CLINICAL BRIEFS

Review of the Clinical Information for SIMPONI™ (golimumab) In Rheumatoid Arthritis

By Jack Alan McCain Jr.

A review of recently published data
with a commentary for managed care decision makers
by Roy Fleischmann, MD

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Review of the Clinical Information For SIMPONI™ (golimumab) in Rheumatoid Arthritis

By Jack Alan McCain Jr.

SIMPONI™ (golimumab) was approved by the U.S. Food and Drug Administration on April 24, 2009, as a monthly subcutaneous blocker of tumor necrosis factor-alpha (TNF-α), indicated for adults with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX). SIMPONI™ also is indicated for treatment of adults with active psoriatic arthritis (PsA), alone or in combination with MTX, and adults with active ankylosing spondylitis (AS).

SIMPONI™ is a fully human $IgG1_K$ monoclonal antibody specific for TNF-α (SIMPONI™ Prescribing Information). SIMPONI™ was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. SIMPONI™ binds to both soluble and transmembrane forms of TNF-α, thus preventing TNF-α from binding with its receptors. SIMPONI™ does not bind with human lymphotoxin. SIMPONI™ is administered monthly in a single 50-mg dose, via a prefilled autoinjector or prefilled syringe. Once-monthly doses of SIMPONI™ 100 mg also were studied. There was no clear evidence of improved American College of Rheumatology (ACR) response with the higher SIMPONI™ dose group (100 mg) compared to the lower SIMPONI™ dose group. This Clinical Brief primarily will report results for the approved dose of SIMPONI™ 50 mg plus MTX in comparison with placebo.

Efficacy of SIMPONI™ in phase 3 RA studies

SIMPONI™ was studied for the treatment of moderately to severely active RA in three phase 3 trials that enrolled different patient populations with respect to previous treatment. These multicenter, randomized, double-blind controlled trials included 1,542 patients age 18 or older with moderately to severely active RA.

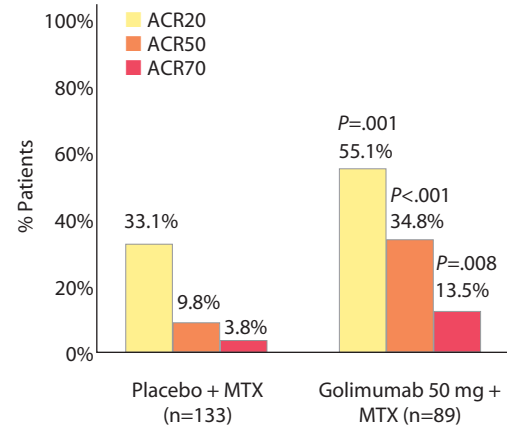
GO-FORWARD. Moderately to severely active RA patients for whom a stable dose of MTX (≥15 mg/week but ≤25 mg/week during the 4 weeks prior to screening) provided an inadequate response and who had not been previously treated with a biologic TNF blocker (N=444) were enrolled in GO-FORWARD (Keystone 2009). Active RA was defined as ≥4 swollen joints out of a total of 66 and ≥4 tender joints out of a total of 68, along with at least two of the following criteria: C-reactive protein (CRP) ≥1.5 mg/dL or erythrocyte sedimentation rate (ESR) ≥28 mm/hour; morning stiffness that persisted for ≥30 minutes; bone erosion confirmed by radiographs or magnetic resonance imaging (MRI); or anti-cyclic citrullinated peptide (anti-CCP) antibody-positive or rheumatoid-factor (RF) positive.

A primary endpoint was the proportion of patients with an ACR20 response at Week 14. Additionally, another endpoint was the change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24. ACR20 response at Week 14 (Figure 1) was achieved by 33.1 and 55.1 percent of the placebo plus MTX and SIMPONI™ 50 mg plus MTX groups, respectively (*P*=.001). At baseline, median HAQ-DI scores were 1.250 in the placebo plus MTX group and 1.375 in the SIMPONI™ 50 mg plus MTX group. At Week 24, median improvement from baseline in HAQ-DI was –0.13 and –0.38 in the placebo plus MTX and SIMPONI™ 50 mg plus MTX groups (*P*<.001), respectively (Keystone 2009).

GO-AFTER. GO-AFTER enrolled moderately to severely active RA patients (N=461) who were previously treated with one or more doses of a TNF-α blocker without a serious adverse event (Smolen 2009). Past experience with an anti-TNF blocker was at least 8 to 12 weeks prior to the administration of the study agent. Patients had a diagnosis of RA for at least 3 months prior to enrollment, and persistent active disease defined as ≥4 swollen joints and ≥4 tender joints. Reasons for anti-TNF blocker discontinuation included inefficacy (58 percent), or reasons unrelated to effectiveness, such as intolerance or accessibility issues (53 percent); more than one reason could exist for the discontinuation (Smolen 2009). At Week 14 (Figure 2), the primary endpoint of patients achieving an ACR20 response was met by 18 percent of patients in the placebo group versus 35 percent of anti-TNF–experienced patients who were given SIMPONI™ 50 mg plus MTX (*P*=.006). By week 24, 34 percent of patients in the placebo group had a minimally clinically important reduction (≥0.25 unit change) in HAQ-DI, compared with 50 percent in the SIMPONI™ 50 mg group (*P*=.0044).

FIGURE 1

Percentage of patients achieving ACR responses at Week 14 in GO-FORWARD

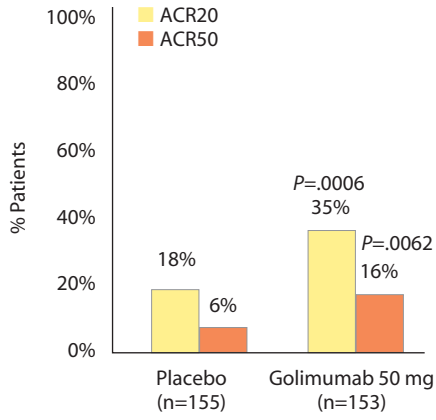


ACR20=Met American College of Rheumatology criteria for symptom improvement of 20 percent from baseline, ACR50=symptom improvement of 50 percent, ACR70=symptom improvement of 70 percent, MTX=methotrexate, RA=rheumatoid arthritis.

Source: Adapted from Keystone 2009

FIGURE 2

Percentage of moderately to severely active RA patients achieving ACR responses at Week 14 in GO-AFTER



If patients were on stable doses of methotrexate, sulfasalazine, and/or hydroxychloroquine at baseline, they were permitted to continue these drugs during the study.

ACR20=Met American College of Rheumatology criteria for symptom improvement of 20 percent from baseline, ACR50=symptom improvement of 50 percent, RA=rheumatoid arthritis.

Source: Adapted from Smolen 2009

GO-BEFORE. A moderately to severely active, MTX-naïve RA population (N=637) was studied in GO-BEFORE (Emery 2009). Eligible patients had received no more than 3 weekly doses of MTX as RA treatment; had ≥4 swollen joints; ≥4 tender joints; and at least two of the following criteria: CRP ≥1.5 mg/dL or ESR ≥28 mm/hour; morning stiffness that persisted for ≥30 minutes; bone erosion confirmed by radiographs or MRI; or anti-CCP antibody-positive or RF positive. Concomitant use of nonsteroidal anti-inflammatory drugs, other analgesics for RA, and oral corticosteroids were permitted if the doses were stable 2 or more weeks prior to initiation of treatment with the study agent and during the study.

The primary endpoint of a difference in the ACR50 response at Week 24 between the combined group of SIMPONI™ 50 mg plus MTX (n=159) and SIMPONI™ 100 mg plus MTX (n=159) versus placebo plus MTX (n=160) was not met (38.4 percent of the combined group versus 29.4 percent of patients in the placebo plus MTX group [P=.053]). The ACR50 response rate at Week 24 was significantly different for SIMPONI™ 50 mg plus MTX (40.3 percent) versus placebo plus MTX (29.4 percent; *P*=.042). The ACR20 response rate at Week 24 was significantly different for SIMPONI™ 50 mg plus MTX (61.6 percent) versus placebo plus MTX (49.4 percent; *P*=.028).

Important Safety Information

Risk of infections. Patients treated with SIMPONI™ are at a higher risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as MTX or corticosteroids. Discontinue SIMPONI™ if a patient develops a serious infection.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients often presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before and during SIMPONI™ use. Treatment for latent infection should be initiated prior to SIMPONI™ use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. 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.**

The risks and benefits of SIMPONI™ treatment should be carefully considered before initiation of therapy in patients with chronic or recurrent infection. Do not start SIMPONI™ in patients with clinically important active infections, including localized infections. Closely monitor patients for the development of signs and symptoms of infection during and after SIMPONI™ treatment, including the possible development of TB in patients who tested negative for latent TB infection prior to therapy initiation.

Other serious infections observed in patients treated with SIMPONI™ included sepsis, pneumonia, cellulitis, abscess, and hepatitis B infection.

Hepatitis B reactivation. The use of TNF-blocking agents including SIMPONI™ has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers. In some cases, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these cases occurred in patients given concomitant immunosuppressants.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before SIMPONI™ initiation. Exercise caution when prescribing SIMPONI™ for patients identified as carriers of HBV and monitor closely for active HBV infection during and following the end of SIMPONI™ therapy. SIMPONI™ should be discontinued in patients who develop HBV reactivation and antiviral therapy should be initiated with appropriate supportive treatment. Exercise caution when considering resumption of SIMPONI™, and monitor patients closely.

Malignancies. In the controlled portions of clinical trials of all TNF-blocking agents including SIMPONI™, more cases of lymphoma have been observed among patients receiving TNF-blocking treatment compared with control patients. In clinical trials, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI™ group compared with an incidence of 0 (95% CI: 0, 0.96) in the placebo group. In clinical trials, the incidence of malignancies other than lymphoma was not increased with exposure to SIMPONI™ and was similar to expected incidence in the general population. The risks and benefits of TNF-blocker therapy must be considered before initiating therapy in patients with a known malignancy or who develop a malignancy.

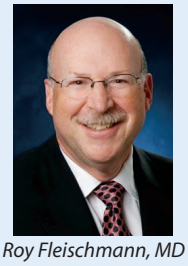
Heart failure. Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported with TNF blockers. Exer-

Rheumatology Considerations

A New Agent for the Treatment of Rheumatoid Arthritis

By Roy Fleischmann, MD, Clinical Professor of Medicine, University of Texas Southwestern Medical Center, and Co-Medical Director, Metroplex Clinical Research Center, Dallas

SIMPONI™ is approved for a monthly 50 mg dose, via subcutaneous (SC) administration and given in addition to methotrexate (MTX), in patients with moderately to severely active rheumatoid arthritis. For these patients, SIMPONI™ may be given in combination with corticosteroids, nonbiologic disease modifying antirheumatic drugs, and/or nonsteroidal anti-inflammatory drugs.



Roy Fleischmann, MD

In clinical trials (Smolen 2009, Keystone 2009, Emery 2009), SIMPONI™ has been shown to be effective in reducing signs and symptoms in patients who are incomplete responders or naïve to MTX, and in those who have experience with anti-tumor necrosis factor (TNF)-α medications. Health care providers should be enthusiastic about an option with a demonstrated safety profile across five clinical studies including moderately to severe active RA, active psoriatic arthritis, and active ankylosing spondylitis patients (SIMPONI™ Prescribing Information). SIMPONI™ also has a once-monthly SC administration via autoinjector that is convenient for patients. SIMPONI™ is intended for use under the guidance and supervision of a physician. Patients also may self-inject after physician approval and proper training.

In summary, SIMPONI™ has shown efficacy in a broad range of patients with moderately to severely active RA and has a demonstrated safety profile in clinical trials that provides an option to patients, physicians, and insurers. Its once-monthly SC administration is a benefit and an important addition to our therapeutic armamentarium.

Disclosure

Roy Fleischmann, MD, has received grant/research support and served as a consultant for Centocor Ortho Biotech Inc.

cise caution and monitor patients with heart failure. Discontinue SIMPONI™ if new or worsening symptoms of heart failure appear.

Demyelinating disorders. TNF-blocking agents have been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis. Exercise caution in considering SIMPONI™ in patients with CNS demyelinating disorders.

Hematologic cytopenias. There have been post marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF blockers. Exercise caution when using SIMPONI™ in patients with significant cytopenias.

Use with other drugs. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections, therefore the use of SIMPONI™ in combination with these products is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. Patients receiving SIMPONI™ can receive vaccinations, except for live vaccines.

Adverse reactions. The most serious adverse reactions were serious infections and malignancies.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI™ as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI™ compared with 2% of patients in the control group.

Cases of new-onset psoriasis, including pustular and palmoplantar, or exacerbation of pre-existing psoriasis have been reported with the use of TNF blockers, including SIMPONI™. Some of these patients required hospitalization. Most patients had improvements following discontinuation of the TNF blocker. Discontinuation of SIMPONI™ should be considered for severe cases and those that do not improve or that worsen despite typical treatment.

Conclusion

SIMPONI™ 50 mg is administered in one dose, once a month SC via a prefilled autoinjector or prefilled syringe and has been demonstrated to improve signs and symptoms in patients with moderately to severely active RA. It has been shown to be efficacious in patients who are incomplete responder or naïve to MTX, as well as those patients who have been previously treated with at least one anti-TNF agent. SIMPONI™ 50 mg is given in combination with MTX for RA. Before prescribing SIMPONI™ 50 mg, please be sure to review the full Prescribing Information and Medication Guide.

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About the Author

Jack Alan McCain Jr. is a freelance medical writer and editor based in Durham, Conn. He is under contract by MediMedia USA, publisher of Managed Care.

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SIMPONI™ (golimumab) Injection, solution for subcutaneous use
See package insert for Full Prescribing Information.

WARNING
RISK OF SERIOUS INFECTIONS

Patients treated with SIMPONI™ are at increased risk for developing serious infections that may lead to hospitalization or death (see Warnings and Precautions). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. SIMPONI™ should be discontinued if a patient develops a serious infection.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before SIMPONI™ use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI™ use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, 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. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with SIMPONI™ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI™, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy (See Warning and Precautions).

INDICATIONS AND USAGE: Rheumatoid Arthritis SIMPONI™, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis. **Psoriatic Arthritis** SIMPONI™, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis. **Ankylosing Spondylitis** SIMPONI™ is indicated for the treatment of adult patients with active ankylosing spondylitis. **CONTRAINDICATIONS:** None. **WARNINGS AND PRECAUTIONS (see Boxed WARNINGS): Serious Infections** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including SIMPONI™. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. 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™ and these biologic products is not recommended (see Warning and Precautions and Drug Interactions). Treatment with SIMPONI™ should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating SIMPONI™ 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. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI™. SIMPONI™ should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI™ should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI™-treated patients and 1.3% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.4 (95% CI: 4.0, 7.2) for the SIMPONI™ group and 5.3 (95% CI: 3.1, 8.7) for the placebo group. Serious infections observed in SIMPONI™-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection. **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. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating SIMPONI™ 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. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating SIMPONI™, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of SIMPONI™ 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 who have 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. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI™ 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. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI™-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. **Invasive Fungal Infections** For SIMPONI™-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. **Hepatitis B Virus Reactivation** The use of TNF-blockers including SIMPONI™ 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. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI™, 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. **Malignancies** The risks and benefits of TNF-blocker treatment including SIMPONI™ 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 SIMPONI™, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI™ group compared with an incidence of 0 (95% CI: 0., 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI™-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] 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. During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was not elevated in the combined SIMPONI™ group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI™-treated patients was similar to that expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] In controlled trials of other TNF-blockers in 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 1-year clinical trial evaluating the use of 50, 100 and 200 mg of SIMPONI™ in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI™ groups compared to none in the control group. Three of the 6 patients were in the 200-mg SIMPONI™ group. **Congestive Heart Failure** Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers. 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™ has not been studied in patients with a history of CHF and SIMPONI™ should be used with caution in patients with CHF. If a decision is made to administer SIMPONI™ to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI™ should be discontinued if new or worsening symptoms of CHF appear. **Demyelinating Disorders** Use of TNF-blockers has been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS). While no trials have been performed evaluating SIMPONI™ in the treatment of patients with MS, another TNF-blocker was associated with increased disease activity in patients with MS. Therefore, prescribers should exercise caution in considering the use of TNF-blockers including SIMPONI™ in patients with CNS demyelinating disorders including MS. **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™ and abatacept is not recommended (see Drug Interactions). **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™, is not recommended (see Drug Interactions). **Hematologic Cytopenias** There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. Although, there were no cases of severe cytopenias seen in the SIMPONI™ clinical trials, caution should be exercised when using TNF-blockers, including SIMPONI™, in patients who have significant cytopenias. **Vaccinations** Patients treated with SIMPONI™ may

receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI™. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI™-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI™-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI™ does not suppress the humoral immune response to the pneumococcal vaccine. **ADVERSE REACTIONS** 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. **Clinical Studies Experience** The safety data described below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA and AS). These 5 trials included 639 control-treated patients and 1659 SIMPONI™-treated patients including 1089 with RA, 292 with PsA, and 277 with AS. The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI™-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI™ in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%). The most serious adverse reactions were: Serious Infections; Malignancies. Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI™-treated patients as compared with 6% and 5% of control-treated patients, respectively. **Infections** In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI™-treated patients compared to 25% of control-treated patients. **Liver Enzyme Elevations** There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI™ in patients with RA, PsA, and AS through Week 16, ALT elevations ≥5 x ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI™-treated patients, and ALT elevations ≥3 x ULN occurred in 2% of control-treated patients and 2% of SIMPONI™-treated patients. Since many of the patients in the Phase 3 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between golimumab and liver elevation is not clear. **Autoimmune Disorders and Autoantibodies** The use of TNF-blockers has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI™ treatment and the development of newly positive anti-dsDNA antibodies. **Injection Site Reactions** In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI™ treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with SIMPONI™ developed anaphylactic reactions. **Psoriasis: New-Onset and Exacerbations** Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI™ should be considered for severe cases and those that do not improve or that worsen despite topical treatments. **Immunogenicity** Antibodies to SIMPONI™ were detected in 57 (4%) of SIMPONI™-treated patients across the Phase 3 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the 3 indications. Patients who received SIMPONI™ with concomitant MTX had a lower proportion of antibodies to SIMPONI™ than patients who received SIMPONI™ without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI™ in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay. The small number of patients positive for antibodies to SIMPONI™ 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™ in an ELISA assay, and are 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™ 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 combined SIMPONI™ groups during the controlled period of the 5 pooled Phase 3 trials through Week 16 in patients with RA, PsA, and AS.

Table 1 **Adverse drug reactions reported by ≥1% of Patients in the Phase 3 trials of RA, AS and PsA through Week 16**[a]

	Placebo ± **DMARDS**	SIMPONI™ ± **DMARDS**
Patients treated	639	1659
Adverse Reaction (Preferred Term)		
Upper respiratory tract infection	37 (6%)	120 (7%)
Nasopharyngitis	31 (5%)	91 (6%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Injection site erythema	6 (1%)	56 (3%)
Hypertension	9 (1%)	48 (3%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Bronchitis	9 (1%)	31 (2%)
Dizziness	7 (1%)	32 (2%)
Sinusitis	7 (1%)	27 (2%)
Influenza	7 (1%)	25 (2%)
Pharyngitis	8 (1%)	22 (1%)
Rhinitis	4 (< 1%)	20 (1%)
Pyrexia	4 (< 1%)	20 (1%)
Oral herpes	2 (< 1%)	16 (1%)
Paraesthesia	2 (< 1%)	16 (1%)

[a] Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low-dose corticosteroids (≤10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials)

DRUG INTERACTIONS: Methotrexate. For the treatment of RA, SIMPONI™ should be used with MTX. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI™ in the treatment of PsA or AS, SIMPONI™ can be used with or without MTX in the treatment of PsA and AS. **Biologic Products for RA, PsA, and/or AS** 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™ with abatacept or anakinra is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information to provide recommendations regarding the concomitant use of SIMPONI™ and other biologic products approved to treat RA, PsA, or AS. **Live Vaccines** Live vaccines should not be given concurrently with SIMPONI™. **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™ 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. **USE IN SPECIFIC POPULATIONS: Pregnancy** Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI™ in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI™ 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 (360 times greater than the maximum recommended human dose-MHRD) 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 (860 times and 310 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 6 months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. **Nursing Mothers** It is not known whether SIMPONI™ 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™, 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. **Pediatric Use** Safety and effectiveness of SIMPONI™ in patients less than 18 years of age have not been established. **Geriatric Use** In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI™-treated patients ages 65 or older (N=155) compared with younger SIMPONI™-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™. **OVERDOSAGE** In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI™ without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMPONI™. There were no SIMPONI™ overdoses in the clinical studies. **PATIENT COUNSELING INFORMATION Patient Counseling** Patients should be advised of the potential benefits and risks of SIMPONI™. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI™ therapy and to read it each time the prescription is renewed. **Infections** Inform patients that SIMPONI™ 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™. **Allergic Reactions** Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect™ autoinjector contains dry natural rubber (a derivative of latex). **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.

References: 1. SEER [database online]. U.S. Population Data—1969-2004. Bethesda, MD; National Cancer Institute. Release date: January 3, 2007. Available at: http://www.seer.cancer.gov/popdata.

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