous golimumab plus MTX group as compared to the placebo plus MTX group. The statistically significant improvement observed in SF-36 PCS scores, as well as the trend towards improvement in MCS and domain scores in the subcutaneous golimumab plus MTX groups provide further supportive evidence of the positive effect of intravenous golimumab in combination with MTX on SF-36 scores observed in Study CNTO148ART3001.

Summary of Efficacy Assessment

Collectively, the SF-36 data from the golimumab clinical program indicate that compared to placebo plus MTX, intravenous golimumab plus MTX improves PCS, MCS, and all eight SF-36 domains in patients with active RA supporting the proposed labeling language of:

> *"...patients receiving SIMPONI ARIA + (b) (4) (MTX) demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36..."*

Assessments of SF-36 were not primary or major secondary endpoints, included in the statistical hierarchy of testing and not controlled for type 1 error for multiple endpoints, thus true statistical significance and p-values could not be calculated. The FDA analyses, conducted by the statistical review team, were in general agreement with the analyses presented by the sponsor.

Of note, these SF-36 results are consistent with the treatment effects observed in other RA products, as described in the published literature.[iii, iv, v, vi, vii]

8. Safety

No new safety information was submitted with this supplement. The safety information from golimumab development program was reviewed in detail with the original BLA submission and resulted in a boxed warning to include:

- Serious infections – Do not start SIMPONI ARIA during an active infection. If an infection develops, monitor carefully, and stop SIMPONI ARIA if infection becomes serious.
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI ARIA, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic.
- Hepatitis B reactivation – Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI ARIA and begin anti-viral therapy.
- Malignancies – More cases of lymphoma have been observed among patients receiving TNF-blockers compared with patients in the control groups. Cases of other malignancies have been observed among patients receiving TNF-blockers.
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI ARIA if new or worsening symptoms occur.
- Demyelinating disease, exacerbation or new onset, may occur.
- Hypersensitivity reactions: Serious systemic hypersensitivity reactions including anaphylaxis may occur.

Overall, the safety data from golimumab RA development program is consistent with the class profile of the TNF inhibitors, with associated inherent risks, such as serious infections, including opportunistic infections and tuberculosis.

9. Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted.

10. Pediatrics

The pediatric issues were discussed in the reviews of the original BLA.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **DSI audits –** The OSI audits were conducted as part of the original BLA
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

The trade name for IV golimumab, Simponi Aria, has already been reviewed and approved.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

None.

- **Physician labeling**

I recommend the following revisions (all to Section 14, Clinical Studies):

1) Proposed SF-36 labeling language:

- Consistent with the applicant's proposed text, describe SF-36 data under a separate subsection "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument and not only as supportive evidence of improvement in physical function.
- Consistent with the applicant's proposed text, for completeness for SF-36 interpretation, include a description of physical component summary (PCS) and mental component summary (MCS) scores. This recommendation is consistent with standard practice in reporting SF-36 results because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores. Further, this approach is consistent with the analysis and reporting of composite endpoints, where the analyses and reporting of the individual components are descriptive without requiring statistical significance, i.e. adjusting for multiplicity.
- (b) (4)

  Proposed labeling revisions (deletions are in ~~*strikethrough*~~):

  *"**Other Health-Related Outcomes**:*

General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + (b) (4) (MTX) demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4) .''

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

Carton and container labels are already approved, and no changes are proposed or warranted.

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

The Patient labeling/Medication guide is a part of REMS and was approved as with the original BLA application. No changes are proposed to the Patient labeling/Medication guide with this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement with revisions to the labeling as discussed in Section 12. Labeling.

- **Risk Benefit Assessment**

The overall risk-benefit profile of IV golimumab in RA remains favorable, as determined at the time of the original BLA approval and is not altered on the basis of this submission. The current submission supports the addition of SF-36 results in Section 14 of the prescribing information. Although the risks of golimumab are not minimal, these are balanced by a number of clinical benefits, which include reduction in patient's signs and symptoms, disease activity, radiographic damage progression, improvement in physical functioning, and general health status.

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

This supplement does not warrant a postmarketing risk evaluation and management strategy (REMS) for intravenous golimumab.

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

This supplement does not warrant new postmarketing requirements or commitments.

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
07/16/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA supplement
Application Number(s)	125433
Priority or Standard	Standard
Submit Date(s)	October 6, 2014
Received Date(s)	October 6, 2014
PDUFA Goal Date	August 6, 2015
Division / Office	DPARP/OND
Reviewer Name(s)	Rachel Glaser, M.D.
Review Completion Date	July 2, 2015
Established Name	Intravenous (IV) Golimumab
Trade Name	Simponi Aria
Therapeutic Class	TNF Inhibitor
Applicant	Janssen Biotech, Inc.
Formulation(s)	Intravenous, 50 mg/4mL Vial
Dosing Regimen	2 mg/kg at Weeks 0 and 4, then every 8 weeks
Indication(s)	Rheumatoid Arthritis (RA), SF-36 claim
Intended Population(s)	Moderate-Severe RA on methotrexate

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this supplement for a general health status claim based on data from SF-36.

1.2 Risk Benefit Assessment

The overall risk-benefit profile of IV golimumab remains favorable, as determined at the time of the original BLA approval, and is not altered on the basis of this submission. The current submission supports the addition of SF-36 results in Section 14 of the prescribing information. Although the risks of IV golimumab are not minimal, these are balanced by the clinical benefits, which include reduction in patient's signs and symptoms and disease activity, inhibition of radiographic joint damage, and improvement in physical functioning and general health status.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This supplement does not warrant postmarketing risk evaluation and management strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

This supplement does not warrant new postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

IV golimumab is a colorless to light yellow solution in a single-use 4 mL glass vial, containing 50 mg of golimumab, 9.5mM L-histidine, 4.5% sorbitol, and 0.015% polysorbate 80 at pH 5.5. IV golimumab is diluted with 0.9% w/v sodium chloride to a final volume of 100 mL. It is administered as an intravenous infusion at a dose of 2 mg/kg over 30 minutes at Weeks 0 and 4, and then every 8 weeks thereafter.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Approved Disease Modifying Anti-Rheumatic Drugs (DMARDs), Immunosuppressants and Therapeutic Biologics for the Treatment of RA in the U.S.

Drug/Product	NDA/BLA	Sponsor	Year of Approval
Sulfasalazine	7-073	Pfizer	1950
Methotrexate	8-085 (PO) 11719 (IV)	Multiple Sponsors	1953
Hydroxychloroquine	9-768	Sanofi-Aventis	1955
Prednisone	Many ANDAs	Multiple Sponsors	1955
Azathioprine	16-324	Prometheus Labs	1968
Penicillamine	19-853	Aton	1970
Auranofin	18-689	Prometheus Labs	1985
Cyclosporin	50-715, 50-625	Novartis	1995, 1990
Leflunomide	20-905	Sanofi-Aventis	1998
Etanercept	103795	Immunex	1998
Infliximab	103772	Centocor	1999
Anakinra	103950	Amgen	2001
Adalimumab	125057	Abbot	2002
Abatacept	125118	Bristol Myers Squibb	2005, 2011
Rituximab	103705	Genentech and Biogen Idec	2006
Certolizumab pegol	125160	UCB Inc	2008
Golimumab	125289	Centocor	2009
Tocilizumab	125276	Genentech	2010, 2013
Tofacitinib citrate	203214	Pfizer	2012
Golimumab IV	125433	Janssen Biotech	2013

Adapted from Table by Dr. Rosemarie Neuner BLA125433 Clinical Review 6/14/13

In addition, there are a number of nonsteroidal anti-inflammatory drugs (NSAIDs) that are approved for the reduction of the signs and symptoms of RA.

2.3 Availability of Proposed Active Ingredient in the United States

Golimumab is an approved therapeutic biologic product that is available and marketed in the U.S. as a subcutaneous formulation (original BLA 125289, approved on November 18, 2009) and as an intravenous formulation (original BLA 125433, approved on July 18, 2013).

2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns associated with the use of TNF inhibitors are listed under the Warnings and Precautions section of the labels for these agents and include: increased susceptibility to serious infections such as opportunistic infections, tuberculosis, histoplasmosis, and reactivation of hepatitis B; increased risk for malignancies particularly lymphomas and hepatosplenic T-cell lymphoma; hepatotoxicity, hypersensitivity reactions, demyelinating disorders, cytopenias, worsening congestive heart failure, autoimmune disorders, and infusion-related/injection-site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IV golimumab was approved for treatment of moderately to severely active rheumatoid arthritis in adult patients on methotrexate on July 18, 2013. The Applicant did not propose inclusion of the SF-36 endpoints in the USPI for IV golimumab based on prior precedent from the FDA's comments on SF-36 during the BLA review for SC golimumab. At that time, the Study Endpoints and Label Development group (SEALD) indicated that SF-36 is a generic health survey that has not been shown to represent a complete, meaningful, interpretable, and appropriate measure of health related quality of life (HRQoL) specific for the RA, psoriatic arthritis, or ankylosing spondylitis populations. Thus, the results for SF-36 were not included in the label. In November 2013, Xeljanz, another treatment for RA, was approved with inclusion of an SF-36 statement. See section 2.6 for details of regulatory history of SF-36 in rheumatoid arthritis. Following this precedent, Janssen submitted the current supplement on October 6, 2014 with a request for consideration of the SF-36 claim in labeling of IV golimumab.

2.6 Other Relevant Background Information

Regulatory History of SF-36 in RA Drug Development

Adapted from regulatory briefing September 20, 2013 by Dr. Nikolay Nikolov

In the 1999 RA Guidance, the SF-36 was mentioned as a validated general health status measure that should be collected in trials intended to support a "prevention of disability" claim, and that patients should not worsen on this measure during the trial. This claim was intended to encourage long-term trials (i.e. 2 to 5 years) in RA. Over time, the claim evolved to "improvement in physical function," and the primary measure used in development programs became the Health Assessment Questionnaire Disability Index (HAQ-DI). Shorter trials were accepted as significant improvement could be observed within 12 to 24 weeks, and it became difficult to justify long-term placebo-controlled trials with the approval of highly effective therapies. SF-36 was included in the labeling for RA products, as supportive data for the HAQ-DI for the claim of improvement in physical function. Between 1998 and 2005, six DMARDs were

approved for the treatment of patients with RA with inclusion of the SF-36. In most of these labels, mention of SF-36 is limited to a descriptive statement that improvements in SF-36 Physical Component Summary (PCS) and the Mental Component Summary (MCS) were observed. The last approved label with SF-36 (Orencia, 2005) contains the statement, "Health-related quality of life was assessed by the SF-36 questionnaire…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)." In 2006, rituximab (Rituxan) was approved for RA but an SF-36 claim was not included in the label because 2 year data were not submitted.

From 2008 through November 2013, the Agency denied proposed labeling for SF-36 claims due to concerns raised by the SEALD team about the SF-36 instrument and, in particular, the use of the SF-36 PCS score and MCS score in RA product labels. These concerns included that (1) SF-36 is a generic health survey that has not been shown to represent a health related quality of life (HRQoL) in RA and (2) PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent and do not measure pure physical or mental functioning and cannot be described in a way that is meaningful. After internal discussion, the review division reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function claim. As a result, SF-36 information from four RA products, golimumab/Simponi, certolizumab/Cimzia, tocilizumab/Actemra, and tofacitinib/Xeljanz, was not included in the product labeling.

In addition to expected pushback from sponsors, who felt that this created an uneven playing field, the decision to no longer include SF-36 in RA product labeling has been questioned by the RA academic and research community. The community's rationale for the importance of SF-36 includes: (1) SF-36 is a legacy instrument with well-known limitations and implications that is widely used by the RA research community throughout the world; (2) SF-36 provides additional important information on the impact of the disease on the patient that is not captured by other outcome measures used in RA trials; (3) SF-36 is utilized throughout the world for health care policy and decision-making. The SF-36 has been extensively studied in the context of RA and other rheumatic diseases with a wealth of data across countries and cultures. The question about the content validity of the SF-36 in RA or other related rheumatic conditions, that the instrument does not measure what it is purported to measure, does not appear to be supported by the abundance of published literature on SF-36. It is ubiquitous in rheumatology and by far the most commonly used generic health status outcome in RA reported in over 150 articles[1]. It was used in 80% of the published clinical studies in RA reporting patient reported outcomes (PROs)[2] indicating that the community understands what SF-36, including the 8 domains and the summary scores, measure. Studies to date have yielded evidence of content, construct, and predictive validity of SF-36. Further, a systematic review of the literature on the measurement properties of physical function scales for use in patients with RA, has identified the SF-36 as a relevant

generic questionnaire with respect to content validity for measuring physical functioning[3], supported by the fact that in RA SF-36 PCS is well correlated with HAQ-DI.

Based on the accumulated clinical data and the evidence of construct validity, responsiveness, and reliability in RA, SF-36 has been shown to:

- Assess disease aspects important to patients
- Provide a multidimensional view of the impact of RA and improvements associated with effective treatment[4]
- Be a sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offer comparison with age- and gender matched norms and with other disease states and co-morbidities[5]
- Be non-redundant with other endpoints[6], [7]
- Reflects impact of early and later disease[8],[9]
- Have generally accepted Minimal Clinically Important Difference (MCID) values for improvement as well as deterioration[10],[11]

An internal Regulatory Briefing meeting was held September 20, 2013 and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), with support of CDER senior management, decided to implement SF-36 in RA labeling as a measure of general health status, rather than its previous use as a supportive measure for improvement in physical function. Inclusion of results of PCS, MCS, and the results of the 8 domains are included to facilitate interpretation. In November 2013, Xeljanz (tofacitinib) was the first RA treatment since 2005 to receive approval for inclusion of an SF-36 claim in the labeling.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical studies to support the supplement, including the analysis datasets and programs, were submitted and reviewed with the original BLA.

3.2 Compliance with Good Clinical Practices

In submission of the original BLA, the applicant certified that the phase 3 trials, C0524T12 and CNTO148ART3001, were conducted in compliance with the following: Good Clinical Practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

3.3 Financial Disclosures

There were no additional financial disclosures submitted with this BLA supplement.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original BLA 125433, as well as in the review of the approved SC formulation in BLA 125289.

4.2 Clinical Microbiology

No new clinical microbiology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125433.

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125433, as well as in the review of the approved SC formulation in BLA 125289.

4.4 Clinical Pharmacology

No new clinical pharmacology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125433.

4.4.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds both soluble and transmembrane forms of human TNFα, inhibiting the biological activity of this proinflammatory cytokine. Elevated levels of TNFα have been implicated in the pathophysiology of chronic inflammatory diseases such as RA, psoriatic arthritis, and ankylosing spondylitis.

4.4.2 Pharmacodynamics

No new pharmacodynamic information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125433.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) profile of IV golimumab was reviewed in the original BLA 125433. No additional PK studies were submitted. While direct comparisons were not provided in the original application, cross-study comparisons and PK modeling indicate that the C_{max} and AUC of the 2 mg/kg every 8 weeks IV dose are approximately 14-fold and 2-3 fold higher respectively than the 50 mg SC dose.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for IV golimumab includes two Phase 3 studies which are summarized in Table 2.

Table 2: Summary of the Phase 3 Studies in RA Submitted for the BLA

Study	Design	Dose Regimen	EP
Dose-Ranging Study			
C0524T12	48 wk, Phase 3, MC, R, DB, PC parallel group study in 643 subjects with RA, followed by a 24 wk extension with 50 mg SC q 4 wks	Dose cohorts: Group 1 (n=129): 2mg/kg q 12 wks + MTX Group 2 (n=128): 2 mg/kg q 12 wks + PBO Group 3 (n=128): 4 mg/kg q 12 wks + MTX Group 4 (n=129): 4 mg/kg q 12 wks + PBO Group 5 (n=129): PBO IV q 12 wks + MTX Early escape at Wk 16 and dose regimen adjustment at Wk 24 if <20% improvement in both T/S JC	1°: ACR50 at Wk 14 2°: ACR20, DAS28 (CRP), SF-36 (PCS) at Wk 14; ACR50 at Wk 24
Confirmatory Clinical Study			
CNT0148-ART3001	52 wk, Phase 3, MC, R, DB, PC, parallel group, adaptive design study in 592 subjects with RA on 15-25 mg/wk MTX, followed by a 48 wk extension with 2 mg/kg IV q 8 wks	Dose cohorts: Group 1 (n=395): 2 mg/kg IV at Wks 0, 4, and then q 8 wks. PBO infusion at Wks 16 and 24. Group 2 (n=197): PBO IV infusion at Wks 0, 4, 12, 16, and 20. Cross over to GOL 2 mg/kg IV at Wks 24, 28, q 8 wks thereafter Early escape for PBO subjects at Wk 16 if < 10% improvement in both T/S JC	1°: ACR20 at Wk 14 2°: DAS28 (CRP) at Wk 14, Wk 14 HAQ, Wk 14 ACR 50; and change in total vDH-S score

Table adapted from presentation by Dr. Rosemary Neuner

5.2 Review Strategy

The applicant conducted two randomized controlled trials, Studies C0524T12 and CNTO148ART3001, in support of efficacy for the BLA supplement. Since study C0524T12 used a dosing regimen different from that of the pivotal efficacy study CNTO148ART3001 and the recommended dosing regimen, the data from that study are considered supportive. The SF-36 was pre-specified and collected as a patient-reported outcome in the protocols of these studies and submitted in the original BLA on September 12, 2012. At the time of the original BLA, the Division denied including SF-36 data in the product labeling citing concerns expressed by the SEALD team that SF-36 is not an optimal PRO for use to support labeling claims and should not be included in product labeling. Refer to the section on Regulatory History of SF-36 in RA Drug Development above. The previously submitted SF-36 data from pivotal trial CNTO148ART3001 and supportive data from C0524T12 are reviewed below. To justify the use of the data from a single study, CNTO148ART3001, as the pivotal evidence of efficacy to support the SF-36 labeling changes, the Agency has also requested analyses of the data, including the Physical Component Score, the Mental Component Score, and the 8 domains of the SF-36, from the pivotal trials of the subcutaneous golimumab rheumatoid arthritis program. These are also reviewed in this document as supportive evidence of efficacy.

5.3 Discussion of Individual Studies/Clinical Trials

Overview of the Clinical Program

Protocol: C0524T12

The pilot study of IV golimumab, C0524T12, in subjects with moderately to severely active RA, was a phase 3 multicenter, randomized, double-blind, placebo-controlled study of 643 subjects randomized to one of five treatment groups, 1) IV golimumab 2 mg/kg at Week 0 and every 12 weeks through Week 48 with methotrexate, 2) IV golimumab 2 mg/kg at Week 0 and every 12 weeks through Week 48 with placebo (sham methotrexate), 3) IV golimumab 4 mg/kg at Week 0 and every 12 weeks through Week 48 with methotrexate, 4) IV golimumab 4 mg/kg at Week 0 and every 12 weeks through Week 48 with placebo, or 5) IV infusions of placebo at Week 0 and every 12 weeks through Week 48 with methotrexate. Study C0524T12, which used an alternative dosing regimen to that used in study CNTO148ART3001 and the recommended dosing regimen, did not meet its primary endpoint of the ACR 50 response at Week 14; however a greater proportion of subjects who received IV golimumab demonstrated improvement in DAS28 and ACR 20 and 50 responses. Response rates were noted to be lower when serum concentrations were below the lower limit of quantification, and based on this observation, the dosing interval was reduced in Study CNTO148ART3001.

Protocol: CNTO148ART3001

The efficacy of the marketed dose of IV golimumab in the treatment of RA was demonstrated by a single pivotal trial, Study CNTO148ART3001. The protocol design of Study CNTO148ART3001 is discussed below.

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, an Anti-TNF-α Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy.

Dates Conducted: This trial was started on September 14, 2009 and completed on November 25, 2011. Database lock was March 1, 2012.

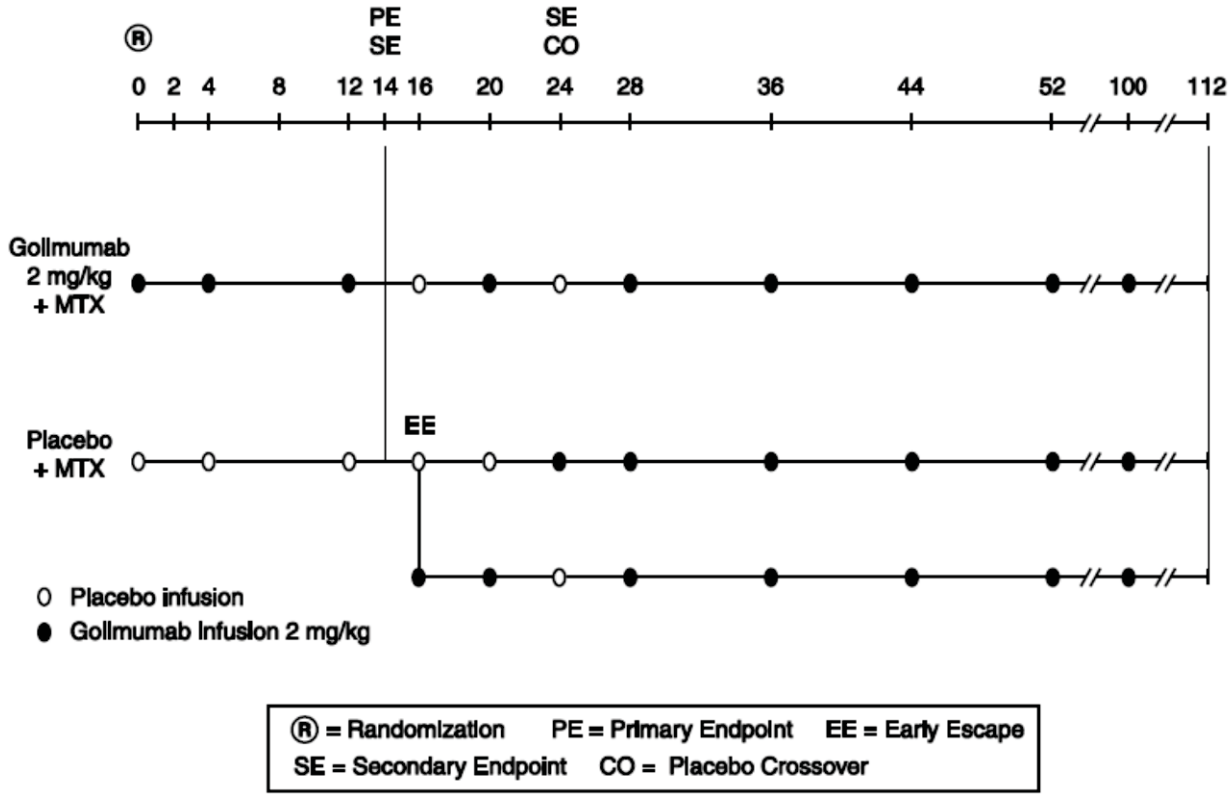
Objectives:
Primary Objective:
To evaluate the clinical efficacy of intravenous (IV) administration of golimumab 2 mg/kg plus methotrexate (MTX) compared with MTX alone in subjects with active rheumatoid arthritis (RA) despite MTX therapy

Secondary Objectives:
- To assess safety parameters
- To assess physical function and disability
- To determine population pharmacokinetics (PK) and pharmacodynamics (PD) of IV golimumab
- To assess effects of IV golimumab on structural damage

Overall Design:
Study CNTO148ART3001 was a 112 week phase 3, multicenter, randomized, double-blind, placebo-controlled trial that included 592 subjects with active rheumatoid arthritis despite treatment with MTX, randomized via a 2:1 ratio stratified by screening C-reactive protein (CRP) level (< 1.5 mg/dL or ≥1.5 mg/dL) to receive:
- IV golimumab infusion 2 mg/kg + MTX
- Placebo infusions + MTX

Study infusions were administered at Weeks 0, 4, and every 8 weeks thereafter through completion of the trial. All subjects continued their stable dose of MTX. Subjects in the placebo group then crossed over to golimumab and received IV golimumab at Weeks 24, 28, and every 8 weeks (q8w) thereafter. Subjects randomized to golimumab received placebo infusions at Weeks 16 and 24 to maintain the blind. At Week 16, subjects in the placebo group who had demonstrated < 10% improvement in both tender and swollen joint count were eligible for early escape therapy of golimumab infusions of 2 mg/kg at Weeks 16 and 20 and q8w thereafter. The figure below details the study scheme.

Figure 1: Study Schema CNTO148ART3001



Source: Applicant's Figure 1; p. 24 of the 24-Week Study Report

Eligibility:

Table 3: Tabular Summary of Major Inclusion and Exclusion Criteria for Study CNTO148ART3001 below summarizes the major inclusion and exclusion criteria for Study CNTO148ART3001.

Table 3: Tabular Summary of Major Inclusion and Exclusion Criteria for Study CNTO148ART3001

Major Inclusion Criteria:

1. Males or females ≥ 18 years old
2. Diagnosis of active RA for at ≥3 months prior to screening defined by 1987 ARA criteria
3. Treated and tolerated MTX a dose of at least 15 mg/week for at least 3 months prior to screening, and have been on a stable dose of MTX ≥ 15 mg/week and ≤ 25 mg/week for at least 4 weeks prior to screening
4. Have active RA, as defined by persistent disease activity with at least 6 swollen and 6 tender joints, at the time of screening and at baseline.
5. CRP ≥ 1.0 mg/dL at screening
6. Anti-cyclic citrullinated peptide (anti-CCP) antibody-positive or rheumatoid factor (RF) positive at screening
7. Subjects using NSAIDs or other analgesics for RA must be on a stable dose for at least 2 weeks prior to first administration of study agent

8. Dose of oral corticosteroids not to exceed prednisone equivalent of ≤10 mg/day that must be stable for at least 2 weeks prior to first administration of study agent. If currently not taking corticosteroids, subjects must have not received oral corticosteroids for at least 2 weeks prior to first administration of study agent
9. Men capable of fathering children and females of childbearing potential must be using adequate birth control measures as listed in the protocol. Females of childbearing potential must test negative for pregnancy
10. Comply with the following tuberculosis (TB) screening criteria: no history of (H/O) latent or active TB prior to screening; no signs/symptoms suggestive of active TB upon medical history and/or physical exam; no recent close contact with a person with active TB or if such contact has occurred evaluation and appropriate treatment for latent TB (if warranted) prior to or simultaneously with first administration of study agent; must have a negative QuantiFERON-TB Gold (and negative TB skin test if QuantiFERON-TB Gold test is not approved/registered in that country) within 6 weeks prior to first administration of study agent; and a negative chest x-ray within 3 months prior to first administration of study agent with no evidence of current active TB or old, inactive TB as read by a qualified radiologist
11. Have the following screening lab test results: hemoglobulin ≥ 8.5 g/dL; WBC≥ 3.5 x 10^3 cells/µL; neutrophils ≥ 1.5 x 10^3 cells/ µL; platelets ≥ 100 x 10^3 cells/µL; ALT and AST ≤ 1.5 x upper limits of normal (ULN); and serum creatinine ≤ 1.5 mg/dL

Major Exclusion Criteria:

1. H/O inflammatory diseases such as psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, or Lyme disease that might confound study evaluations
2. Treated with DMARDs other than MTX or immunosuppressives such as D-penicillamine, hydroxychloroquine, chloroquine, oral or parenteral gold, sulfasalazine, leflunomide, azathioprine, cyclosporine, mycophenolate mofetil during the 4 weeks prior to first administration of study agent
3. Received intra-articular, intra-muscular, or IV corticosteroids including adrenocorticotropic hormone during the 4 weeks prior to first administration of study agent
4. H/O hypersensitivity to human Ig proteins or other components of golimumab
5. Received any commercial or investigation anti-TNF therapy such as infliximab, golimumab, adalimumab, certolizumab pegol, or etanercept
6. Received rituximab, efalizumab, abatacep, natalizumab or other agents that target alpha-4-integrin
7. Received anakinra during the 4 weeks prior to first administration of study agent
8. Received alefacept within the 3 months prior to the first administration of the study agent
9. Used cytotoxic agents such as chlorambucil., cyclophosphamide, nitrogen mustard, or other alkylating agents
10. Treated with any investigational drug within 5 half-lives of that drug prior to the first administration of study agent
11. Pregnant, nursing or planning pregnancy or fathering a child within 6 months after receiving last administration of study agent
12. H/O latent or active granulomatous infection including histoplasmosis, or coccidioidomycosis prior to screening
13. Had bacilli Calmette-Guerin (BCG) vaccination within 12 months of screening
14. Chest X-ray within 3 months prior to first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection including TB

15. H/O nontuberculosis mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening
16. Received or expected to receive any live virus or bacterial vaccination within 3 months prior to first administration of study agent, during the study or within 6 months after the last administration of study agent
17. H/O infected joint prosthesis, or have received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced
18. H/O serious infection, hospitalization for an infection, or treatment with IV antibiotics for an infection within 2 months prior to first administration of study agent.
19. H/O or ongoing chronic/recurrent infectious disease (e.g., chronic renal infection, chronic chest infection, sinusitis, recurrent UTI, or open, draining or infected skin wound or an ulcer)
20. H/O HIV, hepatitis B or C infection
21. H/O demyelinating diseases such as multiple sclerosis or optic neuritis
22. Have current signs/symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, GI, endocrine, pulmonary, cardiac, neurologic, psychiatric or cerebral disease
23. H/O or concurrent CHF, including medically controlled asymptomatic CHF
24. H/O or signs of lymphoproliferative disease
25. H/O malignancy within last 5 years (with the exception of nonmelanoma skin cancer treated without recurrence)
26. H/O transplanted organ with the exception of corneal transplant (>3 months)
27. H/o substance abuse within the last 3 years

Source: Applicant Appendix 1 Protocol and Amendments-52 wk p. 25

Concomitant Medications: The protocol required all subjects to maintain a stable dose of concomitant MTX (15-25 mg/week) through the duration of the study. Temporary discontinuations or reductions in dose of MTX were permitted for abnormal lab test results, side effects, concurrent medical illness, or surgery. Use of folic acid or folinic acid was recommended.

Subjects were permitted to continue stable doses of background NSAIDs, analgesics, and oral corticosteroids (at doses of ≤ 10 mg/day of prednisone or equivalent). Intraarticular steroids were permitted if needed, while intramuscular steroids were prohibited. Short courses of oral corticosteroids (2 weeks or less) or IV steroids for indications other than RA were permitted in the absence of alternative therapy.

Treatment with biological agents, cytotoxic medications, DMARDs other than MTX, systemic immunosuppressive agents, and investigational drugs was prohibited while participating in the trial.

Endpoints:

Primary efficacy endpoint:

The primary efficacy variable was the proportion of subjects with an ACR20 response at Week 14.

Secondary efficacy endpoints:
Major secondary efficacy variables:

- Proportion of subjects with a moderate or good DAS28 Response (using CRP) at Week 14.
- Change from baseline in HAQ-DI at Week 14.
- Proportion of subjects with ACR50 response at Week 24
- Change from baseline in van der Heijde Modified Sharp (vdHS) Score at Week 24.

Other secondary efficacy variables assessed included:

- ACR50 response rate at Week 14
- ACR70 response rate at Weeks 14 and 24
- Proportion of subjects achieving ACR20 response at Week 2
- Proportion of subjects achieving ACR responses of 20, 50, and 70 over time
- Percent improvement from baseline in ACR components over time
- Percent improvement from baseline in ACR components at Weeks 14 and 24
- Proportion of subjects with a moderate or good DAS28 (using CRP) response at Week 24
- Proportion of subjects with a moderate or good DAS28 (CRP) response over time
- Proportion of subjects with a DAS28 (CRP) remission (<2.6) at Week 14 and 24
- Proportion of subjects with a DAS28 (CRP) remission (<2.6) over time
- Change from baseline in DAS28 (CRP) scores over time
- Change from baseline in HAQ-DI score at Week 24
- Improvement from baseline in HAQ-DI score over time
- Proportion of subjects with clinically meaningful improvement (≥0.25) from baseline in the HAQ-DI score at Week 14 and Week 24
- Changes from baseline in Short Form (SF-36) Health Status Survey at Weeks 16 and 24
- Changes from baseline in the physical and mental component summary scores of SF-36
- Summary of change from baseline in the fatigue subset of the FACIT Questionnaire at Weeks 16 and 24
- Proportion of subjects who achieve ≥ 4 point change from baseline in FACIT-Fatigue at Weeks 14 and 24
- Change from baseline in vdHS score at Weeks 52 and 100

Study Monitoring: See Appendix 1 for details of study procedures

Statistical Analysis:
Analysis populations:

1. Intent-to-treat (ITT) Population: defined as all subjects who were randomized regardless of whether or not they received the assigned treatment. The ITT population was used to assess all efficacy endpoints.
2. Treated Population: defined as all subjects who had received at least one IV infusion of study agent. The treated population was used for all safety and clinical pharmacology analyses.

All efficacy endpoints were conducted on the ITT population. The primary endpoint (ACR20 response rate at Week 14) was analyzed by Cochran-Mantel-Haenszel (CMH) test stratified by CRP level at screening with last observation carried forward (LOCF) and nonresponder imputations to account for missing data required to calculate subjects' ACR20 response or early escape subjects, and drop-outs due to treatment failure, respectively. A subject was considered a treatment failure or non-responder if they discontinued study treatment due to unsatisfactory therapeutic effect, required an increase above baseline in their MTX dose, initiated treatment with any prohibited biological product or DMARD, initiated or increased oral corticosteroids, or received IV or IM corticosteroids for treatment of RA.

Secondary endpoints were analyzed by CMH test or chi-square test for binary categorical data or analysis of variance test on van der Waerden normal scores for continuous data. A sequential procedure was used to test the primary endpoint followed by the major secondary endpoints in a prespecified descending order to control for multiplicity. No multiplicity adjustments were prespecified in the statistical analysis plan in analyzing the non-major secondary endpoints. Linear extrapolation was used to impute missing data for the change from baseline in vdHS score and LOCF was used to impute missing data for the other major and the non-major secondary endpoints.

The analysis of safety assessment was conducted on the treated population. Safety assessment included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical exam findings and vital signs. Clinical lab data results for hematology, serum chemistry, urinalysis testing, and changes in serologies (occurrence of ANA and anti-dsDNA antibodies), immunogenicity (occurrence of antibodies to golimumab), vital signs and physical exam were summarized for within treatment changes and for changes from baseline for each treatment group.

6 Review of Efficacy

Efficacy Summary

The efficacy of golimumab in the treatment of active RA was demonstrated by the successful results from a single, international, multicenter, double-blind, randomized, placebo-controlled trial, Study CNTO148ART3001. In this pivotal trial, IV golimumab when administered at a dose and dosing regimen of 2 mg/kg at Week 0 and 4, and then every 8 weeks thereafter was shown to effectively reduce signs and symptoms of active arthritis in subjects with moderate to severe RA with an inadequate response to methotrexate therapy as measured by assessments that included the ACR 20 response rate at Week 14 as the primary endpoint, and ACR50 and DAS 28[CRP] as major secondary endpoints. Positive outcomes were also seen for improvement in physical function and inhibiting progression of joint damage as assessed by the HAQ-DI at Week 14 and vdHS score at Week 24, which were assessed as major secondary endpoints. Improvements in SF-36 composite and domain scores were observed in Study CNTO148ART3001. The change from baseline in SF-36 scores was both statistically significant and clinically relevant, exceeding the minimal clinically important differences. The improvement was further supported by the results of Study C0524T12 with IV golimumab and Study C0524T06 with SC golimumab.

Phase 3 Confirmatory Studies
See section 5.3 for details of the Study CNTO148ART3001 protocol

6.1 Indication

Approved Indication (approved with original BLA 125433):
IV golimumab is approved for the treatment of moderately to severely active RA in combination with MTX

Labeling changes sought with this supplement:

"Other Health-Related Outcomes
General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4) (b) (4) ."

6.1.1 Methods

Brief Description of Short Form 36 (SF-36) Instrument

The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

The SF-36 consists of 36 questions relating to either physical or mental health. One question asks respondents to rate the amount of change experienced in their health in general and the remaining 35 questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitations). The eight domains are age and gender adjusted, and scored 0 (severe impairment) – 100 (no impairment).

Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality of life. The PCS and MCS are reported based on normative-based scoring.

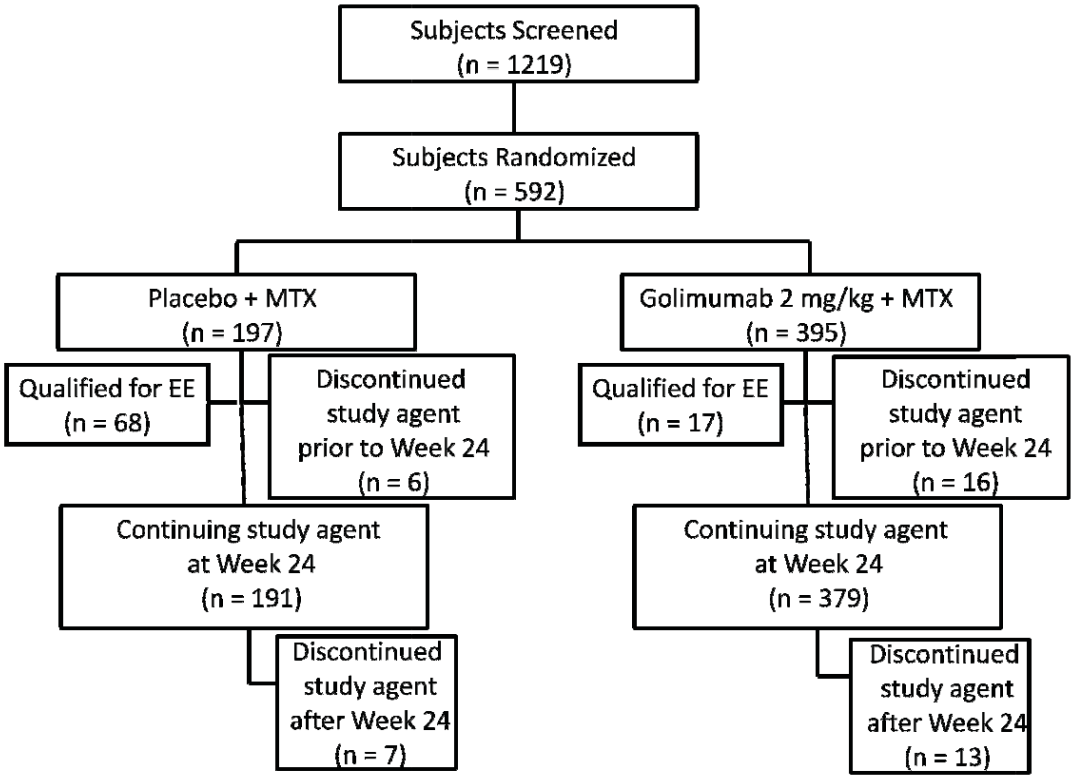
6.1.2 Demographics

Demographic information was reviewed in the original BLA submission. The study population was felt by the clinical reviewer to be representative of patients with moderate to very active RA who could potentially benefit from treatment with IV golimumab.

6.1.3 Subject Disposition

The population in the IV golimumab RA development program consisted of adult subjects with moderate to severely active RA who had an inadequate response to methotrexate. See section 5.3 for detailed inclusion and exclusion criteria. A flow chart of subjects' disposition over the 52-week course of Study CNTO148ART3001 is shown in Figure 2: Subject Disposition through Week 52 of Study CNTO148ART3001The disposition of study subjects who discontinued treatment and reason for discontinuation is displayed in Figure 3.

Figure 2: Subject Disposition through Week 52 of Study CNTO148ART3001



Adapted from Applicant's Figure 3; p. 44 of the 52-Week Study Report

Figure 3: Number of randomized subjects who discontinued study agent through Week 24

	Placebo + MTX	Golimumab 2 mg/kg + MTX	Total
Subjects randomized	197	395	592
Subjects ongoing and continuing study agent	191 (97.0%)	379 (95.9%)	570 (96.3%)
Subjects ongoing and discontinued study agent	3 (1.5%)	5 (1.3%)	8 (1.4%)
Subjects who discontinued study agent and completed post-treatment follow-up	1 (0.5%)	7 (1.8%)	8 (1.4%)
Subjects who discontinued study agent and did not complete post-treatment follow-up	2 (1.0%)	4 (1.0%)	6 (1.0%)
Reason for discontinuing study agent[a]			
Death	1 (0.5%)	0 (0.0%)	1 (0.2%)
Lost to follow-up	0 (0.0%)	1 (0.3%)	1 (0.2%)
Withdrawal of consent	2 (1.0%)	4 (1.0%)	6 (1.0%)
Adverse event	2 (1.0%)	9 (2.3%)	11 (1.9%)
Lack of efficacy	1 (0.5%)	1 (0.3%)	2 (0.3%)
Protocol violation	0 (0.0%)	1 (0.3%)	1 (0.2%)

[a] Percentages calculated with the number of subjects in each group as denominator.
Source: Applicant's Table 6; p. 57 of the 24-Week Study Report

The overall proportion of missing SF-36 questionnaires was low and similar in the two groups (2.1% in the golimumab group and 1.7% in the placebo group) and therefore not expected to substantially influence the analysis and conclusions.

6.1.4 Analysis of Primary and Major Secondary Endpoint(s)

Treatment with IV golimumab was shown to effectively reduce signs and symptoms of active arthritis as measured by ACR 20 response rate at Week 14 as the primary endpoint. Fifty nine percent of the IV golimumab treatment group achieved an ACR 20 response as compared to 25% of the placebo group. The four major secondary endpoints included Disease Activity Index Score [DAS28] response using CRP at Week 14, change from baseline in HAQ-DI at Week 14, ACR 50 Response at Week 24, and change from baseline in vdH-S score at Week 24. Response rates on all of the major secondary endpoints that further assessed signs and symptoms of RA (ACR50 and DAS 28[CRP]), patient reported outcomes (HAQ-DI), and radiographic inhibition of joint damage (vdH-S) were significantly higher in the IV golimumab treatment group as

compared to placebo. For detailed review of the analyses of primary and major secondary endpoints, refer to the original BLA 125433 clinical review.

6.1.5 Analysis of SF-36 Endpoints(s)

Statistical Analysis of SF-36 Data

Thirty six-item Short Form Health Survey (version 2) data was collected and analyzed for all randomized subjects at baseline and Weeks 12, 16, and 24. Changes from baseline in the PCS and MCS scores of SF-36 were summarized by treatment group and compared between groups. An analysis of variance on the van der Waerden normal scores was used to test the treatment group difference for the change from baseline in PCS and for change in MCS, with treatment group and C-reactive protein level at screening as covariates in the model. A norm-based scoring system was used for all 8 subscales of SF-36. The change from baseline in each of the subscales at Weeks 12, 16, and 24 were analyzed by a similar model using treatment group and C-reactive protein level at screening as covariates in the model.

Handling of SF-36 Missing Data

For SF-36 assessments, developer-specified missing data rules for calculating the total score when individual components of the composite endpoints are missing took precedence. For partially answered questionnaires, if more than 50% of the items within each scale were unanswered, the scale score would be assigned to missing. If at least 50% of the items within each scale were answered, the missing item scores were imputed with the average score across the completed items in the same scale. When the total score was non-calculable or missing, the following rules apply to each missing component, after which the total score will be calculated:

1. For change from baseline endpoints, if the baseline value was missing, the median change from baseline value of all subjects in the same stratum (CRP level at screening) was assigned.
2. If the value at a specified time point other than baseline was missing, the missing value was replaced by the last non-missing observation.

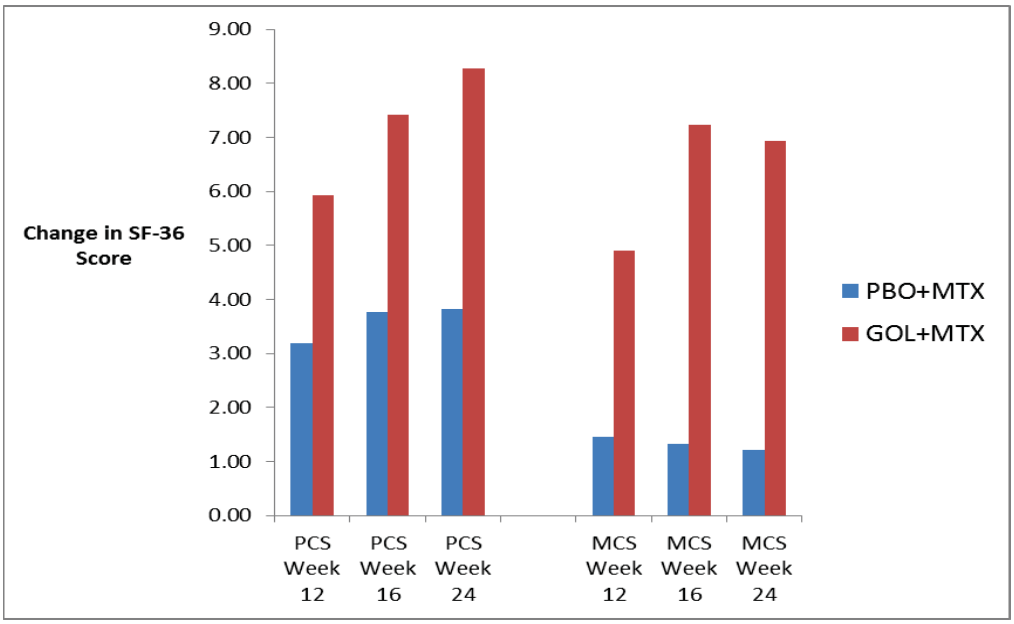
If a subject met the early escape criteria at Week 16, each endpoint or component value after Week 16 was replaced with the corresponding component value at Week 16.

Results of SF-36 Data

Pivotal study CNTO148ART3001:
In Study CNTO148ART3001, subjects who received IV golimumab + MTX showed significantly greater improvement in SF-36 physical component and mental component scores as compared to subjects who received placebo + MTX at Weeks 12, 16, and 24 as seen in Figure 4: Change from baseline in SF-36 PCS and MCS Scores at Weeks

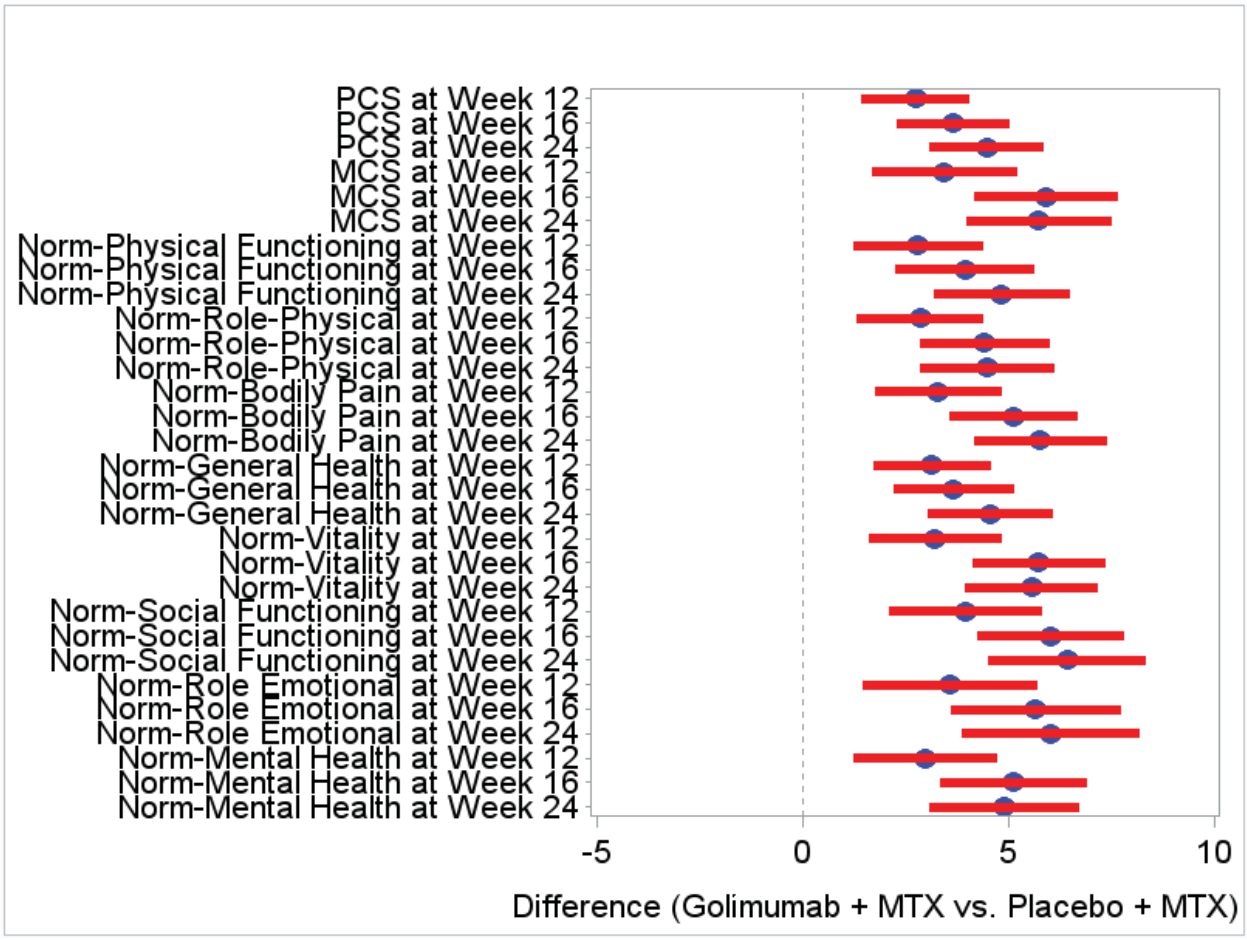
12, 16, and 24 in Study CNTO148ART3001. Significant differences were also seen in all 8 subscales at these timepoints as seen in Figure 5: Change from baseline in SF-36 subscale scores at Weeks 12, 16, and 24 in Study CNTO148ART3001.

Figure 4: Change from baseline in SF-36 PCS and MCS Scores at Weeks 12, 16, and 24 in Study CNTO148ART3001



Source: Adapted from Applicant's Table 2, p. 9 of the Clinical Overview sBLA 125433

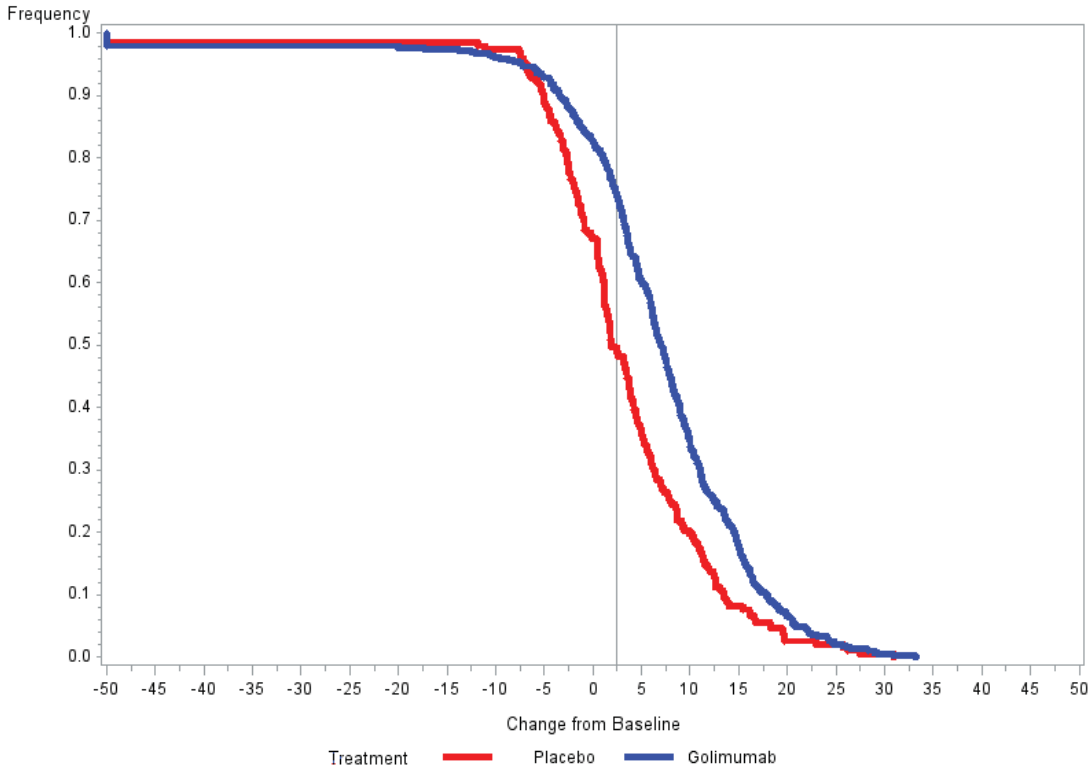
Figure 5: Change from baseline in SF-36 subscale scores at Weeks 12, 16, and 24 in Study CNTO148ART3001



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

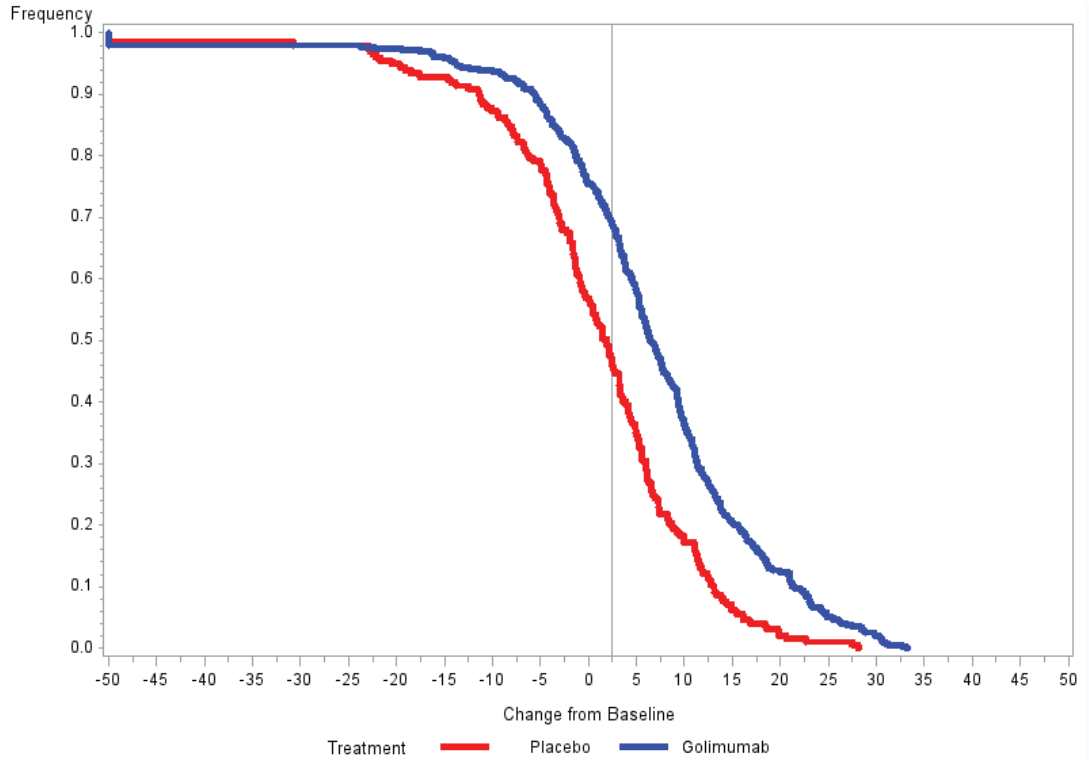
The changes from baseline in the SF-36 composite and subscale scores are equal to or greater than the minimal clinically important difference (MCID) of 2.5-5 points for the composite scores and 5 points for the domain scores proposed in the literature.[12] Sensitivity analysis, conducted by the FDA statistical reviewer, Dr. Yongman Kim, examined the cumulative distribution functions between placebo and treatment showing consistent results with the analyses of the mean change from baseline with clear separation between the golimumab and placebo groups for both PCS and MCS scores at all time points (b) (4), with Week 16 data represented in in Figure 6 and Figure 7 for PCS and MCS, respectively. At Week 16, 74% of subjects in the golimumab + MTX group had a change in PCS score that exceeded the MCID vs. 49% of subjects in the placebo + MTX group, and 69% in the golimumab + MTX group had a change in MCS score that exceeded the MCID vs. 46% of subjects in the placebo + MTX group. Consistent with the observations for PCS and MCS, response rates were higher in the golimumab + MTX group as compared to the placebo + MTX group for all 8 domains of SF-36.

Figure 6: Change from baseline in SF-36 PCS Score at Week 16 in Study CNTO148ART3001, Cumulative Distribution Analysis



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

Figure 7: Change from baseline in SF-36 MCS Score at Week 16 in Study CNTO148ART3001, Cumulative Distribution Analysis



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

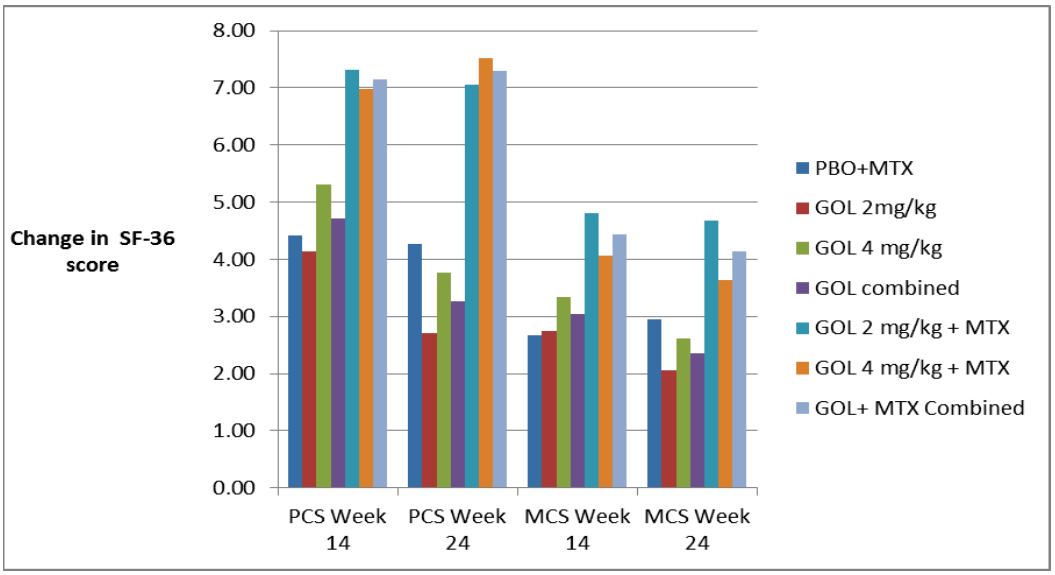
Additional sensitivity analyses conducted by Dr. Kim to examine the effect of missing data and early escape showed similar results, as detailed in the statistical review. The results of Study CNTO148ART3001 demonstrate both statistical and clinically relevant improvement in SF-36 composite and domain scores at all time points tested, supporting improvement in general health status with treatment with IV golimumab in combination with methotrexate over treatment with methotrexate alone.

Supportive studies:

Study C0524T12:
In Study C0524T12, in which subjects received IV golimumab at every 12 week intervals, less than the approved dosing frequency of every 8 weeks, greater changes were seen in the PCS, MCS, and all subscale scores at Weeks 14 and 24 in subjects randomized to receive IV golimumab in combination with MTX as compared to MTX or IV golimumab alone as displayed in Figure 8 and Figure 9. This was statistically significant in the PCS score at both time points. There was numerically greater change from baseline in MCS and all domain scores. The change in SF-36 scores observed in the IV golimumab 2 mg/kg and 4 mg/kg dose groups were similar, suggesting a lack of a dose-response relationship. The improvement in the SF-36 PCS score, as well as the

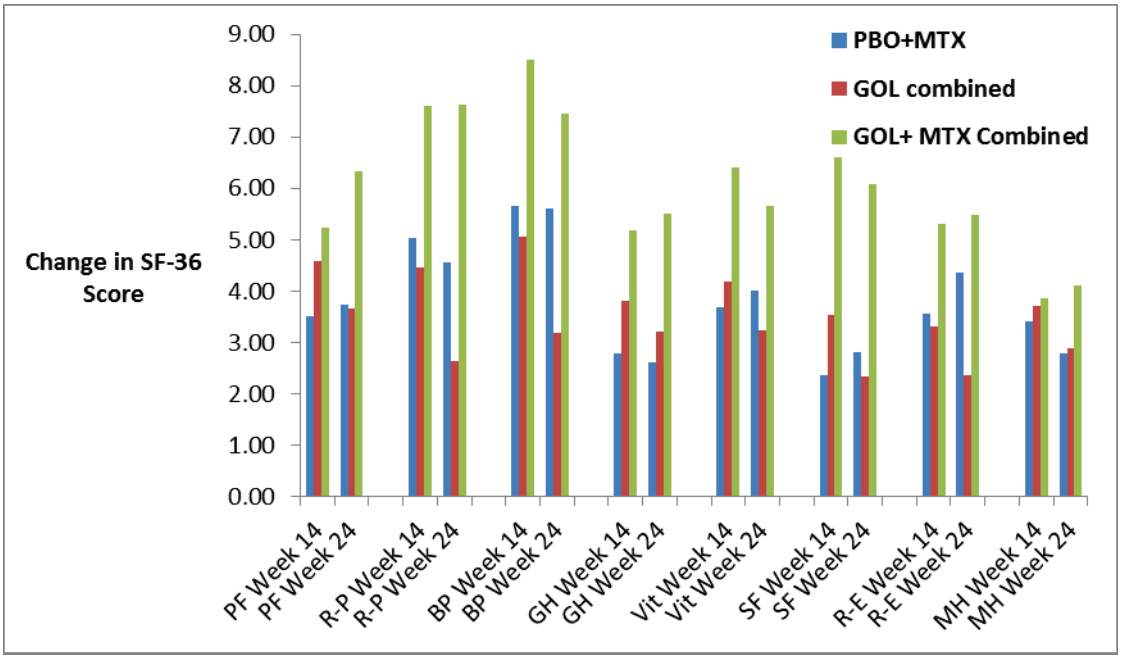
numerical improvement in MCS and domain scores, are supportive of the findings in the pivotal trial.

Figure 8: Change from baseline in SF-36 PCS and MCS Scores at Weeks 14 and 24 in Study C0524T12



Source: Adapted from Applicant Response to IR sBLA 125433 Appendix Table 8

Figure 9: Change from baseline in SF-36 subscale scores at Weeks 14 and 24 in Study C0524T12

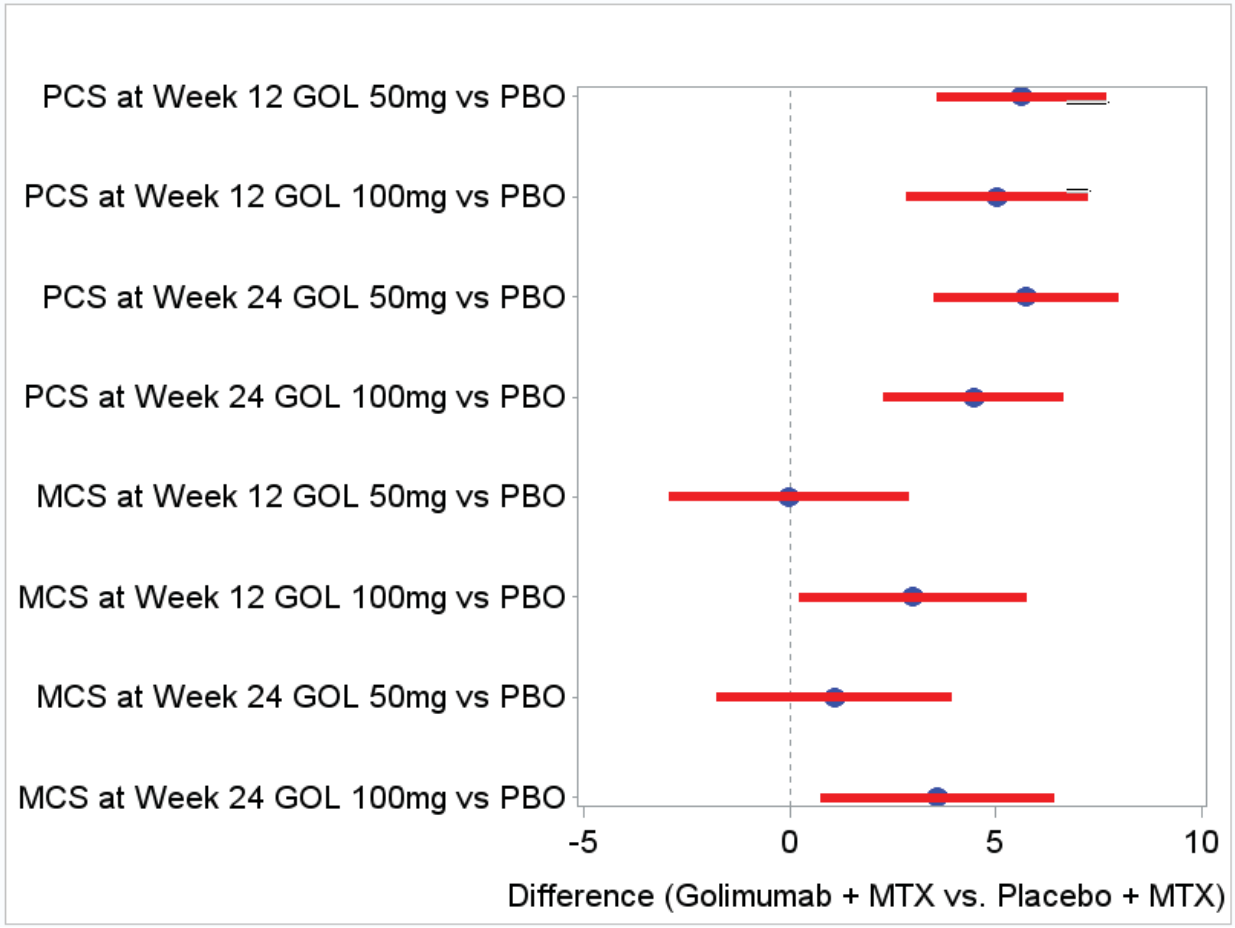


Source: Adapted from Applicant Response to IR sBLA 125433 Appendix Table 10

Study C0524T06 (subcutaneous golimumab):
As requested by the FDA, the applicant provided analyses of the SF-36 data from the subcutaneous golimumab RA program as supportive evidence of efficacy. Study C0524T06 enrolled a population similar to the population in Study CNTO148ART3001 allowing for a comparison of efficacy, including SF-36, across the studies from the SC and IV golimumab programs.

Similar findings to those of study CNTO148ART3001 were observed in study C0524T06, in which subjects were randomized to receive golimumab 50 mg SC + MTX, golimumab 100 mg SC + MTX, golimumab 100 mg SC + placebo, or placebo + MTX. SF-36 was collected and analyzed at baseline, Weeks 14, 24, and 48. Statistically significant differences were seen between SC golimumab + MTX groups as compared to subjects receiving placebo + MTX in PCS score at Weeks 14 and 24, and in MCS score in subjects receiving golimumab 100 mg both with and without MTX at Week 24 as shown in Figure 10. Numerical improvement was seen in all subscales in the golimumab + MTX group as compared to the placebo + MTX group. The statistically significant improvement observed in SF-36 PCS scores, as well as the trend towards improvement in MCS and domain scores in the subcutaneous golimumab + MTX groups are supportive of the positive effect of intravenous golimumab in combination with MTX on SF-36 scores observed in Study CNTO148ART3001.

Figure 10: Change from baseline in SF-36 subscale scores at Weeks 12 and 24 in Study C0524T06



Source: Adapted from FDA statistical analyses by Dr. Yongman Kim

The three studies in MTX incomplete responders demonstrated statistically significant improvement in SF-36 PCS scores, and numerical or statistical improvement in MCS and all subscale scores in subjects receiving golimumab with MTX as compared to those receiving placebo with MTX, demonstrating improvement in general health status with treatment with golimumab in combination with methotrexate over treatment with methotrexate alone.

(b) (4)

6.1.6 Other Endpoints

Not applicable to this submission.

6.1.7 Subpopulations

Not applicable to this submission.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this submission.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable to this submission.

7 Review of Safety

Safety Summary

No new safety information was submitted with this supplement. The safety information from the IV golimumab development program was reviewed in detail with the original BLA submission and resulted in a boxed warning for serious infections and malignancy, as below:

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI ARIA
- Discontinue SIMPONI ARIA if a patient develops a serious infection or sepsis
- Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI ARIA
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Not applicable to this submission.

7.1.2 Categorization of Adverse Events

Not applicable to this submission.

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

Not applicable to this submission.

7.2 Adequacy of Safety Assessments

Not applicable to this submission.

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

Not applicable to this submission.

7.2.2 Explorations for Dose Response

Not applicable to this submission.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this submission.

7.2.4 Routine Clinical Testing

Not applicable to this submission.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable to this submission.

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

Not applicable to this submission.

7.3 Major Safety Results

Not applicable to this submission.

7.3.1 Deaths

Not applicable to this submission.

7.3.2 Nonfatal Serious Adverse Events

Not applicable to this submission.

7.3.3 Dropouts and/or Discontinuations

Not applicable to this submission.

7.3.4 Significant Adverse Events

Not applicable to this submission.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable to this submission.

7.4 Supportive Safety Results

Not applicable to this submission.

7.4.1 Common Adverse Events

Not applicable to this submission.

7.4.2 Laboratory Findings

Not applicable to this submission.

7.4.3 Vital Signs

Not applicable to this submission.

7.4.4 Electrocardiograms (ECGs)

Not applicable to this submission.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable to this submission.

7.4.6 Immunogenicity

Not applicable to this submission.

7.5 Other Safety Explorations

Not applicable to this submission.

7.5.1 Dose Dependency for Adverse Events

Not applicable to this submission.

7.5.2 Time Dependency for Adverse Events

Not applicable to this submission.

7.5.3 Drug-Demographic Interactions

Not applicable to this submission.

7.5.4 Drug-Disease Interactions

Not applicable to this submission.

7.5.5 Drug-Drug Interactions

Not applicable to this submission.

7.6 Additional Safety Evaluations

Not applicable to this submission.

7.6.1 Human Carcinogenicity

Not applicable to this submission.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable to this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable to this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this submission.

7.7 Additional Submissions / Safety Issues

Not applicable to this submission.

8 Postmarket Experience

Not applicable to this submission.

9 Appendices

9.1 Literature Review/References

See section on "Regulatory History of SF-36 in RA Drug Development" above for details on SF-36. The sponsor submitted 2 articles to support this supplement that describe the use of the SF-36 and other instruments to assess the impact of RA on patients and measure health-related quality of life[12, 13] and 1 chapter that contains SF-36 composite score norms in the general U.S. population and in various chronic disorders.[14] For complete list of references, see bibliography below.

9.2 Labeling Recommendations

The trade name for IV golimumab, Simponi Aria, has previously been reviewed and approved.

Proposed SF-36 labeling language:

"Other Health-Related Outcomes

> General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4) ."

The proposed language which includes the results of the summary scores as well as the 8 domains, is consistent with the decision following the Regulatory Briefing on September 20, 2013 to include all of the scores of the SF-36 to facilitate its interpretation as a general health status measure. The language is also consistent with approved language used in describing SF-36 claims for more recently approved products (Xeljanz). (b) (4)

Reviewer proposed SF-36 labeling language:

> ***"Other Health-Related Outcomes***
> General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36."

No changes are proposed to the patient labeling/medication guide with this submission.

9.3 Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted.

[1] Busija L, Pausenberger E, Haines TP, et al. Adult measures of general health and health-related quality of life: Medical Outcomes Study Short Form 36-Item (SF-36) and Short Form 12-Item (SF-12) Health Surveys, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Medical Outcomes Study Short Form 6D (SF-6D), Health Utilities Index Mark 3 (HUI3), Quality of Well-Being Scale (QWB), and Assessment of Quality of Life (AQoL). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S383-412
[2] Ten Klooster PM, Vonkeman HE, Taal E, et al. Performance of the Dutch SF-36 version 2 as a measure of health-related quality of life in patients with rheumatoid arthritis. Health Qual Life Outcomes. 2013; May 8;11:77
[3] Oude Voshaar MA, ten Klooster PM, Taal E, van de Laar MA. Measurement properties of physical function scales validated for use in patients with rheumatoid arthritis: a systematic review of the literature. Health Qual Life Outcomes.2011; Nov 7;9:99
[4] Tugwell P, Idzerda L, Wells GA. Generic quality-of-life assessment in rheumatoid arthritis. Am J Manag Care. 2007;13:S224-S236
[5] http://www.sf-36.org/
[6] Hagen KB, Smedstad LM, Uhliq T, Kvien TK. The responsiveness of health status measures in patients with rheumatoid arthritis: comparison of disease-specific and generic instruments. J Rheumatol. 1999; 26(7):1474-80.
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[8] Kosinski M, Jujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002; (3):321-40
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[11] Strand V, Crawford B. Longterm treatment benefits are best reflected by patient reported outcomes. J Rheumatol. 2007;34(12):2317-9.
[12] Strand V, Singh J. Improved Health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2008;14(4):239-253
[13] Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. Clin Exp Rheumatol 2005;23(Suppl. 39):S43-S52.
[14] Ware J: Chapter 8, Interpretation: norm-based. In *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, the Health Institute, New England Medical Center,8.1-8.42 1994

Appendix 1
Study CNTO148ART3001 Study Schedule of Events

Attachment 1.1 Study Schedule of Events Through Week 112

Assessments[a]	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Consent	X																				
Demography/ med. history	X																				
Physical examination	X													X						X	
Duration of morning stiffness	X	X																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																				
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[b]	X																				
TB screening[b]	X																				
TB evaluation[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of entry criteria	X	X																			
Serum pregnancy test	X																				
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Attachment 1.1 Study Schedule of Events Through Week 112

Assessments[a]	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Randomization		X																			
Infusion[d]		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Rheumatoid factor	X																				
Anti-CCP antibodies	X																				
Efficacy evaluations[e]		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
SF-36		X				X		X		X				X							X
FACIT-F		X				X		X		X				X							X
EQ-5D		X				X		X		X				X							X
HEcon		X		X		X		X		X				X							X
Radiographs of hands and feet		X						X[i]		X				X						X	
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
ANA/anti-dsDNA antibodies		X							X												
Serum biomarkers		X	X	X			X														
Hepcidin		X					X														
DNA markers[f]		X																			
RNA markers		X					X														
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Attachment 1.1 Study Schedule of Events Through Week 112

Assessments[a]	Screen	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk 60	Wk 68	Wk 76	Wk 84	Wk 92	Wk 100	Wk 112
Routine laboratory analyses (except LFTs)	X	X		X		X			X		X		X		X		X		X		X
Liver function tests	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Golimumab concentration[g]		2X	X	2X	X	2X	X	X	2X			2X		2X			2X			2X	
Random golimumab concentration[h]							←X→														
Antibodies to golimumab		X							X					X			X			X	

[a] All assessments are to be completed prior to study agent administration, unless otherwise specified. Subjects will be evaluated every 8 weeks after Week 28 for the purpose of this study. However, treating physicians should monitor subjects for MTX and other therapies in accordance with appropriate clinical practice guidelines. For subjects who discontinue study agent injections, see Section 5.3.2 for required follow-up assessments.

[b] In countries in which QuantiFERON-TB Gold test is not approved/registered, a tuberculin skin test will also be performed.

[c] If TB is suspected at any time during the study, a tuberculin skin test will also be performed in countries in which QuantiFERON-TB Gold test is not approved/registered.

[d] Infusion schedule as outlined in protocol. All subjects must be observed carefully for symptoms of an infusion reaction during the infusion and for 60 minutes after the IV infusion of study agent is complete. If a subject has an infusion reaction, the subject must complete the EQ-5D questionnaire prior to leaving the treatment facility.

[e] Efficacy evaluations include: joint assessment, patient pain assessment, Patient's and Physician's Global Assessments of Disease Activity, and HAQ.

[f] This test is strictly voluntary and results will remain confidential. It is not a requirement for sites and subjects to participate in this study. Samples will be collected for DNA analysis at Week 0.

[g] At each of the Week 0, 4, 12, 20, 36, 52, 76, and 100 visits, 2 samples for serum golimumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected immediately prior to infusion and the other collected one hour after the end of the infusion). For each of the remaining visits, only 1 sample for serum golimumab concentrations will be collected, which should be taken prior to infusion if an infusion of the study agent is administered.

[h] One additional sample for serum golimumab concentration will be collected from all subjects at any time between Weeks 14 and 20 other than at the time of the Week 14, Week 16, and Week 20 visits; this sample must be collected at least 24 hours prior to or after a study agent administration.

[i] Radiographs will be performed for all subjects with < 10% improvement in tender and swollen joints from baseline at Week 16.

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

/s/

RACHEL GLASER
07/02/2015

NIKOLAY P NIKOLOV
07/02/2015
I concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125,433 **Applicant: Janssen** **Stamp Date: 10/06/2014**

Drug Name: golimumab **BLA Type: Standard** **MO: Rachel Glaser, M.D.**

On initial overview of the BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: **C052T12** Study Title: **A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate** Sample Size: 642 Arms: 5 Location in submission: Module 5.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 **A Multicenter, Randomized, Double-Blind, Placebo-**	X			The efficacy has been established for signs and symptoms, physical function, and radiographic

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Indication: RA in patients on concomitant MTX Pivotal Study #2 Indication:				outcomes.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	PREA has been addressed with the original application
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We note your proposal to support the labeling changes in section 14 with results from only study CNTO148ART3001. To support the use of this single study, provide analyses of the data, including the Physical Component Score, the Mental Component Score, and the 8 domains of the SF-36, from the pivotal trials of the subcutaneous golimumab rheumatoid arthritis program.

2. We also note the summary SF-36 Physical Component Score results from study C0524T12. Provide the data for and analyses of the Mental Component Score and the 8 domains of the SF-36 as well.

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Received: October 6, 2014
PDUFA: August 6, 2015

BLA 125433
Simponi Aria (golimumab IV) for Treatment of RA: SF-36 Labeling Claim

MO: Rachel L. Glaser, M.D.
CDTL: Nikolay P. Nikolov, M.D.
Filing/Planning Meeting
November 6, 2014

1

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Executive Summary

- Product: golimumab (TNFα inhibitor)
- Dosing: Intravenous 2 mg/kg at Wks 0 and 4, then q8 Wks
- Population: Adults with mod-to-severe active RA on methotrexate
- Efficacy data on SF-36 from the original BLA
- Proposed labeling:
  - ***"Other Health-Related Outcomes***

    General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4) ."
- Recommendations: Fileable as a standard sBLA
- Key issues:
  - Sponsor's limited justification for including SF-36 in labeling

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Regulatory History

- PreIND/Pre-phase 3 written responses: May 10, 2006
- EOP2 Meeting: May 18, 2009
- Pre-BLA filing meeting: September 23, 2011
- Approval for RA: July 18, 2013
- Request for reconsideration of SF-36 claim in labeling: October 6, 2014

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SF-36 Instrument

- 36 item health status measure
  - 8 domains:
    - Physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems and mental health
  - Physical component summary and mental component summary scores
- Developed in elderly male veterans
- Used widely in different diseases and conditions (COPD, HIV, migraines, IBS, diabetes, surgical procedures, RA, OA, gout, sleep disorders, others)
- Rheumatoid arthritis: Included in > 100 randomized controlled trials, cited in > 450 peer-reviewed studies

https://www.optum.com/content/dam/optum/resources/caseStudies/2577_AravaAventis_CaseStudy_Final.pdf

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SF-36 in RA Product Labeling

- 6 DMARDs approved for RA between 1998 and 2005 with SF-36 claim in Section 14
  - All give PCS results
  - All except leflonomide give MCS results
  - Abatacept labeling identifies "all 8 domains of the SF-36 as well as the PCS and MCS."
- (b) (4)
- Tofacitinib (Xeljanz) received SF-36 claim in Nov. 2013

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SF-36: Regulatory History

- SEALD Concerns:
  - Generic health survey
  - PCS, MCS
    - Weighted scores of all 8 domains
    - Do not measure pure physical or mental functioning
    - PCS should not support physical function claim, but supports overall "health status"
- Community Concerns:
  - Widely used by RA research community
  - Provides info on impact of dz not captured on other measures
  - Utilized for policy and decision-making
- Regulatory Briefing September 20, 2013
  - Recommendations:
    - Use of SF-36 as ancillary claim
    - Supportive of general health status rather than physical function
    - Inclusion of PCS, MCS, and 8 domains in label

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Golimumab IV Confirmatory Trials

Study	Design	Dose Regimen	EP	Status
C0524T12	48 wk, Phase 3, MC, R, DB, PC parallel group study in 642 RA patients	Dose cohorts: Group 1 (n=129): 2mg/kg q 12 wks + MTX Group 2 (n=128): 2 mg/kg q 12 wks + PBO Group 3 (n=128): 4 mg/kg q 12 wks + MTX Group 4 (n=129): 4 mg/kg q 12 wks + PBO Group 5 (n=129): PBO IV q 12 wks + MTX	1º: ACR50 at Wk 14 2º: ACR20, DAS28 (CRP), SF-36 (PCS) at Wk 14; ACR50 at Wk 24	Completed
CNT0148-ART3001	24 wk, Phase 3, MC, R, DB, PC, parallel group , adaptive design study in 592 RA patients on 15-25 mg/wk MTX	Dose cohorts: Group 1 (n=395): 2 mg/kg IV at Wks 0, 4, and then q 8 wks Group 2 (n=197): PBO IV infusion at Wk 0 and then q 4 wks until Wk 24 when crossed-over to GOL 2 mg/kg IV at Wk 28 followed by IV GOL infusions q 8 wks thereafter Early escape for PBO patients at Wk 16 if had < 10% improvement in both T/S JC	1º: ACR20 at Wk 14 2º: DAS28 (CRP) at Wk 14, Wk 14 HAQ, Wk 14 ACR 50; and change in total vDH-S score	Completed

Adapted from slide courtesy of Rosemarie Neuner, MD 7

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SF-36 Data: Treatment Effect Across Select RA Products

	Golimumab (Month 6)	Tofacitinib (Month 3, pooled)	Tocilizumab[2] (Month 6, pooled)		Abatacept[3] (Month 6)
Endpoint	2 mg/kg - PBO	5 mg – PBO	4 mg/kg - PBO	8 mg/kg - PBO	10 mg/kg - PBO
Summary Scores					
Physical, PCS	4.5	3.7	4	4.3	4.9
Mental, MCS	5.7	2.7	2.2	3.7	3.3
Domains					
Physical Function	4.8	3.1	3.3	4.2	4
Role-Physical	4.5	3.2	3.8	4.3	4.6
Bodily Pain	5.8	4.4	4.9	5.6	5.5
General Health	5.7	2.9	2.2	2.8	3.7
Vitality	5.6	3.9	3	3.9	4.3
Social Function	5.5	3.3	2.5	3.8	4.2
Role-Emotional	7.7	2.6	2.5	3.9	4.1
Mental Health	5.6	2.5	2.4	3.2	3.3

[4] Source: FDA Analyses of BLA 125433 (MTX IR population)
[1]Source: FDA Analyses of NDA 203214/0
[3]Source: BLA 125276/0 Summary of Clinical Efficacy, adapted from Tables: etsumsf36pcspooll, etsumsf36mcspooll, etsumsf36pooll
TCZ 4mg/kg + MTX pooled data from WA17822 and WA17823; TCZ 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063 (DMARD IR studies)
[5]Source: BLA 125,118/0 CSR IM101100, adapted from Table S.10.3.1A (MTX IR population)

MCID 3-5 points in PCS and MCS scores, 5 points in domain scores

Adapted from slide courtesy of Nikolay Nikolov, MD 8

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Review of Labeling

- Section 14, Clinical Studies, proposed text:

"Other Health-Related Outcomes

General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4)

- Xeljanz Section 14, Clinical Studies, approved text:

"Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In studies I, IV, and V, patients receiving XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 at Month 3."

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Filing and Planning

- Clinical Filing Checklist:
  - Completed, no omissions
- Advisory Committee:
  - Not recommended
- OSI Audit:
  - Completed with original BLA

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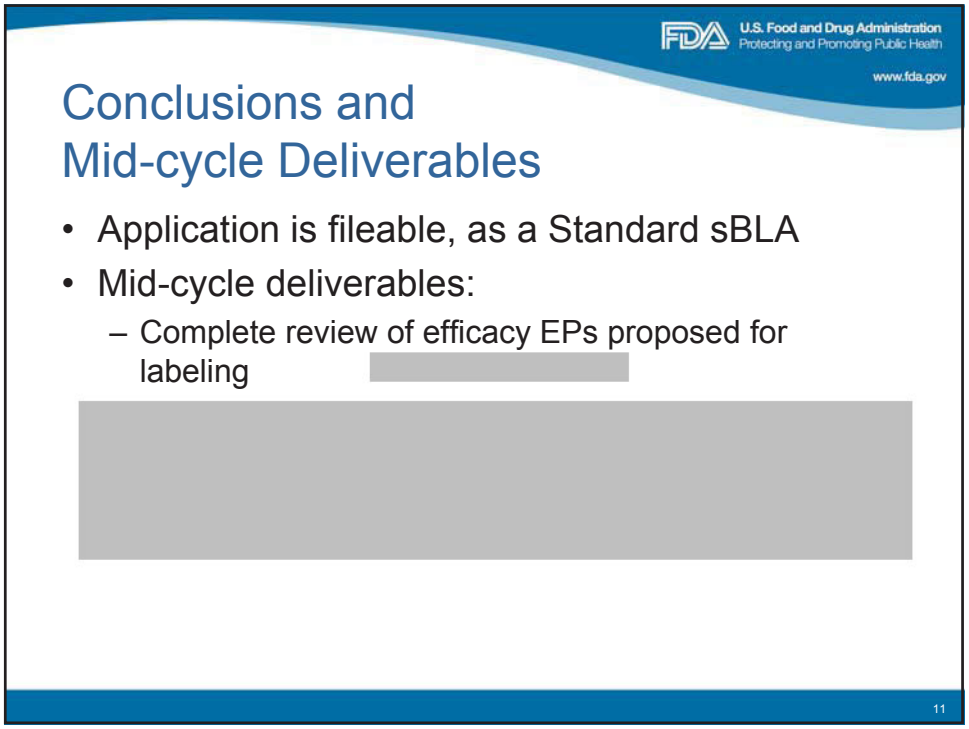
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Conclusions and
Mid-cycle Deliverables
• Application is fileable, as a Standard sBLA
• Mid-cycle deliverables:
– Complete review of efficacy EPs proposed for labeling
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/s/

RACHEL GLASER
11/07/2014

NIKOLAY P NIKOLOV
11/07/2014
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125433 **Applicant: Janssen** **Stamp Date: October 6, 2014**

Drug Name: SIMPONI® ARIA™ (Golimumab) **BLA Type: Efficacy Supplement #014**

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?			Not applicable. No new nonclinical pharmacology or toxicology studies were provided in this supplement.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. No new nonclinical pharmacology or toxicology studies were provided in this supplement.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. No new nonclinical pharmacology or toxicology studies were provided in this supplement.
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)?			Not applicable. See the Pharmacology/Toxicology Review and Evaluation of BLA 125289 dated February 26, 2009.
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).			Not applicable. See the Pharmacology/Toxicology Review and Evaluation of BLA 125289 dated February 26, 2009.
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?			Not applicable. See the Pharmacology/Toxicology Review and Evaluation of BLA 125289 dated February 26, 2009.
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?			Not applicable. See the Pharmacology/Toxicology Review and Evaluation of BLA 125289 dated February 26, 2009.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. No new nonclinical pharmacology or toxicology studies were requested.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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?			A labeling review of nonclinical portions of the product label is not needed at this time.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Not applicable.
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.

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

There will be no Pharmacology and Toxicology Review for this Efficacy Supplement.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

TIMOTHY W ROBISON
11/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125-433
Supplement #:	14
Drug Name:	Simponi Aria (IV golimumab)
Indication(s):	Treatment of Rheumatoid Arthritis (supplement claim: SF-36)
Applicant:	Janssen Biotech, Inc.
Date(s):	Submitted: October 6, 2014
	PDUFA: August 6, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Rachel Glaser, M.D.
	Nikolay Nikolov, M.D.
	Sarah Yim, M.D.
Project Manager:	Christine Ford

Keywords: BLA, clinical studies, SF-36, missing data, rank-ANCOVA

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This supplemental biologic license application (sBLA) considers the addition of the 36-item Short Form Health Survey (SF-36) to Section 14 of the product label. Janssen Biotech Inc. submitted results SF-36 data from study CNTO148ART3001 (hereafter referred to as study 3001) which was reviewed under the approval for intravenous (IV) golimumab in rheumatoid arthritis (RA). Statistical review of the data for signs and symptoms of RA from study 3001 was completed as part of the original statistical review, but review of the SF-36 data was not conducted. My review of this data provides evidence that treatment with golimumab improves SF-36 scores after 24 weeks of treatment. Although SF-36 was not defined as a primary or major secondary endpoint to be controlled for the overall type I error, statistical significance was noted after Bonferroni adjustment was applied.

As additional supportive evidence, I also reviewed SF-36 data from study C0524T12 (hereafter referred to as study 12) that was submitted as part of the original BLA. The results from my analysis of the SF-36 data from this study provided supportive evidence of a treatment benefit although it was not statistically significant.

In conclusion, studies 3011 and 12 taken together, there was evidence that golimumab improves SF-36 scores in RA patients.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Simponi Aria (IV golimumab) is approved for the treatment adult patients with moderate to severe RA in combination with methotrexate (MTX). In this supplemental BLA, the applicant is seeking to include the results from the analyses of SF-36 data from study 3001 in Section 14 of the product label.

2.1.2 History of Drug Development and Regulatory Interactions

The original BLA for Simponi Aria (IV golimumab) was submitted on September 18, 2012 and approved on 18 July 18, 2013. Since the applicant submitted SF-36 data from two studies that were reviewed in the original submission, FDA agreed that the applicant could cross-reference specific source documents from the original BLA.

2.1.3 Specific Studies Reviewed

The focus of this review is on the efficacy data from two phase 3 efficacy trials, study 3001 and study 12. The design of the two studies is described in Table 1. The reader is referred to the original BLA review dated for a detailed review of these studies.

Table 1. Clinical Trials Reviewed

Trial No.	Phase	Design	Treatment Arms	Number of Patients	Dates
3001	3	Multi-center, randomized, double-blind, parallel-group, placebo-controlled	Golimumab 2mg/kg + MTX Placebo + MTX	395 197	09/2009-05/2011
12	3	Multi-center, randomized, double-blind, parallel-group, placebo-controlled	Golimumab 2mg/kg + MTX Golimumab 4mg/kg + MTX Golimumab 2mg/kg Golimumab 4mg/kg Placebo + MTX	129 128 128 129 129	08/2006-07/2008

Source: Excerpted from the Clinical Study Reports for Studies 3001 & 12

2.1.4 Major Statistical Issues

Following is a list of statistical issues found in the submission regarding study 3001:

1. Last observation carried forward (LOCF) imputation for missing data
2. Impact of missing data not examined
3. No multiplicity adjustment for analyses of SF-36 data

These issues will be further discussed in detail in section 5.1.

2.2 Data Sources

The original BLA was submitted on September 18, 2012 and current supplemental BLA was submitted on October 6, 2014 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. The program codes used in statistical analyses and the electronic data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

\\CDSESUB1\EVSPROD\BLA125433\0000\m5\datasets\cnto148art3001\analysis\legacy\datasets\24wk

\\CDSESUB1\EVSPROD\BLA125433\0000\m5\datasets\c0524t12\analysis\legacy\datasets\48wk

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the data submitted in the submission were acceptable in terms of quality and integrity. I was able to derive the individual component scores of the SF-36 instrument for the two studies reviewed and there were no differences between the patient-level data and analysis datasets. The statistical analyses of my derived endpoints were consistent with the applicant's analyses.

3.2 Evaluation of Efficacy

Study 3001 will be discussed in Section 3.2.1 and study 12 will be discussed in Section 3.2.2.

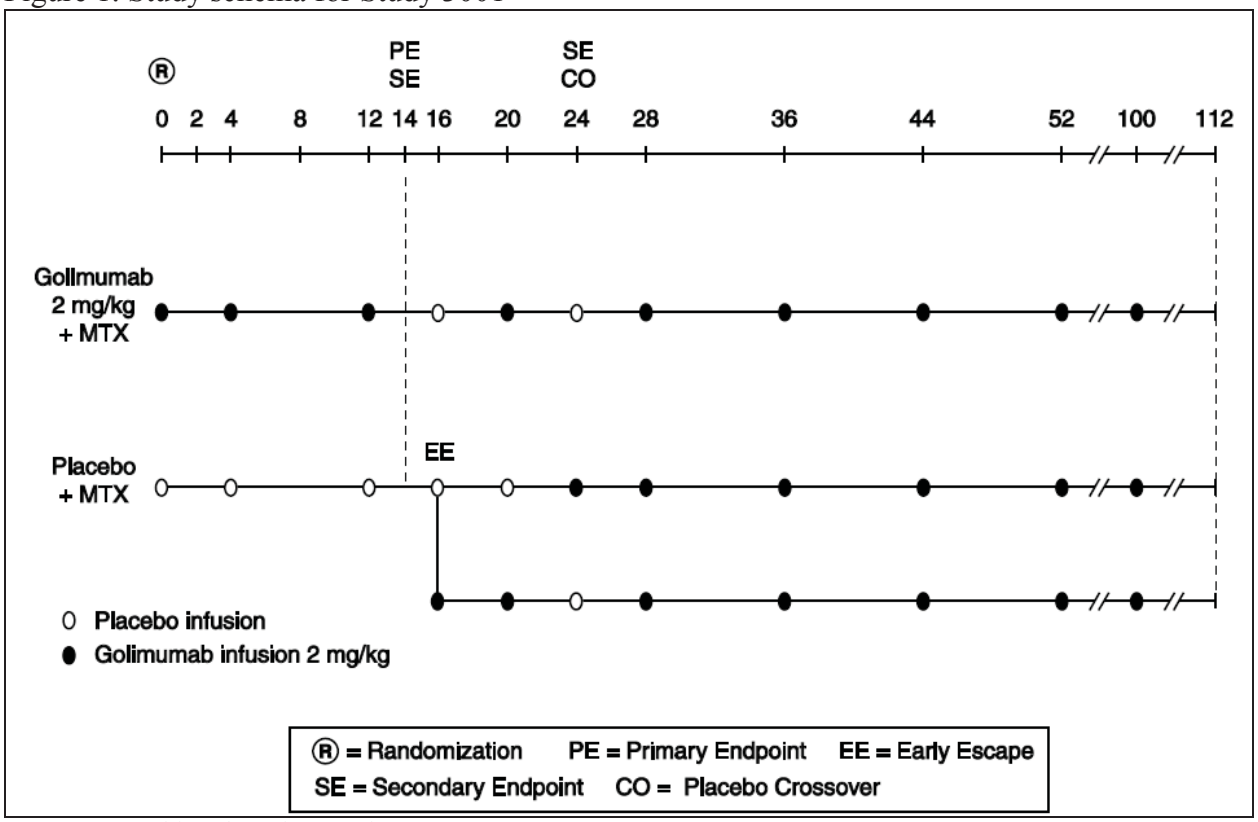
3.2.1 Study 3001

Study Design and Endpoints

Study 3001 was a multicenter, randomized, double-blind, placebo-controlled phase 3 study in which subjects with moderate to severe RA despite MTX therapy. Subjects were randomized to either golimumab IV 2 mg/kg + MTX (hereafter referred to as golimumab) or placebo + MTX (hereafter referred to as placebo) in a 2:1 fashion. Randomization was stratified based upon a screening C-reactive protein (CRP) of < 1.5 mg/dL or ≥ 1.5 mg/dL. Subjects received treatment at Weeks 0 and 4 and then every 8 weeks (q8w). Placebo-treated subjects were eligible for escape at Week 16 if they demonstrated < 10% improvement in both tender and swollen joint count. For a detailed discussion of the study design, the reader is referred to the review of the original BLA.

A schematic of design for Study 3001 is shown in Figure 1.

Figure 1. Study schema for Study 3001



Source: Excerpted from the study protocol (page 19).

Statistical Methodologies

The primary analysis population was the intent-to-treat (ITT) population defined as all randomized patients regardless of whether or not they received the assigned treatment.

The SF-36 is a health-related quality of life instrument that consists of 36 questions and provides a profile of a patient's functional health and well-being. This instrument is divided into of eight subscales scales.

1. physical functioning
2. role-physical
3. bodily pain
4. mental health
5. role-emotional
6. social functioning
7. vitality
8. general health

Two aggregate summary scores, physical component summary (PCS) and mental component summary (MCS) are based on the eight subscales. The PCS, MCS, and the 8 subscales are scored such that a higher score indicates better health. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

For partially answered questionnaires, if more than 50% of the items within each scale were left unanswered, the scale score for the subject was assigned to missing. If at least 50% of the items within each scale were answered, the missing item scores were imputed with the average score for the subject across completed items in the same scale.

The change from baseline in PCS, MCS, and each of the 8 domain scores at Weeks 12, 16 and Week 24 were summarized by treatment group. To test for a treatment difference an analysis of variance on the van der Waerden normal scores was used with treatment group and C-reactive protein level at screening (<1.5 mg/dL or ≥1.5mg/dL) as covariates in the model. Significance was tested using a 2-sided alpha of 0.05.

For subjects that escaped at Week 16, each endpoint or component value after Week 16 was replaced with the corresponding value observed at the time of escape.

The following two rules were applied to all individual and composite endpoints. For composite endpoints, regardless of the number of missing individual components, the missing data rules will be applied for each of the components that are missing, after which the total score will be calculated.

1. For change from baseline endpoints, if the baseline measurement was missing, the median change from baseline value of all subjects in the same stratum (CRP level at screening (< 1.5 mg/dL or ≥ 1.5mg/dL)) will be assigned.
2. If the value at a specified time point other than baseline was missing, the missing value was replaced by the last non-missing observation (including baseline).

It should be noted that the SF-36 assessments have developer-specified missing data rules for calculating the total score when individual components of the composite endpoints are missing. These rules will take precedence over the above. However, since there are no missing data rules when the total score is non-calculable or missing, then the above rules 1 and 2 will apply to the total score for treatment comparisons.

To maintain Type I error among the primary and major secondary endpoints, the endpoints were tested sequentially in a pre-specified manner. However, since SF-36 was not defined as a primary

or major secondary endpoint, there was no way of conducting a formal test with any adjustment for multiplicity.

Patient Disposition, Demographic and Baseline Characteristics

A total of 592 patients (395 golimumab and 197 placebo) were randomized) and the majority (96%) of patients completed the 24 weeks of active treatment. Patient disposition is shown in Table 2. The most common reason for discontinuation was an adverse event.

Table 2. Patients' Accountability through Week 24, N (%) (All Randomized Patients) – Study 3001

	Placebo (N=197)	Golimumab (N=395)
All Randomized Subjects		
N (%)	197 (100)	395 (100)
Subjects Who Completed Study		
N (%)	191 (97)	379 (96)
Subjects Who Discontinued Study		
N (%)	6 (3)	16 (4)
Reason for Discontinuation		
Death	1 (<1)	0
Lack of Efficacy	1 (<1)	1 (<1)
Adverse events	2 (1)	9 (2)
Other	2 (1)	6 (2)

Source: Excerpted from the Clinical Study Report (page 57).

The demographic and baseline disease characteristics were generally well balanced and comparable between the treatment groups and are shown in Table 3. Overall, the mean age was 52 years. Majority of patients were Caucasian and approximately 82% of patients were female. Mean baseline SF-36 PCS score was 31 and mean baseline SF-36 MCS was 38.

Table 3. Patients' Demographic and Baseline Characteristics by Treatment, N (%) – Study 3001

	Placebo (N=197)	Golimumab (N=395)	Total (N=592)
Age at Randomization (yrs)			
Mean (SD)	51.4 (11.3)	51.9 (12.6)	51.8 (12.1)
Median (min-max)	52 (19-78)	53 (18-83)	53 (18-83)
Sex – N(%)			
Male	40 (20)	69 (18)	109 (18)
Female	157 (80)	326 (83)	483 (82)
Race – N(%)			
White	160 (81)	315 (80)	475 (80)
Asian	12 (6)	31 (8)	43 (7)
Other	25 (13)	49 (12)	74 (13)
SF-36 PCS			
Mean (SD)	31 (7)	31 (7)	31 (7)
Median (min-max)	30 (16-51)	31 (13-51)	30 (13-51)
SF-36 MCS			
Mean (SD)	39 (12)	37 (11)	38 (11)
Median (men-max)	38 (12-67)	37 (8-68)	37 (8-68)

Source: Excerpted from the Clinical Study Report (pages 59 & 63).

Results and Conclusions

SF-36 Endpoint – change from Baseline to Week-24

Patients receiving golimumab had a greater mean change from baseline in PCS and MCS composite scores compared to those receiving placebo at Week 24, Results are shown in Table 4. An estimated absolute difference in PCS score was 2.7, 3.6, and 4.5 between the two treatment groups at Weeks 12, 16, and 24, respectively. The estimated absolute difference in MCS score was 3.4, 5.9, and 5.7 between the two treatment groups at Weeks 12, 16, and 24, respectively.

Table 4. Applicant's Analyses on SF-36 Composite Scores (ITT LOCF Imputation) – Study 3001

	Placebo (N=197)	Golimumab (N=395)
PCS		
Change from baseline		
Week 12		
Mean ± SD	3.2 ± 7.4	5.9 ± 7.7
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	3.8 ± 7.5	7.4 ± 8.1
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	3.8 ± 7.3	8.3 ± 8.3
p-value vs. Placebo		<0.001
MCS		
Change from baseline		
Week 12		
Mean ± SD	1.5 ± 9.9	4.9 ± 10.3
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	1.3 ± 9.7	7.2 ± 10.3
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	1.2 ± 10.1	6.9 ± 10.3
p-value vs. Placebo		<0.001

Source: Excerpted from the Clinical Study Report (pages 324 & 325).
Note: p-values based on rank ANOVA with treatment group and CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) as factors.

Sensitivity analyses with respect to missing data gave results that were consistent with the primary analyses and are shown in Table 5. My first sensitivity analysis imputed missing data using the mean of placebo completers. In my second sensitivity analysis, shown in Table 6, I used data obtained after discontinuation of study drug or escape at Week 16.

Table 5. Reviewer's Sensitivity Analyses on SF-36 Composite Scores (ITT Placebo Mean Imputation) – Study 3001

	Placebo (N=197)	Golimumab (N=395)
PCS		
Change from baseline		
Week 12		
Mean ± SD	3.3 ± 7.4	5.9 ± 7.8
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	3.9 ± 7.5	7.4 ± 8.2
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	4.0 ± 7.3	8.3 ± 8.4
p-value vs. Placebo		<0.001
MCS		
Change from baseline		
Week 12		
Mean ± SD	1.7 ± 10.0	4.9 ± 10.4
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	1.5 ± 9.8	7.2 ± 10.4
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	1.2 ± 10.4	6.8 ± 10.5
p-value vs. Placebo		<0.001

Source: Reviewer
Note: p-values based on rank ANOVA with treatment group and CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) as factors.

Table 6. Reviewer's Sensitivity Analyses on SF-36 Composite Scores (ITT Retrieved-Dropouts) – Study 3001

	Placebo (N=197)	Golimumab (N=395)
PCS		
Change from baseline		
Week 12		
Mean ± SD	3.2 ± 7.4	5.9 ± 7.7
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	3.8 ± 7.5	7.4 ± 8.1
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	5.5 ± 7.3	8.3 ± 8.3
p-value vs. Placebo		<0.001
MCS		
Change from baseline		
Week 12		
Mean ± SD	1.5 ± 9.9	4.9 ± 10.3
p-value vs. Placebo		<0.001
Week 16		
Mean ± SD	1.3 ± 9.7	7.2 ± 10.3
p-value vs. Placebo		<0.001
Week 24		
Mean ± SD	3.1 ± 10.0	7.0 ± 10.2
p-value vs. Placebo		<0.001

Source: Reviewer
Note: p-values based on rank ANOVA with treatment group and CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) as factors.

I also examined each individual sub-scale for differences due to treatment. In general, patients receiving golimumab had a greater mean change from baseline in each of 8 domain scores

compared to those receiving placebo at Week 24. Results are shown in Table 7.

Table 7. Applicant's Analyses on SF-36 Domain Scores (ITT LOCF Imputation) – Study 3001

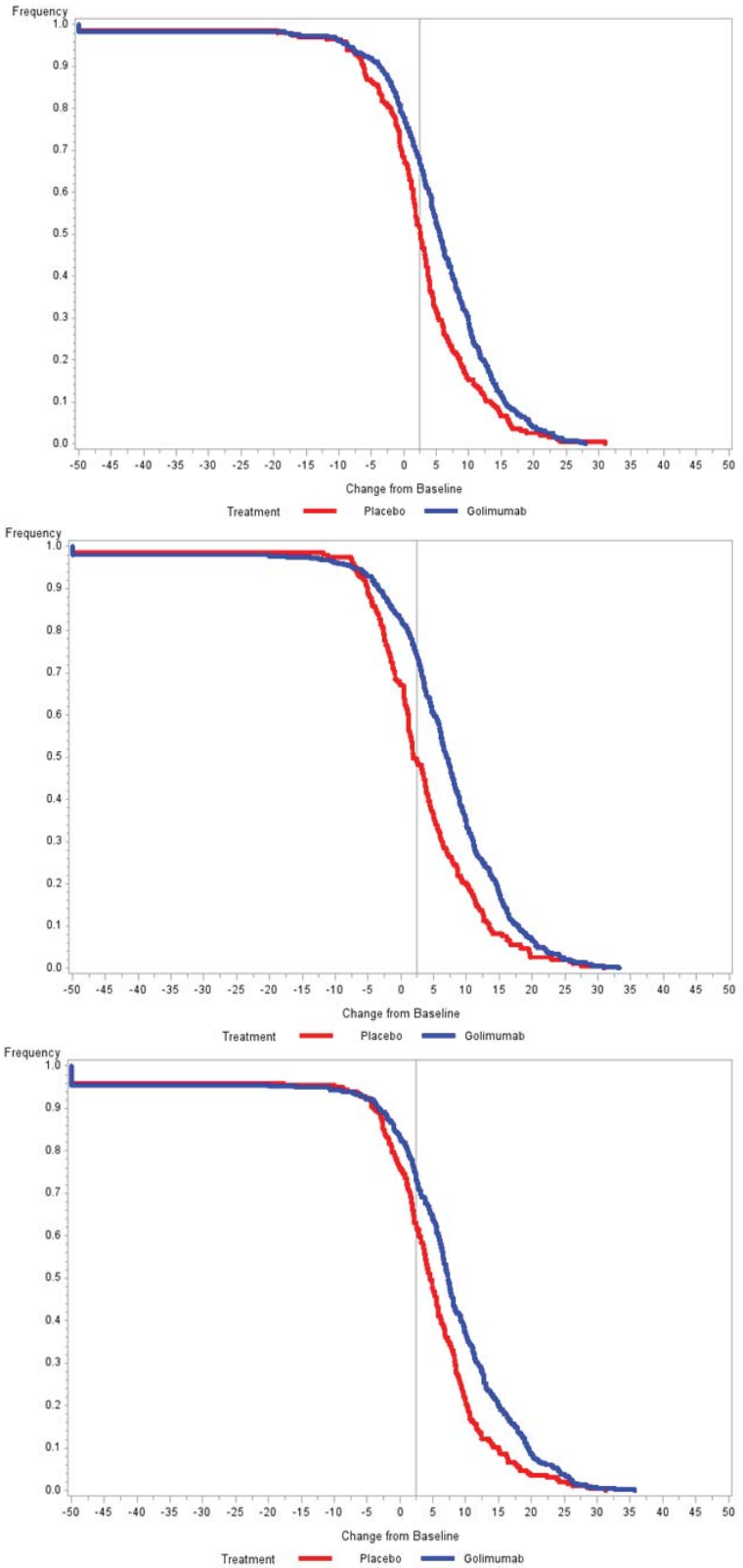
	Placebo (N=197)	Golimumab (N=395)
Physical functioning		
Change from baseline		
Week 12		
Mean ± SD	2.4 ± 9.0	5.2 ± 9.2
Difference vs. Placebo (p-value)		2.8 (<0.001)
Week 16		
Mean ± SD	2.8 ± 9.5	6.7 ± 9.8
Difference vs. Placebo (p-value)		3.9 (<0.001)
Week 24		
Mean ± SD	2.8 ± 10.0	7.6 ± 9.5
Difference vs. Placebo (p-value)		4.8 (<0.001)
Role-physical		
Change from baseline		
Week 12		
Mean ± SD	3.4 ± 8.8	6.3 ± 8.9
Difference vs. Placebo (p-value)		2.9 (<0.001)
Week 16		
Mean ± SD	3.3 ± 8.9	7.7 ± 9.2
Difference vs. Placebo (p-value)		4.4 (<0.001)
Week 24		
Mean ± SD	3.7 ± 9.0	8.2 ± 9.6
Difference vs. Placebo (p-value)		4.5 (<0.001)
Bodily pain		
Change from baseline		
Week 12		
Mean ± SD	4.3 ± 8.7	7.6 ± 9.0
Difference vs. Placebo (p-value)		3.3 (<0.001)
Week 16		
Mean ± SD	5.0 ± 8.5	10.1 ± 9.3
Difference vs. Placebo (p-value)		5.1 (<0.001)
Week 24		
Mean ± SD	4.9 ± 8.6	10.7 ± 9.6
Difference vs. Placebo (p-value)		5.8 (<0.001)
General health		
Change from baseline		
Week 12		
Mean ± SD	1.6 ± 7.6	4.8 ± 8.5
Difference vs. Placebo (p-value)		3.2 (<0.001)
Week 16		
Mean ± SD	2.3 ± 7.7	6.0 ± 8.9
Difference vs. Placebo (p-value)		3.7 (<0.001)
Week 24		
Mean ± SD	2.0 ± 7.6	6.6 ± 9.2
Difference vs. Placebo (p-value)		4.6 (<0.001)
Vitality		
Change from baseline		
Week 12		
Mean ± SD	2.5 ± 8.9	5.8 ± 9.4
Difference vs. Placebo (p-value)		3.3 (<0.001)
Week 16		
Mean ± SD	2.4 ± 8.7	8.2 ± 9.5
Difference vs. Placebo (p-value)		5.8 (<0.001)
Week 24		
Mean ± SD	2.8 ± 9.4	8.4 ± 9.3
Difference vs. Placebo (p-value)		5.6 (<0.001)

Social functioning		
Change from baseline		
Week 12		
Mean ± SD	1.4 ± 10.7	5.3 ± 10.9
Difference vs. Placebo (p-value)		3.9 (<0.001)
Week 16		
Mean ± SD	2.0 ± 10.7	8.0 ± 10.2
Difference vs. Placebo (p-value)		6.0 (<0.001)
Week 24		
Mean ± SD	1.6 ± 10.7	8.0 ± 11.2
Difference vs. Placebo (p-value)		6.4 (<0.001)
Role-emotional		
Change from baseline		
Week 12		
Mean ± SD	2.1 ± 12.4	5.7 ± 12.4
Difference vs. Placebo (p-value)		3.6 (<0.001)
Week 16		
Mean ± SD	1.8 ± 12.1	7.4 ± 11.9
Difference vs. Placebo (p-value)		5.6 (<0.001)
Week 24		
Mean ± SD	1.4 ± 12.7	7.5 ± 12.4
Difference vs. Placebo (p-value)		6.1 (<0.001)
Mental health		
Change from baseline		
Week 12		
Mean ± SD	2.0 ± 10.0	5.0 ± 10.2
Difference vs. Placebo (p-value)		3.0 (<0.001)
Week 16		
Mean ± SD	2.1 ± 9.6	7.2 ± 10.6
Difference vs. Placebo (p-value)		5.1 (<0.001)
Week 24		
Mean ± SD	2.3 ± 10.1	7.1 ± 10.7
Difference vs. Placebo (p-value)		4.8 (<0.001)

Source: Excerpted from the Clinical Study Report (pages 324 & 325).

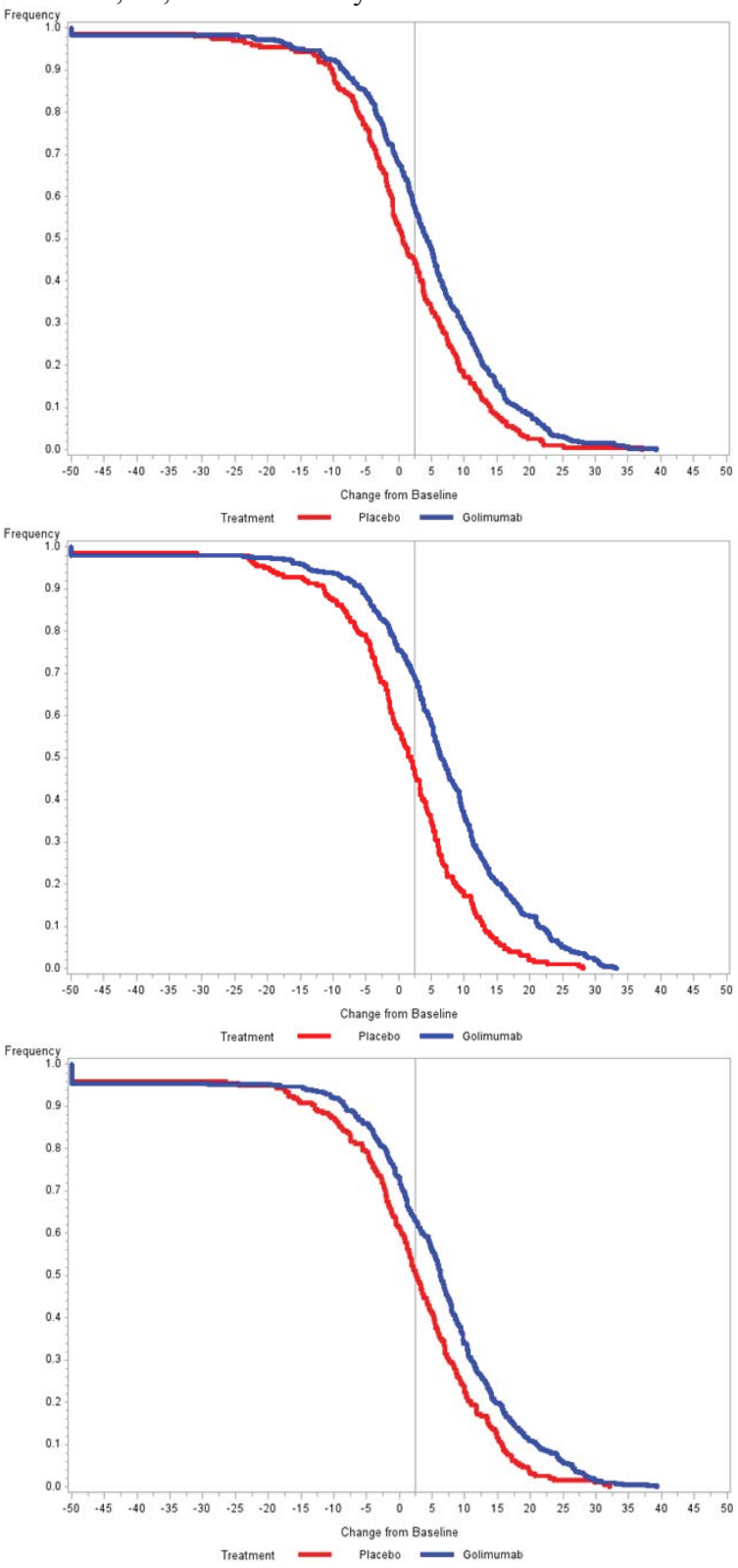
I also conducted a continuous responder analysis, in which cumulative distribution curves for each treatment arm were plotted (Figures 2 & 3). In these plots, all patients who drop out from treatment due to any reason are imputed with value of -50 which is smaller than any observed change. Note that these figures were created to provide a visual display of the benefit of golimumab across the entire range of response at Weeks 12, 16, and 24, respectively. The x-axis shows the absolute change in SF-36 score from baseline at Week X and the y-axis show the corresponding percentage of patients achieving that absolute change in SF-36 score or greater. The positive treatment effect of golimumab was demonstrated by a consistent separation of the curves across all levels of response. As an example, 67% of golimumab-treated patients have at least 2.5 absolute changes in PCS composite score compared to 50% of placebo-treated patients at Week 12 (Figure 2). If we interpret 'at least 2.5 absolute changes' as response, then proportion of responders was 67% and 50% in golimumab group and placebo group, respectively.

Figure 2. Cumulative distribution of absolute change from baseline in PCS composite score at Week 12, 16, and 24 – Study 3001



Source: Reviewer

Figure 3. Cumulative distribution of absolute change from baseline in MCS composite score at Week 12, 16, and 24 – Study 3001



Source: Reviewer

In consultation with the clinical team, a cut-off point of at least 2.5 units in composite score was chosen to perform a responder analysis. The results from this responder analysis supported the results of the primary analysis. Golimumab demonstrated a benefit in SF-36 scores based on SF-36 data. The responder analyses on SF-36 PCS and MCS change from baseline at weeks 12, 16, and 24 were statistically significant (Table 8). Similar results regarding SF-36 domain scores with a cut-off point of at least 5 absolute changes are shown in Figure 5 and Table 13 in the appendix.

Table 8. SF-36 Responder Analyses – Study 3001

	Placebo (N=197)	Golimumab (N=395)	p-value
PCS (with cut of 2.5)			
Week 12	99 (50%)	263 (67%)	<0.001
Week 16	96 (49%)	291 (74%)	<0.001
Week 24	122 (62%)	288 (73%)	0.006
MCS (with cut of 2.5)			
Week 12	87 (44%)	225 (57%)	0.003
Week 16	90 (46%)	271 (69%)	<0.001
Week 24	99 (50%)	248 (63%)	0.004

Note: p-values were based on chi-square test.
Source: Reviewer.

In summary, results from my analyses of SF-36 data in study 3001 showed statistically significant evidence in favor of golimumab. This was supported by my sensitivity analyses that confirmed the robustness of the SF-36 data.

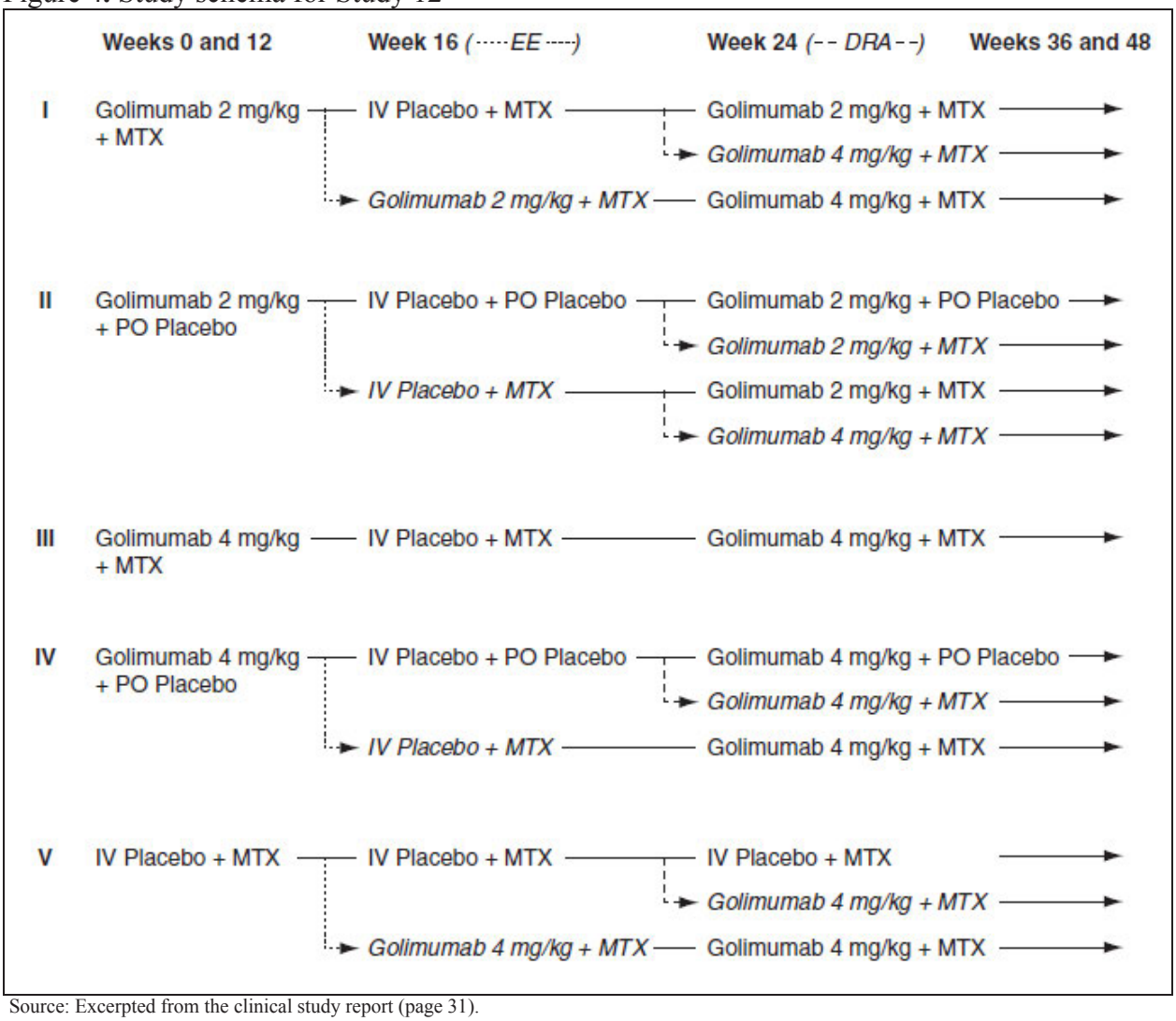
3.2.2 Study 12

Study Design and Endpoints

Study 12 was a randomized, double-blind, placebo-controlled, multicenter, 5-arm study that evaluated the efficacy and safety of IV administration of 2 mg or 4 mg golimumab (given with or without MTX over a period of 30 minutes every 12 weeks) for at least 48 weeks in subjects with active RA despite concurrent MTX therapy. At Week 16 and Week 24, joint assessment results were used to allow subjects to enter early escape and dose regimen adjustment (DRA), respectively, in a blinded fashion. For a detailed discussion of the study design, the reader is referred to the original BLA review.

A schematic of design for Study 12 is shown below (Figure 4).

Figure 4. Study schema for Study 12



Source: Excerpted from the clinical study report (page 31).

Subjects were to be randomized to 5 treatment groups in 1:1:1:1:1 ratio. Randomization was stratified by previous use of anti-TNF treatment and investigational site.

Although there were 5 treatment groups evaluated in this study, I focus on the two treatment groups that were evaluated in study 3001, golimumab 2 mg + MTX (hereafter referred to as golimumab) and placebo + MTX (hereafter referred to as placebo).

Statistical Methodologies

In general, the proposed statistical analysis methods for SF-36 data were similar to the methods used in study 3001.

The change from baseline in PCS and MCS, and each of the 8 domain scores at Weeks 14 and Week 24 were summarized by treatment group. To test for a difference due to treatment an analysis of variance on the van der Waerden normal scores was used with treatment group and prior anti-TNF therapy (yes/no) as covariates in the model. Significance was tested using a 2-sided alpha of 0.05.

For subjects that escaped at Week 16, each endpoint or component value after Week 16 was replaced with the corresponding value observed at the time of escape.

To maintain Type I error among the primary and major secondary endpoints, the endpoints were tested sequentially in a pre-specified manner. However, since SF-36 was not defined as a primary or major secondary endpoint, there was no way of conducting a formal test with any adjustment for multiplicity.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of the 258 patients who were randomized is shown in Table 9. The majority (94%) of patients completed the 24 weeks of active treatment. The most common reason for discontinuations for golimumab patients was adverse event while the most common reason for discontinuations for placebo patients was lack of efficacy.

Table 9. Patients' Accountability Through Week 24, N (%) (All Randomized Patients)

	Placebo (N=129)	Golimumab (N=129)
All Randomized Subjects		
N (%)	129 (100)	129 (100)
Subjects Who Completed Study		
N (%)	122 (95)	120 (93)
Subjects Who Discontinued Study		
N (%)	7 (5)	9 (7)
Reason for Discontinuation		
Lack of Efficacy	4 (3)	1 (1)
Adverse events	1 (1)	3 (2)
Other	2 (1)	5 (4)

Source: Excerpted from the Clinical Study Report (page 57).

The demographic and baseline disease characteristics are shown in Table 10 and were generally well balanced and comparable between the treatment groups and were similar to study 3001. Overall, the mean age was 50 years. Majority of patients were Caucasian and approximately 78% of patients were female. Mean baseline SF-36 PCS score was 30 and mean baseline SF-36 MCS was 43.

Table 10. Patients' Demographic and Baseline Characteristics by Treatment, N (%) – Study 12

	Placebo (N=129)	Golimumab (N=129)	Total (N=258)
Age at Randomization (yrs)			
Mean (SD)	50.2 (11.3)	49.7 (11.1)	50.0 (11.2)
Median (min-max)	51 (41-59)	51 (44-58)	51 (41-59)
Sex – N(%)			
Male	26 (20)	30 (23)	56 (22)
Female	103 (80)	99 (77)	202 (78)
Race – N(%)			
White	92 (71)	88 (69)	180 (70)
Asian	11 (9)	10 (8)	21 (8)
Black	5 (4)	1 (<1)	6 (2)
Other	21 (16)	30 (23)	51 (20)
SF-36 PCS			
Mean (SD)	30 (8)	31 (8)	30 (8)
Median (min-max)	29 (11-53)	29 (17-54)	29 (11-54)
SF-36 MCS			
Mean (SD)	44 (12)	42 (12)	43 (12)
Median (men-max)	43 (15-72)	40 (16-67)	42 (15-72)

Source: Excerpted from the Clinical Study Report (pages 87 & 411).

Results and Conclusions

SF-36 Endpoint – change from Baseline

The only significant difference noted was change from baseline in PCS composite score at Week 14. Patients receiving golimumab had a statistically greater change when compared to those receiving placebo. Results are shown in Table 11.

Table 11. Reviewer's Analyses on SF-36 Composite Scores (ITT LOCF Imputation) – Study 12

	Placebo (N=129)	Golimumab (N=129)
PCS		
Change from baseline		
Week 14		
Mean ± SD	4.4 ± 7.3	7.3 ± 9.3
p-value vs. Placebo		0.007
Week 24		
Mean ± SD	4.9 ± 8.5	7.0 ± 9.3
p-value vs. Placebo		0.059
MCS		
Change from baseline		
Week 14		
Mean ± SD	2.7 ± 11.0	4.8 ± 11.9
p-value vs. Placebo		0.125
Week 24		
Mean ± SD	3.6 ± 10.9	4.8 ± 11.2
p-value vs. Placebo		0.515

Note: p-values based on rank ANOVA with treatment group and prior anti-TNF therapy (yes/no) as factors.

In general, regardless of the subscale and week, patients receiving golimumab had a numerically greater mean change from baseline when compared to those receiving placebo. There was no difference in bodily pain scores at Week 24. The changes at Week 14 for physical functioning, vitality, and social functioning were statistically significant and the change in physical functioning at Week 24 was statistically significant. Results are shown in Table 12.

Table 12. Reviewer's Analyses on SF-36 Domain Scores (ITT LOCF Imputation) – Study 12

	Placebo (N=129)	Golimumab (N=129)
Physical functioning		
Change from baseline		
Week 14		
Mean ± SD	3.5 ± 8.3	5.7 ± 9.8
p-value vs. Placebo		0.027
Week 24		
Mean ± SD	3.9 ± 9.8	6.6 ± 9.6
p-value vs. Placebo		0.013
Role-physical		
Change from baseline		
Week 14		
Mean ± SD	5.0 ± 9.9	7.9 ± 14.4
p-value vs. Placebo		0.169
Week 24		
Mean ± SD	5.4 ± 11.4	7.8 ± 13.5
p-value vs. Placebo		0.246
Bodily pain		
Change from baseline		
Week 14		
Mean ± SD	5.7 ± 8.7	8.4 ± 10.0
p-value vs. Placebo		0.023
Week 24		
Mean ± SD	6.9 ± 9.1	6.8 ± 10.2
p-value vs. Placebo		0.803
General health		
Change from baseline		
Week 14		
Mean ± SD	2.8 ± 8.2	5.0 ± 9.6
p-value vs. Placebo		0.097
Week 24		
Mean ± SD	3.1 ± 8.4	5.3 ± 10.0
p-value vs. Placebo		0.097
Vitality		
Change from baseline		
Week 14		
Mean ± SD	3.7 ± 9.4	6.9 ± 10.2
p-value vs. Placebo		0.008
Week 24		
Mean ± SD	4.8 ± 9.0	6.1 ± 10.3
p-value vs. Placebo		0.281
Social functioning		
Change from baseline		
Week 14		
Mean ± SD	2.4 ± 12.3	7.2 ± 11.5
p-value vs. Placebo		0.002
Week 24		
Mean ± SD	3.5 ± 11.4	6.6 ± 11.5
p-value vs. Placebo		0.052
Role-emotional		
Change from baseline		

Week 12		
Mean ± SD	3.6 ± 13.9	5.3 ± 15.8
p-value vs. Placebo		0.414
Week 24		
Mean ± SD	4.8 ± 13.8	6.4 ± 14.4
p-value vs. Placebo		0.338
Mental health		
Change from baseline		
Week 14		
Mean ± SD	3.4 ± 11.6	4.4 ± 10.2
p-value vs. Placebo		0.623
Week 24		
Mean ± SD	3.5 ± 11.1	4.1 ± 11.1
p-value vs. Placebo		0.787

Note: p-values based on rank ANOVA with treatment group and prior anti-TNF therapy (yes/no) as factors.

In general, regardless of the domain, there was a numerical trend in favor of golimumab for the change from baseline at weeks 14 and 24. However, statistical significance was only noted for the change in PCS scores at Week 14.

3.3 Evaluation of Safety

No new safety information was provided in the supplement.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Not applicable.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

During my review of the application, two statistical issues were identified in study 3001, the approach to handle missing data and multiplicity. SF-36 in study 12 was considered exploratory and these issues were not applicable.

For the analyses of SF-36, the applicant pre-specified LOCF for imputation of missing data. However, as dropout rates were low, 3-7%, I did not consider this an issue. However, LOCF imputation for early escapers at Week 16 was a concern as there were more placebo patients that escaped early. My concerns were alleviated as the results from my sensitivity analysis that imputed

an early escaper's data after Week 16 with the mean score from completers among placebo showed that the results were consistent with the applicant's analysis. I also conducted a retrieved dropout analysis using obtained data after discontinuation of study medication. In all cases, there was a significant treatment effect in favor of golimumab.

To maintain the overall Type I error among the primary and major secondary endpoints, the endpoints were tested sequentially. However, SF-36 was not a pre-specified primary or major secondary endpoint and was not included in the sequential testing strategy. When I applied a conservative Bonferroni correction to adjust for multiplicity in a post hoc fashion, all endpoints including SF-36 were statistically significant.

5.2 Conclusions and Recommendations

In conclusion, my analyses of the SF-36 data from studies 3001 and 12 provide evidence that golimumab improves SF-36 scores in patients with moderate to severe RA in combination with MTX.

Further, there was substantial evidence of efficacy of IV golimumab for the treatment of rheumatoid arthritis based on consistent findings in the domains of reducing signs and symptoms of RA as measured by ACR20 and DAS28 responses. The reader is referred to the original BLA review for a detailed review.

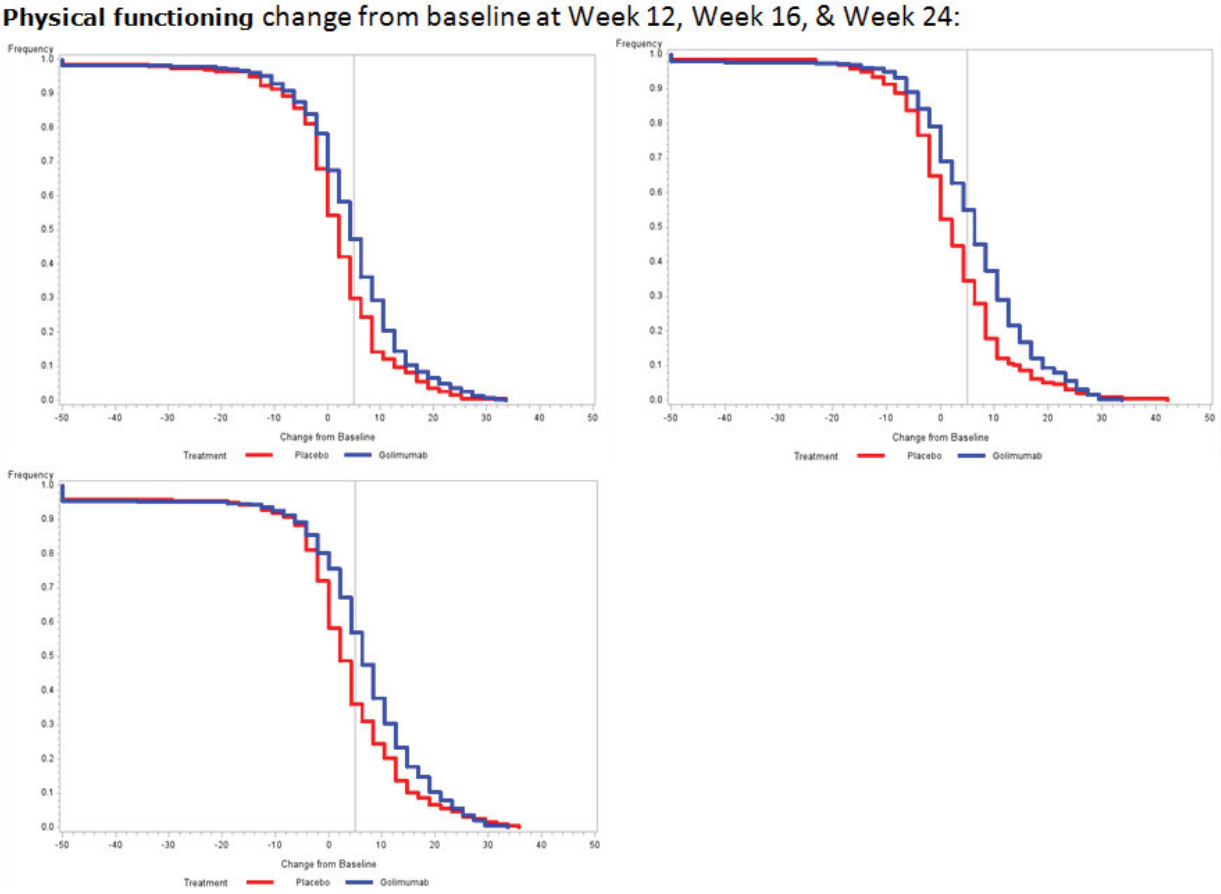
5.3 Labeling Recommendations

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the SF-36 data analysis results and their interpretation.
However, we recommend that results from secondary and exploratory analyses that were not adjusted for multiplicity be not presented except for endpoints agreed as clinically important.

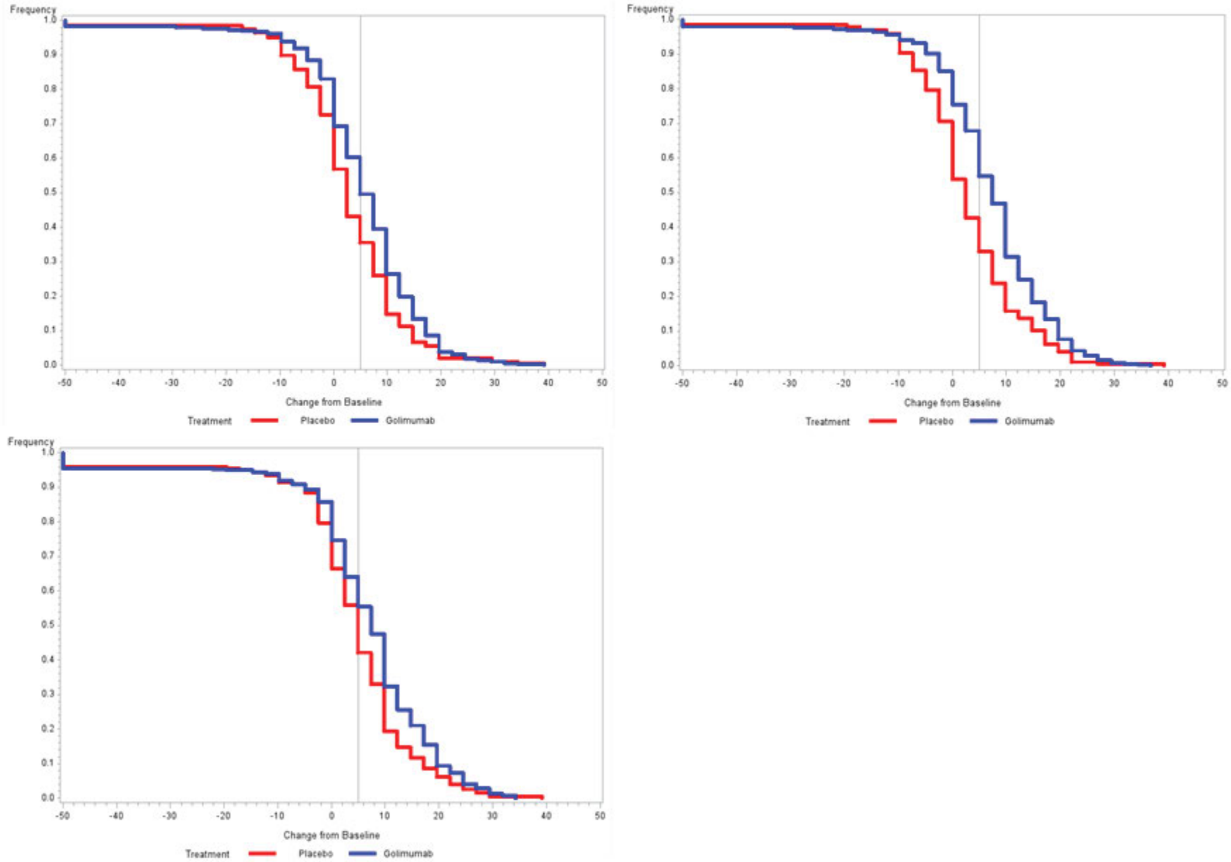
> ***Other Health-Related Outcomes***[i]
> General health status was assessed by the 36-item Short Form Health Survey (SF-36). In Trial 1, patients receiving SIMPONI ARIA + MTX demonstrated greater improvement from baseline compared with placebo + MTX in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 (b) (4).

APPENDIX

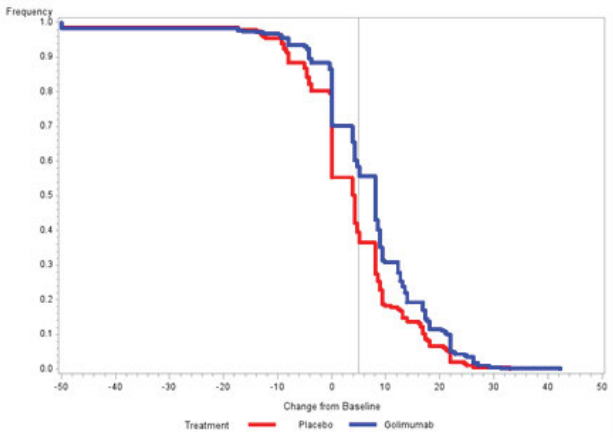
Figure 5. Cumulative distribution of absolute change from baseline in SF-36 domain scores – Study 3001

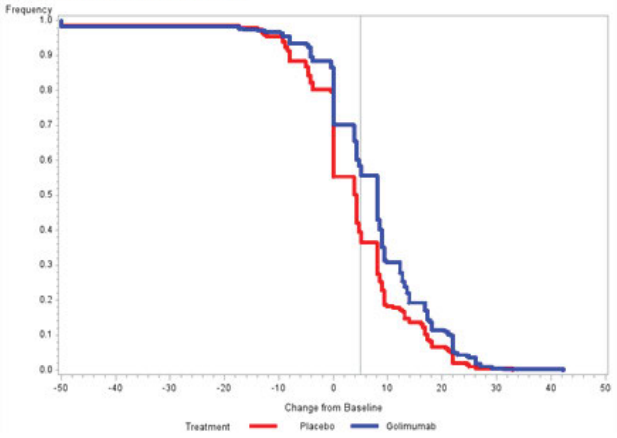


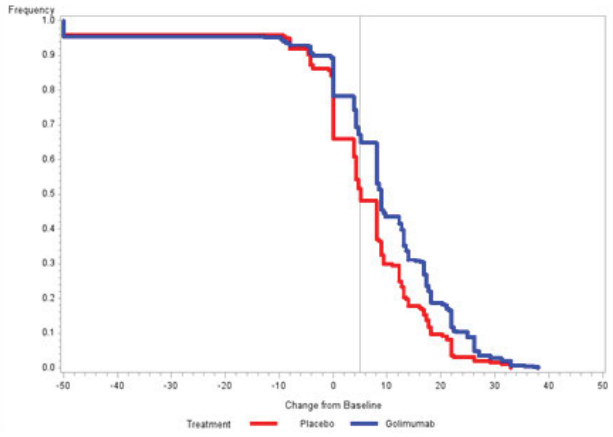
Role-physical change from baseline at Week 12, Week 16, & Week 24:



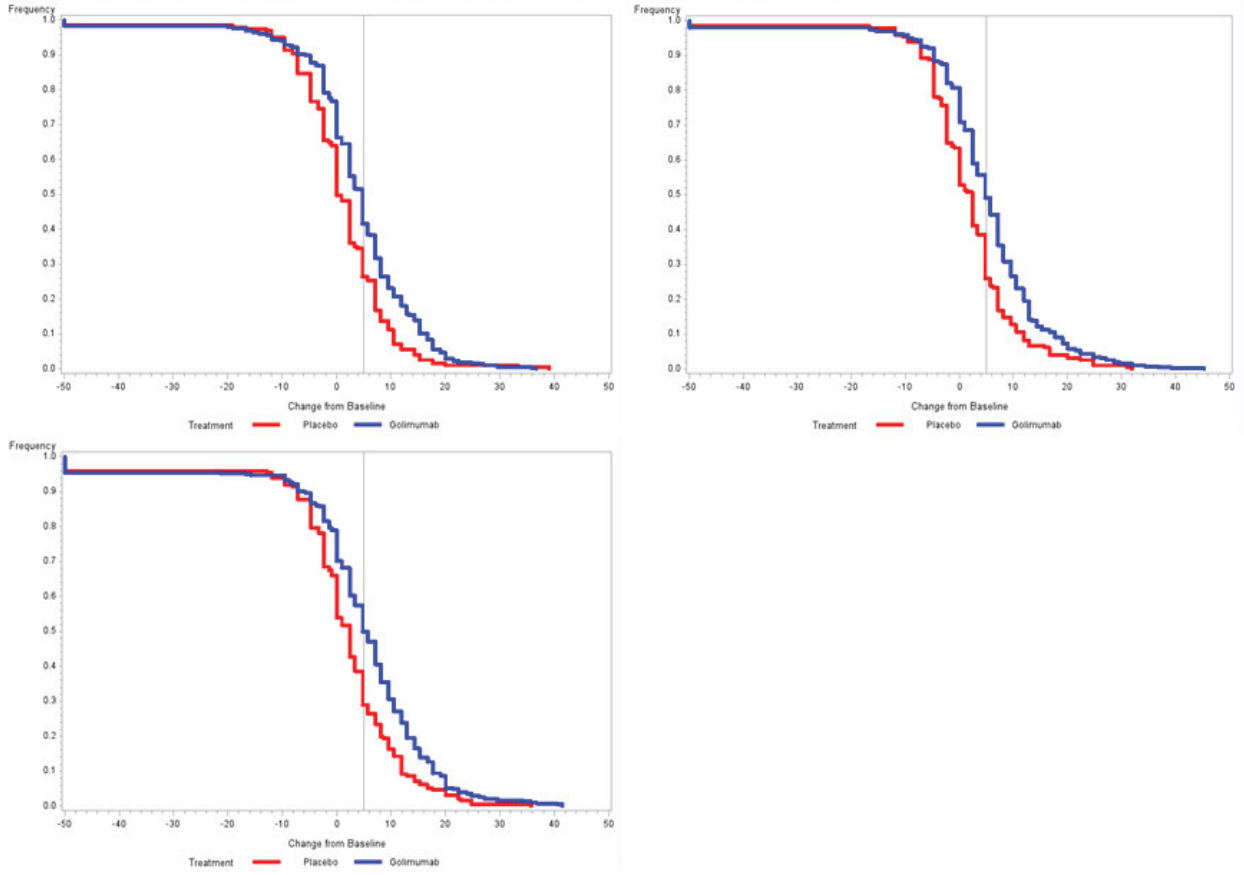
Bodily pain change from baseline at Week 12, Week 16, & Week 24:



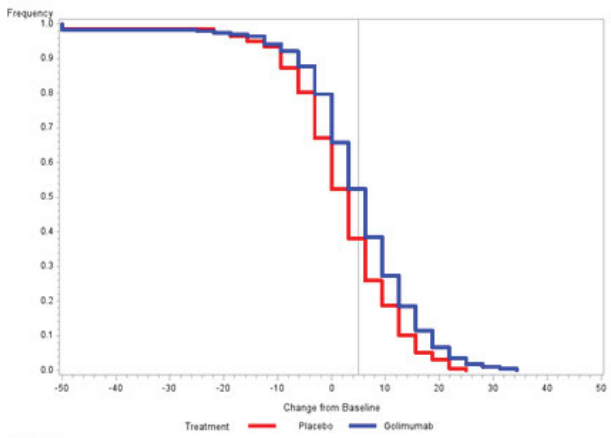


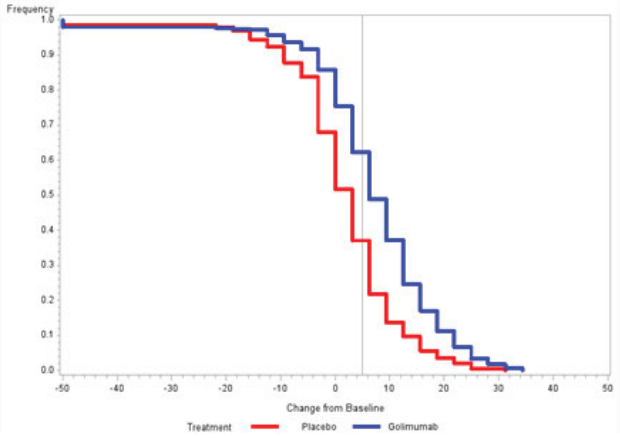


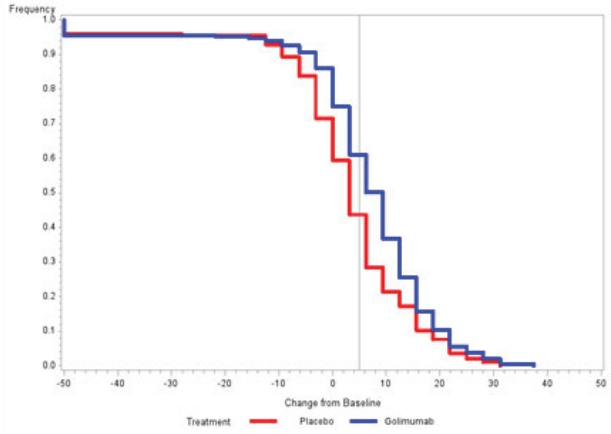
General health change from baseline at Week 12, Week 16, & Week 24:



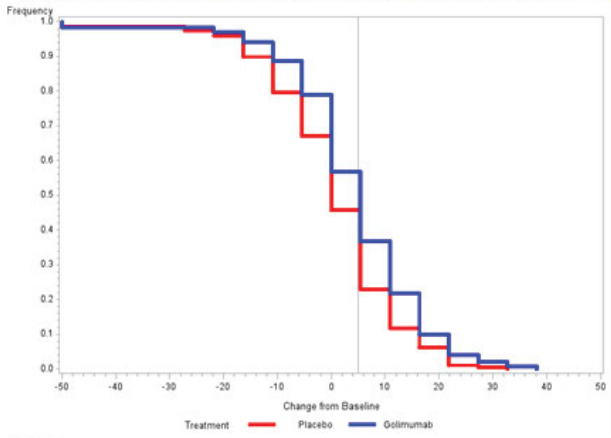
Vitality change from baseline at Week 12, Week 16, & Week 24:

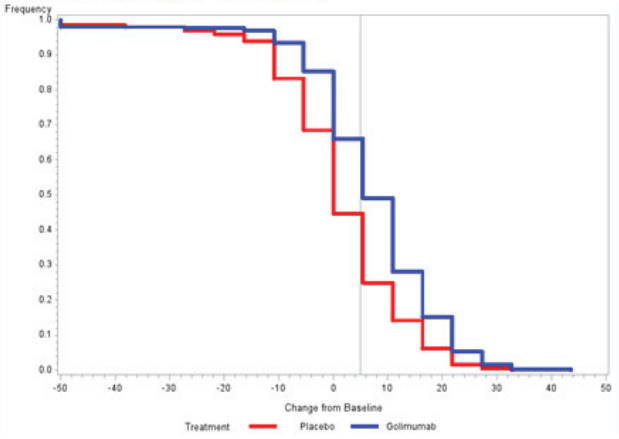


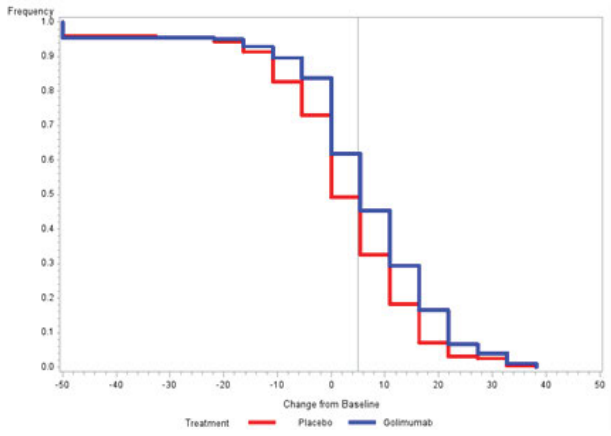




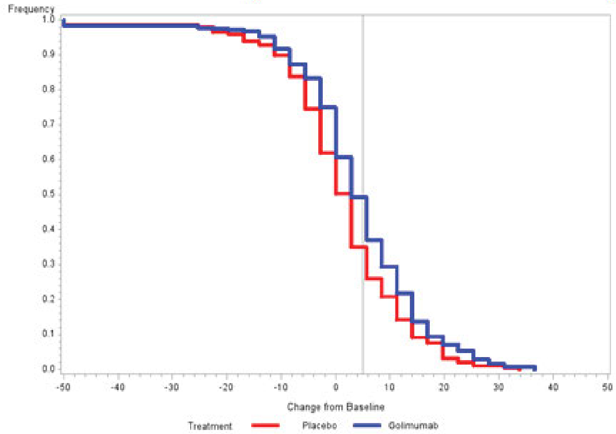
Social functioning change from baseline at Week 12, Week 16, & Week 24:

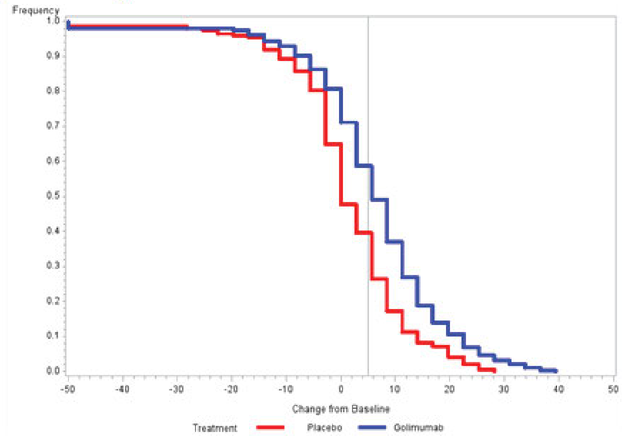


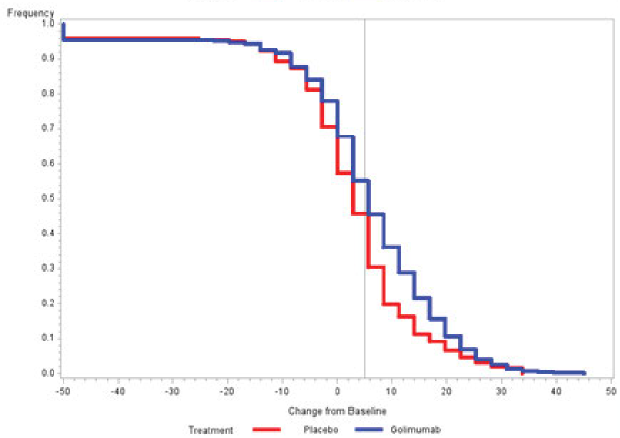




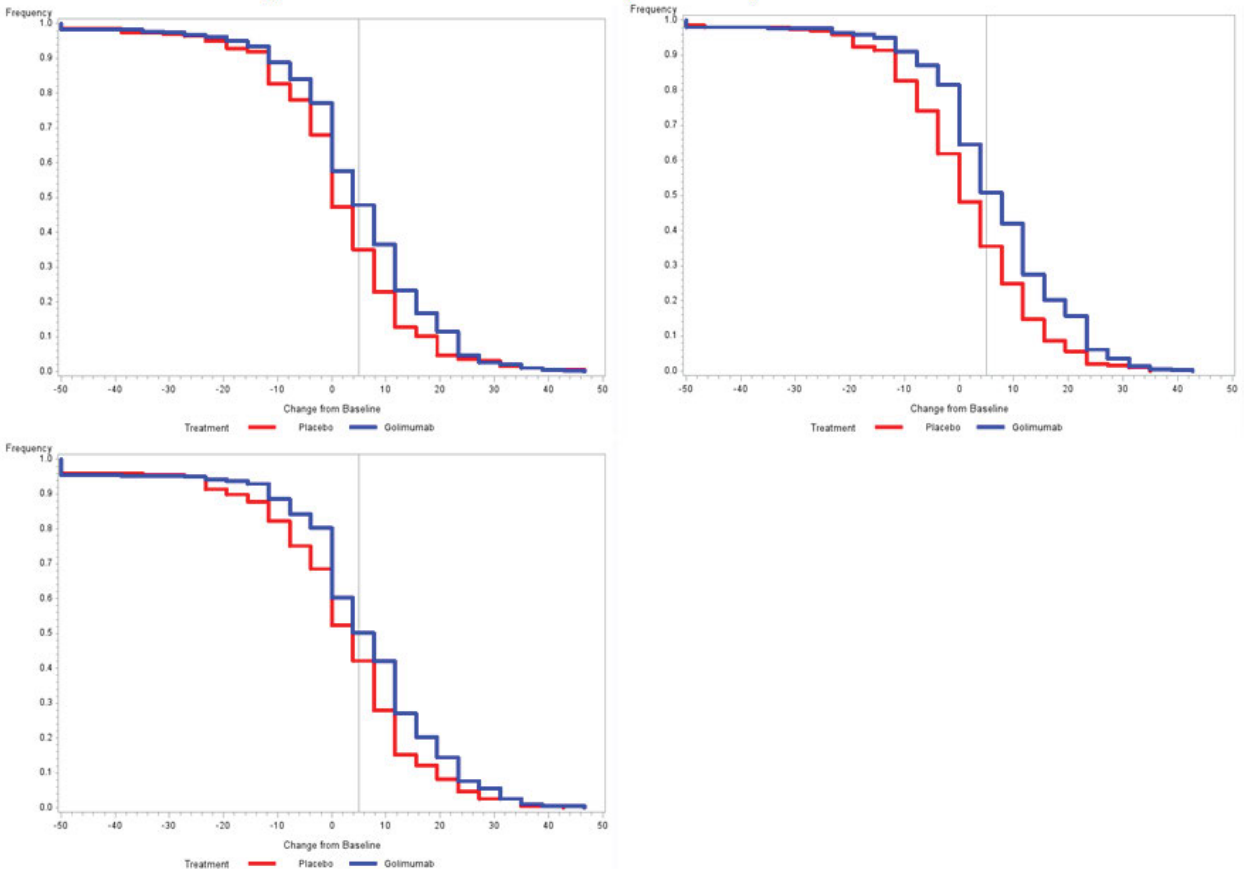
Mental health change from baseline at Week 12, Week 16, & Week 24:



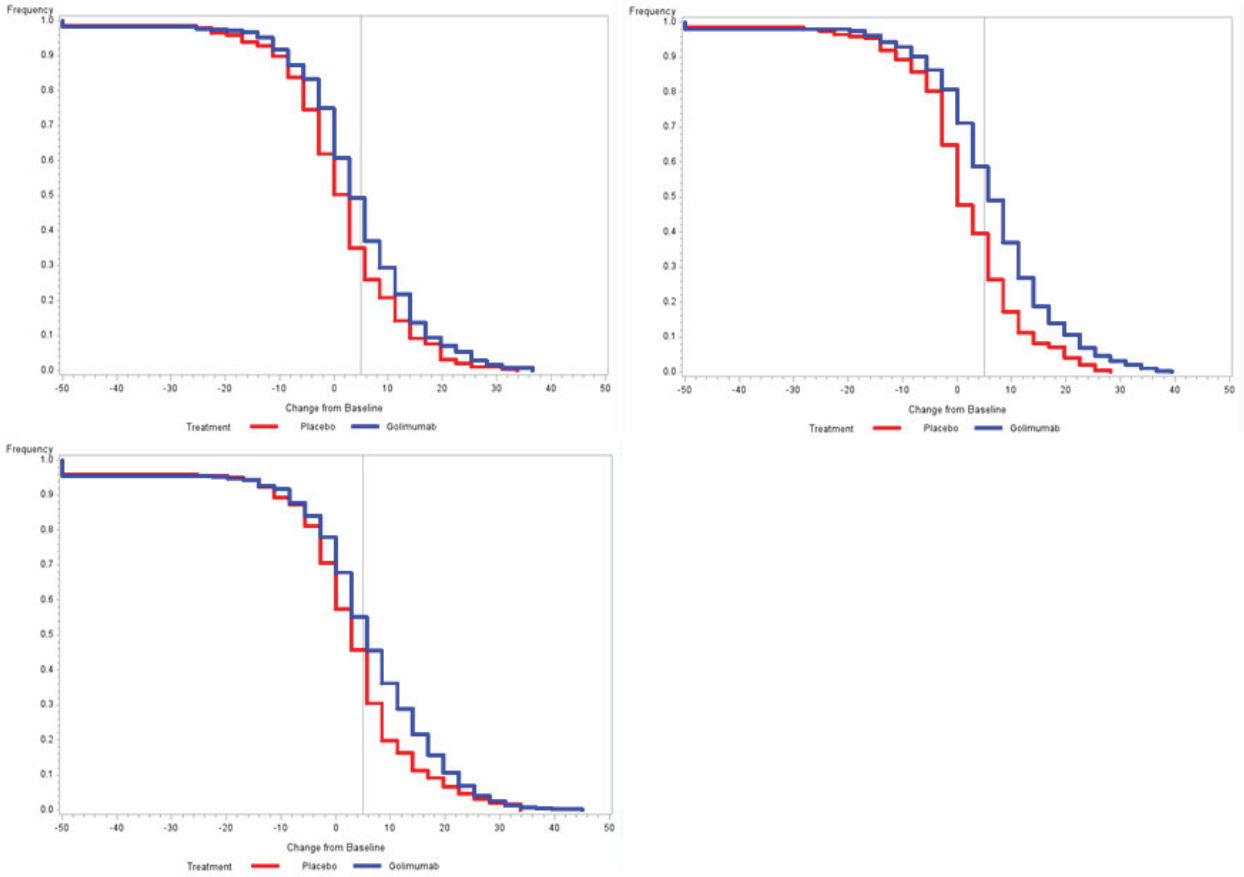




Role-emotional change from baseline at Week 12, Week 16, & Week 24:



Mental health change from baseline at Week 12, Week 16, & Week 24:



Source: Reviewer.

Table 13. Proportion (%) of SF-36 Responders – Study 3001

	Placebo (N=197)	Golimumab (N=395)
PCS (with cut of 2.5)		
Week 12	50	67
Week 16	49	74
Week 24	62	73
MCS (with cut of 2.5)		
Week 12	44	57
Week 16	46	69
Week 24	50	63
Physical functioning (with cut of 5)		
Week 12	30	47
Week 16	35	55
Week 24	36	57
Role-physical (with cut of 5)		
Week 12	36	50
Week 16	33	55
Week 24	42	55
Bodily pain (with cut of 5)		
Week 12	40	58
Week 16	41	66
Week 24	52	67
General health (with cut of 5)		
Week 12	26	42
Week 16	26	49
Week 24	29	50
Vitality (with cut of 5)		

Week 12	38	52
Week 16	37	62
Week 24	44	61
Social functioning (with cut of 5)		
Week 12	46	57
Week 16	45	66
Week 24	49	62
Role-emotional (with cut of 5)		
Week 12	35	48
Week 16	36	51
Week 24	42	50
Mental health (with cut of 5)		
Week 12	35	49
Week 16	40	59
Week 24	46	55

Source: Reviewer.

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/s/

YONGMAN KIM
07/01/2015

DAVID M PETULLO
07/01/2015
I concur.

STATISTICS FILING CHECKLIST FOR BLA 125-433

BLA Number: 125-433 **Applicant:** Janssen **Stamp Date:** October 6, 2014

Drug Name: golimumab **NDA Type:** Standard

On **initial** overview of the NDA application for RTF: **Study CNTO148ART3001**

	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	SF-36 claim based on data from a single study submitted in the original submission
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	SF-36 claim based on data from a single study submitted in the original submission
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

Comment:

Please identify and list any potential review issues to be forwarded to the Applicant 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.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as			X	

STATISTICS FILING CHECKLIST FOR BLA 125-433

BLA Number: 125-433 **Applicant:** Janssen **Stamp Date:** October 6, 2014

Drug Name: golimumab **NDA Type:** Standard

On **initial** overview of the NDA application for RTF: **Study CNTO148ART3001**

	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	SF-36 claim based on data from a single study submitted in the original submission
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	SF-36 claim based on data from a single study submitted in the original submission
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

Comment:

Please identify and list any potential review issues to be forwarded to the Applicant 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.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as			X	

described by applicant appears adequate.				

Brief Summary of Pivotal Studies

Trial ID	Design	Treatment/ Sample Size	Endpoint	Preliminary Findings
CNTO148ART3001	A 52-weeks, placebo-controlled, multicenter parallel study	golimumab/395 Placebo/197	Primary: ACR20 response at Week 14	Primary: golimumab vs Placebo (Difference = 33.6%; p-value <0.001).
			Major Secondary: DAS28(CRP) response at Week 14, Improvement from baseline in HAQ score at Week 14, ACR50 response at Week 24.	Major Secondary: DAS28(CRP): golimumab vs Placebo (Difference = 41.2%; p-value <0.001) HAQ: golimumab vs Placebo (Difference = 0.306; p-value <0.001) ACR50: golimumab vs Placebo (Difference = 21.7%; p-value <0.001)
			Other Secondary: SF-36 PCS, MCS, 8 Domains at Weeks 12, 16, and 24	Other Secondary: SF-36 PCS, MCS, 8 Domains at Weeks 12, 16, and 24: golimumab vs Placebo (all p-values <0.001)

Submission location: \\CDSESUB1\EVSPROD\BLA125433\125433.enx

STATISTICS FILING CHECKLIST FOR BLA 125-433

Additional information regarding the data:

	Information regarding the data	Comments
1	Dataset location	\\Cdsesub1\evsprod\BLA125433\0000\m5\datasets\cnto148art3001
2	Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
3	Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	
4	List the dataset(s) that contains the primary endpoint(s)	adql.xpt
5	Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	None identified.

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/s/

YONGMAN KIM
11/07/2014

GREGORY P LEVIN
11/10/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125433Orig1s14

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 8, 2015

To: Paul Imm, Associate Director Immunology, Global Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1110	**Fax number:** 301-796-9728
Email: pimm@its.jnj.com	**Phone number:** 301-796-3420

Subject: BLA 125433/S-014 Simponi Aria (golimumab IV)
FDA labeling comments

Total no. of pages including cover: **31**

Comments: ***Response requested no later than cob Monday July 13, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

We refer to Simponi Aria supplemental BLA 125433/014 and have the following labeling edits provided in the attached marked up label. Additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the clean version of your proposed labeling submitted January 12, 2015.

Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) July 13, 2015. Your response will subsequently need to be submitted officially to the BLA.

If you have any questions, please contact me at 301-796-3420.

Drafted by: RGlaser, NNikolov/ 6.30.2015
cford/ 7.7.2015

Cleared thru: SBarnes/ 7.7.2015

Finalized: cford/ 7.7.2015

Following this page 28 pages have been withheld in full as draft labeling (b) (4)

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/s/

CHRISTINE H CHUNG
07/08/2015

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: February 26, 2014

To: Paul Imm, Associate Director Immunology, Global Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1110	**Fax number:** 301-796-9728
Email: pimm@its.jnj.com	**Phone number:** 301-796-3420

Subject: BLA 125433/S-014 Simponi Aria (golimumab IV)
FDA Request for information - Clinical

Total no. of pages including cover: **3**

Comments: ***Response requested no later than cob Tuesday March 3, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

We refer to supplemental BLA 125433/14 for Simponi Aria and have the following request for information.

In Table 9 of your submission dated December 23, 2014 (response to clinical information request dated November 10, 2014), you include change from baseline in SF-36 PCS scores through Week 14 in study C0524T12. Provide the same information (change from baseline) for SF-36 MCS scores through Week 14 in study C0524T12.

Send your responses to me via secure email at christine.ford@fda.hhs.gov no later than close of business Tuesday, March 3, 2015. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by:	RGlaser, NNikolov/ 2.25.15 cford/ 2.26.2015
Cleared thru:	SBarnes/ 2.26.2015
Finalized:	cford/ 2.26.2015

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/s/

CHRISTINE H CHUNG
02/26/2015

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application:	BLA 125433/S-014
Name of Drug:	Simponi Aria (golimumab for infusion)
Applicant:	Janssen Biotech, Inc. (JBI)
Receipt Date:	October 6, 2014
Labeling amendment:	January 12, 2015

Background and Summary Description:

JBI submitted this prior approval labeling supplement with clinical data (SE8) to add SF-36 results to the USPI.

Review:

I compared the labeling submitted on January 12, 2015, with the last approved USPI for S-013 on December 19, 2014. There were no other changes proposed other than those provided for in this supplement and as requested by FDA in labeling IR dated December 29, 2014, that included comments from DMPP (see attached).

Recommendations:

Pending approval recommendations from the review teams (clinical and biometrics) and labeling agreement with the applicant, this supplement should be approved.

Christine Ford, R.Ph.	January 27, 2015
Regulatory Project Manager	Date
Sandy Barnes	January 27, 2015
Chief, Project Management Staff	Date

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: December 29, 2014

To: Paul Imm, Associate Director Immunology, Global Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1110	**Fax number:** 301-796-9728
Email: pimm@its.jnj.com	**Phone number:** 301-796-3420

Subject: BLA 125433 Simponi Aria (golimumab IV)
FDA labeling comments to Medguide

Total no. of pages including cover: **10**

Comments: Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

We refer to BLA 125433 for Simponi Aria and recommend that the following changes be made to the Medication Guide for consistency of information with the approved Prescribing Information as well as the Medication Guide for Simponi. You may submit these changes as an amendment to pending S-014 (preferred) or as a new supplement.

If you have any questions, please contact me at 301-796-3420.

Drafted by:	DMPP/ 12.18.2014 cford/ 12.19.2014
Cleared thru:	SBarnes, RNeuner, SYim/ 12.29.2014
Finalized:	cford/ 12.29.2014

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/s/

CHRISTINE H CHUNG
01/27/2015

SANDRA L BARNES
01/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Christine Ford, RPM, DPARP, x-63420

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
12/15/2014		BLA 125433 S-014	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Simponi Aria (IV golimumab)	Standard		2 weeks after scpi forwarded

NAME OF FIRM:	PDUFA Date: 8/6/2015
Janssen Biotech, Inc.	

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: \\CDSESUB1\evsprod\BLA125433\125433.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
This is a consult for evaluation and review of the revised USPI for intravenous golimumab. This is a SE8, "labeling supplement with clinical data" to add SF-36 language (health-related outcomes, changes only in section 14 under Clinical Studies) to the USPI.
Cover Letter: \\CDSESUB1\evsprod\BLA125433\0050\m1\us\cover.pdf
Annotated labeling: \\cdsesub1\evsprod\bla125433\0050\m1\us\draft-labeling-text-annotated.doc
\\cdsesub1\evsprod\bla125433\0050\m1\us\draft-labeling-text-annotated.pdf

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☑ eMAIL ☐ HAND

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/s/

CHRISTINE H CHUNG
12/15/2014

Therapeutic Biological Establishment Evaluation
Initial 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[i] 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/BsUFA goal date: 8/6/2015

Applicant Name:	Janssen Biotech, Inc.
U.S. License #:	1864
STN(s):	125433/014
Product(s):	Simponi Aria (IV golimumab)

Short summary of application: This is a supplemental BLA to add SF-36 language (health-related outcomes, changes only in section 14 under Clinical Studies) to the USPI (labeling supplement with clinical data).

FACILITY INFORMATION

Manufacturing Location:

Firm Name:	Janssen Biologics (Ireland)
Address:	Barnahely, Ringaskiddy, Co. Cork, Ireland
FEI:	3007029098

Short summary of manufacturing activities performed:
Drug substance manufacturer and raw material testing.
Drug product SIMPONI FVP (IV) DP release and stability testing.

FACILITY INFORMATION

Manufacturing Location:

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)

Short summary of manufacturing activities performed:

(b) (4)

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, 2333 CB Leiden, The Netherlands
FEI: 3002806632

Short summary of manufacturing activities performed:
Drug Substance manufacturing, raw material testing.
Drug product SIMPONI FVP (IV) DP release and stability testing.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: (b) (4)
Address:
FEI: (b) (4)

Short summary of manufacturing activities performed:
(b) (4)

[i]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."

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/s/

CHRISTINE H CHUNG
12/15/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: November 10, 2014

To: Paul Imm, Associate Director Immunology, Global Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Janssen Biotech, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 215-986-1110	**Fax number:** 301-796-9728
Email: pimm@its.jnj.com	**Phone number:** 301-796-3420

Subject: BLA 125433/S-014 Simponi Aria (golimumab IV)
FDA Request for information - Clinical

Total no. of pages including cover: **3**

Comments: ***Response requested by cob Friday January 16, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

We refer to supplemental BLA 125433/14 for Simponi Aria dated October 6, 2014, and have the following request for information.

1. We note your proposal to support the labeling changes in section 14 with results from only study CNTO148ART3001. To support the use of this single study, provide analyses of the data, including the Physical Component Score, the Mental Component Score, and the 8 domains of the SF-36, from the pivotal trials of the subcutaneous golimumab rheumatoid arthritis program.

2. We also note the summary SF-36 Physical Component Score results from study C0524T12. Provide the data for and analyses of the Mental Component Score and the 8 domains of the SF-36 as well.

Send your responses to me via secure email at christine.ford@fda.hhs.gov by close of business Friday, January 16, 2015. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

Drafted by:	RGlaser, NNikolov/ 11.7.2014 cford/ 11.10.2014
Cleared thru:	SBarnes/ 11.10.2014
Finalized:	cford/ 11.10.2014

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/s/

CHRISTINE H CHUNG
11/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125433/S-014

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT

Janssen Biotech, Inc.
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Attention: Paul Imm, Pharm.D.
Associate Director, Global Regulatory Affairs

Dear Dr. Imm:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 125433/S-014

PRODUCT NAME: Simponi Aria (golimumab for infusion)

DATE OF SUBMISSION: October 6, 2014

DATE OF RECEIPT: October 6, 2014

This supplemental application proposes to add SF-36 results to labeling.

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 5, 2014, in accordance with 21 CFR 601.2(a).

CONTENT OF LABELING

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.

FDAAA TITLE VIII RESPONSIBILITIES

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).

SUBMISSION REQUIREMENTS

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.

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).

If you have questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG
10/20/2014