

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

SIMPONI (golimumab) Injection, solution for subcutaneous use  
Initial U.S. Approval: 2009

**WARNINGS: SERIOUS INFECTIONS**

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal, and other opportunistic infections have occurred in patients receiving SIMPONI (5.1).
- SIMPONI should be discontinued 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 (5.1).
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1).

**MALIGNANCY**

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member (5.2).

**RECENT MAJOR CHANGES**

Boxed Warning, MALIGNANCY	11/2009
Warnings and Precautions, Malignancies (5.2)	11/2009
Warnings and Precautions, Demyelinating disorders (5.4)	5/2010

**INDICATIONS AND USAGE**

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

- Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate (1.1)
- Active Psoriatic Arthritis (PsA) in adults, alone or in combination with methotrexate (1.2)
- Active Ankylosing Spondylitis in adults (AS) (1.3)

**DOSAGE AND ADMINISTRATION**

Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis (2.1)

- 50 mg administered by subcutaneous injection once a month.

**DOSAGE FORMS AND STRENGTHS**

- 50 mg/0.5 mL in a single dose prefilled SmartJect autoinjector (3)
- 50 mg/0.5 mL in a single dose prefilled syringe (3)

**CONTRAINDICATIONS**

- None (4)

**WARNINGS AND PRECAUTIONS**

- Serious Infections – Do not start SIMPONI during an active infection. If an infection develops, monitor carefully, and stop SIMPONI if infection becomes serious (5.1).
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI, consider empiric antifungal therapy for those who reside 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 and begin anti-viral therapy (5.1).
- Malignancies – The incidence of lymphoma was seen more often than in the general U.S. population. Cases of other malignancies have been observed among patients receiving TNF-blockers (5.2).
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI if new or worsening symptoms occur (5.3).
- Demyelinating disease, exacerbation or new onset, may occur (5.4).

**ADVERSE REACTIONS**

Most common adverse reactions (incidence > 5%): upper respiratory tract infection, nasopharyngitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 1-800-457-6399 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Abatacept – increased risk of serious infection (5.1, 5.5, 7.2)
- Anakinra – increased risk of serious infection (5.1, 5.6, 7.2).
- Live vaccines – should not be given with SIMPONI (5.8, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2010

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1 **FULL PRESCRIBING INFORMATION**  
2

3 **WARNINGS**

4 **SERIOUS INFECTIONS**

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

9  
10 **SIMPONI should be discontinued if a patient develops a serious infection.**

11 **Reported infections include:**

- 12  
13  
14 • **Active tuberculosis, including reactivation of latent tuberculosis. Patients with**  
15 **tuberculosis have frequently presented with disseminated or extrapulmonary disease.**  
16 **Patients should be tested for latent tuberculosis before SIMPONI use and during**  
17 **therapy. Treatment for latent infection should be initiated prior to SIMPONI use.**
- 18  
19 • **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and**  
20 **pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may**  
21 **present with disseminated, rather than localized, disease. Antigen and antibody**  
22 **testing for histoplasmosis may be negative in some patients with active infection.**  
23 **Empiric anti-fungal therapy should be considered in patients at risk for invasive**  
24 **fungal infections who develop severe systemic illness.**
- 25  
26 • **Bacterial, viral, and other infections due to opportunistic pathogens.**

27  
28 **The risks and benefits of treatment with SIMPONI should be carefully considered prior to**  
29 **initiating therapy in patients with chronic or recurrent infection.**

30  
31 **Patients should be closely monitored for the development of signs and symptoms of infection**  
32 **during and after treatment with SIMPONI, including the possible development of**  
33 **tuberculosis in patients who tested negative for latent tuberculosis infection prior to**  
34 **initiating therapy [see Warning and Precautions (5.1)].**

35  
36 **MALIGNANCY**

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

40  
41  
42 **1 INDICATIONS AND USAGE**

43 **1.1 Rheumatoid Arthritis**

44 **SIMPONI, in combination with methotrexate, is indicated for the treatment of adult patients with**  
45 **moderately to severely active rheumatoid arthritis.**  
46

47 **1.2 Psoriatic Arthritis**  
48 SIMPONI, alone or in combination with methotrexate, is indicated for the treatment of adult  
49 patients with active psoriatic arthritis.  
50

51 **1.3 Ankylosing Spondylitis**  
52 SIMPONI is indicated for the treatment of adult patients with active ankylosing spondylitis.  
53

## 54 **2 DOSAGE AND ADMINISTRATION**

55 **2.1 Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis**  
56 The SIMPONI dose regimen is 50 mg administered by subcutaneous (SC) injection once a month.

57 For patients with rheumatoid arthritis (RA), SIMPONI should be given in combination with  
58 methotrexate and for patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS),  
59 SIMPONI may be given with or without methotrexate or other non-biologic DMARDs. For  
60 patients with RA, PsA, or AS, corticosteroids, non-biologic DMARDs, and/or NSAIDs may be  
61 continued during treatment with SIMPONI.  
62

63 **2.2 Monitoring to Assess Safety**  
64 Prior to initiating SIMPONI and periodically during therapy, patients should be evaluated for  
65 active tuberculosis and tested for latent infection [*see Warnings and Precautions (5.1)*].  
66

67 **2.3 General Considerations for Administration**  
68 SIMPONI is intended for use under the guidance and supervision of a physician. After proper  
69 training in subcutaneous injection technique, a patient may self inject with SIMPONI if a  
70 physician determines that it is appropriate. Patients should be instructed to follow the directions  
71 provided in the Medication Guide [*see Medication Guide (17.3)*]. To ensure proper use, allow the  
72 prefilled syringe or autoinjector to sit at room temperature outside the carton for 30 minutes prior  
73 to subcutaneous injection. Do not warm SIMPONI in any other way.  
74 Prior to administration, visually inspect the solution for particles and discoloration through the  
75 viewing window. SIMPONI should be clear to slightly opalescent and colorless to light yellow.  
76 The solution should not be used if discolored, or cloudy, or if foreign particles are present. Any  
77 leftover product remaining in the prefilled syringe or prefilled autoinjector should not be used.  
78 NOTE: The needle cover on the prefilled syringe as well as the prefilled syringe in the  
79 autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by  
80 persons sensitive to latex.  
81 Injection sites should be rotated and injections should never be given into areas where the skin is  
82 tender, bruised, red, or hard.  
83

84 **3 DOSAGE FORMS AND STRENGTHS**

85  
86 **SmartJect™ Autoinjector**

87 Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch)  
88 providing 50 mg of SIMPONI per 0.5 mL of solution.

89  
90 **Prefilled Syringe**

91 Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5  
92 mL of solution.

93  
94 **4 CONTRAINDICATIONS**

95 None.

96  
97 **5 WARNINGS AND PRECAUTIONS (see Boxed WARNINGS)**

98 **5.1 Serious Infections**

99 Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral,  
100 protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers  
101 including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis,  
102 candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly  
103 reported with TNF-blockers. Patients have frequently presented with disseminated rather than  
104 localized disease, and were often taking concomitant immunosuppressants such as methotrexate or  
105 corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated  
106 with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these  
107 biologic products is not recommended [*see Warning and Precautions (5.5, 5.6) and Drug*  
108 *Interactions (7.2)*].

109  
110 Treatment with SIMPONI should not be initiated in patients with an active infection, including  
111 clinically important localized infections. The risks and benefits of treatment should be considered  
112 prior to initiating SIMPONI in patients:

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

119  
120 Patients should be closely monitored for the development of signs and symptoms of infection  
121 during and after treatment with SIMPONI. SIMPONI should be discontinued if a patient develops  
122 a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection  
123 during treatment with SIMPONI should undergo a prompt and complete diagnostic workup  
124 appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be  
125 initiated, and the patient should be closely monitored.

126  
127 In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections  
128 were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. In the  
129 controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of

130 serious infections per 100 patient-years of follow-up was 5.4 (95% CI: 4.0, 7.2) for the SIMPONI  
131 group and 5.3 (95% CI: 3.1, 8.7) for the placebo group. Serious infections observed in SIMPONI-  
132 treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal  
133 infections, and hepatitis B infection.

### 134 135 **Tuberculosis**

136 Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients  
137 receiving TNF-blockers, including patients who have previously received treatment for latent or  
138 active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent  
139 infection prior to initiating SIMPONI and periodically during therapy.

140  
141 Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to  
142 reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with  
143 tuberculin skin testing should be considered a positive test result when assessing if treatment for  
144 latent tuberculosis is needed prior to initiating SIMPONI, even for patients previously vaccinated  
145 with Bacille Calmette-Guerin (BCG).

146  
147 Anti-tuberculosis therapy should also be considered prior to initiation of SIMPONI in patients  
148 with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot  
149 be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors  
150 for tuberculosis infection. Consultation with a physician with expertise in the treatment of  
151 tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is  
152 appropriate for an individual patient.

153  
154 Patients should be closely monitored for the development of signs and symptoms of tuberculosis  
155 including patients who tested negative for latent tuberculosis infection prior to initiating therapy.  
156 Tuberculosis should be strongly considered in patients who develop a new infection during  
157 SIMPONI treatment, especially in patients who have previously or recently traveled to countries  
158 with a high prevalence of tuberculosis, or who have had close contact with a person with active  
159 tuberculosis. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA,  
160 and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-  
161 treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary  
162 and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a  
163 high incidence rate of TB.

### 164 165 **Invasive Fungal Infections**

166 For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic,  
167 invasive fungal infection should be suspected if they develop a serious systemic illness.  
168 Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being  
169 performed. Antigen and antibody testing for histoplasmosis may be negative in some patients  
170 with active infection. When feasible, the decision to administer empiric antifungal therapy in  
171 these patients should be made in consultation with a physician with expertise in the diagnosis and  
172 treatment of invasive fungal infections and should take into account both the risk for severe fungal  
173 infection and the risks of antifungal therapy.

176 **Hepatitis B Virus Reactivation**

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

182  
183 Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before  
184 initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to  
185 prescribing TNF-blockers, including SIMPONI, to patients who are carriers of HBV. Adequate  
186 data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in  
187 HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require  
188 treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of  
189 active HBV infection throughout therapy and for several months following termination of therapy.

190  
191 In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy  
192 with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers  
193 after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise  
194 caution when considering resumption of TNF-blockers in this situation and monitor patients  
195 closely.

196  
197 **5.2 Malignancies**

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

207  
208 The risks and benefits of TNF-blocker treatment including SIMPONI should be considered prior  
209 to initiating therapy in patients with a known malignancy other than a successfully treated non-  
210 melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who  
211 develop a malignancy.

212  
213 In the controlled portions of clinical trials of TNF-blockers including SIMPONI, more cases of  
214 lymphoma have been observed among patients receiving anti-TNF treatment compared with  
215 patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the  
216 Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up  
217 was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI group compared with an incidence of 0  
218 (95% CI: 0., 0.96) in the placebo group. In the controlled and uncontrolled portions of these  
219 clinical trials in 2347 SIMPONI-treated patients with a median follow-up of 1.4 years, the  
220 incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population  
221 according to the SEER database (adjusted for age, gender, and race). Patients with RA and other  
222 chronic inflammatory diseases, particularly patients with highly active disease and/or chronic

223 exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the  
224 general population for the development of lymphoma, even in the absence of TNF-blocking  
225 therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-  
226 blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker  
227 therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the  
228 general population for the development of leukemia.

229  
230 During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and  
231 AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was  
232 not elevated in the combined SIMPONI group compared with the placebo group. In the controlled  
233 and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in  
234 SIMPONI-treated patients was similar to that expected in the general U.S. population according to  
235 the SEER database (adjusted for age, gender, and race).<sup>1</sup>

236  
237 In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients  
238 with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide)  
239 a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled  
240 group. In an exploratory 1-year clinical trial evaluating the use of 50, 100 and 200 mg of  
241 SIMPONI in 309 patients with severe persistent asthma, 6 patients developed malignancies other  
242 than NMSC in the SIMPONI groups compared to none in the control group. Three of the 6  
243 patients were in the 200 mg SIMPONI group.

### 245 **5.3 Congestive Heart Failure**

246 Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with  
247 TNF-blockers. In several exploratory trials of other TNF-blockers in the treatment of CHF, there  
248 were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring  
249 hospitalization or increased mortality. SIMPONI has not been studied in patients with a history of  
250 CHF and SIMPONI should be used with caution in patients with CHF. If a decision is made to  
251 administer SIMPONI to patients with CHF, these patients should be closely monitored during  
252 therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

### 254 **5.4 Demyelinating Disorders**

255 Use of TNF-blockers, of which SIMPONI is a member, has been associated with cases of new  
256 onset or exacerbation of central nervous system (CNS) demyelinating disorders, including  
257 multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré  
258 syndrome. In clinical trials, cases of central demyelination, MS, and peripheral demyelinating  
259 polyneuropathy have been reported in patients treated with SIMPONI [*see Adverse Reactions*  
260 (6.1)]. Prescribers should exercise caution in considering the use of TNF-blockers, including  
261 SIMPONI, in patients with central or peripheral nervous system demyelinating disorders.  
262 Discontinuation of SIMPONI should be considered if these disorders develop.

### 264 **5.5 Use with Abatacept**

265 In controlled trials, the concurrent administration of another TNF-blocker and abatacept was  
266 associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and  
267 the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated

268 improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers  
269 including SIMPONI and abatacept is not recommended [*see Drug Interactions (7.2)*].  
270

### 271 **5.6 Use with Anakinra**

272 Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was  
273 associated with a greater portion of serious infections and neutropenia and no additional benefits  
274 compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-  
275 blockers, including SIMPONI, is not recommended [*see Drug Interactions 7.2*].  
276

### 277 **5.7 Hematologic Cytopenias**

278 There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic  
279 anemia, and thrombocytopenia in patients receiving TNF-blockers. Although, there were no cases  
280 of severe cytopenias seen in the SIMPONI clinical trials, caution should be exercised when using  
281 TNF-blockers, including SIMPONI, in patients who have significant cytopenias.  
282

### 283 **5.8 Vaccinations**

284 Patients treated with SIMPONI may receive vaccinations, except for live vaccines. No data are  
285 available on the response to live vaccination or the risk of infection, or transmission of infection  
286 after the administration of live vaccines to patients receiving SIMPONI. In the Phase 3 PsA study,  
287 after pneumococcal vaccination, a similar proportion of SIMPONI-treated and placebo-treated  
288 patients were able to mount an adequate immune response of at least a 2-fold increase in antibody  
289 titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated  
290 patients, the proportions of patients with response to pneumococcal vaccine were lower among  
291 patients receiving MTX compared with patients not receiving MTX. The data suggest that  
292 SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine.  
293

## 294 **6 ADVERSE REACTIONS**

295 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
296 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of  
297 another drug and may not reflect the rates observed in clinical practice.  
298

### 299 **6.1 Clinical Studies Experience**

300 The safety data described below are based on 5 pooled, randomized, double-blind, controlled  
301 Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA, and AS) [*see*  
302 *Clinical Studies (14.1, 14.2 and 14.3)*]. These 5 trials included 639 control-treated patients and  
303 1659 SIMPONI-treated patients including 1089 with RA, 292 with PsA, and 278 with AS. The  
304 proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase  
305 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI-treated patients and 3% for  
306 placebo-treated patients. The most common adverse reactions leading to discontinuation of  
307 SIMPONI in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine  
308 aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%).  
309

310 The most serious adverse reactions were:

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

313 Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions  
314 reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and

315 6% of SIMPONI-treated patients as compared with 6% and 5% of control-treated patients,  
316 respectively.

317

### 318 **Infections**

319 In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in  
320 28% of SIMPONI-treated patients compared to 25% of control-treated patients [for Serious  
321 Infections, *see Warnings and Precautions (5.1)*].

322

### 323 **Liver Enzyme Elevations**

324 There have been reports of severe hepatic reactions including acute liver failure in patients  
325 receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI in patients with RA, PsA, and  
326 AS through Week 16, ALT elevations  $\geq 5 \times$  ULN occurred in 0.2% of control-treated patients and  
327 0.7% of SIMPONI-treated patients and ALT elevations  $\geq 3 \times$  ULN occurred in 2% of control-  
328 treated patients and 2% of SIMPONI-treated patients. Since many of the patients in the Phase 3  
329 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the  
330 relationship between SIMPONI and liver enzyme elevation is not clear.

331

### 332 **Autoimmune Disorders and Autoantibodies**

333 The use of TNF-blockers has been associated with the formation of autoantibodies and, rarely,  
334 with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with  
335 RA, PsA, and AS through Week 14, there was no association of SIMPONI treatment and the  
336 development of newly positive anti-dsDNA antibodies.

337

### 338 **Injection Site Reactions**

339 In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI-treated  
340 patients had injection site reactions compared with 2% of control-treated patients. The majority of  
341 the injection site reactions were mild and the most frequent manifestation was injection site  
342 erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with  
343 SIMPONI developed anaphylactic reactions.

344

### 345 **Psoriasis: New-Onset and Exacerbations**

346 Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been  
347 reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-  
348 existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients  
349 were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these  
350 patients required hospitalization. Most patients had improvement of their psoriasis following  
351 discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when  
352 they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI should be  
353 considered for severe cases and those that do not improve or that worsen despite topical  
354 treatments.

355

### 356 **Immunogenicity**

357 Antibodies to SIMPONI were detected in 57 (4%) of SIMPONI-treated patients across the Phase 3  
358 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the three  
359 indications. Patients who received SIMPONI with concomitant MTX had a lower proportion of  
360 antibodies to SIMPONI than patients who received SIMPONI without MTX (approximately 2%

361 versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI in the  
362 Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as  
363 measured by a cell-based functional assay. The small number of patients positive for antibodies to  
364 SIMPONI limits the ability to draw definitive conclusions regarding the relationship between  
365 antibodies to golimumab and clinical efficacy or safety measures.  
366 The data above reflect the percentage of patients whose test results were considered positive for  
367 antibodies to SIMPONI in an ELISA assay, and are highly dependent on the sensitivity and  
368 specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay  
369 may be influenced by several factors including sample handling, timing of sample collection,  
370 concomitant medications, and underlying disease. For these reasons, comparison of the incidence  
371 of antibodies to SIMPONI with the incidence of antibodies to other products may be misleading.  
372

### 373 Other Adverse Reactions

374 Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the  
375 combined SIMPONI groups during the controlled period of the 5 pooled Phase 3 trials through  
376 Week 16 in patients with RA, PsA, and AS.  
377

**Table 1. Adverse Drug Reactions Reported by  $\geq 1\%$  of Patients in the Phase 3 Trials of RA, PsA, and AS through Week 16<sup>a</sup>**

	Placebo $\pm$ DMARDs	SIMPONI $\pm$ 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%)

378 a Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids ( $\leq 10$  mg  
379 of prednisone/day or equivalent), and/or NSAIDs during the trials.  
380  
381

382 ***Less common clinical trial adverse drug reactions***

383 Adverse drug reactions that occurred <1% during the SIMPONI clinical trials included the  
384 following events listed by system organ class:

385 *Nervous system disorders:* central nervous system demyelinating disorders (such as multiple  
386 sclerosis), peripheral demyelinating polyneuropathy

387

388 **7 DRUG INTERACTIONS**

389 **7.1 Methotrexate**

390 For the treatment of RA, SIMPONI should be used with methotrexate (MTX) [*see Clinical Studies*  
391 (14.1)]. Since the presence or absence of concomitant MTX did not appear to influence the  
392 efficacy or safety of SIMPONI in the treatment of PsA or AS, SIMPONI can be used with or  
393 without MTX in the treatment of PsA and AS [*see Clinical Studies (14.1) and Clinical*  
394 *Pharmacology (12.3)*].

395

396 **7.2 Biologic Products for RA, PsA, and/or AS**

397 An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers  
398 used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI  
399 with abatacept or anakinra is not recommended [*see Warnings and Precautions (5.5 and 5.6)*]. A  
400 higher rate of serious infections has also been observed in RA patients treated with rituximab who  
401 received subsequent treatment with a TNF-blocker. There is insufficient information to provide  
402 recommendations regarding the concomitant use of SIMPONI and other biologic products  
403 approved to treat RA, PsA, or AS.

404

405 **7.3 Live Vaccines**

406 Live vaccines should not be given concurrently with SIMPONI [*see Warnings and Precautions*  
407 (5.8)].

408

409 **7.4 Cytochrome P450 Substrates**

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

417

418 **8 USE IN SPECIFIC POPULATIONS**

419 **8.1 Pregnancy**

420 Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI in  
421 pregnant women. Because animal reproduction and developmental studies are not always  
422 predictive of human response, it is not known whether SIMPONI can cause fetal harm when  
423 administered to a pregnant woman or can affect reproduction capacity. SIMPONI should be used  
424 during pregnancy only if clearly needed.

425

426 An embryofetal developmental toxicology study was performed in which pregnant cynomolgus  
427 monkeys were treated subcutaneously with golimumab during the first trimester with doses up to  
428 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD)

429 and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood  
430 samples collected at the end of the second trimester showed that fetuses were exposed to  
431 golimumab during gestation. In this study, *in utero* exposure to golimumab produced no  
432 developmental defects to the fetus.  
433

434 A pre- and post-natal developmental study was performed in which pregnant cynomolgus  
435 monkeys were treated with golimumab during the second and third trimesters, and during lactation  
436 at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady  
437 state human blood levels for maternal animals and neonates, respectively) and has revealed no  
438 evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum  
439 from the time of birth and for up to six months postpartum. Exposure to golimumab during  
440 gestation and during the postnatal period caused no developmental defects in the infants.  
441

### 442 **8.3 Nursing Mothers**

443 It is not known whether SIMPONI is excreted in human milk or absorbed systemically after  
444 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of  
445 the potential for adverse reactions in nursing infants from SIMPONI, a decision should be made  
446 whether to discontinue nursing or to discontinue the drug, taking into account the importance of  
447 the drug to the mother.  
448

449 In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was  
450 administered subcutaneously during pregnancy and lactation, golimumab was detected in the  
451 breast milk at concentrations that were approximately 400-fold lower than the maternal serum  
452 concentrations.  
453

### 454 **8.4 Pediatric Use**

455 Safety and effectiveness of SIMPONI in pediatric patients less than 18 years of age have not been  
456 established.  
457

### 458 **8.5 Geriatric Use**

459 In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious  
460 infections, and AEs in SIMPONI-treated patients ages 65 or older (N = 155) compared with  
461 younger SIMPONI-treated patients. Because there is a higher incidence of infections in the  
462 geriatric population in general, caution should be used in treating geriatric patients with  
463 SIMPONI.  
464

## 465 **10 OVERDOSAGE**

466 In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of  
467 intravenous SIMPONI without serious adverse reactions or other significant reactions. The  
468 highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000  
469 mg of SIMPONI. There were no SIMPONI overdoses in the clinical studies.  
470

## 471 **11 DESCRIPTION**

472 SIMPONI (golimumab) is a human IgG1 $\kappa$  monoclonal antibody specific for human tumor  
473 necrosis factor alpha (TNF $\alpha$ ) that exhibits multiple glycoforms with molecular masses of  
474 approximately 150 to 151 kilodaltons. SIMPONI was created using genetically engineered mice

475 immunized with human TNF, resulting in an antibody with human-derived antibody variable and  
476 constant regions. SIMPONI is produced by a recombinant cell line cultured by continuous  
477 perfusion and is purified by a series of steps that includes measures to inactivate and remove  
478 viruses.

479  
480 The SIMPONI drug product is a sterile solution of the golimumab antibody supplied as either a  
481 single dose prefilled syringe (with a passive needle safety guard) or a single dose prefilled  
482 autoinjector. The Type 1 glass syringe has a coated stopper. The fixed stainless steel needle (5  
483 bevel, 27G, half-inch) is covered with a needle shield to prevent leakage of the solution through  
484 the needle and to protect the needle during handling prior to administration. The needle shield is  
485 made of a dry natural rubber containing latex.

486  
487 SIMPONI does not contain preservatives. The solution is clear to slightly opalescent, colorless to  
488 light yellow with a pH of approximately 5.5. SIMPONI is provided in one strength: 50 mg of the  
489 golimumab antibody in 0.5 mL of solution. Each 0.5 mL of SIMPONI contains 50 mg of the  
490 golimumab antibody, 0.44 mg of L-histidine and L-histidine monohydrochloride monohydrate,  
491 20.5 mg of sorbitol, 0.08 mg of polysorbate 80, and Water for Injection.

## 492 493 **12 CLINICAL PHARMACOLOGY**

### 494 **12.1 Mechanism of Action**

495 Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane  
496 bioactive forms of human TNF $\alpha$ . This interaction prevents the binding of TNF $\alpha$  to its receptors,  
497 thereby inhibiting the biological activity of TNF $\alpha$  (a cytokine protein). There was no evidence of  
498 the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab  
499 antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human  
500 monocytes expressing transmembrane TNF in the presence of complement or effector cells.  
501 Elevated TNF $\alpha$  levels in the blood, synovium, and joints have been implicated in the  
502 pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic  
503 arthritis, and ankylosing spondylitis. TNF $\alpha$  is an important mediator of the articular inflammation  
504 that is characteristic of these diseases. Golimumab modulated the *in vitro* biological effects  
505 mediated by TNF in several bioassays, including the expression of adhesion proteins responsible  
506 for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of  
507 proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

### 508 509 **12.2 Pharmacodynamics**

510 In clinical studies, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix  
511 metalloproteinase 3 (MMP-3), intercellular adhesion molecule (ICAM)-1 and vascular endothelial  
512 growth factor (VEGF) were observed following SIMPONI administration in patients with RA,  
513 PsA, and AS.

### 514 515 **12.3 Pharmacokinetics**

516 Following subcutaneous (SC) administration of SIMPONI to healthy subjects and patients with  
517 active RA, the median time to reach maximum serum concentrations ( $T_{max}$ ) ranged from 2 to 6  
518 days. A SC injection of 50 mg SIMPONI to healthy subjects produced a mean maximum serum  
519 concentration ( $C_{max}$ ) of approximately 2.5  $\mu\text{g/mL}$ . SIMPONI exhibited dose-proportional  
520 pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10.0 mg/kg

521 following a single intravenous (IV) dose. Following a single IV administration over the same  
522 dose range in patients with active RA, mean systemic clearance of SIMPONI was estimated to be  
523 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg. The  
524 volume of distribution for SIMPONI indicates that SIMPONI is distributed primarily in the  
525 circulatory system with limited extravascular distribution. Median terminal half-life values were  
526 estimated to be approximately 2 weeks in healthy subjects and patients with active RA, PsA or  
527 AS. By cross-study comparisons of mean  $AUC_{inf}$  values following an IV or SC administration of  
528 SIMPONI, the absolute bioavailability of SC SIMPONI was estimated to be approximately 53%.  
529

530 When 50 mg SIMPONI was administered SC to patients with RA, PsA or AS every 4 weeks,  
531 serum concentrations appeared to reach steady state by Week 12. With concomitant use of  
532 methotrexate (MTX), treatment with 50 mg SIMPONI SC every 4 weeks resulted in a mean  
533 steady-state trough serum concentration of approximately 0.4-0.6  $\mu\text{g/mL}$  in patients with active  
534 RA, approximately 0.5  $\mu\text{g/mL}$  in patients with active PsA, and approximately 0.8  $\mu\text{g/mL}$  in  
535 patients with active AS. Patients with RA, PsA and AS treated with SIMPONI 50 mg and MTX  
536 had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of  
537 golimumab, respectively compared with those treated with SIMPONI 50 mg without MTX. The  
538 presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% [*see Adverse*  
539 *Reactions (6.1)*]. For RA, SIMPONI should be used with MTX. In the PsA and AS trials, the  
540 presence or absence of concomitant MTX did not appear to influence clinical efficacy and safety  
541 parameters [*see Drug Interactions (7.1) and Clinical Studies (14.1)*].  
542

543 Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or  
544 sulfasalazine did not influence the apparent clearance of SIMPONI.  
545

546 Population PK analyses showed there was a trend toward higher apparent clearance of SIMPONI  
547 with increasing weight. However, across the PsA and AS populations, no meaningful differences  
548 in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-  
549 experienced and TNF-blocker-naïve patients (Study RA-2) did show evidence of a reduction in  
550 clinical efficacy with increasing body weight, but this effect was observed for both tested doses of  
551 SIMPONI (50 mg and 100 mg). Therefore, there is no need to adjust the dosage of SIMPONI  
552 based on a patient's weight.  
553

554 Population PK analyses suggested no PK differences between male and female patients after body  
555 weight adjustment in the RA and PsA trials. In the AS trial, female patients showed 13% higher  
556 apparent clearance than male patients after body weight adjustment. Subgroup analysis based on  
557 gender showed that both female and male patients achieved clinically significant response at the  
558 proposed clinical dose. Dosage adjustment based on gender is not needed.  
559

560 Population PK analyses indicated that PK parameters of SIMPONI were not influenced by age in  
561 adult patients. Patients with age  $\geq 65$  years had apparent clearance of SIMPONI similar to  
562 patients with age  $< 65$  years. No ethnicity-related PK differences were observed between  
563 Caucasians and Asians, and there were too few patients of other races to assess for PK differences.  
564

565 Patients who developed anti-SIMPONI antibodies generally had lower steady-state serum trough  
566 concentrations of SIMPONI.

567  
568 No formal study of the effect of renal or hepatic impairment on the PK of golimumab was  
569 conducted.  
570

## 571 **13 NONCLINICAL TOXICOLOGY**

### 572 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

573 Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic  
574 potential. Mutagenicity studies have not been conducted with golimumab. A fertility study  
575 conducted in mice using an analogous anti-mouse TNF $\alpha$  antibody showed no impairment of  
576 fertility.  
577

## 578 **14 CLINICAL STUDIES**

### 579 **14.1 Rheumatoid Arthritis**

580 The efficacy and safety of SIMPONI were evaluated in 3 multicenter, randomized, double-blind,  
581 controlled trials (Studies RA-1, RA-2, and RA-3) in 1542 patients  $\geq$  18 years of age with  
582 moderately to severely active RA, diagnosed according to the American College of Rheumatology  
583 (ACR) criteria, for at least 3 months prior to administration of study agent. Patients were required  
584 to have at least 4 swollen and 4 tender joints. SIMPONI was administered subcutaneously at  
585 doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected  
586 and analyzed through Week 24. Patients were allowed to continue stable doses of concomitant  
587 low dose corticosteroids (equivalent to  $\leq$  10 mg of prednisone a day) and/or NSAIDs and patients  
588 may have received oral MTX during the trials.  
589

590 Study RA-1 evaluated 461 patients who were previously treated (at least 8 to 12 weeks prior to  
591 administration of study agent) with one or more doses of a biologic TNF-blocker without a serious  
592 adverse reaction. Patients may have discontinued the biologic TNF-blocker for a variety of  
593 reasons. Patients were randomized to receive placebo (n = 155), SIMPONI 50 mg (n = 153), or  
594 SIMPONI 100 mg (n = 153). Patients were allowed to continue stable doses of concomitant  
595 MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the trial. The use of other  
596 DMARDs including cytotoxic agents or other biologics was prohibited.  
597

598 Study RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15  
599 mg/week of MTX and who had not been previously treated with a biologic TNF-blocker. Patients  
600 were randomized to receive background MTX (n = 133), SIMPONI 50 mg + background MTX (n  
601 = 89), SIMPONI 100 mg + background MTX (n = 89), or SIMPONI 100 mg monotherapy (n =  
602 133). The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was  
603 prohibited.  
604

605 Study RA-3 evaluated 637 patients with active RA who were MTX-naïve and had not previously  
606 been treated with a biologic TNF-blocker. Patients were randomized to receive MTX (n = 160),  
607 SIMPONI 50 mg + MTX (n = 159), SIMPONI 100 mg + MTX (n = 159), or SIMPONI 100 mg  
608 monotherapy (n = 159). For patients receiving MTX, MTX was administered at a dose of 10  
609 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The use of other  
610 DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.  
611

612 The primary endpoint in Study RA-1 and Study RA-2 was the percentage of patients achieving an  
613 ACR 20 response at Week 14 and the primary endpoint in Study RA-3 was the percentage of  
614 patients achieving an ACR 50 response at Week 24.

615  
616 In Studies RA-1, RA-2, and RA-3, the median duration of RA disease was 9.4, 5.7, and 1.2 years;  
617 and 99%, 75%, and 54% of the patients used at least one DMARD in the past, respectively.  
618 Approximately 77% and 57% of patients received concomitant NSAIDs and low dose  
619 corticosteroids, respectively, in the 3 pooled RA trials.

### 621 **Clinical Response**

622 In the 3 RA trials, a greater percentage of patients treated with the combination of SIMPONI and  
623 MTX achieved ACR responses at Week 14 (Studies RA-1 and RA-2) and Week 24 (Studies RA-  
624 1, RA-2, and RA-3) versus patients treated with the MTX alone. There was no clear evidence of  
625 improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower  
626 SIMPONI dose group (50 mg). In Studies RA-2 and RA-3, the SIMPONI monotherapy groups  
627 were not statistically different from the MTX monotherapy groups in ACR responses. Table 2  
628 shows the proportion of patients with the ACR response for the SIMPONI 50 mg and control  
629 groups in Studies RA-1, RA-2, and RA-3. In the subset of patients who received SIMPONI in  
630 combination with MTX in Study RA-1, the proportion of patients achieving ACR 20, 50 and 70  
631 responses at week 14 were 40%, 18%, and 13%, respectively, in the SIMPONI 50 mg + MTX  
632 group (N = 103) compared with 17%, 6%, and 2%, respectively, in the placebo + MTX group (N  
633 = 107). Table 3 shows the percent improvement in the components of the ACR response criteria  
634 for the SIMPONI 50 mg + MTX and MTX groups in Study RA-2. The percent of patients  
635 achieving ACR 20 responses by visit for Study RA-2 is shown in Figure 1. ACR 20 responses  
636 were observed in 38% of patients in the SIMPONI 50 mg + MTX group at the first assessment  
637 (Week 4) after the initial SIMPONI administration.

638  
639

**Table 2. Studies RA-1, RA-2, and RA-3 Proportion of Patients with an ACR Response<sup>a</sup>**

	Study RA-1 Active RA previously treated with one or more doses of TNF-blockers		Study RA-2 Active RA, despite MTX		Study RA-3 Active RA, MTX Naïve	
	Placebo ± DMARDs <sup>b</sup>	SIMPONI 50 mg ± DMARDs <sup>b</sup>	Background MTX	SIMPONI 50 mg + Background MTX	MTX	SIMPONI 50 mg + MTX
N <sup>c</sup>	155	153	133	89	160	159
<b>ACR 20</b>						
Week 14	18%	35%	33%	55%	NA	NA
Week 24	17%	34%	28%	60%	49%	62%
<b>ACR 50</b>						
Week 14	6%	16%	10%	35%	NA	NA
Week 24	5%	18%	14%	37%	29%	40%
<b>ACR 70</b>						
Week 14	2%	10%	4%	13%	NA	NA
Week 24	3%	12%	5%	20%	16%	24% <sup>d</sup>
a	Approximately 78% and 58% of the patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and NSAIDs, respectively, during the 3 pooled RA trials.					
b	DMARDs in Study RA-1 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ, and SSZ, respectively).					
c	N reflects randomized patients.					
d	Not significantly different from MTX monotherapy.					
NA	Not applicable, as data was not collected at Week 14 in Study RA-3.					

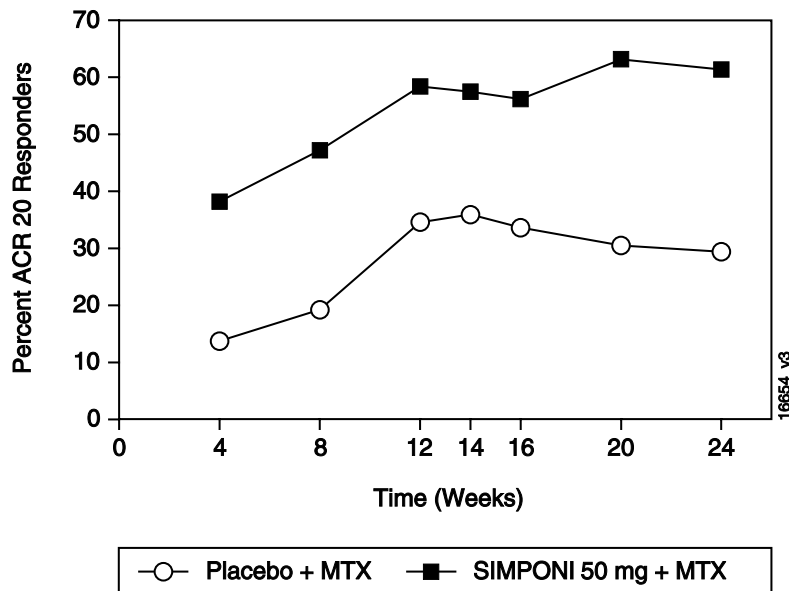
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643

**Table 3. Study RA-2 – Median Percent Improvement from Baseline in the Individual ACR Components at Weeks 14<sup>a</sup>**

	<b>Background MTX</b>	<b>SIMPONI 50 mg + Background MTX</b>
N <sup>b</sup>	133	89
<b>Number of swollen joints (0-66)</b>		
Baseline	12	13
Week 14	38%	62%
<b>Number of tender joints (0-68)</b>		
Baseline	21	26
Week 14	30%	60%
<b>Patient’s assessment of pain (0-10)</b>		
Baseline	5.7	6.1
Week 14	18%	55%
<b>Patient’s global assessment of disease activity (0-10)</b>		
Baseline	5.3	6.0
Week 14	15%	45%
<b>Physician’s global assessment of disease activity (0-10)</b>		
Baseline	5.7	6.1
Week 14	35%	55%
<b>HAQ score (0-3)</b>		
Baseline	1.25	1.38
Week 14	10%	29%
<b>CRP (mg/dl)</b>		
Baseline	0.8	1.0
Week 14	2%	44%
<p>Note: Baseline values are medians.</p> <p>a In Study RA-2, about 70% and 85% of patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs during the trials, respectively.</p> <p>b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.</p>		

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646

647 **Figure 1. Study RA - 2 – Percent of Patients Achieving ACR 20 Response by Visit: Randomized**  
648 **Patients\***  
649



\* The same patients may not have responded at each timepoint.

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### **Physical Function Response in Patients with RA**

In Studies RA-1 and RA-2, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24: 0.25 vs. 0.05 in RA-1, 0.47 vs. 0.13 in RA-2, respectively. Also in Studies RA-1 and RA-2, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at Week 24: 44% vs. 28%, 65% vs. 35%, respectively.

### **14.2 Psoriatic Arthritis**

The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) despite NSAID or DMARD therapy (Study PsA). Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF-blocker was not allowed. Patients were randomly assigned to placebo (n = 113), SIMPONI 50 mg (n = 146), or SIMPONI 100 mg (n = 146) given subcutaneously every 4 weeks. Patients were allowed to receive stable doses of concomitant MTX ( $\leq 25$  mg/week), low dose oral corticosteroids (equivalent to  $\leq 10$  mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

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678

Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). The

679 median duration of PsA disease was 5.1 years, 78% of patients received at least one DMARD in  
680 the past, and approximately 48% of patients received MTX, and 16% received low dose oral  
681 steroids.

682  
683 **Clinical Response in Patients with PsA**

684 SIMPONI ± MTX, compared with placebo ± MTX, resulted in significant improvement in signs  
685 and symptoms as demonstrated by the proportion of patients with an ACR 20 response at Week 14  
686 in Study PsA (see Table 4). There was no clear evidence of improved ACR response with the  
687 higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).  
688 ACR responses observed in the SIMPONI-treated groups were similar in patients receiving and  
689 not receiving concomitant MTX. Similar ACR 20 responses at Week 14 were observed in patients  
690 with different PsA subtypes. However, the number of patients with arthritis mutilans was too  
691 small to allow meaningful assessment. SIMPONI 50 mg treatment also resulted in significantly  
692 greater improvement compared with placebo for each ACR component in Study PsA (Table 5).  
693 Treatment with SIMPONI resulted in improvement in enthesitis and skin manifestations in  
694 patients with PsA. However, the safety and efficacy of SIMPONI in the treatment of patients with  
695 plaque psoriasis has not been established.

696  
697 The percent of patients achieving ACR 20 responses by visit for Study PsA is shown in Figure 2.  
698 ACR 20 responses were observed in 31% of patients in the SIMPONI 50 mg + MTX group at the  
699 first assessment (Week 4) after the initial SIMPONI administration.

700  
701 **Table 4. Study PsA - Proportion of Patients with ACR Responses**

	Placebo ± MTX <sup>a</sup>	SIMPONI 50 mg ± MTX <sup>a</sup>
N <sup>b</sup>	113	146
<b>ACR 20</b>		
Week 14	<b>9 %</b>	<b>51 %</b>
Week 24	12 %	52 %
<b>ACR 50</b>		
Week 14	2 %	30 %
Week 24	4 %	32 %
<b>ACR 70</b>		
Week 14	1 %	12 %
Week 24	1 %	19 %
a In Study PsA, about 48%, 16%, and 72% of the patients received stable doses of MTX (≤ 25 mg/day), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively. b N reflects randomized patients. Bold text indicates primary endpoint		

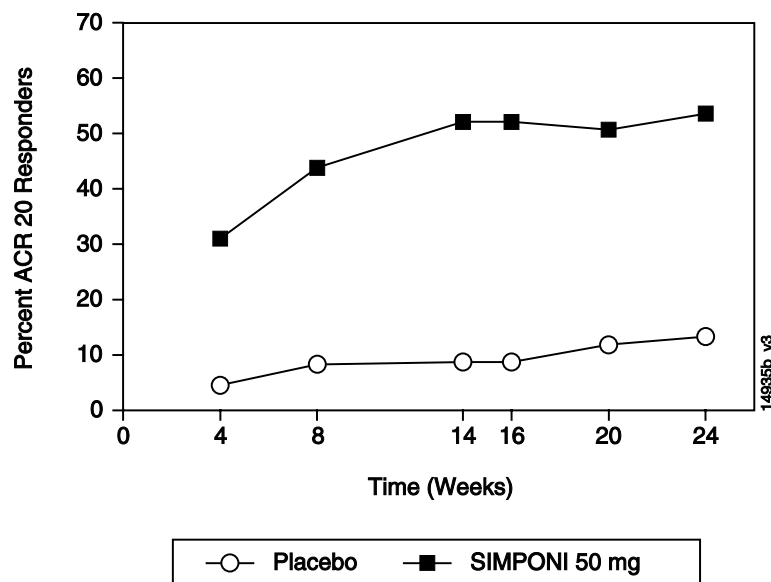
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**Table 5. Study PsA - Percent Improvement in ACR Components at Week 14**

	Placebo± MTX <sup>a</sup>	SIMPONI 50 mg ± MTX <sup>a</sup>
N <sup>b</sup>	113	146
<b>Number of swollen joints (0-66)</b>		
Baseline	10.0	11.0
Week 14	8 %	60 %
<b>Number of tender joints (0-68)</b>		
Baseline	18.0	19.0
Week 14	0 %	54 %
<b>Patient's assessment of pain (0-10)</b>		
Baseline	5.4	5.8
Week 14	-1 %	48 %
<b>Patient's global assessment of disease activity (0-10)</b>		
Baseline	5.2	5.2
Week 14	2 %	49 %
<b>Physician's global assessment of disease activity (0-10)</b>		
Baseline	5.2	5.4
Week 14	7 %	59 %
<b>HAQ score (0-10)</b>		
Baseline	1.0	1.0
Week 14	0 %	28 %
<b>CRP (mg/dL) (0-10)</b>		
Baseline	0.6	0.6
Week 14	0 %	40 %
<p>Note: Baseline are median values</p> <p>a In Study PsA, about 48%, 16%, and 78% of the patients received stable doses of MTX (<math>\leq 25</math> mg/day), low dose corticosteroids (equivalent to <math>\leq 10</math> mg of prednisone a day), and NSAIDs, respectively.</p> <p>b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint</p>		

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Figure 2. Study PsA – Percent of ACR 20 PsA Responders by Visit: Randomized Patients\*



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\* The same patients may not have responded at each timepoint.

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### Physical Function Response in Patients with PsA

In Study PsA, SIMPONI 50 mg demonstrated a greater improvement compared to placebo in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24 (0.33 and -0.01, respectively). In addition, the SIMPONI 50 mg group compared to the placebo group had a greater proportion of HAQ responders ( $\geq 0.3$  change from baseline) at Week 24: 43% vs. 22%, respectively.

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### 14.3 Ankylosing Spondylitis

The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 356 adult patients with active ankylosing spondylitis according to modified New York criteria for at least 3 months (Study AS). Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI)  $\geq 4$  and VAS for total back pain of  $\geq 4$ , on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they were previously treated with a biologic TNF-blocker or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (n = 78), SIMPONI 50 mg (n = 138), or SIMPONI 100 mg (n = 140) administered subcutaneously every 4 weeks. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), low dose corticosteroids (equivalent to < 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

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The primary endpoint was the percentage of patients achieving an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

734 In Study AS, the median duration of AS disease was 5.6 years, median duration of inflammatory  
735 back pain was 12 years, 83% were HLA-B27 positive, 24% had prior joint surgery or procedure,  
736 and 55% received at least one DMARD in the past. During the trial, the use of concomitant  
737 DMARDs and/or NSAIDs was as follows: MTX (20%), SSZ (26%), HCQ (1%), low dose oral  
738 steroids (16%), and NSAIDs (90%).

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740 **Clinical Response in Patients with AS**

741 In Study AS, SIMPONI ± DMARDs treatment, compared with placebo ± DMARDs, resulted in a  
742 significant improvement in signs and symptoms as demonstrated by the proportion of patients with  
743 an ASAS 20 response at Week 14 (see Table 6). There was no clear evidence of improved ASAS  
744 response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose  
745 group (50 mg). Table 7 shows the percent improvement in the components of the ASAS response  
746 criteria for the SIMPONI 50 mg ± DMARDs and placebo ± DMARDs groups in Study AS.

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748 The percent of patients achieving ASAS 20 responses by visit for Study AS is shown in Figure 3.  
749 ASAS 20 responses were observed in 48% of patients in the SIMPONI 50 mg + MTX group at the  
750 first assessment (Week 4) after the initial SIMPONI administration.

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752 **Table 6. Study AS – Proportion of ASAS Responders at Weeks 14 and 24**

	<b>Placebo ± DMARDs<sup>a</sup></b>	<b>SIMPONI 50 mg ± DMARDs<sup>a</sup></b>
N <sup>b</sup>	78	138
<b>Responders, % of patients</b>		
<b>ASAS 20</b>		
Week 14	<b>22%</b>	<b>59%</b>
Week 24	23%	56%
<b>ASAS 40</b>		
Week 14	15%	45%
Week 24	15%	44%
<p>a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively.</p> <p>b N reflects randomized patients.</p> <p>Bold text indicates primary endpoint</p>		

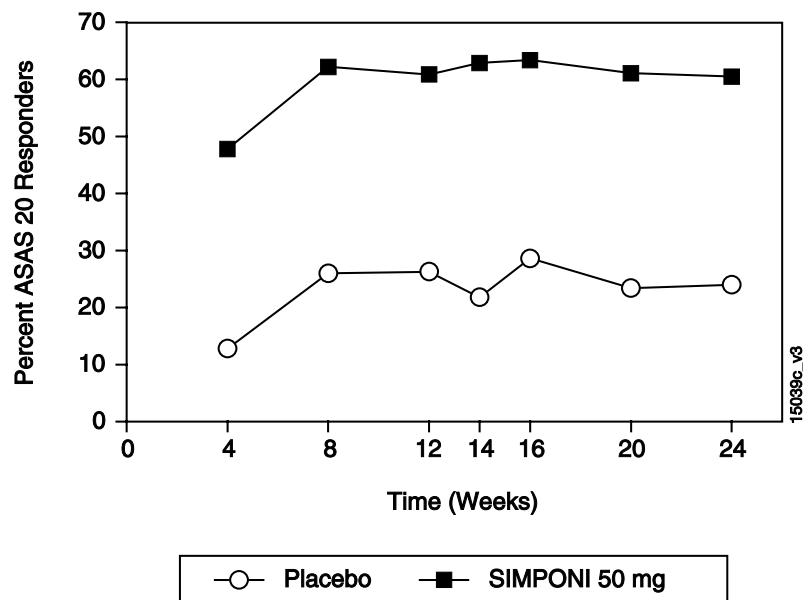
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**Table 7. Study AS – Median Percent Improvement in ASAS Components at Week 14**

	Placebo ± DMARDs <sup>a</sup>	SIMPONI 50 mg ± DMARDs <sup>a</sup>
<b>N<sup>b</sup></b>	78	138
<b>ASAS components</b>		
<b>Patient global assessment (0-10)</b>		
Baseline	7.2	7.0
Week 14	13%	47%
<b>Total back pain (0-10)</b>		
Baseline	7.6	7.5
Week 14	9%	50%
<b>BASFI (0-10)<sup>c</sup></b>		
Baseline	4.9	5.0
Week 14	-3%	37%
<b>Inflammation (0-10)<sup>d</sup></b>		
Baseline	7.1	7.1
Week 14	6%	59%
a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively. b N reflects randomized patients c BASFI is Bath Ankylosing Spondylitis Functional Index d Inflammation is the mean of two patient-reported stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI)		

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**Figure 3. Study AS – Percent of AS Patients Achieving ASAS 20 Response by Visit: Randomized Patients\***



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\* The same patients may not have responded at each timepoint.

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**15 REFERENCES**

1. SEER [database online]. US Population Data – 1969-2004. Bethesda, MD: National Cancer Institute. Release date: January 3, 2007. Available at: <http://seer.cancer.gov/popdata/>.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Each SIMPONI prefilled autoinjector or prefilled syringe is packaged in a light-blocking, cardboard outer carton. SIMPONI is available in packs of 1 prefilled syringe NDC 57894-070-01 or 1 prefilled SmartJect autoinjector NDC 57894-070-02.

**Prefilled SmartJect Autoinjector**

Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch) providing 50 mg of SIMPONI per 0.5 mL of solution.

**Prefilled Syringe**

Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5 mL of solution.

**Storage and Stability**

SIMPONI must be refrigerated at 2°C to 8°C (36°F to 46°F) 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 beyond the expiration date (EXP) on the carton or the expiration date on the prefilled syringe (observed through the viewing window) or the prefilled SmartJect autoinjector.

**17 PATIENT COUNSELING INFORMATION**

See Medication Guide (17.3)

**17.1 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).

809 **Other Medical Conditions**

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

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814 **17.2 Instruction on Injection Technique**

815 The first self-injection should be performed under the supervision of a qualified healthcare  
816 professional. If a patient or caregiver is to administer SIMPONI, he/she should be instructed in  
817 injection techniques and their ability to inject subcutaneously should be assessed to ensure the  
818 proper administration of SIMPONI [*see Medication Guide (17.3)*].

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820 Prior to use, remove the prefilled syringe or the prefilled SmartJect autoinjector from the  
821 refrigerator and allow SIMPONI to sit at room temperature outside of the carton for 30 minutes  
822 and out of the reach of children.

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824 Do not warm SIMPONI in any other way. For example, do not warm SIMPONI in a microwave  
825 or in hot water.

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827 Do not remove the prefilled syringe needle cover or SmartJect autoinjector cap while allowing  
828 SIMPONI to reach room temperature. Remove these immediately before injection.

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830 Do not pull the autoinjector away from the skin until you hear a first “click” sound and then a  
831 second “click” sound (the injection is finished and the needle is pulled back). It usually takes  
832 about 3 to 6 seconds but may take up to 15 seconds for you to hear the second “click” after the  
833 first “click”. If the autoinjector is pulled away from the skin before the injection is completed, a  
834 full dose of SIMPONI may not be administered.

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836 A puncture-resistant container for disposal of needles and syringes should be used. Patients or  
837 caregivers should be instructed in the technique of proper syringe and needle disposal, and be  
838 advised not to reuse these items.

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843 Centocor Ortho Biotech Inc.  
844 Horsham, PA 19044  
845 US License No. 1821

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847 Revised: 7/2010

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