9.4.4 Study C0524T08 (Study 8) – PsA

A detailed description of the protocol and the safety results for Study C0524T08 (i.e., Study 8, GO-REVEAL) are presented in this section. Since Study 8 was the only trial of golimumab in patients with PsA, the efficacy results are presented in Section 6.2 [i.e., Indication – Treatment of [redacted] Psoriatic Arthritis (PsA)]. The description of the protocol for Study 8 described below is based on the original protocol (there were no amendments to the original protocol) and amendment 1 of the SAP (dated May 14, 2007). There were no significant changes from the original SAP to amendment 1 of the SAP. See Table 9.4.1 for the amendments to the Study 8 protocol and SAP. b(4)

Table 9.4.1: Amendments to the Study 8 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	August 25, 2005
SAP	Original SAP	December 20, 2006
	Amendment 1 to SAP[1]	May 14, 2007[1]

Date of 24-week data base lock was on June 6, 2007
1 Amendment 1 to the SAP was the last amendment to the SAP before the first data base lock.
Adapted from the protocol and SAP for Study 8

In Study 8, the first patient consented on December 12, 2005 and the last patient completed Week 24 on May 14, 2007. The last protocol (the original protocol) and the final SAP (amendment 1) occurred prior to the 24-week database lock in Study 8.

Title: Study 8 (GO-REVEAL) is entitled, "A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic Arthritis"

Objectives: The primary objective of this trial is to evaluate the efficacy of SC injections of golimumab in patients with active PsA by assessing reduction in signs and symptoms of PsA and inhibition of progression of structural damage. The major secondary objectives of this trial are to evaluate the efficacy of golimumab in achieving sustained arthritis response, improving psoriatic skin lesions, improving physical function, improving quality of life, and to assess the safety of golimumab in patients with active PsA.

Overall Design: Randomized, DB, placebo-control, multi-center, global, 3-arm, 5-year Phase 3 trial of golimumab in patients with active PsA who never have received any biologic anti-TNF product (e.g., infliximab, etanercept, adalimumab), rituximab, natalizumab, or a cytotoxic agent. Patients may take stable doses of concomitant NSAIDs, MTX (≤ 25 mg/week), and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent) but may not take systemic or topical psoriasis treatments/medications during the study. There will be 3 main treatment periods in Study 8 (see Figure 9.4.2):

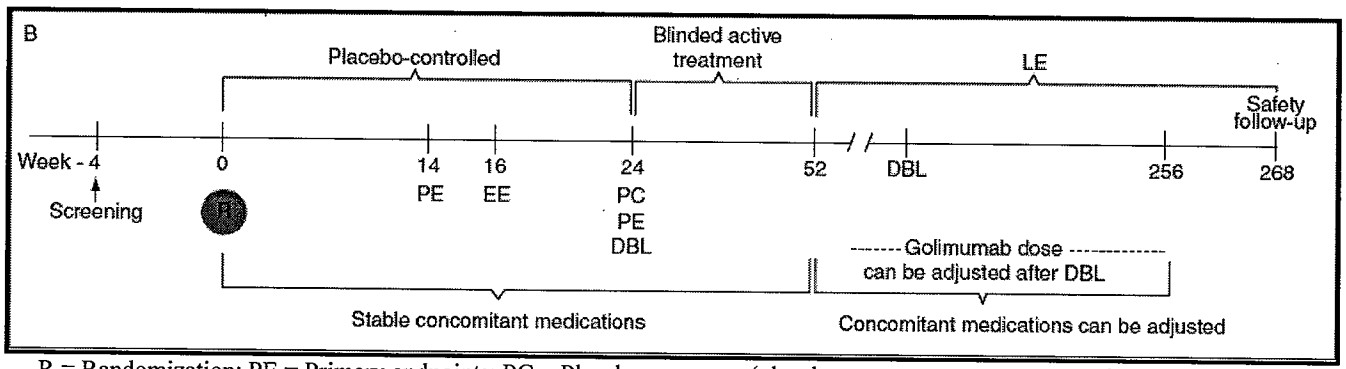
1. DB, placebo-controlled period (Week 0 to Week 24) with two parts:
   - 16-week period from Week 0 to Week 16

- 8-week period from Week 16 to Week 24 (where at Week 16 patients could enter into an escape phase for lack of efficacy)

2. DB, dose-ranging control period (Week 24 to 52) in which the placebo group will crossover to blinded treatment with golimumab.

3. 4-year, LE period from Week 52 to Week 256. The initial part of the LE period will be DB but the time period after the Week 52 database lock will be open-label (the Week 52 database lock will occur when the last patient completes the 52-week controlled portion of the study).

Figure 9.4.2: Study 8 schema



R = Randomization; PE = Primary endpoints; PC = Placebo crossover (placebo group crosses over to receive golimumab 50 mg once every 4 weeks); DBL = database lock (the 24-week DBL occurs after the last patient enrolled completes the Week 24 visit); LE long-term extension; EE = early escape (patient having < 10% improvement in both tender & swollen joint counts)
Reference: Adapted from the original protocol of Study 8, Page 23

Eligibility Criteria: Table 9.4.3 displays the eligibility criteria in Study 8.

Table 9.4.3: Eligibility Criteria in Study 8

Inclusion Criteria: To have been eligible to participate in the study, patients have to meet all of the following criteria:	**Exclusion Criteria:** If patients have any of the following conditions, they are not eligible to participate in the study:
1. ≥ 18 years old and have PsA (for at least 6 months prior to first administration of study agent) 2. **Have active PsA** at the time of screening and at baseline, as characterized by ≥ 3 swollen joints and ≥ 3 tender joints, **despite current or previous DMARD therapy** (i.e., taking a DMARD for at least 3 months, or evidence of DMARD intolerance) **or NSAID therapy** (i.e., taking an NSAID for at least 4 weeks). 3. **Have active plaque psoriasis** with a qualifying target lesion ≥ 2 cm in diameter, but not on axilla, inframammary area, or groin and are negative for RF. 4. Have at least 1 of the PsA subsets: DIP joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. 5. If using **oral corticosteroids**, must be on a stable dose equivalent to ≤ 10 mg of prednisone/day for at least 2 weeks prior to first	1. Have other inflammatory diseases (e.g., RA, ankylosing spondylitis, systemic lupus erythematosus, Lyme disease) that might confound the evaluations of benefit from the golimumab therapy. 2. **Received any biologic anti-TNF product** (e.g., infliximab, etanercept, adalimumab), rituximab, natalizumab, or a cytotoxic agent (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents). 3. Within 4 weeks prior to the first administration of study agent, received systemic immunosuppressives (e.g., cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine); DMARDs other than MTX (e.g., SSZ, HCQ, chloroquine, gold preparations, D-penicillamine, anakinra); or intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone). 4. Within 4 weeks prior to the first administration of study

administration of study agent. If currently not using corticosteroids, must not have received oral corticosteroids for at least 2 weeks prior to the baseline visit.
6. If using **MTX**, should have started treatment at least 3 months prior to the first administration of study agent, be on a stable dose (≤ 25 mg/week) for at least 4 weeks prior to the first administration of the study agent, and have no serious toxic side effects attributable to MTX. If currently not using MTX, must have not received MTX for at least 4 weeks prior to the first administration of the study agent.
7. If using **NSAIDs**, must be on a stable dose for at least 2 weeks prior to the first administration of study agent. If currently not using NSAIDS, must not have received NSAIDs for at least 2 weeks prior to the first administration of the study agent.
8. If using **systemic psoriasis** treatments [e.g., systemic retinoids, cyclosporine, psoralen with ultraviolet light A (PUVA)], must not have received these treatments for at least 4 weeks prior to the first administration of study agent.
9. If using **topical psoriasis medications/treatments** [e.g., corticosteroids (with the exception of low-potency corticosteroids used on the face and/or groin), keratolytics (with the exception of salicylic acid shampoos), coal tar (with the exception of coal tar shampoos), anthralin, vitamin D3 analogues, topical tacrolimus, and retinoids], ultraviolet B light (UVB), or tanning beds, must not have received these treatments for at least 2 weeks prior to the first administration of study agent. Acceptable low-potency corticosteroids include 2.5% concentration or less of hydrocortisone cream or equivalent.
10. Considered eligible according to the following TB screening criteria:
    - 7.1. No history of latent or active TB prior to screening.
    - 7.2. No signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - 7.3. No recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study drug.
    - 7.4. Within 1 month prior to the first administration of study agent, either have negative diagnostic TB test results (defined as both a negative tuberculin skin test and a negative QuantiFERON-TB Gold test), or have a newly identified positive diagnostic TB test result (defined as either a positive tuberculin skin test or a positive QuantiFERON-TB Gold test) during screening in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study drug.
    - 7.5. Have posterior-anterior and lateral chest radiographs, taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
11. Screening laboratory test results:
    - 11.1 Hemoglobin ≥ 8.5 g/dL.
    - 11.2 White blood cells ≥ 3.5 x 10^9 cells/L.

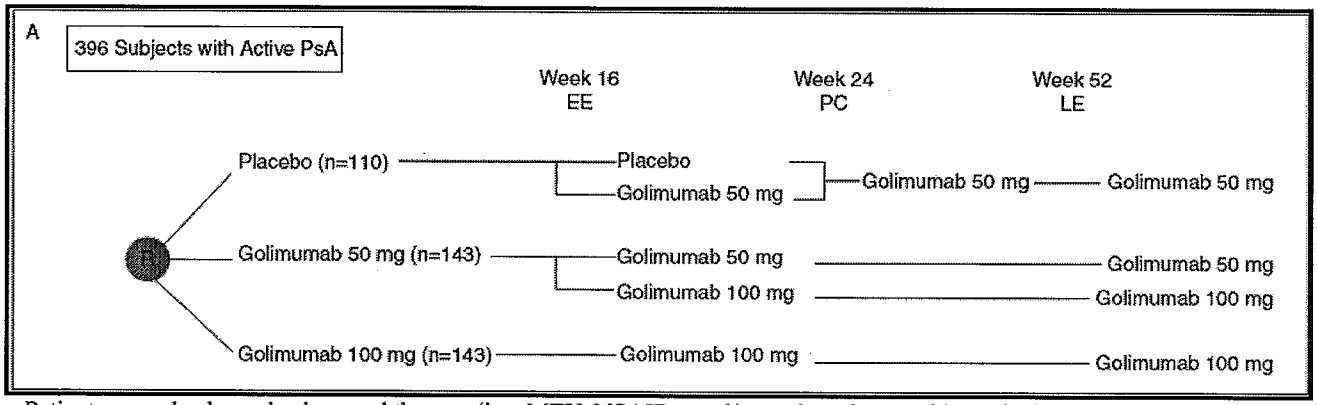
agent, received leflunomide (irrespective of undergoing a drug elimination procedure), or within 3 months prior to the first administration of study received leflunomide agent and have not undergone a drug elimination procedure.
5. Within 3 months prior to the first administration of the study agent received alefacept or efalizumab.
6. Received any investigational agent within 5 half-lives prior to the first administration of study agent.
7. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic nonremitting cystitis), an open, draining, or infected skin wound, or an ulcer. History of an infected joint prosthesis, or received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
8. Known to be infected with HIV, hepatitis B, or hepatitis C.
9. Had a serious infection (e.g., hepatitis, pneumonia, pyelonephritis, or sepsis) or have been hospitalized for an infection or within 2 months prior to administration of study agent have been treated with IV antibiotics for an infection. Although, less serious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) do not have to be considered exclusionary.
10. History of active or latent granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis.
11. Within 6 months prior to screening had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, Pneumocystis carinii, aspergillosis).
12. Received, or are expected to receive during the trial (within 3 months before the first administration of study agent or within 6 months after the last administration of study agent) any live virus or bacterial vaccination.
13. History of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease (e.g., lymphadenopathy of unusual size or location, or clinically significant splenomegaly).
14. Known malignancy with the exception of a non-melanoma skin cancer that has been treated with no evidence of recurrence.
15. Have a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to first study agent administration).
16. Have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.
17. Had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.
18. History of known demyelinating diseases such as multiple sclerosis or optic neuritis.
19. History of, or concurrent, CHF, including medically controlled, asymptomatic CHF.
20. Current signs or symptoms of severe, progressive, or

11.3 Neutrophils $\geq 1.5 \times 10^9$ cells/L. 11.4 Platelets $\geq 100 \times 10^9$ cells/L. 11.5 ALT and AST levels not exceeding 1.5 times the ULN. 11.6 Creatinine not exceeding 1.5 mg/dL. 12. Women of childbearing potential (WOCP) or men capable of fathering children must be using adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study and for 6 months after receiving the last administration of study drug. WOCP must test negative for pregnancy. 13. Are willing and able to adhere to the study visit schedule and other protocol requirements and are capable of providing informed consent, which must be obtained prior to any study-related procedures.	uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease. 21. Known hypersensitivity to human immunoglobulin proteins or other components of golimumab. 22. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years. 23. Unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access. 24. Participating in another trial with an investigational agent or procedure. 25. Pregnant, nursing, or planning a pregnancy or fathering a child within 6 months after receiving the last administration of study agent.

Reference: Adapted from the original protocol for Study 8, Pages 28-32

Treatments: Patients will receive study treatment during the DB and LE periods (see Figure 9.4.4). Golimumab will be supplied as a sterile liquid (liquid in a vial or LiV) for SC injection and once available, golimumab may also be supplied as a sterile liquid for SC injection in prefilled syringe (PFS).

Figure 9.4.4: Treatments in Study 8[1]



Patients may also be on background therapy (i.e., MTX, NSAIDs, and/or oral corticosteroids equivalent to $\leq$ 10 mg prednisone/day).
Reference: Adapted from the original protocol of Study 8, Page 23

DB, Placebo-Control Period: Patients will be randomized 1:1.3:1.3 to 1 of the following 3 treatment groups: Groups 1, 2, and 3 (see Table 9.4.5 and Figure 9.4.4).

Table 9.4.5: Treatment groups at randomization in the DB, placebo-control period (Week 0 to 24) in Study 8[1]

Group #	Dosing
Group 1	**placebo SC injections once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**
Group 2	**golimumab 50 mg SC once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**
Group 3	**golimumab 100 mg SC once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**

1 Patients who escape at Week 16 may receive different treatment at Week 16 and Week 20 (see Table 9.4.6).
2 Patients may take stable doses of concomitant MTX, NSAIDs, and/or oral steroids equivalent to $\leq$ 10 mg prednisone/day during the study.
Reference: Adapted from the original protocol of Study 8, Page 24

At Week 16 during the DB Period, any patient who has < 10% improvement from baseline in both swollen and tender joint counts will enter early escape in a double-blinded fashion (see the treatments for the patients who enter escape in Table 9.4.6 and Figure 9.4.4). Patients who do not enter early escape will continue the treatment assigned at randomization (see Table 9.4.6 and Figure 9.4.4).

Table 9.4.6: Treatments for patients who enter escape at Week 16[1] in Study 8

Group #	Treatment prior to escape	Treatment during escape
Group 1	Placebo	**Add golimumab 50 mg** SC at Weeks 16 and 20[2]
Group 2	Golimumab50 mg	**Increase golimumab to 100 mg** SC at Weeks 16 and 20[2]
Group 3	Golimumab100 mg	Continue golimumab 100 mg SC at Weeks 16 and 20 (no change)[2]

1 For patients who enter escape at Week 16, they will be treated in a DB fashion at Week 16 and Week 20. All groups will receive golimumab every 4 weeks (i.e., at Week 16 and Week 20).
2 Patients may take stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.
Reference: Adapted from the original protocol of Study 8, Page 24

DB, Dose-Ranging-Control Period: Treatment during the DB, dose-ranging control period will start at Week 24 and continue every 4 weeks through Week 48. All patients in the placebo group will crossover to receive blinded golimumab 50 mg SC every 4 weeks and patients in the original golimumab treatment groups will continue their treatments (see Table 9.4.7 and Figure 9.4.4)

Table 9.4.7: Treatments for patients during the DB, dose-ranging control period in Study 8[1]

Group #		Treatment during Week 24 to Week 52
Group 1	For patients who did not escape	**Cross over to golimumab 50 mg SC mg** every 4 weeks at Weeks 24, 28, 32, 36, 40, 44, and 48.
	For patients who entered escape	Continue golimumab 50 mg SC mg every 4 weeks at Weeks 24, 28, 32, 36, 40, 44, and 48 (no change).
Group 2	For patients who did not escape	Continue golimumab 50 mg SC every 4 weeks at Weeks 24, 28, 32, 36, 40, 44, and 48. (no change)
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks at Weeks 24, 28, 32, 36, 40, 44, and 48. (no change)
Group 3	For all patients	Continue golimumab 100 mg SC every 4 weeks at Weeks 24, 28, 32, 36, 40, 44, and 48. (no change)

1 All groups will receive golimumab every 4 weeks. Patients may take stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.
Reference: Adapted from the original protocol of Study 8, Page 25

LE Period: Treatment during the Long-Term Extension (LE) Period in Study 8 will start at Week 52 and continue every 4 weeks through Week 252 (see Table 9.4.8 and Figure 9.4.4). The blind will be maintained during the LE Period until the last patient completes the Week 52 evaluations and the 52-week database is locked.

Table 9.4.8: Treatments during the Long-Term Extension Period from Week 52 to 252 in Study 8[1]

Group #	Prior Treatment	Treatment during Week 52 through Week 252
Group 1	golimumab50	Continue golimumab 50 mg SC every 4 weeks **(option to increase to golimumab 100 mg SC every 4 weeks after 52-week DBL)**
Group 2	golimumab50	Continue golimumab 50 mg SC every 4 weeks **(option to increase to golimumab 100 mg SC every 4 weeks after 52-week DBL)**
	golimumab100	Continue golimumab 100 mg SC every 4 weeks
Group 3	golimumab100	Continue golimumab 100 mg SC every 4 weeks

1 All groups will receive golimumab starting at Week 52 every 4 weeks until Week 252. The blind will be maintained in LE Period until after the last patient finishes the 52-week evaluations and the 52-week database is locked. Therefore, during the initial part of LE, the treatments will be double-blinded. After the 52-week DBL, doses of concomitant therapy (i.e., MTX, NSAIDs, and/or oral corticosteroids) may be adjusted.
Reference: Adapted from the original protocol of Study 8, Pages 25-26

Concomitant Medication:

MTX: Patients are allowed to receive stable, concomitant MTX (≤ 25 mg/week) until the 52-week database is locked. After the 52-week database lock, MTX will not be considered one of the study agents, and the MTX dose can be adjusted at the investigator's discretion. It is recommended that all patients taking MTX should receive at least 5 mg oral folic acid or oral folinic acid weekly.

Corticosteroids: Patients treated with oral corticosteroids for PsA should receive a stable dose equivalent to ≤ 10 mg prednisone per day for at least 2 weeks prior to their first administration of the study agent and continue to receive this dose through Week 52. Long-term (> 2 weeks) oral or IV corticosteroids used for indications other than PsA are not allowed through Week 52. IM or epidural administration of corticosteroids is not allowed up to Week 52 and IV administration of corticosteroids for PsA are not allowed up until Week 52. Inhaled, otic, ophthalmic, intranasal and other routes of mucosal delivery of corticosteroids are allowed throughout the course of the study. Patients may receive up to 2 intra-articular, tendon sheath, or bursal corticosteroid injections in no more than 2 affected sites during the first 52 weeks of the study.

NSAIDs and other Analgesics: Patients treated with NSAIDs, including aspirin, and other analgesics, should receive the usual marketed doses approved in the country in which the study is being conducted, and should have been on a stable dose at least 2 weeks prior to the first administration of the study agent and during the first 52 weeks of the trial. The dose may be reduced and the type of NSAIDs or other analgesics may be changed if the patient develops unacceptable side effects. Whenever possible, short-acting NSAIDs and other analgesics should not be administered within 6 hours before study evaluations. Long-acting NSAIDs can be maintained at their usual dosing intervals before study evaluations.

Systemic Therapy for Psoriasis: Concurrent use of systemic therapy for psoriasis (e.g., PUVA, systemic retinoids, cyclosporine) is not permitted within 4 weeks prior to first administration of study agent and through Week 256.

Topical Treatments for Psoriasis: Concurrent use of topical medications/treatments for psoriasis [e.g., corticosteroids (with the exception of low-potency corticosteroids, defined as ≤ 2.5% concentration of hydrocortisone cream or equivalent, used on the face and/or groin), keratolytics (with the exception of

salicylic acid shampoos), coal tar (with the exception of coal tar shampoos), anthralin, vitamin D3 analogues, topical tacrolimus, and retinoids), Ultraviolet B light (UVB), or tanning beds are not permitted at least 2 weeks prior to first administration of study drug and through Week 52. The treatments that are permitted should not be taken prior to an evaluation on the day of a study visit. UVB, tanning beds, and topical or intralesional treatments for psoriasis are not permitted from Week 52 to Week 256.

Disease-modifying Antirheumatic Drugs (DMARDs) and Systemic Immunosuppressives: DMARDs (other than stable doses of MTX) and systemic immunosuppressives are prohibited within the 4 weeks prior to the first administration of the study agent through Week 52 of the study. After the 52-week DBL, the MTX dose can be adjusted and new DMARDs and/or immunosuppressives (with the exception of
cyclosporine and tacrolimus) may be added.

Biologic Agents, Cytotoxic Agents, and Investigational Drugs: The use of biologic agents (e.g., anakinra, etanercept, adalimumab, infliximab, alefacept, efalizumab, rituximab, natalizumab), cytotoxic agents (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, other alkylating agents), or investigational drugs is not allowed during the entire 5-year study including LE

Study Monitoring and Evaluations: Table 9.4.9 presents the schedule of procedures and evaluations in Study 8. All post-baseline visits through Week 52 must have occurred within ± 7 days except the Week 12, 14, and 16 visits must have occurred within ± 3 days.

Table 9.4.9: Schedule of procedures and evaluations through Week 24 in Study 8

Assessments[a]	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 14[b]	Wk 16	Wk 20	Wk 24[b]	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52
Consent	X															
Demography/medical history	X															
Physical (including skin) exam	X								X							X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Weight	X					X			X							X
Chest x-ray[c]	X															
Tuberculin skin test[c]	X															
QuantiFERON-TB Gold test[c]	X															
Review of entry criteria	X	X														
Serum pregnancy test[d]	X															
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
IVRS notification of swollen and tender joint count		X					X									
Study Agent Injection		X	X	X	X		X	X	X	X	X	X	X	X	X	X[e]
PsA evaluations[f]	X	X	X	X		X	X	X	X	X	X		X			X
Dactylitis/Enthesitis		X				X			X							X
HAQ		X	X	X		X	X	X	X	X	X		X			X

HEcon		X		X			X		X							X
SF-36		X				X			X							X
Psoriasis BSA (%)		X														
PASI		X	X	X		X	X	X	X	X	X		X			X
Target lesion assessment		X				X			X							X
Nails (NAPSI and Nail PGA)		X				X			X							X
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent Injection site evalution		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses	X	X	X	X		X		X	X	X	X	X		X		X
CRP		X	X	X		X	X	X	X	X	X		X			X
Rheumatoid factor (RF)	X															
ANA/anti-dsDNA		X				X										X
Golimumab concentration		X	X	X	X	X	X	X	X							X
Population PK							←	X[g]	→							
Antibodies to golimumab		X							X							X
Antipneumococcal antibody					X		X									
Pneumococcal vaccine IM injection[h]					X											
Serum-based PD markers (approximately 150 subjects[i])		X	X			X			X							
Protein profiling (approximately 100 of the 150 subjects above[i])		X	X			X										
Anemia markers		X				X										
Photographs of skin lesions[i]		X				X			X							
Radiographs of hands and feet[j]		X							X							X

a All assessments are to be completed prior to study agent injection, except at Week 14 (no study agent injection) and unless otherwise specified.
b Primary and secondary endpoints.
c Also performed at any time during the study if TB is suspected.
d In addition to the screening evaluation, the pregnancy test may be repeated at any time (including during the long-term extension).
e Long-term extension starts with the Week 52 injection.
f PsA evaluations included joint assessment, duration of morning stiffness, pain assessment, and patient and physician global assessments on VAS and Likert scales. At screening, evaluation included joint assessment only.
g One additional sample will be collected from all subjects at any time between Weeks 16 to 24, other than at visits at Weeks 16, 20, or 24. This sample must be collected at least 24 hours prior to or after a study agent injection.
h After blood sample for antipneumococcal antibody is collected.
i Performed at selected study sites.
j Performed within ± 4 weeks of the scheduled date for Week 0, and within ± 2 weeks of the scheduled date for subsequent radiographs.
Reference: Adapted from the original protocol of Study 8, Attachment 1.1, Pages 85-87

Efficacy Endpoints:

Co-Primary Efficacy Endpoints: The co-primary efficacy endpoints in Study 8 were the proportion of patients with an ACR 20 response at Week 14 and the change from baseline in the total radiographic scores of the hands and the feet at Week 24.

ACR response at Week 14: A patient was classified as having achieved an ACR 20 response if both of the following were achieved at Week 14:

1. An improvement of $\geq 20\%$ from baseline in both the swollen joint count (66 is the maximum number of swollen joints) and tender joint count (68 is the maximum number of tender joints); and

2. An improvement of ≥ 20% from baseline in ≥ 3 of the following 5 assessments:

    2.1. Patient's assessment of pain using a Visual Analog Scale (VAS)
    2.2. Patient's global assessment of disease activity, using a VAS
    2.3. Physician's global assessment of disease activity, using a VAS
    2.4. Patient's assessment of physical function as measured by the HAQ disability index
    2.5. CRP

Total Modified vdH-S Score at Week 24: The inhibition of progression of structural damage will be measured by the change from baseline in total modified van der Heijde (vdH-S) score, modified for the purpose of PsA, for hands and feet at Week 24. The modification for PsA includes addition of distal inter-phalangeal (DIP) joints of both hands scored for joint erosion (JE) and joint space narrowing (JSN), and assessments of radiographic features known as "pencil in cup" (PIC) and "gross osteolysis" (GO) that are specific to PsA. The total modified vdH-S score, which ranges from 0 (best score) to 528 (worst score), is the sum of the maximum JE score for both hands and feet and the maximal JSN score (see Table 9.4.10):

1. The JE score is a summary of erosion severity in 40 joints of the hands (20 joints per hand) and 12 joints in the feet (6 in each foot). Erosions in each hand joint are scored, according to number of erosions and surface area involved, from 0 (no erosion) to 7 (GO). A score of 6 in a hand joint is applied to PIC abnormalities. However, for the hand JE score, a score of 5, 6, or 7 will all be considered to be a score of 5. Thus, the maximum JE score for all the hand joints is 200 (5 times 40 joints). Erosions in each foot joint are scored, according to number of erosions and surface area involved, from 0 (no erosion) to 12 (GO). A score of 11 in a foot joint is applied to PIC abnormalities. However, for the foot JE score, a score of 10, 11, or 12 will all be considered to be a score of 10. Thus, the maximum JE score for all the foot joints is 120 (10 times 12 joints). The maximum total JE score for both the hands and the feet is 320.
2. The JSN score summarizes the severity of JSN in 40 joints in the hands and 12 joints of the feet. Assessment of JSN is scored from 0 to 4, with 0 indicating no JSN and with 4 indicating absence of a joint space, presumptive evidence of ankylosis, or complete luxation. The maximum score for JSN score in all 40 hand joints is 160 (4 times 40 joints) and the maximum score for JSN score in all 12 feet joints is 48 (4 times 12 joints). Thus, the total maximum JSN score for both hands and feet is 208.

Table 9.4.10: Range of total modified vdH-S scores

	Hand	Foot	Total (Hands and Feet)
Joint Erosion (JE)	**0-200**	**0-120**	**0-320**
Joint Space Narrowing (JSN)	**0-160**	**0-48**	**0-208**
JE and JSN	**0-360**	**0-168**	**0-528**

Reference: Adapted from amendment 1 of the SAP for Study 8, Table 2, Page 32

Secondary Efficacy Endpoints: The 4 secondary efficacy endpoints in Study 8 were the following (without a pre-specified order):

1. The proportion of patients with an ACR 20 response at Week 24
2. Improvement from baseline in the HAQ score at Week 24: The baseline HAQ disability index score minus the Week 24 HAQ disability index score (positive values indicate less disability and negative values indicate more disability). The HAQ disability index assesses the degree of difficulty a patient has in performing the following 8 activities over the previous week: dressing & grooming (C1), arising (C2), eating (C3), walking (C4), hygiene (C5), reach (C6), grip (C7), and activities (C8). Each of the categories has component questions and for each of the components, patients are asked to record the amount of difficulty they had in performing the activities (i.e., without ANY difficulty = 0, with SOME difficulty = 1, with MUCH difficulty = 2, and UNABLE to do = 3). Each of the component scores may be adjusted if the patient used an aid, device, or assistance. The highest score recorded by the patient for any component question determines the score for that category. The HAQ is calculated as the sum of the category scores divided by the number of categories answered. The HAQ is not computed if the patient does not have scores for at least 6 of the 8 categories.
3. For patients with $\geq$ 3% total body surface area (BSA) of psoriasis skin involvement at baseline, the proportion of patients with a Psoriatic Area and Severity Index (PASI) 75 response at Week 14. In the PASI system, the body is divided into 4 areas: the head (h), trunk (t), upper limbs (u), and lower limbs (l) account for 10%, 30%, 20%, and 40% of total BSA, respectively. These 4 areas are assessed separately for erythema (E), induration (I), and scaling (S) on a 0 (none) to 4 (very severe) scale. The scale for estimating the area (A) of involvement for psoriatic lesions varies from 0 (no involvement) to 6 (90%-100% involvement). The total PASI score ranges from 0 to 72. The proportion of patients who achieve a PASI 75 are the percent of patients who achieve $\geq$ 75% improvement from the baseline PASI score. The PASI score is calculated by using the following equation:

$$\mathbf{PASI = 0.1A_h(E_h + I_h + S_h) + 0.3A_t(E_t + I_t + S_t) + 0.2A_u(E_u + I_u + S_u) + 0.4A_l(E_l + I_l + S_l)}$$

4. Change from baseline the physical component summary score (PCS) of the 36-item short form health survey (SF-36) at Week 14.

140 Other Pre-Specified Endpoints Related to Signs and Symptoms: The following are the 140 other pre-specified endpoints related to signs and symptoms:

ACR Response Endpoints

1. 4 endpoints: proportion of patients achieving ACR 50 response and ACR 70 response at Week 14 and Week 24.
2. 21 endpoints: proportion of patients achieving ACR 20, ACR 50, and ACR 70 response at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).
3. 2 endpoints: ACR-N index of improvement at Week 14 and Week 24 (for the definition of ACR-N improvement see Table 9.1.9 in the study report for Study 5).
4. 7 endpoints: ACR-N index of improvement at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).

ACR Component Endpoints

5. 14 endpoints: percent improvement from baseline in each of the 7 ACR components at Week 14 and Week 24.
6. 21 endpoints: percent improvement from baseline in swollen joint counts, tender joint counts, and CRP at each visit through Week 24 (7 visits).

Change in DAS 28 Endpoints

7. 7 endpoints: change from baseline in DAS 28 (CRP) at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits). See Table 9.1.10 for the definition of the DAS 28 (CRP).

DAS Response Endpoints

8. 2 endpoints: proportion of patients with Disease Activity Index 28 (DAS 28) response using CRP at Week 14 and Week 24 (for the definition of a DAS 28 response see the study report for Study 5).
9. 7 endpoints: proportion of patients achieving DAS 28 (CRP) response at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).

PsA Response Endpoints

10. 2 endpoints: proportion of patients achieving PsA response criterion (PsARC) at Weeks 14 and 24 (see Table 9.4.11).
11. 7 endpoints: proportion of patients achieving PsARC at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).

Dactylitis, Enthesitis, and Stiffness Endpoints

12. 2 endpoints: **proportion of patients with ≥ 1 digit with dactylitis at Week 14** and 24. Dactylitis will be assessed in 10 fingers and 10 toes (20 digits).
13. 7 endpoints: percent change in the dactylitis score at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).
14. 2 endpoints: percent change in the dactylitis score at Week 14 and 24. The dactylitis score ranges from 0 to 60 [each of the 20 digits is scored on a 0 (no dactylitis) to 3 (severe dactylitis)] scale.
15. 7 endpoints: proportion of patients with ≥ 1 digit with dactylitis at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).
16. 2 endpoints: percentage change from baseline in the entheses score based on the modified Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index at Week 14 and Week 24. The 15 entheses sites are each evaluated for tenderness (0 is not tender and 1 is tender) so the modified MASES score is the sum of the scores for each entheses site and can range from 0 to 15.
17. 2 endpoints: proportion of patients with ≥ 1 site with enthesitis, using the modified MASES, at Week 14 and 24.
18. 7 endpoints: proportion of patients with ≥ 1 site with enthesitis at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).
19. 2 endpoints: the change from baseline in duration of morning stiffness at Week 14 and Week 24 (based on the mean duration of morning stiffness during the previous week).
20. 7 endpoints: change from baseline in duration of morning stiffness at Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits).

ACR Response by PK Endpoints

21. 8 endpoints: Efficacy by PK analysis: the proportion of patients who achieve an ACR 20 response at Week 14 who have a trough serum golimumab concentration at Week 12 of < 0.2 μg/mL, ≥ 0.2 to < 1 μg/mL, ≥ 1 to < 2 μg/mL, and ≥ 2 μg/mL. Also the proportion of patients who achieve an ACR 20 response at Week 24 who have a trough serum golimumab concentration at Week 24 of < 0.2 μg/mL, ≥ 0.2 to < 1 μg/mL, ≥ 1 to < 2 μg/mL, and ≥ 2 μg/mL. The proportion of patients will be determined for the following two groups: the combined golimumab groups with and without concomitant MTX. The 4 categories of trough serum golimumab concentrations can be changed based on observed PK data.

Table 9.4.11: PsA response criterion (PsARC)

Patients are considered to achieve a PsA response criterion (PsARC) if they have improvement in at least 2 (1 of which must be tender or swollen joint score) of the following 4 assessments and no worsening in any of the 4 assessments:
1. Improvement (decrease by ≥ 1) in the patient global assessment of the disease on a 1 (none) to 5 (very severe) Likert scale (worsening is an increase by ≥ 1)
2. Improvement (decrease by ≥ 1) in the physician global assessment of the disease on a 1 (none) to 5 (very severe) Likert scale (worsening is an increase by ≥ 1)
3. Improvement (decrease by ≥ 30%) in the tender joint score on a 0 (no tenderness) to 3 (severe tenderness) scale (worsening is an increase by ≥ 30%)
4. Improvement (decrease by ≥ 30%) in the swollen joint score on a 0 (no swelling) to 3 (severe swelling) scale (worsening is an increase by ≥ 30%)

Other Pre-Specified Endpoints: There were multiple other pre-specified endpoints related to HAQ, joint structural damage, quality of life, and skin and nail assessments.

Statistics:

Populations: The pre-specified populations for Study 8 were:

1. **Intent-to-Treat (ITT) Population** includes patients who are randomized regardless of whether or not they receive the assigned treatment. The ITT population will be used for the efficacy analyses.
2. **Treated Population** includes patients who received at least one SC study agent administration. The treated population will be used for the clinical pharmacology and safety analyses

Database Locks: The 4 database locks will occur at Weeks 24, 52, 104, and 268 after all patient evaluations through Weeks 24, 52, 104, and 268, respectively.

Methods for the Co-Primary Efficacy Endpoints: The co-primary efficacy endpoints will be evaluated in a sequential manner to protect the Type 1 error. The ACR 20 response at Week 14 will be analyzed first and if this endpoint is statistically significant than the radiographic endpoint at Week 24 will be considered.

There will be 2-tiered testing for the first co-primary efficacy endpoint (i.e., ACR 20 response at Week 14):

1. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) CMH test stratified by baseline MTX use (yes/no), will be between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group.
2. If this is significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$ for each comparison, between golimumab100 & placebo and golimumab50 and placebo will be performed.

There will be 2-tiered testing for the second co-primary efficacy endpoint (i.e., change from baseline in total modified vdH-S score, modified for PsA, of the hands and feet at Week 24):

1. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) analysis of variance (ANOVA) on the van der Waerden normal scores with treatment and baseline MTX use (yes/no) as factors, will be between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group.
2. If this is significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$ for each comparison, between golimumab100 & placebo groups and golimumab50 and placebo groups will be performed.

According to the SAP, a positive trial is defined as a statistically significant global test (i.e., combined golimumab groups versus the placebo group) **and** at least one statistically significant pair-wise test (i.e., golimumab100 group versus placebo or golimumab50 group versus placebo) for the first co-primary efficacy endpoint (i.e., ACR 20 response at Week 14).

Handling of Treatment Failure, Dropouts, and Missing Data for the ACR 20 at Week 14 Co-Primary Efficacy Endpoint: Patients, who meet ≥ 1 of the following treatment failure criteria prior to Week 14, will be considered to not have achieved an ACR 20 response at Week 14:

1. Initiate treatment with new DMARDs, systemic immunosuppressives, or biologics for the treatment of PsA or increase the MTX dose above baseline for the treatment of PsA;
2. Discontinue study agent injections due to an unsatisfactory therapeutic effect; or
3. Initiate treatment with oral, IV, or IM corticosteroids for PsA, or increase the dose of oral corticosteroids for the treatment of PsA above the baseline dose.

Patients with missing data for all of the ACR components at Week 14 will be considered as ACR 20 non-responders at Week 14. If patients have missing data but have data for ≥ 1 ACR component at Week 14, the following rules will be applied:

1. For any ACR component, **if all the component values are missing from baseline through Week 14,** the percent improvement from baseline at Week 14 will be imputed with 0%.
2. For any ACR component, **if the component value at Week 14 is missing**, the missing component will be replaced by the last non-missing observation (LOCF).
3. For any ACR component, **if the component value at baseline is missing,** the median component value of all patients at baseline in the same stratum (use of MTX: Yes/No) will be assigned.

For 4 of the 6 ACR components (i.e., patient's assessment of pain, patient's assessment of global disease activity, HAQ, and the physician's global assessment of disease activity), if the baseline value is 0 and the post-baseline value is not 0, then set the baseline to 0.1. If both baseline and post-baseline values of a component are equal to 0, then set the percentage change from baseline to 0. This is the zero divisor rule.

If patients have a joint injection and/or surgical joint procedure, prior to the date of randomization, the affected joint(s) will be analyzed according to the impact of the joint injection and/or the surgical procedure on the evaluability of the involved joints (see Table 9.4.12). If a joint is considered unevaluable at baseline due to a joint injection(s)/surgical joint procedure(s) prior to the date of randomization, it will be considered as unevaluable during the entire study, and will overrule the actual joint assessment.

Table 9.4.12: Joint evaluability for joints with a joint procedure/injection prior to randomization

Procedures/ Injection	Prior to Randomization
Synovectomy	Not evaluable
Arthrodesis	Not evaluable
Joint replacement	Not evaluable
Amputation	Not evaluable
Needle aspiration (Arthrocentesis)	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Steroid injection (IA, tendon sheath, bursa)	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Excision/Resection	Not evaluable
Arthroscopy-surgery	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Arthroscopy-diagnose	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Bunionectomy	Not evaluable
Chondroplasty	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Synovial cyst	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Needle biopsy-synovium	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Osteotomy	Not evaluable
Radio synovectomy	Not evaluable
Arthrotomy	Not evaluable
Fracture reduction	Not evaluable
Tendon surgery	Not evaluable
Bursal surgery	Not evaluable

Reference: Adapted from amendment 1 of the SAP for Study 8, Appendix 1.1, Page 115the original protocol of Study 8, Attachment 1.1, Pages 85-87

If patients who receive a surgical joint procedure(s) for the treatment of PsA during the study, then that affected joint(s) will be analyzed using the worst score [severe tender (3) and severe swollen (3) for joint scores] from the time of the first such procedure onward, regardless of the actual examination

findings. For patients who have received a concomitant joint injection(s) such as intra-articular, tendon sheath or bursal corticosteroid injections during the study (for PsA or for any other indication), then that affected joint(s) will be analyzed using the worst score [severe tender (3) and severe swollen (3) for joint scores] from the time of the first such injection onward for the next 90 days, regardless of the actual examination findings.

For patients who have an incomplete set of evaluable joints the joint count/score will be adjusted to a 68 joint count/score for tenderness and 66 joint count/scores for swelling by dividing the number of affected joints/score by the number of evaluable joint/score and multiplying by 68 for tenderness and 66 for swelling.

Methods for the Secondary Efficacy Endpoints: Analyses of the 4 secondary efficacy endpoints will only be considered if positive test results are achieved for the first co-primary efficacy endpoint (i.e., ACR 20 response at Week 14). There will be no multiplicity adjustments for the 4 secondary endpoints. For all
these endpoints, the first test will compare the combined golimumab groups versus placebo. If the result is significant, then pair-wise comparisons of golimumab100 versus placebo and golimumab50 versus placebo will be performed. The ACR 20 response at Week 24 and the PASI 75 response at Week 14 will both use a 2-sided CMH test with stratification by the patients baseline MTX usage (yes/no). The improvement from baseline in the HAQ score at Week 24 and the change in the PCS of the SF-36 at Week 14 will both use a 2-sided analysis of variance on the van der Waerden normal scores with treatment and baseline MTX usage (yes/no) as a factor.

Methods for the Other Pre-Specified Endpoints: There were no multiplicity adjustments for the 140 pre-specified signs and symptoms endpoints or the multiple other pre-specified endpoints relating to HAQ, joint structural damage, quality of life, and skin and nail assessments.

Study 8 Results

For the disposition, baseline demographics, baseline disease characteristics, and the efficacy results in Study 8 see Section 6.2. For the safety results see Section 7.6.4 (Drug-Disease Interactions). For the protocol deviations and exposure results see below.

Protocol Deviations: Table 9.4.13 displays the protocol deviations in Study 8 through Week 24. A similar proportion of patients in the treatment groups did not meet eligibility criteria and had a SC agent deviation. Most of the patients who did not meet eligilibility criteria entered the study and continued study treatment. There was some variability in the receipt of study agent administration including outside the protocol-specified window (within 3-7 days of the study visit).

Table 9.4.13: Protocol deviations in Study 8 through Week 24

	Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100± MTX (n=146)
Patients who did not meet eligibility criteria	3%	3%	1%
Patients with SC study agent administration deviation	22%	25%	26%
Received administration outside protocol-specified window	15%	22%	23%
Missed an administration	8%	3%	6%
Received an incorrect study agent or incorrect dose	0%	0%	1%

Reference: Adapted from Final Study Report for Study 8; Table 10, Page 82; Table 11, Page 84

Exposure: Table 9.4.14 displays the SC exposure of golimumab through Week 24 in Study 8. Patients may have received concomitant stable MTX during the Treatment Period. At baseline, 48%, 49%, and 47% of the patients in the placebo, golimumab50, and golimumab100 groups received concomitant MTX (weekly doses were 15, 15, and 16 mg, respectively).

Table 9.4.14: Cumulative dose of SC golimumab received through Week 24 in Study 8[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	Placebo ± MTX[2] (n=113)	Golimumab50 ± MTX[2] (n=146)	Golimumab100 ± MTX[2,3] (n=146)	Placebo to Golimumab50 ± MTX[2] (n=51)	Golimumab50 to Golimumab100± MTX[2] (n=28)
Mean number of SC administrations	4.6	5.4	5.9	2.0	2.0
Mean duration of follow-up	19.4 weeks	22.2 weeks	24.0 weeks	8.1 weeks	8.2 weeks
Mean (SD) cumulative SC golimumab dose	0 (0) mg	271 (50) mg	586 (62) mg	99 (7) mg	196 (19) mg

1 For the 24-week dataset, SC administrations of placebo or golimumab occurred at Weeks 0, 4, 8, 12, 16, and 20 (up to 6 SC administrations). Evaluations were performed at Week 24 and then the database was locked after all patients completed the 24 week data.

2 Patients may have taken stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks. The treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses.

3 Patients in the golimumab100 group who escaped continued to receive golimumab100 at Week 16

Reference: Adapted from Final Study Report for Study 8, Table 29, Page 150.

9.4.5 Study C0524T09 (Study 9) – AS

There were no significant changes from the original SAP to amendment 1 of the SAP.

A detailed description of the protocol and the safety results for Study C0524T09 (i.e., Study 9, GO-RAISE) are presented in this section. Since Study 9 was the only trial of golimumab in patients with AS, the efficacy results are presented in Section 6.3 [i.e., Indication – Treatment of [redacted], of Ankylosing Spondylitis (AS)]. The description of the protocol for Study 9 described below is based on amendment 1 of the protocol (dated May 11, 2007) and amendment 1 of the SAP (dated May 14, 2007). See Table 9.5.1 for the dates of all amendments to the protocol and SAP for Study 9. b(4)

Table 9.5.1: Amendments to the Study 9 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	August 25, 2005
	Amendment 1[1]	May 11, 2007[1]
SAP	Original SAP	December 18, 2006
	Amendment 1 to SAP[2]	May 14, 2007[2]

Date of 24-week data base lock was on June 20, 2007
1 Amendment 1 of the protocol was the last amendment to the protocol before the 24-week database lock
2 Amendment 1 to the SAP was the last amendment to the SAP before the 24-week data base lock.
Adapted from the protocol and SAP for Study 9

In Study 9, the first patient consented on December 13, 2005 and the last patient completed Week 24 on May 15, 2007. The last protocol (amendment 1) and the final SAP (amendment 1) occurred prior to the 24-week database lock in Study 9. There were no significant changes to the protocol in amendment 1 to protocol 9. There were several data handling rule changes in amendment 1 of the SAP for the Bath AS Functional Index (BASFI) secondary endpoint in Study 9 (see Dr. Joan Buenconsejo's review, the statistical reviewer for the AS indication, for more details). However, there were no changes in the data handling rules for the primary efficacy endpoint in Study 9.

Title: Study 9 (GO-RAISE) is entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis"

Objectives: The primary objective of this trial is to assess the efficacy of SC injections of golimumab in patients with active AS as measured by reduction in the signs and symptoms of active AS at Week 14. The secondary objectives are to assess the overall safety of golimumab; the effects of golimumab on physical function, range of motion, structural damage, and quality of life; and the population PK and PD effects of golimumab in patients with AS.

Overall Design: Randomized, DB, placebo-control, multi-center, global, 3-arm, 5-year Phase 3 trial of golimumab in patients with active AS (both a BASDAI score of ≥ 4 and a VAS score for total back pain of ≥ 4) who have had an inadequate response to 3 months of maximal NSAIDs or is unable to

tolerate a 3 month maximal NSAID therapy because of intolerance, toxicity, or contraindications to NSAIDs. Patients with complete ankylosis of the spine and patients who have received any biologic anti-TNF product (e.g., infliximab, etanercept, adalimumab), rituximab, natalizumab, or a cytotoxic agent will be excluded. Patients may take stable doses of concomitant NSAIDs, MTX (≤ 25 mg/week), SSZ, HCQ, and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent). There will be 3 main treatment periods in Study 9 (see Figure 9.5.2):

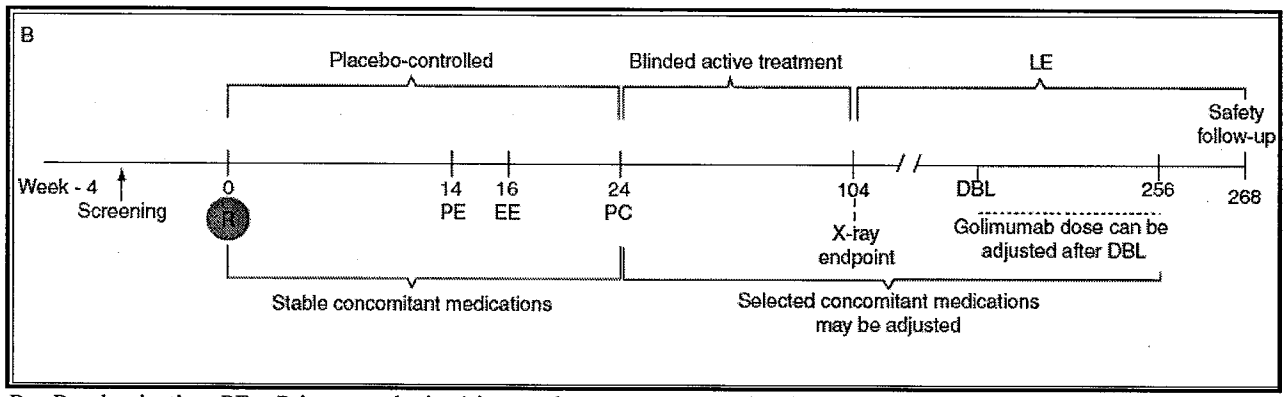
1. 0.5 year, DB, placebo-controlled period (Week 0 to Week 24) with two parts:

   - 16-week period from Week 0 to Week 16
   - 8-week period from Week 16 to Week 24 (where at Week 16 patients could enter into an escape phase for lack of efficacy)

2. 1.5 year, DB, dose-ranging control period (Week 24 to 104) in which the placebo group will crossover to blinded treatment with golimumab.

3. 3-year, LE period from Week 104 to Week 256. The initial part of the LE period will be DB but the time period after the Week 104 database lock will be open-label (the Week 104 database lock will occur when the last patient completes the 104-week controlled portion of the study).

Figure 9.5.2: Study 9 schema



R = Randomization; PE = Primary endpoint (signs and symptoms at Week 14); PC = Placebo crossover (placebo group crosses over to receive golimumab 50 mg once every 4 weeks); DBL = database lock (the 24-week DBL occurs after the last patient enrolled completes the Week 24 visit); LE long-term extension; EE = early escape (patient having < 20% improvement in the total back pain and morning stiffness)
Reference: Adapted from amendment 1 of the protocol of Study 9, Page 20

Eligibility Criteria: Table 9.5.3 displays the eligibility criteria in Study 9

Table 9.5.3: Eligibility Criteria in Study 9

Inclusion Criteria: To have been eligible to participate in the study, patients have to meet all of the following criteria:	Exclusion Criteria: If patients have any of the following conditions, they are not eligible to participate in the study:
1. ≥ 18 years old and have a diagnosis of **definite AS** (for at least 3 months prior to first administration of study agent), as defined by the **modified New York criteria**. Both the radiographic criterion (i.e.,	1. Have other inflammatory diseases (e.g., RA, PsA, SLE, Lyme disease) that might confound the evaluations of benefit from the golimumab therapy.

grade ≥ 2 sacroiliitis bilaterally or grade 3 to 4 sacroiliitis unilaterally) and at least 1 of the following clinical criteria must be met:
- Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes
- Limitation of chest expansion relative to normal values corrected for age and sex

2. Have symptoms of **active disease** at screening and at baseline, as evidenced by both a BASDAI score of ≥ 4 and a VAS score for total back pain of ≥ 4, each on a scale of 0 to 10 cm.
3. Either has an **inadequate response** to 3 months of continuous therapy with maximal recommended doses of **NSAIDs, or is unable to receive a full 3 months of maximal NSAID** therapy because of intolerance, toxicity, or contraindications to NSAIDs.
4. If using oral corticosteroids, must be on a stable dose equivalent to ≤ 10 mg of prednisone/day for at least 2 weeks prior to first administration of study agent. If currently not using corticosteroids, must not have received oral corticosteroids for at least 2 weeks prior to the first administration of the study agent.
5. If using MTX, SSZ, or HCQ, should have started treatment at least 3 months prior to the first administration of study agent and should have no serious toxic side effects attributable to the DMARD. MTX (not to exceed 25 mg/week), SSZ, or HCQ doses should be stable for at least 4 weeks prior to the first administration of the study agent. If currently not using MTX, SSZ, or HCQ, must have not received these DMARDs for at least 4 weeks prior to the first administration of the study agent.
6. If using NSAIDs, must be on a stable dose for at least 2 weeks prior to the first administration of study agent. If currently not using NSAIDS, must not have received NSAIDs for at least 2 weeks prior to the first administration of the study agent.
7. Considered eligible according to the following TB screening criteria:
   7.1. No history of latent or active TB prior to screening.
   7.2. No signs or symptoms suggestive of active TB upon medical history and/or physical examination.
   7.3. No recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study drug.
   7.4. Within 1 month prior to the first administration of study agent, either have negative diagnostic TB test results (defined as both a negative tuberculin skin test and a negative QuantiFERON-TB Gold test), or have a newly identified positive diagnostic TB test result (defined as either a positive tuberculin skin test or a positive QuantiFERON-TB Gold test) during screening in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study drug.
   7.5. Have posterior-anterior and lateral chest radiographs, taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
8. Screening laboratory test results:
   11.1 Hemoglobin ≥ 8.5 g/dL.
   11.2 White blood cells ≥ 3.5×10^9 cells/L.
   11.3 Neutrophils ≥ 1.5×10^9 cells/L.
   11.4 Platelets ≥ 100×10^9 cells/L.
   11.5 ALT and AST levels not exceeding 1.5 times the ULN.
   11.6 Serum creatinine ≤ 1.5 mg/dL.
9. Women of childbearing potential (WOCP) or men capable of fathering children must be using adequate birth control measures (e.g.,

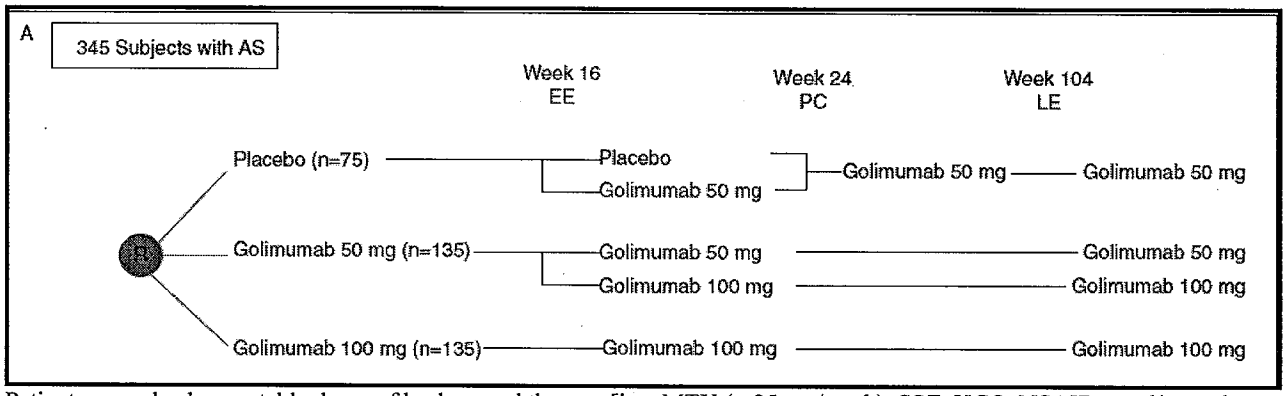
2. Have complete ankylosis of the spine, defined as bridging syndesmophytes present at all intervertebral levels of the cervical and lumbar spine visualized on lateral-view spinal radiographs.
3. Received any biologic anti-TNF product (e.g., infliximab, etanercept, adalimumab), rituximab, natalizumab, or a cytotoxic agent (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents).
4. Within 4 weeks prior to the first administration of study agent, received systemic immunosuppressives (e.g., cyclosporine, mycophenolate mofetil, azathioprine); DMARDs other than MTX, SSZ, or HCQ (e.g., gold preparations, D-penicillamine); or intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone).
5. Within 4 weeks prior to the first administration of study agent, received leflunomide (irrespective of undergoing a drug elimination procedure), or within 3 months prior to the first administration of study received leflunomide and have not undergone a drug elimination procedure.
6. Within 3 months prior to the first administration of the study agent received alefacept or efalizumab.
7. Received any investigational agent within 5 half-lives prior to the first administration of study agent.
8. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic non-remitting cystitis), an open, draining, or infected skin wound, or an ulcer. History of an infected joint prosthesis, or received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
9. Known to be infected with HIV, hepatitis B, or hepatitis C.
10. Had a serious infection (e.g., hepatitis, pneumonia, pyelonephritis, or sepsis) or have been hospitalized for an infection or within 2 months prior to administration of study agent have been treated with IV antibiotics for an infection. Although, less serious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) do not have to be considered exclusionary.
11. History of active or latent granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis.
12. Within 6 months prior to screening had a non-tuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, Pneumocystis carinii, aspergillosis).
13. Received, or are expected to receive during the trial (within 3 months before the first administration of study agent or within 6 months after the last administration of study agent) any live virus or bacterial vaccination.
14. History of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease (e.g., lymphadenopathy of unusual size or location, or clinically significant splenomegaly).
15. Known malignancy with the exception of a non-melanoma skin cancer that has been treated with no evidence of recurrence.
16. Have a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to first study agent administration).
17. Have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.
18. Had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.
19. History of known demyelinating diseases such as multiple sclerosis or optic neuritis.
20. History of, or concurrent, CHF, including medically controlled, asymptomatic CHF.
21. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease.

abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study and for 6 months after receiving the last administration of study drug. WOCP must test negative for pregnancy. 10. Are willing and able to adhere to the study visit schedule and other protocol requirements and are capable of providing informed consent, which must be obtained prior to any study-related procedures.	22. Known hypersensitivity to human immunoglobulin proteins or other components of golimumab. 23. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years. 24. Unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access. 25. Participating in another trial with an investigational agent or procedure. 26. Pregnant, nursing, or planning a pregnancy or fathering a child within 6 months after receiving the last administration of study agent.

Reference: Adapted from the amendment 1 of the protocol for Study 9, Pages 24-29

Treatments: Patients will receive study treatment during the DB and LE periods (see Figure 9.5.4). Golimumab will be supplied as a sterile liquid (liquid in a vial or LiV) for SC injection and once available, golimumab may also be supplied as a sterile liquid for SC injection in prefilled syringe (PFS).

Figure 9.5.4: Treatments in Study 9[1]



Patients may also be on stable doses of background therapy [i.e., MTX (≤ 25 mg/week), SSZ, HCQ, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day].
Reference: Adapted from amendment 1 of the protocol of Study 9, Page 20

DB, Placebo-Control Period: Patients will be randomized 1:1.8:1.8 to 1 of the following 3 treatment groups: Groups 1, 2, and 3 (see Table 9.5.5 and Figure 9.5.4).

Table 9.5.5: Treatment groups at randomization in the DB, placebo-control period (Week 0 to 24) in Study 9[1]

Group #	Dosing
Group 1	**placebo SC injections once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**
Group 2	**golimumab 50 mg SC once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**
Group 3	**golimumab 100 mg SC once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20)[2]**

1 Patients who escape at Week 16 may receive different treatment at Week 16 and Week 20 (see Table 9.5.6).
2 Patients may take stable doses of concomitant NSAIDs, MTX (≤ 25 mg/week), SSZ, HCQ, and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent) during the study.
Reference: Adapted from amendment 1 of the protocol for Study 9, Page 21

At Week 16 during the DB Period, any patient who has < 20% improvement from baseline in both total back pain **and** morning stiffness will enter early escape in a double-blinded fashion (see the

treatments for the patients who enter escape in Table 9.5.6 and Figure 9.5.4). Total back pain is assessed over the past week (using a 0-10 cm VAS where 0 is no pain and 10 is most severe pain) and morning stiffness will be assessed using the mean of qualitative morning stiffness and the quantitative morning stiffness in the Bath AS disease activity index (BASDAI) on a 0 to 10 cm VAS. Patients who do not enter early escape will continue the treatment assigned at randomization (see 9.5.6 and Figure 9.5.4).

Table 9.5.6: Treatments for patients who enter escape at Week 16[1] in Study 9

Group #	Treatment prior to escape	Treatment during escape
Group 1	**Placebo**	**Add golimumab 50 mg** SC at Weeks 16 and 20[2]
Group 2	**Golimumab50 mg**	**Increase golimumab to 100 mg** SC at Weeks 16 and 20[2]
Group 3	**Golimumab100 mg**	Continue golimumab 100 mg SC at Weeks 16 and 20 (no change)[2]

1 Patients who enter escape at Week 16 will be treated in a DB fashion at Week 16 and Week 20. All groups who escape will receive golimumab every 4 weeks (i.e., at Week 16 and Week 20).
2 Patients may take stable doses of concomitant NSAIDs, MTX (≤ 25 mg/week), SSZ, HCQ, and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent) during the study.
Reference: Adapted from amendment 1 of the protocol for Study 9, Page 21

DB, Dose-Ranging-Control Period: Treatment during the DB, dose-ranging control period will start at Week 24 and continue every 4 weeks through Week 100. All patients in the placebo group will crossover to receive blinded golimumab 50 mg SC every 4 weeks and patients in the original golimumab treatment groups will continue their treatments (see Table 9.5.7 and Figure 9.5.4).

Table 9.5.7: Treatments for patients during the DB, dose-ranging control period in Study 9[1]

Group #		Treatment during Week 24 to Week 100
Group 1	For patients who did not escape	**Cross over to golimumab 50 mg SC mg** every 4 weeks starting at Week 24 and ending on Week 100 (no change).
	For patients who entered escape	Continue golimumab 50 mg SC mg every 4 weeks starting at Week 24 and ending on Week 100 (no change).
Group 2	For patients who did not escape	Continue golimumab 50 mg SC every 4 weeks starting at Week 24 and ending on Week 100 (no change).
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks starting at Week 24 and ending on Week 100 (no change).
Group 3	For all patients	Continue golimumab 100 mg SC every 4 weeks starting at Week 24 and ending on Week 100 (no change).

1 The doses of concomitant NSAIDs, MTX, SSZ, HCQ, and/or oral corticosteroids may be decreased during this blinded, dose-ranging portion of the study.
Reference: Adapted from amendment 1 of the protocol for Study 9, Page 21

LE Period: Treatment during the Long-Term Extension (LE) Period in Study 9 will start at Week 104 and continue every 4 weeks through Week 252 (see Table 9.5.8 and Figure 9.5.4). The blind will be maintained during the LE Period until the last patient completes the Week 104 evaluations and the 104-week database is locked.

Table 9.5.8: Treatments during the Long-Term Extension Period from Week 104 to 252 in Study 9[1]

Group #	Prior Treatment	Treatment during Week 104 through Week 252
Group 1	golimumab50	Continue golimumab 50 mg SC every 4 weeks **(option to increase to golimumab 100 mg SC every 4 weeks after 104-week DBL)**
Group 2	golimumab50	Continue golimumab 50 mg SC every 4 weeks **(option to increase to golimumab 100 mg SC every 4 weeks after 104-week DBL)**
	golimumab100	Continue golimumab 100 mg SC every 4 weeks
Group 3	golimumab100	Continue golimumab 100 mg SC every 4 weeks

1 All groups will receive golimumab starting at Week 104 every 4 weeks until Week 252. The blind will be maintained in LE Period until after the last patient finishes the 104-week evaluations and the 104-week database is locked. Therefore, during the initial part of LE, the treatments will be double-blinded. After the 104-week DBL, doses of concomitant therapy (i.e., MTX, SSZ, HCQ, NSAIDs, and/or oral corticosteroids) may be adjusted.
Reference: Adapted from amendment 1 of the protocol for Study 9, Pages 22-23

Concomitant Medication:

MTX, SSQ, and/or SSZ: Patients are allowed to receive stable, concomitant MTX (≤ 25 mg/week), SSZ, and/or HCQ until the 104-week database is locked. Every effort should be made to maintain stable doses of MTX, SSZ, and HCQ through Week 24 of the study and starting at Week 24, MTX, SSZ, or HCQ doses can be decreased. After the 104-week database lock, MTX, SSZ, HCQ can be increased, decreased, or started. It is recommended that all patients taking MTX should receive at least 5 mg oral folic acid or oral folinic acid weekly.

Corticosteroids: Patients treated with oral corticosteroids should receive a stable dose equivalent to ≤ 10 mg prednisone per day for at least 2 weeks prior to their first administration of the study agent and continue to receive this dose through Week 24. If there are no adequate alternatives, patients could receive short courses (≤ 2 weeks) of oral or IV corticosteroids for the treatment of non-AS conditions (e.g., stress-dose steroids, therapy for limited infections, exacerbation of asthma or COPD). IM or IV administration of corticosteroids for the treatment of AS is not allowed up to Week 104. Inhaled and intranasal corticosteroids for conditions other than AS are allowed throughout the course of the study. Patients may receive up to 2 intra-articular, tendon sheath, or bursal corticosteroid injections in no more than 2 affected sites during the first 104 weeks of the study.

NSAIDs and other Analgesics: Patients treated with NSAIDs, including aspirin, and other analgesics, should receive the usual marketed doses approved in the country in which the study is being conducted, and should have been on a stable dose at least 2 weeks prior to the first administration of the study agent and during the first 104 weeks of the trial. The dose may be reduced and the type of NSAIDs or other analgesics may be changed if the patient develops unacceptable side effects. Whenever possible, short-acting NSAIDs and other analgesics should not be administered within 6 hours before study evaluations. Long-acting NSAIDs can be maintained at their usual dosing intervals before study evaluations.

Disease-modifying Antirheumatic Drugs (DMARDs) and Systemic Immunosuppressives: DMARDs (other than stable doses of MTX, SSZ, and HCQ) and systemic immunosuppressives are prohibited within the 4 weeks prior to the first administration of the study agent through Week 104 of the study. After the 104-week DBL, the MTX, SSZ, and HCQ dose can be adjusted and new DMARDs may be added.

Biologic Agents, Cytotoxic Agents, and Investigational Drugs: The use of biologic agents (e.g., anakinra, etanercept, adalimumab, infliximab, alefacept, efalizumab, rituximab, natalizumab), cytotoxic agents (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, other alkylating agents), or investigational drugs is not allowed during the entire 5-year study including LE.

Study Monitoring and Evaluations: Table 9.5.9 presents the schedule of procedures and evaluations in Study 9. All post-baseline visits through Week 52 must have occurred within ± 7 days except the Week 12, 14, and 16 visits must have occurred within ± 3 days.

Table 9.5.9: Schedule of procedures and evaluations through Week 52 in Study 9

Assessments[a]	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 14[b]	Wk 16	Wk 20	Wk 24[b]	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52
Consent	X															
Demography/medical history	X															
Physical exam	X								X							X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Weight	X					X			X							X
Chest x-ray	X															
Tuberculin skin test	X															
QuantiFERON-TB Gold test	X															
Review of entry criteria	X	X														
Serum pregnancy test[c]	X															
HLA-B27 status		X														
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
IVRS notification of total back pain and morning stiffness		X					X									
Study agent injection (every 4 weeks)		X	X	X	X		X	X	X	X	X	X	X	X	X	X
AS response evaluations[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Musculoskeletal assessments[e]		X				X			X							X
Jenkins Sleep questionnaire		X				X			X							X
HEcon		X		X			X		X							X
SF-36		X				X			X							X
X-rays of cervical and lumbar spine	X															
MRI of spine[g]	X					X										
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study agent injection site evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses	X	X	X	X		X		X	X	X	X	X		X		X
CRP	X	X	X	X		X		X	X		X			X		X
ANA/anti-dsDNA antibodies		X				X										X
Golimumab concentration		X	X	X	X	X	X	X	X							X
Population PK							←	X[a]	→							
Antibodies to golimumab		X							X							X
Serum-based PD biomarkers (approximately 150 subjects)[f]		X	X			X			X							
Protein profiling (approximately 100 of the 150 subjects above)[f]		X	X			X										
Anemia markers		X				X										

a All assessments are to be completed prior to study agent injection, except at Week 14 (no study agent injection), unless otherwise specified.
b Primary and secondary endpoints.
c In addition to the screening evaluation, the pregnancy test may be repeated at any time (including during the long-term extension).
d Evaluations include BASDAI, BASFI, patient's global, total back pain, and night back pain assessments.
e Evaluations include BASMI, enthesitis index, and chest expansion.
f Performed at selected study sites.
g If TB is suspected at any time during the study, chest x-ray, tuberculin skin test, and QuantiFERON-TB Gold test should be performed.
h One additional sample for golimumab concentration will be collected from all subjects at any time between Weeks 16 to 24, other than at visits at Weeks 16, 20, or 24. This sample must be collected at least 24 hours prior to or after a study agent injection. Reference: Adapted from amendment 1 of the protocol for Study 9, Attachment 1.1, Pages 69-70

Efficacy Endpoints:

Primary Efficacy Endpoint: The primary efficacy endpoint in Study 9 was the proportion of patients with an ASAS 20 response at Week 14. A patient was classified as having achieved an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14 if both of the following was achieved at Week 14:

1. A relative improvement of ≥ 20% from baseline **and** an absolute improvement from baseline of ≥ 1 on a 0 to 10 cm scale in ≥ 3 of the following 4 domains:

   - Patient global using a 0-10 cm VAS, where 0 is very well and 10 is very poor
   - Total back pain, using the average total back pain over the past week on a 0-10 cm VAS, where 0 is no pain and 10 is the most severe pain.
   - Function using the Bath AS Functional Index (BASFI) on a 0-10 cm VAS (see Table 9.5.10).
   - Mean of the last two stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI) on a 0-10 cm VAS (see Table 9.5.10 for the definition of the BASDAI).

2. Absence of deterioration from baseline (deterioration defined as ≥ 20% worsening and absolute worsening of ≥ 1 on a 0 to 10 cm scale) in the potential remaining domain.

Secondary Efficacy Endpoints: The 3 secondary efficacy endpoints in Study 9 were the following (without a pre-specified order):

1. The proportion of patients with an ASAS 20 at Week 24.
2. The change from baseline in the BASFI score at Week 14 (see Table 9.5.10).
3. The change from baseline in the Bath AS Metrology Index (BASMI) score at Week 14 (see Table 9.5.10).

Table 9.5.10: The Bath AS Function, Disease Activity, and Metrology Indexes (i.e., BASFI, BASDAI, and BASMI)

Instrument	Definition	Range
Bath AS Functional Index (BASFI)	**A functional instrument (a higher score indicates worse function), was calculated as the mean of 10 scales (8 and 2 scales are related to the functional capacity of a patient and the patient's ability to cope with everyday life, respectively).**	**0 to 10**
Bath AS Disease Activity Index (BASDAI)	**A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS.**	**0 to 10**
Bath AS Metrology Index (BASMI)	**Comprises of the sum of 5 measures of hip and spine mobility [i.e., tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe).**	**0 to 10**

105 Other Pre-Specified Endpoints Related to Signs and Symptoms: The following are the 105 other pre-specified endpoints related to signs and symptoms:

ASAS Endpoints

1. 7 endpoints: proportion of ASAS 20 responders over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
2. 2 endpoints: proportion of patients with an ASAS 40 response at Week 14 and Week 24 (i.e., a 40% improvement in 3 of the 4 ASAS domains with an absolute improvement of at least 2 cm on a 0 to 10 cm scale, and no deterioration in the remaining domain).
3. 2 endpoints: proportion of patients with an ASAS 5/6 response at Weeks 14 and 24. ASAS 5/6 is a 20% improvement from baseline in 5 of the following 6 domains: total back pain (VAS 0 to 10 cm), patient global (VAS 0 to 10 cm), function (BASFI score), the mean morning stiffness score in the BASDAI (VAS 0 to 10 cm), CRP, and spine mobility (lumbar side flexion).

Enthesitis Endpoints

4. 21 endpoints: change from baseline for each of the three enthesitis indexes (i.e., Berlin, UCSF, and MASES) over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].

BASDAI Endpoints

5. 8 endpoints: proportion of patients with a $\geq$ 20%, 50%, 70%, and 90% improvement from baseline in the BASDAI at Weeks 14 and 24.
6. 7 endpoints: proportion of patients with a BASDAI score < 3 over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
7. 7 endpoints: change in BASDAI score from baseline over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].

Other Sign and Symptom Endpoints

8. 1 endpoint: proportion of patients at Week 14 with low AS disease activity (i.e., score less than 2 out of 10 in the 4 domains — patient global, total back pain, BASFI, stiffness).
9. 7 endpoints: percentage change from baseline in the patient's Global Assessment of Disease Activity (0-10 VAS) over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
10. 7 endpoints: percentage change from baseline in the patient's Assessment of Total Back Pain (0-10 VAS) over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
11. 7 endpoints: the percentage change from baseline in the stiffness score [the mean of the two morning stiffness questions (each used a 0-10 VAS) in the BASDAI (i.e., overall level of stiffness and duration of stiffness from the time of awakening)] over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
12. 7 endpoints: percentage change in the CRP from baseline over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
13. 7 endpoints: change from baseline in chest expansion (i.e., the difference between the circumference of the chest in maximal inspiration and maximal expiration) over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].
14. 7 endpoints: change from baseline in Night Back Pain for the past week (0-10 VAS) over time [i.e., Weeks 4, 8, 12, 14, 16, 20, and 24 (7 visits)].

BASFI Endpoints

15. 1 endpoint: change from baseline in the BASFI at Week 24.
16. 2 endpoints: of the patients with a baseline BASFI ≥ 2, the proportion with an improvement from baseline of at least 2 units in the BASFI at Week 14 and Week 24.

BASMI Endpoints

17. 1 endpoint: change from baseline in the BASMI at Week 24.
18. 2 endpoints: of the patients with a baseline BASMI ≥ 1, the proportion with an improvement from baseline of at least 1 unit in the BASMI at Week 14 and Week 24.

ASAS Response by PK Endpoints

19. 2 endpoints: ASAS 20 response at Weeks 14 and 24 by trough serum golimumab concentration (i.e., < 0.2, 0.2-1.0, 1.0-2, ≥ 2.0 µg/ml — these categories may be changed depending on actual data).

Other Pre-Specified Endpoints: There were multiple other pre-specified endpoints related to vertebral structural damage using MRIs and radiographs of the spine and quality of life.

Statistics:

Populations: The pre-specified populations for Study 9 were:

1. **Intent-to-Treat (ITT) Population** includes patients who are randomized regardless of whether or not they receive the assigned treatment. The ITT population will be used for the efficacy analyses.
2. **Treated Population** includes patients who received at least one SC study agent administration. The treated population will be used for the clinical pharmacology and safety analyses

Database Locks: The 3 database locks will occur at Weeks 24, 104, and 268 after all patient evaluations through Weeks 24, 104, and 268, respectively.

Methods for the Primary Efficacy Endpoint: There will be 2-tiered testing for the primary efficacy endpoint (i.e., ASAS 20 response at Week 14):

1. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) CMH test stratified by screening CRP (≤ 1.5 mg/dL, > 1.5 mg/dL), was between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group.
2. If this is significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$ for each comparison, between golimumab100 & placebo and golimumab50 and placebo was performed. According to the SAP, a positive trial occurred if at least one these two pairwise comparisons were significant.

Handling of Treatment Failures, Dropouts, and Missing Data for the ASAS 20 at Week 14 Primary Efficacy Endpoint: Patients who met ≥ 1 of the following treatment failure criteria prior to Week 14 were considered to not have achieved an ASAS 20 response at Week 14:

1. Initiated treatment with new DMARDs, systemic immunosuppressives, or biologics for the treatment of AS or increased the SSZ, MTX, or HCQ dose above baseline for the treatment of AS;
2. Discontinued study agent due to an unsatisfactory therapeutic effect; or
3. Initiated treatment with oral, IV, or IM corticosteroids for AS, or increased the dose of oral corticosteroids for the treatment of AS above the baseline dose.

Patients with missing data for all of the ASAS components at Week 14 will be considered as ASAS 20 non-responders at Week 14. If patients have missing data but have data for ≥ 1 ASAS component at Week 14, the following rules will be applied:

1. For any ASAS component, if all the component values are missing from baseline through Week 14, the percent improvement from baseline at Week 14 for that component will be imputed with 0%.
2. For any ASAS component, if the component value at Week 14 is missing and the baseline value is present, the missing component will be replaced by the last non-missing observation (LOCF).
3. For any ASAS component, if the component value at baseline is missing but a post-baseline value is observed prior to or at Week 14, the median component value of all patients at baseline in the same stratum (screening CRP ≤ 1.5 mg/dL or > 1.5 mg/dL) will be used to impute the baseline value.

If the baseline value of an ASAS component is 0, then for purposes of calculating ASAS 20, the percent change from baseline will be determined as follows (i.e., zero divisor rule):

1. If the post-baseline component value is also 0, set the percent change equal to 0;
2. If the post-baseline component value is > 0, then calculate the percent change as though the baseline value were 0.1.

Methods for the Secondary Efficacy Endpoints: There will be no multiplicity adjustments for the 3 secondary endpoints. For all 3 secondary endpoints, the first test will compare the combined golimumab groups versus placebo. If the result is significant, then pair-wise comparisons of golimumab100 versus placebo and golimumab50 versus placebo will be performed.

The proportion of patients with an ASAS 20 response at Week 24 was analyzed by a 2-sided CMH test with stratification by screening CRP. The change from baseline in the BASFI score and the BASMI score at Week 14 used an analysis of variance on the van der Waerden normal scores, based on screening CRP level.

Methods for the Other Pre-Specified Endpoints: There were no multiplicity adjustments for the 105 pre-specified signs and symptoms endpoints or the multiple other pre-specified endpoints relating to vertebral structural damage using MRIs and radiographs of the spine and quality of life.

Study 9 Results

For the disposition, baseline demographics, baseline disease characteristics, and the efficacy results in Study 9 see Section 6.3. For the safety results see Section 7.6.4 (Drug-Disease Interactions). For the protocol deviations and exposure see below.

Protocol Deviations: Table 9.5.11 displays the protocol deviations in Study 9 through Week 24. A similar proportion of patients in the treatment groups did not meet eligibility criteria and SC agent deviation. Most of the patients who did not meet eligilibility criteria entered the study and continued study treatment. There was some variability in the receipt of study agent administration including outside the protocol-specified window (within 3-7 days of the study visit).

Table 9.5.11: Protocol deviations in Study 9 through Week 24

	Placebo ± DMARDs (n=77)	Golimumab50 ± DMARDs (n=138)	Golimumab100 ± DMARDs (n=140)
Patients who did not meet eligibility criteria	6%	4%	2%
Patients with SC study agent administration deviation	40%	33%	35%
Received administration outside protocol-specified window	35%	31%	29%
Missed an administration	8%	6%	7%
Received an incorrect study agent or incorrect dose	1%	0%	1%

Reference: Adapted from Final Study Report for Study 9; Table 7, Page 73; Table 8, Page 75

Exposure: Table 9.5.12 displays the SC exposure of golimumab through Week 24 in Study 9.

Table 9.5.12: Cumulative dose of SC golimumab received through Week 24 in Study 9[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	Placebo ± DMARDs[2] (n=77)	Golimumab50 ± DMARDs[2] (n=138)	Golimumab100 ± DMARDs[2,3] (n=140)	Placebo to Golimumab50 ± DMARDs[2] (n=41)	Golimumab50 to Golimumab100± ± DMARDs[2] (n=25)
Mean number of SC administrations	4.8	5.4	5.8	2.0	1.9
Mean duration of follow-up	19.5 weeks	22.4 weeks	24.1 weeks	8.0 weeks	7.9 weeks
Mean (SD) cumulative SC golimumab dose	0 (0) mg	269 (54) mg	581 (63) mg	100 (0) mg	192 (28) mg

1 For the 24-week dataset, SC administrations of placebo or golimumab occurred at Weeks 0, 4, 8, 12, 16, and 20 (up to 6 SC administrations). Evaluations performed at W24 and then the database was locked after all patients completed the W24 data.
2 Patients may have taken stable doses of concomitant DMARDS (i.e., MTX, SSZ, and/or HCQ), NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks. The treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses.
3 Patients in the golimumab100 group who escaped continued to receive golimumab100 at Week 16
Reference: Adapted from Final Study Report for Study 9, Table 34, Page 138.

CLINICAL FILING CHECKLIST FOR ORIGINAL BLA SUBMISSION

BLA Number: 125289/0000

Product Name: golimumab (SIMPONI)
Applicant: Centocor
BLA Type: original submission
Stamp Date: June 24, 2008

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			PLR format Includes Patient Information Sheet
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Neither, golimumab is a biologic and is neither a 505(b)(1) or 505(b)2
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR ORIGINAL BLA SUBMISSION

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			Particular analyses were requested and provided
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional CRFs have been requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			