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APPLICATION NUMBER:

125289

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 125289
Submission Code	0000
Letter Date	June 24, 2008
Stamp Date	June 24, 2008
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Reviewer Name	Eric Brodsky, M.D.
Through	Sarah Okada, M.D.
Review Completion Date	March 9, 2009
Established Name	golimumab
(Proposed) Trade Name	Simponi
Therapeutic Class	TNF inhibitor
Applicant	Centocor
Priority Designation	Standard
Proposed Presentation	Pre-filled syringe (by auto-injector or needle safety guard)
Proposed Dosing Regimen	50 mg given subcutaneously once a month
Proposed Indications	[redacted] adult patients with moderate to severely active rheumatoid arthritis (RA), with active psoriatic arthritis (PsA), and active ankylosing spondylitis (AS)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend **approval** of Biologic License Application (BLA) 125289 for Simponi (golimumab) for [redacted] adult patients with moderately to severely active **rheumatoid arthritis (RA)**, moderately to severely active **psoriatic arthritis (PsA)**, and moderately to severely active **ankylosing spondylitis (AS)**, with revisions to the proposed label. [redacted] b(4)

For all three indications, recommend **approval** of only the lower dose regimen [**50 mg of golimumab given subcutaneously (SC) once monthly**] since there was no clear evidence of improved efficacy with the higher dose regimen (100 mg of golimumab given SC once every 4 weeks) and there was a suggestion of increased toxicity of the higher dose regimen. For the RA indication, recommend that golimumab should be used with MTX because the efficacy of golimumab monotherapy in the treatment of the signs and symptoms of RA was not clearly established. For the PsA indication, recommend that golimumab be used with or without MTX because the efficacy of golimumab with or without MTX in the treatment of the signs and symptoms of PsA was established.

1.2 Risk Benefit Analysis

Overview of the Clinical Program

Centocor submitted BLA 125289 on June 24, 2008 to support the approval of Simponi (golimumab), a biologic TNF inhibitor (human monoclonal antibody to TNF), for [redacted] of adult patients with moderately to severely active RA, PsA, and AS. Centocor proposes one dose regimen for all three indications [50 mg of golimumab given subcutaneously (SC) once monthly]. b(4)
Centocor argues that golimumab will be beneficial because it is more convenient than the other approved TNF inhibitors that are given SC (the 2 approved TNF inhibitors for SC use for RA, PsA, and AS are given either once a week or once every two weeks).

Centocor submitted the results from the **24-week controlled portions of 5 ongoing Phase 3 trials** as the primary basis for the efficacy and safety of SC golimumab for the treatment of signs and symptoms of RA, PsA, and AS. Results from an additional 8 studies were also submitted as supportive evidence of efficacy and safety. Centocor plans to [redacted] b(4)
These 5 Phase 3 trials are 5-year, ongoing, randomized, double-blind, controlled, trials of 50 mg and 100 mg of SC golimumab given every 4 weeks [see Table 5.1 in Section 5.1 (Tables of Clinical Studies) and Section 5.3 (Discussion of Individual Studies) for more details on the design of these trials]:

1. Study 5: 4-arm, MTX-controlled, global (18% of the patients from the United States) trial in 634 treated patients with **active RA** who were **MTX-naive** (primary efficacy endpoint was the proportion of ACR50 responders at Week 24)

2. Study 6: 4-arm, background MTX-controlled, global (16% of the patients from the United States) trial in 444 treated patients with **active RA despite MTX therapy** (primary efficacy endpoint was the proportion of ACR20 responders at Week 14)
3. Study 11: 3-arm, placebo-controlled, global (58% of the patients from the United States) trial in 459 treated patients with **active RA who "must have previously received at least 1 dose of etanercept, adalimumab, or infliximab"** without a clinically serious adverse reaction (primary efficacy endpoint was the proportion of ACR20 responders at Week 14).
4. Study 8: 3-arm, placebo-controlled, global (22% of the patients from the United States) trial in 405 treated patients with **active PsA** who may have received stable doses of MTX (primary efficacy endpoint was the proportion of ACR20 responders at Week 14).
5. Study 9: 3-arm, placebo-controlled, global (24% of the patients from the United States) trial in 355 treated patients with **active AS despite NSAID therapy or was unable to tolerate NSAIDs** (primary efficacy endpoint was the proportion of ASAS20 responders at Week 14).

Patients in these 5 Phase 3 trials may have received stable doses of MTX, oral corticosteroids ($\leq$ 10 mg prednisone/day or equivalent) and/or NSAIDs during the trial and patients in Studies 11 and 9 may have also received stable doses of hydroxychloroquine and/or sulfasalazine during the trial. In Studies 5, 6, 8, and 9, patients who received a biologic TNF inhibitor was excluded; however, in Study 11 patients must have previously received $\geq$ 1 dose of a biologic TNF inhibitor prior to enrollment. Patients were allowed to enter early escape if they had active disease at Week 16 in Studies 6, 11, 8, and 8 and at Week 28 in Study 5. Patients in Studies 6, 11, 8, and 9 were allowed to receive open-label golimumab in a long-term extension up to 4.5 additional years. Patients in Study 5 with active disease were allowed to receive open-label golimumab or receive open-label MTX if they had quiescent disease (no swollen or tender joints) in a long-term extension up to 4 additional years.

In the entire safety database of 13 completed studies of golimumab, 2894 patients received at least one dose of golimumab (2868 and 26 patients received at least one dose of SC and IV golimumab, respectively). In the 5 Phase 3 rheumatology trials, 2210, 2057, and 1768 patients received at least 4, 24, and 52 weeks, respectively, of the proposed SC golimumab dose (50 mg) or a higher dose (100 mg) as of the last safety cut off date — patients may have been counted more than once. One dose of SC golimumab was considered to be 4 weeks of treatment due to the 2-week half life of golimumab and maintenance dose interval (every 4 weeks). As of the last safety cut-off date, the mean (SD) number of SC administrations of 50 mg and 100 mg of golimumab were 15 (8) and 17 (8), respectively, in the 5 Phase 3 trials.

Summary of Efficacy

Three adequate and well-controlled trials in patients with RA, one adequate and well-controlled trial in patients with PsA, and one adequate and well-controlled trial in patients with AS supports the efficacy of golimumab in the three indications. One trial in PsA and one trial in AS were sufficient to support the efficacy of golimumab in these indications because data from the three RA trials provided independent substantiation of the efficacy of golimumab for RA, and PsA and AS are considered sufficiently closely related that efficacy in RA could be extrapolated to support the efficacy of golimumab in these two diseases.

Major Efficacy Results for RA: The combination of golimumab 50 mg given SC every 4 weeks (golimumab50) and weekly oral MTX demonstrated efficacy for the treatment of signs and symptoms (based on the ACR response at Weeks 14 and 24) in three different populations of patients with moderately to severely active RA (e.g., different disease refractoriness and disease durations). There was no clear evidence of improved efficacy with the higher dose combination [golimumab 100 mg given SC every 4 weeks (golimumab100) and weekly MTX]. In patients with early RA (mean disease duration of 3.5 years) who were naive to MTX (Study 5), the golimumab monotherapy group and MTX monotherapy group appeared to have similar efficacy in reducing the signs and symptoms of active RA. The efficacy of golimumab was similar to the efficacy of the 3 approved TNF inhibitors (infliximab, etanercept, and adalimumab) in the treatment of signs and symptoms in the 3 distinct RA populations.

The golimumab combination groups demonstrated an improvement in physical function in RA, using HAQ responders — the proportion of patients with a change in HAQ from baseline at Week 24 greater or equal to 0.22 [a minimally clinically important difference (MCID) in RA].

Major Efficacy Results for PsA: Golimumab50 demonstrated efficacy for reducing the signs and symptoms in patients with moderately to severely active PsA, based on a large absolute treatment margin of 42% compared to placebo group in the ACR 20 response at Week 14 in Study 8. Golimumab50 demonstrated efficacy for the ACR response with or without concomitant MTX. There was no clear evidence of improved efficacy with the higher dose (golimumab100). Golimumab50 demonstrated an improvement in physical function in PsA, using HAQ responders — the proportion of patients with a change in HAQ from baseline at Week 24 greater or equal to 0.3 [a minimally clinically important difference (MCID) in PsA].

Major Efficacy Results for AS: Golimumab50 demonstrated efficacy for reducing the signs and symptoms in patients with moderately to severely active AS, based on large absolute treatment margin of 37% compared to placebo in the ASAS 20 response at Week 14 in Study 9. There was no clear evidence of improved efficacy with the higher dose (golimumab100).

Summary of Safety

Overall golimumab had a similar safety profile as the 4 other approved TNF inhibitors. The exposure-adjusted incidence rates of deaths in the golimumab groups were below published background rates in the RA, PsA, and AS populations. In the controlled portions of the 5 Phase 3 trials, the combined golimumab group had a lower or similar proportion of SAEs, adverse events leading to discontinuation (DAEs), and AEs compared to the placebo control group. In the controlled and uncontrolled portions of the rheumatology Phase 2 and Phase 3 trials, the golimumab group had a lower exposure-adjusted incidence of serious infections compared to the placebo group. There were 7 golimumab-treated patients who had tuberculosis and 4 who had invasive fungal infections (2 cases of histoplasmosis, 1 case of coccidioidomycosis, and 1 case of pneumocystosis) in the 13 submitted golimumab studies through the last safety cut-off date (no placebo-treated patients developed tuberculosis or invasive fungal infections). Although in the controlled portions of the 5 Phase 3 trials the golimumab and placebo groups had a similar proportion of serious infections, a slightly greater proportion of patients in the golimumab groups compared to the placebo group had an infection AE and had an infection AE that required oral or parental anti-microbial therapy. Overall, the incidence and types of serious infections noted with golimumab are consistent with those seen with other TNF inhibitors.

In the rheumatology trials, the exposure-adjusted incidence of malignancies was similar in the golimumab and placebo groups and was similar to the expected rate in the general U.S. population according to the SEER database. There were 3 and 0 lymphomas in the golimumab and placebo groups, respectively, and the exposure-adjusted incidence of lymphomas in the golimumab groups were slightly greater than the expected rate in the general U.S. population according to the SEER database, a finding consistent with data from RA patients regardless of treatment, and also consistent with the experience with other TNF inhibitors in rheumatic disease. In an asthma trial, which included a higher golimumab dose (200 mg), there was a 3.5 fold higher incidence of malignancy other than NMSC in the golimumab group compared to the expected rate in the general U.S. population according to the SEER database. Susceptibility to malignancies in the asthma trial might be dose-related, since higher doses of TNF inhibitors were studied or might be related to the higher doses of oral corticosteroids used (for the patients who used steroids, the mean daily oral dose of prednisone equivalents was 13 and 7 mg in the asthma and rheumatology trials, respectively).

The proportion of golimumab-treated patients who developed human anti-golimumab antibodies was low. No golimumab-treated patient in the controlled portions of the 5 Phase 3 trials developed an anaphylactic reaction or serum sickness and there was no significant difference in the proportion of patients in the golimumab and placebo groups who developed urticaria, hypersensitivity, and/or rash. In the controlled portions of the 5 Phase 3 trials, 3.2%, 6.8%, and 9.1% of the patients in the placebo, golimumab50, and golimumab100 groups, respectively, had injection site reactions.

There was no significant difference in the exposure-adjusted rates of congestive heart failure, demyelinating disorders, autoimmune disorders, new auto-antibody formation, and serious hematological cytopenias in the golimumab-treated and placebo-treated patients. There were no "true" Hy's law cases (not confounded by baseline liver disease or concomitant hepatotoxic products) and a similar proportion of patients in the golimumab and placebo groups had post-baseline ALT elevations with similar degree of elevations.

The marketing of the prefilled syringe (PFS) presentations of golimumab was supported by no differences in the immunogenicity, allergic-type reactions, and safety after multiple-dose administration of the liquid-in-vial (LIV) and PFS presentations and the demonstration of bioequivalence of the presentations by AUC.

There was some suggestion that the golimumab100 regimen had greater toxicity than the golimumab50 regimen. The golimumab100 regimen had a greater exposure-adjusted incidence of death and serious infections in the controlled and uncontrolled portions of the Phase 3 trials and also had a greater proportion of infection AEs and infection AEs that required anti-microbial therapy in the controlled portions of the Phase 3 trials compared to the golimumab50 regimen.

The 5 Phase 3 trials appropriately excluded patients who were at increased risk of developing TNF inhibitor associated AEs (e.g., patients with ongoing or recurrent infections, a recent serious infection, a known malignancy except NMSC, a history of demyelinating disease, or a history of congestive heart failure) and patients at higher risk of developing active tuberculosis. Thus, the incidence of TNF-inhibitor associated AEs in the clinical trials may not reflect the incidence of these reactions if golimumab were used in clinical practice. However there is an extensive post-marketing clinical experience with other TNF inhibitors and experience with golimumab would likely be similar.

In summary, the safety profile of SC golimumab in reducing the signs and symptoms of RA, PsA, and AS appears to be consistent with the safety profile of approved TNF inhibitors. There were no unexpected safety concerns and there is no evidence to suggest that golimumab had greater risks compared to four approved TNF inhibitors. As with the four approved TNF inhibitors, the golimumab labeling should include Boxed Warnings for serious infections including tuberculosis and invasive fungal infections and Warnings for lymphoma and other malignancies and the FDA should institute a REMS with a Medication Guide, a Communication Plan, and an Assessment of REMS pertaining to the risk of serious infections including tuberculosis and invasive fungal infections.

Risk-Benefit Assessment
Overall, the results support the efficacy and safety of the:

1. Combination of golimumab 50 mg given SC every 4 weeks (golimumab50) and weekly oral MTX for reducing the signs and symptoms and the improvement of physical function in patients with moderately to severely active RA
2. Golimumab50 with or without MTX for reducing the signs and symptoms and the improvement of physical function in patients with moderately to severely active PsA
3. Golimumab50 for reducing the signs and symptoms in patients with moderately to severely active AS.

There have been no comparative trials of golimumab to the other approved TNF inhibitors in the treatment of RA, PsA, or AS. Although cross-study comparisons have major limitations, golimumab appeared to have similar efficacy and safety as the other TNF inhibitors in the treatment of RA, PsA, and AS.

1.3 Recommendations for Postmarketing Risk Management Activities

All approved TNF inhibitors in the United States (infliximab, etanercept, adalimumab, certolizumab pegol) require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of these products outweigh their risks. This was based on the FDA's review of serious infections associated with the use of TNF inhibitors particularly tuberculosis and invasive fungal infections (e.g., histoplasmosis, coccidioidomycosis, and blastomycosis). Since the safety profile of golimumab appeared similar to the other TNF inhibitors including the risk of serious infections, a REMS should be instituted to educate health care providers about the increased risk of serious infections including tuberculosis and invasive fungal infections. Centocor's proposed REMS that includes a Medication Guide, a Communication Plan, and a Time Table for Assessment of the REMS (at 1.5, 3, and 7 years after approval) is acceptable.

1.4 Recommendations for Postmarketing Study Commitments

Studies to achieve compliance with PREA
For adult RA: Polyarticular juvenile idiopathic arthritis (PJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2007, studies in PJIA are mandated. With this submission, Centocor requests a deferral for pediatric patients age 2-16 with PJIA because studies of golimumab in adult RA are completed and are ready for approval. This request has historically been granted for other therapeutic biologics, and should

also be granted for golimumab, because it is ethically desirable to have adequate safety experience in adults before proceeding with extensive studies in pediatric patients. Centocor has requested a partial waiver for pediatric patients ages 0-2 with PJIA, since these studies would be highly impracticable because PJIA is extremely rare in this age group. This, too, has been historically granted, and should be granted for golimumab.

Centocor's proposed pediatric plan for PJIA includes

[redacted] b(4)

Centocor plans to submit a pediatric study protocol for their proposed PK/safety/efficacy trial in the third or fourth quarter of 2009, with study initiation anticipated in the first quarter of 2010, and with submission of the final study report in 2013. While this is acceptable, an argument could be made that a PK/safety study in PJIA patients would be adequate.

Since the effects of TNF inhibitors in the treatment of PJIA are similar to their effects in adult RA (e.g., etanercept, adalimumab), and the efficacy and safety of golimumab in adult RA appears similar to the three approved TNF inhibitors for adult RA, efficacy of golimumab from the adult RA trials can be extrapolated to PJIA. Therefore, only PK, safety, and immunogenicity data in pediatric patients with PJIA from aged 2 to 16 years old should be sufficient to satisfy PREA and demonstration of efficacy should not be required. The exposure-response of golimumab in adult RA should form the basis for dose stimulations in the pediatric patients with PJIA.

For adult PsA and adult AS: The juvenile equivalents of PsA and AS are extremely rare, because pediatric patients with JIA do not typically develop sufficient distinguishing features of PsA or AS for specific diagnoses to be made during childhood. Therefore the Agency has historically granted waivers for pediatric studies in these two indications because studies would be highly impracticable.

2 Introduction and Regulatory Background

2.1 Product Information

Proposed Trade Name (established name): Simponi (golimumab)

Proposed Indications: The following are the three proposed indications:

1. "SIMPONI, in combination with methotrexate, is indicated for [redacted] adult patients with moderate to severely active rheumatoid arthritis. [redacted]
2. "SIMPONI, alone or in combination with methotrexate, is indicated for [redacted] active arthritis in adult patients with psoriatic arthritis." b(4)
3. "SIMPONI is indicated for [redacted] adult patients with active disease."

Proposed Age Group: Adult patients

Proposed Dose Regimen for All Indications: 50 mg of golimumab administered subcutaneously once a month.

Pharmacologic Class: TNF inhibitor

Chemical Class: New Molecular Entity

Description: Golimumab is a human IgG monoclonal antibody with molecular mass of about 150,000 daltons that reduces the binding of soluble and transmembrane forms of TNF to its receptors.

How supplied: Golimumab is supplied as a solution (50 mg of the golimumab antibody in 0.5 mL of solution) in a pre-filled syringe (PFS) or contained in an auto-injector.

See Table 2.1 for the differences in the route of administration, presentation, dosing regimen, and antibody type between Centocor's approved TNF inhibitor (infliximab) and Centocor's proposed TNF inhibitor (golimumab).

Table 2.1: Comparisons between infliximab and golimumab

	Infliximab (approved)	Golimumab (proposed)
Route of administration	Only IV	SC [redacted] b(4)
Presentation	Lyophilized concentrate	Auto-injector or prefilled syringe
Weight based dosing	Weight-based dosing	Not weight based; rather, one fixed dose
Dose in Rheumatologic Indications	**RA: 3 mg/kg** (for patients with incomplete response, may increase dose up to 10 mg/kg) **PsA & AS: 5 mg/kg**	**Dose is identical in all rheumatologic indications** **RA, PsA, & PsA:** 50 mg SC once monthly
Dosing Frequency in Rheumatologic Indications	**RA & PsA:** At Weeks 0, 2, & 6 then **every 8 weeks** thereafter (for RA patients with incomplete response, may change frequency to every 4 weeks) **AS:** At Weeks 0, 2, and 6 then **every 6 weeks** thereafter	**RA, PsA, & PsA:** Once monthly
Type of antibody (possible reactions)	**Chimeric** (Hypersensitivity WARNINGS)	**Fully Human** (lower risk of immunogenicity and hypersensitivity reactions)

2.2 Tables of Currently Available Treatments for Proposed Indications

Rheumatoid Arthritis: There are over 15 products that are approved in the United States to treat RA. Table 2.2 displays the approved small molecule products and Table 2.3 displays the 6 approved biologic products for the treatment of RA in the United States. The 2008 American College of Rheumatology (ACR) recommendations for the use of TNF inhibitors in the treatment of RA depends many factors including the disease activity, the duration of disease (less than or greater than 6 months), and features of poor prognosis (Saag 2008). Biologic treatments for RA include anti-cytokine therapies including three TNF inhibitors and an IL-1 receptor antagonist; T-cell costimulation modulating therapy (abatacept); and B-cell depleting therapy (rituximab).

Table 2.2: Approved small molecule tablets for the treatment of RA in the United States[1]

	Product	NDA	Sponsor	Year of Approval[2]
1	Sulfasalazine (AZULFIDINE)	7-073	Pfizer	1950
2	Methotrexate sodium (METHOTREXATE SODIUM)	8-085 (PO) 11-719 (IV)	Multiple	1953
3	Hydroxychloroquine (PLAQUENIL)	9-768	Sanofi-Aventis	1955
4	Prednisone	Many ANDAs	Multiple	1955
5	Azathioprine (IMURAN)	16-324	Prometheus Labs	1968
6	Penicillamine (CUPRIMINE)	19-853	Aton	1970
7	Auranofin (RIDAURA)	18-689	Prometheus Labs	1985
8	Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE)	50-715 50-625	Novartis	1995 1990
9	Leflunomide (ARAVA)	20-905	Sanofi-Aventis	1998

1 Other formulations (e.g., solutions) are not included in this table. In addition, steroids and NSAIDs are approved for reduction of the signs and symptoms of RA.
2 The initial approval of these small molecules may have not been for RA.

Table 2.3: Approved biologic products for the treatment of RA in the United States

	Product	BLA (sponsor)	Year Approved for RA[1]	Characteristics	ROA
1	Infliximab (REMICADE®)	103772 (Centocor)	1999	Monoclonal antibody (TNF inhibitor)	IV
2	Etanercept (ENBREL®)	103795 (Immunex)	1998	Fusion protein (TNF inhibitor)	SQ
3	Anakinra (KINERET®)	103950 (Amgen)	2001	Human IL-1 receptor antagonist (IL-1 inhibitor)	SQ
4	Adalimumab (HUMIRA®)	125057 (Abbott)	2002	Monoclonal antibody (TNF inhibitor)	SQ
5	Abatacept (ORENCIA®)	125118 (Bristol Myers Squibb)	2005	Fusion protein (costimulation modulator – inhibits T-cell activation)	IV
6	Rituximab (RITUXAN®)	103705 (Genentech & Biogen Idec)	2006	Monoclonal antibody [anti-CD20 (B-cell depleter)]	IV

1 Infliximab was originally approved in 1998 for Crohn's Disease and rituximab was originally approved for non-Hodgkin's Lymphoma in 1997

Psoriatic Arthritis: Compared to RA, there are fewer products approved in the United States to treat PsA. Table 2.4 presents the approved products for the treatment of PsA in the United States.

Table 2.4: Approved products for the treatment of PsA in the United States[1]

	Product	NDA/BLA (sponsor)	Year Approved for PsA[2]	Characteristics	ROA
1	Infliximab (REMICADE®)	103772 (Centocor)	2005	Monoclonal antibody (TNF inhibitor)	IV
2	Etanercept (ENBREL®)	103795 (Immunex)	2002	Fusion protein (TNF inhibitor)	SQ
3	Adalimumab (HUMIRA®)	125057 (Abbott)	2005	Monoclonal antibody (TNF inhibitor)	SQ

1 Steroids are also approved for the treatment of PsA (i.e., betamethasone, cortisone, prednisolone, triamcinolone, methylprednisolone, and dexamethasone).
2 Infliximab was originally approved in 1998 for Crohn's Disease, etanercept was originally approved in 1998 for RA, and adalimumab was originally approved in 2002 for RA

Ankylosing Spondylitis: Compared to RA, there are fewer products approved in the United States to treat AS. Table 2.5 presents the approved products for the treatment of AS in the United States.

Table 2.5: Approved products for the treatment of AS in the United States[1]

	Product	NDA/BLA (sponsor)	Year Approved for AS[2]	Characteristics	ROA
1	Etanercept (ENBREL®)	103795 (Immunex)	2003	Fusion protein (TNF inhibitor)	SQ
2	Infliximab (REMICADE®)	103772 (Centocor)	2004	Monoclonal antibody (TNF inhibitor)	IV
3	Adalimumab (HUMIRA®)	125057 (Abbott)	2006	Monoclonal antibody (TNF inhibitor)	SQ

1 NSAIDs (e.g., celecoxib, diclofenac, indomethacin, naproxen, sulindac) and steroids (e.g., betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone) are also approved for the treatment of AS.

2 Etanercept was originally approved in 1998 for RA, infliximab was originally approved in 1998 for Crohn's Disease, and adalimumab was originally approved in 2002 for RA.

2.3 Availability of Proposed Active Ingredient in the United States

Golimumab is not approved in the United States or any other country.

2.4 Important Safety Issues With Consideration to Related Drugs

There are four biologic TNF inhibitors that are approved in the United States (see Table 2.6) for multiple inflammatory diseases in adults (RA, PsA, AS, psoriasis, Crohn's disuse, and ulcerative colitis) and two pediatric diseases [pediatric Crohn's disease and Juvenile Idiopathic Arthritis (JIA)]. Of the four approved biologic TNF inhibitors, three are approved for RA, PsA, and AS and one biologic TNF inhibitor has [redacted] b(4)

Table 2.6: Approved biologic TNF inhibitors in the United States

	Product	BLA (Sponsor)	Year of Approval	Description	ROA	Indications	
						Adult	Pediatric
1	Infliximab (REMICADE®)	BLA 103772 (Centocor)	1998	Monoclonal antibody	IV	RA, PsA, AS, Ps, CD, UC	CD
2	Etanercept (ENBREL®)	BLA 103795 (Immunex)	1998	Fusion Protein	SC	RA, PsA, AS, Ps	JIA
3	Adalimumab (HUMIRA®)	BLA 125057 (Abbott)	2002	Monoclonal antibody	SC	RA, PsA, AS, Ps, CD	JIA
4	Certolizumab Pegol (CIMZIA®)	BLA 125160 (UCB)	2008	Fab fragment conjugated to PEG	SC	[redacted] CD	None
5	Golimumab (SIMPONI™)	BLA 125289 (Centocor)	N/A	Monoclonal antibody	SC	RA[1], PsA[1], AS[1]	N/A

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Table 2.7 displays adverse reactions that have been associated with the use of TNF inhibitors and appear the Boxed Warnings, Warnings, or Precautions section of at least one biologic TNF inhibitor

product label. See Section 7.4 (Specific Safety Concerns of TNF Inhibitors) for an evaluation of the association of golimumab with these known TNF inhibitor adverse events.

Table 2.7: Safety concerns with TNF inhibitors

Location in label[1]	Safety Concerns
Boxed Warnings	**1. Serious infections including bacterial sepsis, tuberculosis, invasive fungal infections, and other opportunistic infections** **2. Tuberculosis** **3. Histoplasmosis** **4. Hepatosplenic T-cell Lymphoma**
Warnings/Precautions	**1. Infections including hepatitis B reactivation** **2. Malignancies** **3. Hepatotoxicity** **4. Hypersensitivity disorders** **5. Demyelinating disorders (e.g., multiple sclerosis)** **6. Adverse outcomes in patients with heart failure** **7. Pancytopenia, leukopenia, neutropenia, thrombocytopenia** **8. Autoimmune disorders (e.g., lupus-like syndrome)** **9. Infusion-related reactions/Injection-site reactions** **10. Use with anakinra or abatacept not recommended**

1 All TNF inhibitor labels do not contain all of these safety concerns

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

See Table 2.8 for the important Pre-BLA submission interactions between the FDA and Centocor regarding the clinical development program of SC golimumab for RA, PsA, and AS. In general, the FDA agreed with Centocor's proposed study designs and endpoints for the Phase 3 trials to support these three indications. The FDA agreed with Centocor's proposed safety database (1000 to 1500 patients exposed to the proposed golimumab dose or higher for at least one year), assuming there were no unexpected safety signals. For specific FDA concerns regarding the clinical development program of SC golimumab for the three indications see Table 2.8.

Centocor originally planned to submit the golimumab BLA for [redacted] RA, PsA, and AS in February 2008. To comply with the FDA's requirements to support the PFS presentations, Centocor collected additional safety and immunogenicity clinical data of the PFS presentation which delayed the golimumab BLA submission to June 2008. See Section 7.7.1 (Safety and Immunogenicity of the To-Be-Marketed Presentation) for more details on the required immunogenicity and safety data for the PFS presentation.

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Table 2.8: Pre-BLA submission interactions between the FDA and Centocor regarding the development of SC golimumab for RA, PsA, and AS

Meeting Date (Date minutes finalized)	Type of Meeting	Indication	FDA recommendations
8/21/07 (9/21/07)	Pre-BLA Meeting[1]	RA, PsA, AS	1. Centocor's proposed safety analyses are acceptable to support the safety of golimumab for RA, PsA, and AS; however, additional pooled safety analyses of the three Phase 3 RA trials and the five Phase 3 rheumatology trials through Week 24 were requested by the FDA. 2. The efficacy of golimumab in the Phase 3 trials through Week 24 was based solely on the liquid in vial (LIV) presentation of golimumab. However, Centocor proposed only marketing pre-filled syringe (PFS) presentations. To support the registration of the PFS presentations, Centocor proposed submission of comparability data, safety and immunogenicity results of a single-dose bioequivalence study of LIV and PFS (Study 24), and the safety/efficacy results of the LIV in the 5 Phase 3 trials. Since PFS may have greater immunogenicity than LIV because of increased aggregates, the FDA stated that safety and immunogenicity clinical data after multiple dosing of PFS compared to LIV was required prior to marketing PFS. Centocor proposed to submit additional safety and immunogenicity data to satisfy the FDA requirements, as described below. Analyses of patient reported safety data (via the interactive voice response system, IVRS) from the 5 Phase 3 trials from approximately 1100 and 800 patients after self-injection of ≥ 1 and ≥ 3 doses of PFS, respectively; and analyses of safety data (by IVRS and clinic visits) and immunogenicity data from approximately 300 and 60 patients after self-injection of ≥ 1 and ≥ 3 doses of PFS, respectively. Analyses of the comparison of immunogenicity rates between patients remaining on LIV compared to those switching from LIV to PFS. The FDA agreed that Centocor's proposal was adequate to provide sufficient data for the evaluation of potential differences in immunogenicity and safety between the LIV and PFS presentations.[1]
4/5/06 (N/A)	Letter to Centocor	RA	The design of Study 11 [redacted] of efficacy in patients with an [redacted] b(4)
4/19/05 (5/16/05)	EOPII Meeting[6]	AS	Only one trial in AS is required and only one trial in PsA is required to support the AS and PsA indications because in principle, golimumab would be the fourth TNF inhibitor in the United States. However, if an unexpected safety signal arises then additional data may be required.
3/21/05 (5/19/05)	EOPII Meeting[5]	PsA	The physical function results will need to be maintained through 2 years [redacted] b(4)
3/8/05 (4/6/05)	EOPII Meeting[2]	RA	The FDA recommended that an additional arm be added to Study 5 (MTX naive) — golimumab monotherapy group. Centocor added the additional treatment group to Study 5.
3/25/04 (4/22/04)	Type C Mtg.[3]	RA, PsA, AS	1. In Study 6 (inadequate MTX response), patients should have an adequate response to at least 15 mg of MTX per week (not at least 10 mg of MTX per week). 2. For PsA, the FDA recommended enrolling patients with all subtypes to make the results generalizable to all PsA subpopulations. 3. [redacted], 2 years of data is generally required (at least one year of blinded data).[4] b(4) 4. The FDA stated that Centocor's proposed safety database in RA (1150), in PsA (420), and in AS (300) was acceptable from a safety standpoint given that golimumab would be the fourth TNF inhibitor in the United States. The FDA stated that about 1000-1500 RA patients would need golimumab exposure for a year at the proposed or higher doses.

1 Pre-BLA meeting for the submission of SC golimumab for the treatment of the signs and symptoms of RA, PsA, and AS
2 End of Phase 2 meeting to discuss the proposed Phase 3 clinical development program of SC golimumab for the treatment of signs and symptoms of RA, [redacted] b(4)
3 The Type C meeting discussed the clinical development program of SC golimumab for RA, PsA, and AS
4 The FDA requirements for improvement of physical function have changed. Only 6 months of data are required (proportion of patients with change in HAQ from baseline ≥ 0.3) [redacted]
5 The EOPII meeting for the PsA indications on April 21, 2005 was also a Pre-IND meeting.
6 The EOPII meeting for the AS indication on April 19, 2005 was also a Pre-IND meeting.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic BLA submission was well-organized and complete and there were no major amendments.

3.2 Compliance with Good Clinical Practices

According to Centocor, the 5 Phase 3 trials were conducted in compliance with good clinical practice (GCP) guidelines, as described in the 1996 International Committee on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP; U.S. Code of Federal Regulations (CFR) dealing with clinical studies, informed consent, and institutional review board (IRB) regulations; the European Union Directive; the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects), and other applicable local/regional regulations and guidelines regarding the conduct of clinical studies. A signed informed consent form was obtained for each patient prior to enrollment and IRB approval was obtained by the investigators.

As is customary for new molecular entities such as golimumab, the Division of Scientific Investigations (DSI) was requested to perform routine audits of clinical sites (see Table 3.1). The 2 individual sites were chosen because they represented the highest enrolling US sites. No site comprised more than 5% to 9% of the total study population in each trial and thus no single site was identified that would alter the overall study results. No sites were identified as requiring an inspection "for-cause," e.g., due to excessive efficacy results, unusual safety findings, or financial reasons.

Table 3.1: The two clinical sites chosen for DSI audits

Site# (Name, Address, Phone#)	Study #	Patients Enrolled	Patients Randomized
Site# 7404 **Dr. Antony Hou & Dr. Eugene P. Boling** **510 N 13th Avenue, Suite 302** **Upland, CA 91786 (909-982-4252)**	**Study 11 (RA)** **Study 8 (PsA)**	**10** **15**	**9** **7**
Site# 7434 **Frederick T. Murphy, DO** **Altoona Center for Clinical Research** **1125 Old Route 220 North** **Duncansville, PA 16635 (814-693-0300)**	**Study 11 (RA)** **Study 8 (PsA)**	**12** **15**	**8** **12**

DSI found that the sites adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. DSI found no evidence of under-reporting of AEs and no regulatory violations at the two clinical sites. According to DSI, Studies 11 and 8 appeared to be well-conducted at the two audited sites and the data generated at the sites appear acceptable to support the proposed indications.

3.3 Financial Disclosures

Centocor submitted FDA Form 3454 certifying that Centocor did not enter into "any financial arrangement" with the overwhelming majority of investigators in the golimumab studies whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CRF 54.2(a). Centocor listed all these investigators. In addition, Centocor certified that each of these investigators was required to disclose to Centocor whether the investigator had a proprietary interest in golimumab or a significant equity interest in Centocor as defined in 21 CRF 52.2(b). Finally, Centocor certified that no listed investigator was the recipient of significant payments as defined in 21 CRF 54.2(f).

Approximately 190 sites treated patients in one or more of the 5 Phase 3 trials in RA, PsA, and AS. Of these 190 sites, 8 investigators had received significant payments from Centocor in the past 10 years or had significant equity interest in Johnson and Johnson, the parent company of Centocor. Of these 8 investigators, 5 received grants from Centocor to conduct research or to support fellowship training, 2 had significant stock in Johnson and Johnson, and 1 investigator's husband received significant stock and salary from Johnson and Johnson. Centocor submitted form 3455 certifying to the specific financial interest of these 8 investigators. See Table 3.2 for the 8 investigators who had patients who received study agent in one or more of the 5 Phase 3 trials.

In Studies 6, 11, 8, and 9, few patients received study agent at the sites directed by investigators that had financial interest. Even if these results were excluded the overall results and conclusions from Studies 6, 11, 8, and 9 would be unchanged.

Study 5 included the most investigators that had financial interest with Centocor (five investigators). However, Study 5 was the only Phase 3 trial that failed to reach its pre-specified primary efficacy endpoint. Therefore it is unlikely that their financial interest affected the results in Study 5.

Therefore, there is no clear evidence that the financial interest of these investigators changed the overall results in the 5 Phase 3 trials.

Table 3.2: Eight investigators in the 5 Phase 3 trials that had financial interest[1]

	Investigator	Study 5	Study 6	Study 11	Study 8	Study 9
1	[redacted]	R		R		
2		R				
3	[redacted]	R				
4		S				
5	[redacted]	S				
6			R			
7	[redacted]		S[2]			
8					R	R

b(6)

1 R denotes that the investigator received research money from Centocor or money for fellowship
S denotes that the investigator has significant stock in Johnson and Johnson.
2 [redacted] spouse received stock and salary from Centocor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

According to Dr. Kurt Brorson, the Division of Monoclonal Antibody reviewer, the manufacture of Simponi is well controlled, leading to a product that meets standards for purity and potency and is free from endogenous or adventitious infectious agents. According to Dr. Brorson, the manufacturing conditions have been sufficiently validated and a consistent product is produced from multiple production runs.

In October 2008 during the BLA review, Centocor notified the FDA of adventious virus detection from numerous cell culture harvest samples from golimumab. These assays were performed by the [redacted] However, after a FDA inspection of the [redacted] facility, the root cause was judged to be a non-optimized assay at [redacted] because the controls were found to be positive and the false positive results were not replicated at two other contract testing laboratories using advanced techniques. b(4)

According to Dr. Brorson, the current assay for detection of adventitious virus contamination in the unprocessed bulk harvest is a sub-optimal assay and Dr. Brorson recommends a post-marketing commitment to optimize the existing assay or develop an improved assay for detecting adventitious virus contamination in the unprocessed bulk harvest (see Dr. Brorson's review for more details).

Dr. Brorson found an increased number of subvisible particles in the pre-filled syringe (PFS) presentation, compared to the liquid in a vial (LIV) presentation of golimumab. Given this difference in chemical comparability and that only the LIV presentation was used to support the safety and efficacy of SC golimumab in the 5 Phase 3 trials through Week 24, additional clinical immunogenicity and safety data of the PFS presentation was required prior to marketing of the PFS presentation. There was no evidence of differences in safety or immunogenicity between the LIV and PFS presentations in the long-term extensions [see Section 7.7.1 (Safety and Immunogenicity of the To-Be-Marketed Presentation) for more details].

There are no chemistry, manufacturing, or control issues that would prevent approval of golimumab.

4.2 Clinical Microbiology

Golimumab is not an anti-microbial product. There are no clinical microbiology issues that would prevent approval of golimumab.

4.3 Preclinical Pharmacology/Toxicology

According to Dr. Gary Bond, the pharmacology/toxicology reviewer, the cynomolgus monkey was chosen as a pharmacologically relevant species for non-clinical safety evaluations of golimumab because golimumab demonstrated the ability to neutralize significant amount of TNFα from cynomolgus monkeys, but not TNFα from other animals (e.g., dog, rabbit, mouse, and rat).

According to Dr. Bond, the pivotal non-clinical studies of golimumab in cynomolgus monkeys included two 6-month chronic toxicology studies of SC and IV golimumab [which included cardiovascular, respiratory, and central nervous system (CNS) pharmacological evaluations], an embryofetal development study of SC golimumab, and a pre-/post-natal development study of SC golimumab. According to Dr. Bond, there was no evidence of known TNF inhibitor toxicities in the non-clinical studies of golimumab including infections, malignancy, severe liver injury, autoimmune disorders, and demyelinating CNS disorders. The No Observed Adverse Effect Levels (NOAELs) in the pivotal monkey studies were the highest doses tested (50 mg/kg twice weekly) and there were adequate safety margins for the chronic studies of golimumab in humans even after consideration of the reduced potency of golimumab binding to and neutralizing cynomolgus TNFα compared to human TNFα. According to Dr. Bond, these studies demonstrated anticipated pharmacological actions of TNF inhibitors that were considered clinically monitorable and reversible.

According to Dr. Bond, carcinogenicity studies of golimumab could not be done because golimumab did not have pharmacological activity in the species that are used for carcinogenicity testing (rodents).

Overall, there were no pharmacology/toxicology issues that would prevent approval of golimumab.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. Elevated TNFα levels have been implicated in the pathophysiology of several chronic inflammatory diseases such as RA, PsA, and AS, and TNFα is an important mediator of the articular inflammation that is characteristic of these diseases.

4.4.2 Pharmacodynamics

Multiple pharmacodynamic markers of inflammation (e.g., TNFα, IL-6, MMP-3, ICAM-1, IL-8, and VEGF); autoantibodies (rheumatoid factor and anti-cyclic citrullinated peptide antibodies); and serum markers of bone and cartilage metabolism (e.g., BAP, Osteocalcin, PINP, and PYD) were evaluated at baseline and at Weeks 4, 14, and/or 24 in the 5 Phase 3 trials.

Since the relationship between changes in all of these PD biomarkers and the efficacy of products for the treatment of the signs and symptoms of RA, PsA, and AS has not been clearly established and since other well-established clinically meaningful efficacy parameters (e.g., ACR response, ASAS response) were evaluated in the Phase 3 trials, these results were not reviewed. See Sections 6.1.4, 6.2.4, and 6.3.4 for analyses of the sign and symptoms endpoints for the RA, PsA, and AS indications, respectively.

4.4.3 Pharmacokinetics

Three single-dose, PK Phase 1 studies of SC golimumab (either 50 mg or 100 mg) were conducted in healthy subjects (Studies 13, 23, and 24). The mean apparent total systemic clearance (CL/F) of golimumab was 12-18 mL/day/kg, the mean apparent volume of distribution during terminal phase (Vz/F) of golimumab was 224-262 mL/kg, and mean apparent half life ($T_{1/2}$) of golimumab was 11-14 days. See Section 7.7.1 (Safety and Immunogenicity of the To-Be-Marketed Presentation) for the PK results of Study 24 [a single-dose Phase 1 bioequivalence study of two presentations of golimumab (LIV and PFS)].

Two randomized, double-blind, placebo-control ascending dose Phase 1 studies of IV and SC golimumab in patients with active RA (Studies 466-1 and 466-2) demonstrated that the mean CL/F of golimumab was 10-13 mL/day/kg, the mean Vz/F of golimumab was 214-737 mL/kg, and mean $T_{1/2}$ of golimumab was 12-24 days.

According to Dr. Lei Zhang, the clinical pharmacology reviewer, the volume of distribution of golimumab in the Phase 1 studies indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution. According to Dr. Zhang, based on cross-study comparisons of the mean AUC values following IV and SC administration of golimumab, the absolute bioavailability of SC golimumab was estimated to be approximately 53%.

According to Dr. Zhang, there was no clear relationship between golimumab trough concentrations and the primary efficacy endpoint results in the Phase 3 trials (ACR 50 response at Week 24 in Study 5, ACR 20 response in Studies 6 and 8, and ASAS response at Week 14 in Study 9). No exposure-response evaluation was performed in Study 11 because no population PK was performed in Study 11.

According to Dr. Zhang, population PK analyses demonstrated that concomitant medications including NSAIDs, corticosteroids, sulfasalazine, and hydroxychloroquine had no affect on the PK of golimumab. Population PK analyses identified three covariates that altered the PK of golimumab [body weight, MTX use, and presence of anti-golimumab antibodies (HAHA)]. Patients with increased body weight, compared to patients with lower body weight, had increased clearance and lower exposure. Patients who did not receive MTX, compared to MTX users, had a 20 to 40 percent decreased trough concentrations of golimumab. Finally, patients with HAHA had lower golimumab serum concentrations. However, since there was a lack of an exposure-response and lack of a dose-response, Dr. Zhang does not recommend any dose adjustment based on body weight, use of MTX, or other covariates.

According to Dr. Zhang, pro-inflammatory cytokines including TNFα have reduced the expression level of multiple CYP enzymes including CYP3A4. Since golimumab decreases TNFα serum levels, golimumab could theoretically contribute to a relative increase in the expression of CYP3A4 and the levels of CYP3A4 substrates could decrease. Therefore, Dr. Zhang recommends a post-marketing commitment to study these theoretical DDIs with golimumab.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Centocor submitted the following data from **13 completed studies** of golimumab in their BLA to support the approval of SC golimumab for [redacted] RA, PsA, and AS: b(4)

1. **5 Phase 3 studies in RA, PsA, and AS**: Final study reports of the 24-week data and safety data from the last safety cut-off date from ongoing, 5-year, randomized, double-blind, controlled, global Phase 3 trials of SC golimumab in patients with active RA (i.e., Studies 5, 6, and 11), Phase 3 trial in patients with active PsA (i.e., Study 8), and Phase 3 trial in patients with active AS, i.e., Study 9 (see Table 5.1).
2. **1 Phase 2 study in RA**: Final study report for the 1 completed, 1-year, randomized, double-blind, MTX-controlled, dose-ranging, 5-arm Phase 2 trial of SC golimumab in patients with active RA despite MTX therapy, i.e., Study 2 (see Table 5.2).
3. **1 Phase 2 study in asthma**: Final study report for the 1 completed, 1-year, randomized, double-blind, placebo-control, Phase 2 trial of SC golimumab in patients with severe persistent asthma who are symptomatic despite inhaler steroids and long-acting $beta_2$-agonists, i.e., Study 3 (see Table 5.2).
4. **2 Phase 1 studies in RA**: Final study reports for 1 completed Phase 1 study of SC golimumab in patients with active RA, i.e., Study 466-2, and 1 completed Phase 1 study of IV golimumab in patients with active RA, i.e. Study 466-1 (see Table 5.3).

[redacted] b(4)

6. **3 Phase 1 studies in healthy subjects**: Final study reports for 3 completed Phase 1 studies of SC golimumab in healthy subjects, i.e., Studies 13, 23, and 24 (see Table 5.3).

Table 5.1: Five ongoing, 5-year, randomized, double-blind, controlled, global Phase 3 trials of SC golimumab in patients with RA, PsA, and AS

Study Name and Design[1,2]	Treatment Groups[3]	Allowed Concomitant Medications[4]
RA		
Study 5 (GO-BEFORE): R, DB, MTX-controlled, global, 4-arm, 5-year Phase 3 trial in patients with **active RA** who are **MTX-naive** (i.e., have not received more than 3 weekly doses of MTX for RA at any time). EE at Week 28 if < 20% improvement in both swollen and tender joint counts.	1. MTX (n=160) 2. Golimumab100 (n=159) 3. Golimumab50 & MTX (n=159) 4. Golimumab100 & MTX (n=159)	≤ 10 mg prednisone/day and/or NSAIDs
Study 6 (GO-FORWARD): R, DB, PC, global, 4-arm, 5-year Phase 3 trial in patients with **active RA despite MTX therapy**[2]. EE at Week 16 if < 20% improvement in both swollen and tender joint counts.	1. Background MTX (n=133) 2. Golimumab100 (n=133) 3. Golimumab50 & background MTX (n=89) 4. Golimumab100 & background MTX (n=89)	≤ 10 mg prednisone/day and/or NSAIDs
Study 11 (GO-AFTER): R, DB, PC, global, 3-arm, 5-year Phase 3 trial in patients with **active RA** who must have previously received ≥ 1 dose of a biologic TNF inhibitor without a clinically serious adverse reaction. EE at Week 16 if < 20% improvement in both swollen and tender joint counts.	1. Placebo ± DMARDS (n=155) 2. Golimumab50 ± DMARDS (n=153) 3. Golimumab100 ± DMARDS (n=153)	MTX, HCQ, SSZ, ≤ 10 mg prednisone/day, and/or NSAIDs
PsA		
Study 8 (GO-REVEAL): R, DB, PC, global, 3-arm, 5-year Phase 3 trial in patients with **active PsA** (≥ 3 swollen joints and ≥ 3 tender joints) **despite NSAID or DMARD therapy**. Must have active plaque psoriasis (≥ 2 cm in diameter). Cannot receive topical or systemic psoriasis treatments during the study.	1. Placebo ± MTX (n=113) 2. Golimumab50 ± MTX (n=146) 3. Golimumab100 ± MTX (n=146)	MTX (≤ 25 mg/week), ≤ 10 mg prednisone/day, and/or NSAIDs
AS		
Study 9 (GO-RAISE): R, DB, PC, global, 3-arm, 5-year Phase 3 trial in patients with **active AS** (BASDAI score ≥ 4 out of 10 and total back pain score ≥ 4 out of 10) who have had an **inadequate response to NSAIDs or** are **unable to tolerate NSAIDs**. Cannot have complete ankylosis of the spine	1. Placebo ± DMARDS (n=78) 2. Golimumab50 ± DMARDS (n=138) 3. Golimumab100 ± DMARDS (n=140)	MTX (≤ 25 mg per week), HCQ, SSZ, 10 mg prednisone/day, and/or NSAIDs

EE is early escape

1 Studies C0524T05, C0524T06, C0524T11, C0524T08, and C0524T09 are abbreviated as Studies 5, 6, 11, 8, and 9 in this review, respectively.

2 Patients who received rituximab, natalizumab, or a cytotoxic agent were excluded from all 5 of these Phase 3 Studies. In Studies 5, 6, 8, and 9, patients who received a biologic TNF inhibitor was excluded; however, in Study 11 patients must have received ≥ 1 dose of a biologic TNF inhibitor to be included.

3 Golimumab50 and golimumab100 are 50 mg and 100 mg of golimumab given subcutaneously every 4 weeks, respectively. MTX is given orally once weekly. For Study 5, 10 mg of MTX (given once weekly) was started at Week 0 and escalated to 20 mg by Week 8. In Study 6, patients must have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have a MTX dose of ≥ 15 mg/week and ≤ 25 mg/week and stable for at least 4 weeks prior to screening.

4 In all 5 Phase 3 studies, patients may have taken concomitant stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day. In Study 8, patients may not take systemic or topical psoriasis treatments/medications during the study.

Reference: Adapted from the tabular listing of studies, Pages 1-39.

Table 5.2: One completed Phase 2 trial of SC golimumab in patients with RA and one completed Phase 2 trial of SC golimumab in patients with asthma[1]

Design	Treatment Groups
Phase 2 RA (Study 2)	
R, DB, MTX-controlled, one-year, **phase 2** trial of SC golimumab in patients with **active RA with insufficient response to MTX** (≥ 10 mg once weekly) who have not previously been treated with anti-TNF therapy	1. background MTX (W0-19) then cross-over to infliximab 3 mg/kg at Weeks 20,22, 28, and then q 8 weeks (n=25) 2. golimumab50 & background MTX (n=37) 3. golimumab50 every 2 weeks (W0-18) then golimumab50 every 4 weeks (W20-W48) & background MTX (n=32) 4. golimumab100 & background MTX (n=33) 5. golimumab100 every 2 weeks (W0-18) then golimumab100 every 4 weeks (W20-W48) & background MTX (n=35)
Phase 2 Asthma (Study 3)	
R, DB, PC, **phase 2** trial of SC golimumab in patients with severe persistent **asthma** who are symptomatic despite inhaler steroids and long-acting beta$_2$-agonists	1) Placebo (W0-W52) 2) W0 75 mg then 50 mg q 4 weeks (W4-52) 3) W0 150 mg then 100 mg q 4 weeks (W4-52) 4) W0 300 mg then 200 mg q 4 weeks (W4-52) (n= 78, 77, 76, 78)

1 Studies C0524T02 and C0524T03 are abbreviated as Studies 2 and 3 in this review, respectively. Study 3 (asthma) was terminated early by Centocor because golimumab did not demonstrate efficacy in the co-primary efficacy endpoints or the major secondary endpoints and because of the golimumab-associated toxicities (e.g., serious infections, malignancies).

b(4)

Reference: Adapted from the tabular listing of studies, Pages 1-39.

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Table 5.3: Three completed Phase 1 studies of golimumab in patients with active RA and [redacted] and 3 completed Phase 1 studies in healthy subjects

Study[1]	Design	Treatment Groups
RA		
466-1	R, DB, PC, **single ascending dose phase 1** study of **IV golimumab** in patients with **active RA**	Single IV infusion of placebo (n=10) or 0.1, 0.3, 1, 3, 6, or 10 mg/kg of golimumab (n=26)
466-2	R, DB, PC, **single ascending dose** and **multiple dose phase 1** trial of SC golimumab in patients with **active RA**	**SAD:** (5-arm) placebo or single dose of 0.3, 0.6, 1, or 3 mg/kg of golimumab (n=9, 5, 5, 5, 5) **Multiple-Dose:** placebo or 0.3 or 1 mg/kg of golimumab q 2 weeks (Weeks 0, 2, and 4 for 3 administrations) (n=9, 6, 8)
[redacted]		
1	[redacted]	
Healthy subjects		
13	Open-label, **single-dose**, PK, **phase 1** study of 100 mg of SC golimumab in **healthy male subjects**	golimumab 100 mg SC (n=30)
23	Single-blind, **single**-dose, PK, **phase 1** study of SC golimumab in **healthy Caucasian and Japanese male subjects**	1. golimumab 100 mg SC (n=26) 2. golimumab 50 mg SC (n=25)
24	R, open-label, **single-dose, bioequivalence** (auto-injector or LiV via syringe/needle), **phase 1** study of 100 mg of SC golimumab study in **healthy subjects**	1. golimumab 100 mg via autoinjector (n=77) 2. golimumab 100 mg via syringe/needle (n=79)

b(4)

1 Studies C0466T01 and C0466T02 are abbreviated as Studies 466-1 and 466-2 in this review, respectively. Studies C0524T01, C0524T13, C0524T23, and C0524T24 are abbreviated as Studies 1, 13, 23, and 24 in this review, respectively.
Reference: Adapted from the tabular listing of studies, Pages 1-39.

Centocor also submitted deaths and nonfatal SAEs as of the last safety update (i.e., the 120-Day Safety Update) from 7 ongoing studies of golimumab (see Table 5.4): 1 Phase 3 trial of IV golimumab (i.e., Study 12), 1 Phase 1 bioavailability study (i.e., Study 14), 1 study of SC golimumab in Japanese patients with RA (i.e., Study JPN-01/JPN-02), 3 trials in patients with ulcerative colitis (i.e., Studies 16, 17, and 18), and 1 bioavailability study in healthy subjects (i.e., Study 15).

Table 5.4: Seven ongoing studies of golimumab (i.e., 3 in patients with RA, 3 in patients with UC, and 1 in healthy subjects)

Study Name and Design[1]	ROA	Treatment Groups	Subjects Planned[2]
RA			
Study 12: R, DB, MC, global, MTX-control, **5-arm, Phase 3** trial of golimumab in patients with **active RA with insufficient response to MTX (with possible prior exposure to anti-TNF).** Possible EE at W16 and W24; then LE from W48 to W120 patients will switch to SC golimumab. Primary efficacy endpoint is proportion of patients with ACR50 response at W14.	**IV**[3]	Treatments from W0 to W48 (5 infusions) 1. MTX once weekly 2. golimumab 2 mg/kg q 12 weeks 3. golimumab 4 mg/kg q 12 weeks 4. golimumab 2 mg/kg q 12 weeks & MTX 5. golimumab 4 mg/kg q 12 weeks & MTX	625
Study 14: R, open-label, MC, multiple-dose, bioavailability **Phase 1** U.S. study of golimumab administered SC and IV in patients with **active RA**	**IV and SC**	1. golimumab 100 mg SC, every 4 weeks (W0-W20) 2. golimumab 2 mg/kg IV on Days 1 and 85	45
Study JPN-01/ JPN-02: Open-label, dose-controlled, MC, PK, **single-dose and multiple-dose, Phase 1** study of golimumab in Japanese patients with **active RA**	**SC**	Single dose followed by multiple dose every 4 weeks: 1. golimumab 0.6 mg/kg SC, n=9 2. golimumab 1 mg/kg SC, n=11 3. golimumab 3 mg/kg SC, n=9	27
Ulcerative Colitis			
Study 16: R, DB, PC, MC, global, **induction Phase 3** trial of golimumab in patients with **active UC with inadequate response to at least one conventional UC therapy (i.e., oral steroids, azathioprine, or 6-MP)**	**IV**	Single dose 1. placebo 2. golimumab 1 mg/kg 3. golimumab 2 mg/kg 4. golimumab 4 mg/kg Further doses to be determined; maximum duration 16 weeks of dosing	676
Study 17: R, DB, PC, MC, global, **induction Phase 3** trial of golimumab in patients with **active UC with inadequate response to at least one conventional UC therapy (i.e., oral steroids, azathioprine, or 6-MP)**	**SC**	Two doses at W0 and W2 1. placebo 2. golimumab 100 mg at W0 and 50 mg at W2 3. golimumab 200 mg at W0 and 100 mg at W2 4. golimumab 400 mg at W0 and 200 mg at W2 Further doses to be determined; maximum duration 18 weeks of dosing	676
Study 18: R, DB, PC, MC, global, **maintenance Phase 3** trial of golimumab in patients with **UC with clinical response to golimumab in Study 16 or 17**	**SC**	Maintenance dosing through Week 68 1. placebo every 4 weeks 2. golimumab 50 mg every 4 weeks 3. golimumab 100 mg every 4 weeks Extension dosing through Week 228	1350
Healthy Subjects			
Study 15: R, open-label, single-dose, parallel bioavailability **Phase 1** study of SC golimumab administered in 3 locations (i.e., upper arm, abdomen, and thigh) in **healthy male subjects**	**SC & IV**	1. golimumab 100 mg IV, n=23 2. golimumab 100 mg SC, n=55	78

1 Study JNSO12-JPN-01/JPN-02 was abbreviated as Study JPN-01/ JPN-02 in this review. Studies C0524T12, C0524T14, C0524T15, C0524T16, C0524T17, and C0524T18 are abbreviated as Studies 12, 14, 15, 16, 17, and 18 in this review, respectively.
2 As of June 4, 2008
3 In the long-term extension in Study 12 (W48-W120), patients will be switched from IV golimumab to SC golimumab.
Reference: Adapted from the tabular listing of studies, Pages 1-39.

5.2 Review Strategy

Efficacy: Studies 5, 6, and 11 served as the critical trials for the evaluation of the **efficacy** of SC golimumab in the treatment of signs and symptoms of **RA.** These trials were adequate and well-controlled, had acceptable endpoints, and included three distinct RA populations with different mean durations of disease. The efficacy results in the 3 RA trials were not pooled because the populations, treatments assigned at randomization, and concomitant medications for RA were heterogeneous. For the efficacy evaluation of Studies 5, 6, and 11 see the individual study reports in Sections 9.4.1, 9.4.2, and 9.4.3, respectively, and see Section 6.1.4 (Analysis of Sign and Symptom Endpoints — RA).

Study 8 served as the critical trial for the evaluation of the **efficacy** of SC golimumab in the treatment of signs and symptoms of **PsA.** This trial was well-controlled and had acceptable endpoints. One trial in PsA could support the efficacy of SC golimumab in the treatment of PsA because the efficacy of SC golimumab in the 3 Phase 3 RA trials could be extrapolated to support the efficacy of SC golimumab in PsA (the efficacy of TNF inhibitors have been established in these two arthritis populations). Study 9 served as the critical trial for the evaluation of the **efficacy** of SC golimumab in the treatment of signs and symptoms of **AS** and was well-controlled with acceptable endpoints. Similar to PsA, one trial in AS was considered sufficient to support the efficacy of SC golimumab in the treatment of AS due to evidence of efficacy in RA, a related rheumatic disease. For the efficacy evaluation of PsA, see Section 6.2.4 (Analysis of Sign and Symptom Endpoints – PsA) and for the efficacy evaluation of AS, see Section 6.3.4 (Analysis of Sign and Symptom Endpoints – AS).

Safety: See Table 5.5 for the overview of the major **safety** evaluations of SC golimumab for the treatment of signs and symptoms of RA, PsA, and AS. The pooled safety results from the 3 Phase 3 RA trials, the pooled safety results from the 5 rheumatology Phase 3 trials, the safety results from the individual safety reports, and safety analyses of specific TNF inhibitor safety concerns (e.g., infections, malignancies) in the pooled 5 rheumatology Phase 3 trials served as the major safety analyses for the RA indication. The pooled safety results from the 5 rheumatology Phase 3 trials, the safety results from Study 8, and safety analyses of specific TNF inhibitor safety concerns (e.g., infections, malignancies) served as the major safety analyses for the PsA indication. The pooled safety results from the 5 rheumatology Phase 3 trials, the safety results from Study 9, and safety analyses of specific TNF inhibitor safety concerns (e.g., infections, malignancies) served as the major safety analyses for the AS indication.

For the individual study reports, the pooled results from the 3 Phase 3 RA trials, the pooled results from the 5 rheumatology Phase 3 trials, and specific TNF inhibitor safety in the pooled 5 rheumatology Phase 3 trials, the safety analyses were evaluated through Week 24 — **the common, double-blind controlled period**. For the Week 24 analyses, the treatment groups included the treatment groups assigned at randomization and the escape treatment groups. In addition, infections and malignancies in the **controlled and uncontrolled portions** of the pooled 5 rheumatology Phase 3 trials were analyzed through the last safety cut-off date and the observed exposure adjusted events were compared to the expected rate of events. Finally, for Study 5, the only study with a double-blind control period longer than 24 weeks, safety analyses were conducted **through Week 52** to help evaluate the possibility of time-dependency for adverse reactions (see the individual study report for Study 5 in Section 9.4.1).

Additional sources for the safety evaluation of SC golimumab for the treatment of RA, PsA, and AS included safety data from 1 Phase 2 trial in RA and 6 Phase 1 studies in patients with RA, patients [redacted] and in healthy subjects.

Finally, the safety results of SC golimumab in patients with asthma (Study 3) will be discussed in Section 7.7.2 (Safety in Asthma trial). The safety results of this trial are important because a greater proportion of patients in the golimumab groups had serious infections and malignancies, compared to the placebo control group. The relevance of these safety results to the safety of SC golimumab in the proposed rheumatology populations will be discussed in Section 7.6.4 (Drug-Disease Interactions).

Table 5.5: Major safety analyses in the BLA review

<table>
<tr><th rowspan="2">Trials</th><th rowspan="2">Individual Study Reports</th><th colspan="3">Pooled Analyses</th></tr>
<tr><th>Pooled Trials in Each Indication</th><th colspan="2">Pooled Phase 3 Trials in RA, PsA, and AS</th></tr>
<tr><td rowspan="3">RA Phase 3 trials</td><td>Safety in Study 5 (Section 9.4.1)</td><td rowspan="3">Pooled Phase 3 RA trials[1] (Section 7.6.4)</td><td rowspan="4">Pooled Phase 3 RA, PsA, and AS trials[2] (Sections 7.3, 7.4, 7.5, 7.6)</td><td rowspan="4">Specific safety concerns of TNF inhibitors[3] (Section 7.4)</td></tr>
<tr><td>Safety in Study 6 (Section 9.4.2)</td></tr>
<tr><td>Safety in Study 11 (Section 9.4.3)</td></tr>
<tr><td>PsA Phase 3 trial</td><td>Safety in Study 8 Section 7.6.4</td><td>N/A</td></tr>
<tr><td>AS Phase 3 trial</td><td>Safety in Study 9 Section 7.6.4</td><td>N/A</td><td></td><td></td></tr>
<tr><td>RA Phase 2 trial (Study 2)</td><td colspan="3"></td><td></td></tr>
</table>

1. The pooled RA Phase 3 trials were Studies 5, 6, and 11. The safety analyses were through Week 24 (the common, double-blind controlled period in the 3 trials).
2. The pooled RA, PsA, and AS trials were Studies 5, 6, 11, 8 (Ps), and 9 (AS). The safety analyses were through Week 24 (the common, double-blind controlled period in the 5 trials).
3. Specific safety concerns of TNF inhibitors include infections, malignancies, immunogenicity, and hepatotoxicity. Two types of safety analyses were performed: 1) through Week 24 (the common, double-blind controlled period in the 5 trials) and 2) the controlled and uncontrolled data through the last safety cut-off date (some of the analyses included all 5 Phase 3 trials and some included all 5 Phase 3 trials and the Phase 2 RA trial).

5.3 Discussion of Individual Studies

Centocor submitted 24-week results of 5 Phase 3 trials to support the efficacy and safety of golimumab for the treatment of the signs and symptoms of RA (i.e., Studies 5, 6, and 11), PsA (Study 8), and AS (Study 9). Below is an overview of the design of these 5 Phase 3 trials. See Section 9.4 for the complete individual study reports for these 5 trials.

RA Trials (i.e., Studies 5, 6, and 11)

Study 5 (Study C0524T05, GO-BEFORE): Study 5 is an ongoing, **5-year**, randomized, double-blind, MTX-controlled, global (82% of the patients from Europe, Australia, Canada, New Zealand, Latin America, Mexico, and Asia and 18% of the patients from the United States), 4-arm, Phase 3 trial of SC golimumab in 634 treated patients with **active RA** who were **MTX-naive** (i.e., have not received more

than 3 weekly doses of MTX for RA at any time) and had never received a TNF inhibitor, rituximab, natalizumab, or a cytotoxic agent. Patients may have taken stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day. The use of DMARDs or systemic immunosuppressive products (other than the study agents) was prohibited through Week 52 of the study and the use of other biologic agents, cytotoxic agents, and investigational agents was prohibited during the entire 5-year study.

Patients were randomized 1:1:1:1 to one of the following four treatment groups: MTX once weekly, golimumab 100 mg once every 4 weeks, golimumab 50 mg once every 4 weeks and MTX once weekly, and golimumab 100 mg once every 4 weeks and MTX once weekly. Oral MTX was initially given 10 mg once weekly and then escalated by Week 20 to 20 mg once weekly. At Week 28, if patients had less than 20% improvement in both swollen and tender joint counts, patients entered early escape (EE) in a double-blinded fashion (all patients received golimumab during EE). Patients who did not enter EE continued their treatment assigned at randomization. During long-term extension (Week 52 to Week 256), the blind was maintained until after the last patient finished the 52-week evaluations. After the 52-week database was locked in the long-term extension (LE), the treatments were given under open-labeled conditions. During LE, almost all patients received open-labeled golimumab 50 mg or 100 mg every 4 weeks. Patients in the initial MTX monotherapy group who had quiescent disease (i.e., did not escape at Week 28 and had no swollen or tender joints at Week 52) continued to receive MTX monotherapy during the long-term extension.

The primary efficacy endpoint (signs and symptoms) in Study 5 was the proportion of patients with an ACR 50 response at Week 24. The primary statistical comparison (for superiority), using a 2-sided (α = 0.05) Cochran-Mantel-Haenszel (CMH) test was between the combined low and high dose combination groups (i.e., golimumab50 & MTX and golimumab100 & MTX, respectively) versus the MTX monotherapy group. If this was significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$, between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX was to be performed.

Study 6 (Study C0524T06, GO-FORWARD): Study 6 is an ongoing, **5-year**, randomized, double-blind, placebo-controlled, global (84% of the patients from Europe, Australia, Canada, New Zealand, Latin America, Mexico, and Asia and 16% of the patients from the United States), 4-arm, Phase 3 trial in 444 treated patients with **active RA despite MTX therapy** who have never received a TNF inhibitor, rituximab, natalizumab, or a cytotoxic agent. Patients must have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have had a stable MTX dose (≥ 15 mg/week and ≤ 25 mg/week) for at least 4 weeks prior to screening. Patients may have taken stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day. The use of DMARDs or systemic immunosuppressive products (other than the study agents) was prohibited through Week 52 of the study and the use of other biologic agents, cytotoxic agents, and investigational agents was prohibited during the entire 5-year study.

Patients were randomized 3:3:2:2 to one of the following four treatment groups: background MTX only, SC golimumab 100 mg once every 4 weeks, SC golimumab 50 mg once every 4 weeks and background MTX, and SC golimumab 100 mg once every 4 weeks and background MTX. At Week 16 during the DB Period, any patient who had < 20% improvement from baseline in both swollen and

tender joint counts entered EE in a double-blinded fashion and received SC golimumab. Patients who did not enter early escape continued the treatment assigned at randomization. At Week 24 to Week 52, all patients received SC golimumab in double-blind fashion and then during the LE (Weeks 52 to 256), all patients received SC golimumab. The initial part of the LE period was double-blind but the time period after the Week 52 database lock was open-label.

The first co-primary efficacy endpoint was the proportion of patients with an ACR 20 response at Week 14. The second co-primary efficacy endpoint (i.e., improvement in HAQ at Week 24) was only to have been considered if the first co-primary endpoint was positive. The primary statistical comparison (for superiority) for the first co-primary endpoint, using a 2-sided ($\alpha = 0.05$) chi-square test, was between the combined low and high dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) versus the MTX monotherapy group. If this was significant, a comparison (for superiority) between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX was performed. For the second co-primary efficacy endpoint a 2-sided analysis of variance on the van der Waerden normal scores ($\alpha = 0.05$) between the combined low and high dose combination groups versus the MTX monotherapy group was performed. If this was significant, a comparison (for superiority) between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX was performed.

Study 11 (Study C0524T11, GO-AFTER): Study 11 is an ongoing, **5-year**, randomized, double-blind, placebo-control, multi-center, global (58% of the patients from the United States and 42% of the patients from Europe, Australia, Canada, and New Zealand), 3-arm, Phase 3 trial of golimumab in 459 treated patients with **active RA who "must have previously received at least 1 dose of etanercept, adalimumab, or infliximab"** without a clinically serious adverse reaction. Patients may have never received rituximab, natalizumab, or a cytotoxic agent. Patients may have taken stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, NSAIDs, and/or corticosteroids equivalent to $\leq$ 10 mg prednisone/day during the study.

Patients were randomized 1:1:1 into one of the following three treatment groups: placebo SC injections, golimumab 50 mg SC once every 4 weeks, or golimumab 100 mg SC once every 4 weeks. At Week 16 during the DB Period, any patient who had < 20% improvement from baseline in both swollen and tender joint counts entered EE in a double-blinded fashion. Patients who did not enter EE continued the treatment assigned at randomization. All patients who entered EE received SC golimumab in a double-blind fashion. At Week 24 to Week 252, all patients entered LE and all patients received SC golimumab. In the LE, patients received golimumab in a double-blind fashion until the last patient finished the 24-week evaluations. Following the 24-week database lock, all patients received open-label SC golimumab.

The primary efficacy endpoint in Study 11 was the proportion of patients with an ACR 20 response at Week 14. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) CMH test, was between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group. If this was significant, a comparison (for superiority) between golimumab100 & placebo and golimumab50 and placebo was performed.

PsA Trial (i.e., Study 8)

Study 8 (Study C0524T08, GO-REVEAL) is an ongoing, **5-year**, randomized, double-blind, placebo-control, multi-center, global (78% of the patients were from Europe and Canada and 22% of the patients were from the United States), 3-arm, Phase 3 trial of golimumab in 405 treated 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 have taken stable doses of concomitant MTX (≤ 25 mg/week), oral corticosteroids (≤ 10 mg prednisone/day or equivalent), and/or NSAIDs, but may not have taken systemic or topical psoriasis treatments/medications during the study.

Patients were randomized to 1:1.3:1.3 (to obtain 110, 143, and 143 patients) to one of the following three treatment groups: placebo SC injections, golimumab 50 mg SC once every 4 weeks, or golimumab 100 mg SC once every 4 weeks. At Week 16 during the DB Period, any patient who had < 10% improvement from baseline in both swollen and tender joint counts entered EE and all patients received SC golimumab in a double-blinded. Patients who did not enter EE continued their treatment assigned at randomization. During the double-blind control Period from Week 24 to Week 52, all patients received SC golimumab in double-blind fashion. Patients who entered LE at Week 52 received SC golimumab until Week 252. In the LE, patients received golimumab in a double-blind fashion until the last patient finished the 52-week evaluations. Following the 52-week database lock, all patients received open-label SC golimumab.

The first co-primary efficacy endpoint in Study 8 was the proportion of patients with an ACR 20 response at Week 14. The second co-primary efficacy endpoint (i.e., the change from baseline in the total radiographic scores of the hands and the feet at Week 24) was only to have been considered if the first co-primary endpoint was positive. For the first co-primary endpoint, the primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) CMH test, was between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group. If this was significant, a comparison (for superiority) between golimumab100 & placebo and golimumab50 and placebo was performed.

AS Trial (i.e., Study 9)

Study 9 (Study C0524T09, GO-RAISE) is an ongoing, **5-year**, randomized, double-blind, placebo-control, multi-center, global (54% of the patients were from Europe and Canada, 23% of the patients were from Asia, and 24% of the patients were from the United States), 3-arm, Phase 3 trial of golimumab in 355 treated patients with **active AS** (both a BASDAI score of ≥ 4 and a VAS score for total back pain of ≥ 4) who had an inadequate response to 3 months of maximal NSAIDs or was 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 were excluded. Patients may have taken stable doses of concomitant NSAIDs, MTX (≤ 25 mg/week), SSZ, HCQ, and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent).

Patients were randomized 1:1.8:1.8 (to obtain 75, 135, and 135 patients) to one of the following three treatment groups: placebo SC injections, golimumab 50 mg SC once every 4 weeks, or golimumab 100 mg SC once every 4 weeks. At Week 16 during the DB Period, any patient who had less than

20% improvement from baseline in both total back pain and morning stiffness, as measured in the Bath AS disease activity index (BASDAI), entered EE and received SC golimumab in a double-blinded fashion. Patients who did not enter early escape continued their treatment assigned at randomization. From Week 24 to Week 100, patients received double-blinded SC golimumab and from Week 104 to Week 252, during the LE, patients received SC golimumab. The blind was maintained during the LE Period until the last patient completed the Week 104 evaluations and the 104-week database was locked.

The primary efficacy endpoint in Study 9 was the proportion of patients with an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14 (see the final study report for Study 9 in Section 9.4 for a definition of an ASAS 20 response). The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) CMH test, was between the combined golimumab groups (i.e., golimumab50 and golimumab100) versus the placebo group. If this was significant, a comparison (for superiority) between golimumab100 & placebo and golimumab50 and placebo was performed.