Golimumab

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Golimumab, a human anti-TNFα IgG1κ monoclonal antibody, was approved in the US and Canada in April 2009 as a treatment for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and is undergoing regulatory review in the EU for these indications. The product was developed by Centocor and Janssen Pharmaceutical KK (Johnson & Johnson subsidiaries), in collaboration with Schering-Plough and Mitsubishi Tanabe Pharma. Golimumab faces numerous protein therapeutic competitors on the market, but, as the first patient-administered, once-monthly dosed anti-TNFα drug, it will likely be an attractive option for patients.

Introduction

Tumor necrosis factor (TNF)α is a pro-inflammatory cytokine that serves a key role in the pathogenesis of a variety of immunological diseases. The protein is targeted by the marketed fusion protein etanercept, and a total of four marketed monoclonal antibodies (mAbs). The most recent anti-TNFα market entrant, golimumab, was approved in April 2009 by the US Food and Drug Administration (FDA) and Health Canada as a treatment for three separate conditions. The product is indicated for the treatment of moderately-to-severely active rheumatoid arthritis (RA) when given to adults in combination with methotrexate (MTX), active psoriatic arthritis (PsA) when given to adults as a single agent or in combination with methotrexate, and active ankylosing spondylitis (AS) in adults. During the course of clinical development, golimumab was also studied as a treatment for ulcerative colitis (UC) and severe persistent asthma, although the product has not been approved for these indications.

Reduction of TNFα levels has been shown to ameliorate symptoms of diseases characterized by inflammation due to autoimmune or hyper-immune reactions.¹ The most prevalent of these diseases is arthritis, which affects approximately 20% of US adults,² and can manifest itself in a variety of ways. The rheumatoid and psoriatic forms have similar symptoms, including joint pain and stiffness, but PsA is specifically associated with the occurrence of psoriasis. Early treatment of RA and PsA may slow disease progression and thereby lessen joint and bone destruction. AS, which is also a chronic rheumatic disease, is characterized by pain and stiffness due to inflammation specifically of the axial skeleton, sacroiliac joints and entheses. Prior to the introduction of anti-TNFα therapeutics, rheumatic conditions including RA, PsA and AS were commonly treated with non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and naproxen, or disease-modifying anti-rheumatic drugs (DMARDs) such as MTX and corticosteroids.

Characterization and Preclinical Evaluation

Golimumab is a full-size antibody with a molecular mass of approximately 150 kilodaltons that exhibits multiple glycoforms. The mAb binds to both soluble and transmembrane forms of TNFα. The product was originally isolated from a hybridoma clone produced by HuMab (Medarex) transgenic mice that had been immunized with human TNFα. The golimumab-secreting clone was selected after being assayed for human light and heavy chains, and for TNFα-binding. The commercial product is produced in a recombinant cell line cultured by continuous perfusion.

The binding affinity for the target is 17 pM as assessed by surface plasmon resonance, and 1.4 pM in solution.³ The molecule is heat-stable, with Tm = 74.9°C as determined by differential scanning colorimetry, and demonstrates no self-association or aggregation at concentrations from 0.12–0.65 mg/mL as assessed by analytical ultracentrifugation. Liquid formulations are stable at 100 mg/mL. The marketed product is provided at a 50 mg/0.5 mL dose.

The safety of long-term administration and the immune-modulating effects of golimumab were assessed in cynomolgus macaques.⁴ A total of 16 animals were treated for up to six months with either saline, 10 mg/kg golimumab or 50 mg/kg golimumab doses administered twice per week by subcutaneous (SC) injection. Immune system function was assessed by the degree to which the macaques mounted an immune response, i.e., production of IgG and IgM, to keyhole limpet hemocyanin (KLH). No signs of toxicity were associated with treatment in animals that received golimumab for up to six months. No histopathological changes were observed in lymphoid tissues, and no affect on antibody response to KLH was observed after exposure to the mAb. In addition, no animal developed an infection.

Since arthritis affects women at approximately twice the rate of men, assessing the effects of golimumab on pregnancy and the
growth and development of neonates was an important aspect of preclinical development. Golimumab was administered to cynomolgus macaques throughout pregnancy and lactation to determine whether the mAb affected the immune system of the developing fetus. Embryo-fetal development was assessed after pregnant macaques (12–14 per group) were treated with twice-weekly subcutaneous injections of golimumab at doses of either 25 or 50 mg/kg during gestation day (GD) 20 to 50. Peri- and post-natal development was assessed after a similar treatment regimen was administered from GD50 through lactation day 33 (12 macaques per group). The mAb was transported across the placenta, with concentrations in cord blood about half that of maternal blood by GD100, but no treatment related adverse effects were observed in the fetuses or infants.

First in Humans Study

The pharmacokinetic (PK) properties and safety of golimumab were assessed in a placebo-controlled, dose escalating Phase 1 study of subjects with rheumatoid arthritis. A total of six doses (0.1, 0.3, 1, 3, 6 and 10 mg/kg) given as a single intravenous infusion were studied; six subjects were included in each group. The median half-life was approximately 11–19 days in subjects who received 3 mg/kg or higher doses. Additionally, Bayesian estimates suggested that the half-life of the mAb was in the 2–3 week range. The PK of golimumab were adequately described by a 2-compartment population PK model, and appeared to be linear over the dose range included in the study. Subjects were evaluated for up to 16 weeks after the infusion of golimumab. Adverse events (AE) were generally mild to moderate; headache was the only AE that appeared to correlate dose.

Clinical Trials Overview

Golimumab has been studied in at least 13 clinical studies that assessed safety and efficacy, some of which are ongoing. These studies have involved over 4,000 patients, and are listed at www.clinicaltrials.gov. It should be noted that a Phase 2 study of golimumab in patients with severe persistent asthma listed at the web site, NCT00675649, was withdrawn prior to recruitment. Specifically, the product was evaluated in five Phase 3 and two Phase 2/3 studies in RA, one Phase 3 study in PsA, one Phase 3 study in AS, one Phase 3 and two Phase 2/3 studies in ulcerative colitis, and one Phase 2 study in asthma. Five of the studies of golimumab were described by creative nicknames: GO-FORWARD (for patients with active RA despite MTX treatment), GO-BEFORE (MTX-treatment naïve patients), GO-AFTER (for patients previously treated with biologic anti-TNFα agents), GO-REVEAL (randomized evaluation in active psoriatic arthritis) and GO-RAISE (active ankylosing spondylitis patients).

Clinical Studies in Rheumatoid Arthritis

Golimumab was evaluated in a variety of RA patient populations. Studies included individuals who had active RA despite treatment specifically with MTX (one Phase 2, two Phase 3, one Phase 2/3 studies), those who had active RA despite therapy with any DMARD (one Phase 2/3 studies) or biologic TNFα inhibitors (one Phase 3 study), as well as patients who were naïve to therapy (one Phase 3 study). Results from completed studies indicate that SC or intravenous (IV) golimumab is safe and efficacious in treating several RA symptoms as assessed by primary endpoints such as ACR20 (20% improvement of symptoms based on American College of Rheumatology criteria). The FDA approval in April 2009 was given for use of golimumab as a treatment of moderately-to-severely active rheumatoid (RA) when given to adults in combination with MTX.

Phase 2 and 3 studies in patients resistant to MTX. Two Phase 3, one Phase 2/3 and one Phase 2 study were initiated to test the efficacy of golimumab alone or in combination with MTX in patients who had active RA despite prior treatment with MTX. Two different modes of drug administration, SC and IV, were evaluated. Three of the four studies are currently active, although no new patients are being enrolled.

A Phase 2 multicenter, randomized, double-blind, placebo-controlled study (NCT00207714) was conducted to test the efficiency of golimumab in treating RA symptoms in 196 patients with active RA despite MTX therapy. Data was collected between December 2003 and February 2006. Patients received MTX and were given either placebo, SC golimumab (50 or 100 mg) every 2 weeks or SC golimumab (50 or 100 mg) every 4 weeks (total of five study groups). The primary endpoints of the study were ACR20 at week 16 and the secondary endpoint is percentage improvement from ACR20 (week 16). The primary end point was attained; 61% of golimumab plus MTX recipients achieved an ACR20 response compared with 37% of placebo plus MTX recipients (p = 0.010). Serious adverse events were reported in 9% of patients in all golimumab groups combined, and also in 6% of placebo recipients. The study concluded that treatment with golimumab in conjunction with MTX effectively decreased the indications of RA and was generally well-tolerated in patients who do not respond well to MTX (Table 1).

Data collected during the course of the study were also analyzed to assess the effect of golimumab on inflammatory biomarkers such as E-selectin, interleukin (IL)-18, serum amyloid A (SAA) and matrix metalloproteinase (MMP)-9. Conclusions of the study were that, compared to MTX-only therapy, treatment with golimumab plus MTX resulted in greater and more rapid reductions in the serum levels of these markers, as well as tissue inhibitor of MMP-9 and C-reactive protein, as early as week 4, and the reductions continued through week 16. In addition, the magnitudes of the decrease in SAA, E-selectin, and MMP-9 at week 4 were larger for patients who had responded to therapy at week 16 compared to those who did not, which suggests that these biomarkers might be used to predict patient response.

The GO-FORWARD Phase 3 study (NCT00264550) involved 444 MTX-resistant RA patients. In addition to MTX, patients received placebo, 50 mg or 100 mg golimumab administered subcutaneously every 4 weeks; a fourth group received 100 mg golimumab and placebo instead of MTX. The double-blind controlled phase extended to week 52, and the study included an
**Table 1. Clinical studies in approved indications: Rheumatoid arthritis**

### NCT00207714.
**Phase 2 trial MTX-resistant RA patients (n = 196)**

Study conditions and dosage:
Patients divided into 5 groups: (1) Placebo every 2 wks, (2) 50 or (3) 100 mg sc golimumab every 2 wks, (4) 50 or (5) 100 mg sc golimumab every 4 wks. After wk 20 placebo patients were administered infliximab (3 mg/kg) at wk 20, 22, 28, 36 and 44. Golimumab/MTX patients received 50 or 100 mg sc golimumab every 4 wks.

| Results | ACR data (combined groups) | Placebo |
|---------|---------------------------|---------|
|         | Golimumab                 |         |
| ACR20   | 61.3% (p = 0.010)         | 37.1%   |
| ACR50   | 30.7% (p = 0.003)         | 5.7%    |
| ACR70   | 12.4% (p = 0.028)         | 0%      |

**ACR data 100 mg golimumab only**

| ACR20 | 79.4 (p < 0.001) |

Reference 7

### NCT00264550.
**GO-FORWARD:**
**Phase 3 trial MTX-resistant RA patients (n = 444)**

Study conditions and dosage:
In addition to MTX (15–25 mg every wk or 4 wks for placebo) patients received placebo, 50 or 100 mg sc golimumab administered every 4 weeks up to wk 20. A fourth group received 100 mg golimumab and placebo instead of MTX. Study extended to wk 52 with an open label extension of up to 5 years.

| Results | Co-primary end points | Co-secondary end points |
|---------|-----------------------|-------------------------|
| ACR20 (wk 14) | 50 mg | 100 mg | ACR20 (wk 24) | 50 mg | 100 mg |
| Golimumab + MTX | 55.1% | 56.2% | Golimumab + MTX | 59.6% | 59.6% |
| Golimumab + placebo | 44.4% (p = 0.059) | Golimumab + placebo | 35.3% |
| MTX + placebo | 33.1% | MTX + placebo | 27.8% |
| ACR50 (wk 14) | 50 mg | 100 mg | ACR50 (wk 24) | 50 mg | 100 mg |
| Golimumab + MTX | 34.8% | 29.2% | Golimumab + MTX | 37.1% | 32.6% |
| Golimumab + placebo | 20.3% | Golimumab + placebo | 19.5% |
| MTX + placebo | 9.8% | MTX + placebo | 13.5% |
| ACR70 (wk 14) | 50 mg | 100 mg | ACR70 (wk 24) | 50 mg | 100 mg |
| Golimumab + MTX | 13.5% | 9% | Golimumab + MTX | 20.2% | 14.6% |
| Golimumab + placebo | 7.5% | Golimumab + placebo | 11.3% |
| MTX + placebo | 3.8% | MTX + placebo | 5.3% |

**Co secondary end points continued.**

| DAS 28 response(using ESR) |
|----------------------------|
| 14 wks | 24 wks |
| Golimumab + MTX | 73% | 74.2% |
| Golimumab + placebo | 59.4% | 51.9% |
| MTX + placebo | 44.4% | 42.1% |

Reference 9

Open label extension up to five years. The co-primary end points were ACR.20 at week 14 and a health-associated questionnaire-disability index (HAQ-DI) score at week 24 (Table 1).

Of the patients who were co-administered MTX, ACR20 response were achieved at week 14 in 33% of those receiving placebo, and 55% and 56% of those receiving 50 mg or 100 mg golimumab, respectively. ACR20 response was observed in 44% of patients receiving 100 mg golimumab and placebo. At week 24, improvement from baseline in HAQ-DI were equivalent in the MTX plus placebo and the golimumab plus placebo groups (HAQ-DI = -0.13), but significantly different in both golimumab plus MTX groups (HAQ-DI = -0.38 and -0.50 for 50 mg and
Table 1. Clinical studies in approved indications: Rheumatoid arthritis

| NCT00361335. | Phase 3 MTX-resistant RA patients (n = 643) |
|---------------|---------------------------------------------|
| 30 min iv infusion of golimumab (2 or 4 mg/kg) or placebo every 12 wks at 0, 12, 24, 36 and 48 wks with/without MTX. Placebo recipients got golimumab at 4 mg/kg every from wk 24 onwards. STUDY ONGOING. | |

| Results | Primary endpoint | Secondary endpoint |
|---------|------------------|--------------------|
| ACR50 (wk 14) | ACR50 (wk 14) | ACR50 (wk 24) and Moderate or good DAS28 response (wk 14) |

| References | No peer reviewed literature published as of May 2009 |

| NCT00727987. | Phase 2/3 trial May 2008 (expected n = 240) |
|---------------|---------------------------------------------|
| All patients received MTX (6–8 mg/wk) every 4 wks. In addition patients received either: - sc golimumab 50 mg until wk 152 (increased to 100 mg from wk 16 if early escape was seen) - sc golimumab 100 mg until wk 152 - placebo every 4 wks until wk 12, followed by sc golimumab 50 mg every 4 wks there on | |

| Results | Primary end point: ACR20 STUDY ONGOING |
|---------|----------------------------------------|

| References | No peer reviewed literature published as of May 2009 |

| NCT00771251. | Phase 2/3 trial in patients not receiving MTX therapy (n = 285) |
|---------------|---------------------------------------------|
| 50 or 100 mg SC injections of golimumab every 4 wks from the first administration until wk 116. The placebo group received injections every 4 wks from the first administration until week 12 and then 50 mg SC golimumab injections every 4 wks from wk 16 until wk 116 | |

| Results | Primary end point | Secondary end point |
|---------|------------------|--------------------|
| ACR20 | ACR 50, ACR 70, ACR 90, Changes in the DAS28, and the HAQ |

| References | No peer reviewed literature published as of May 2009 |

| NCT002399546. | GO AFTER: |
|---------------|---------------------------------------------------|
| Phase 3 trial Patients treated with at least 1 TNFα agent (n = 461) | |
| Sc golimumab (50 or 100 mg) or placebo every 4 wks for 24 wks. After wk 24 all patients were to receive sc golimumab (50 or 100 mg) every 4 wks for 4.5 yrs. | |

| Results | Primary end point | Effect of golimumab on recipient of one TNFα agent vs. 2 TNFα agents |
|---------|------------------|------------------------------------------------|
| ACR20 (wk 14) | ACR20(wk 14) | Patients who received 2 TNFα agents |
| Golimumab | 50 mg | 100 mg | Patients who received 2 TNFα agents |
| 35% | 38% | Golimumab | 38% |
| Placebo | 18% | 16% | Placebo |

| Secondary end points | Patients receiving one TNFα agent |
|---------------------|----------------------------------|
| ACR20 (wk 24) | ACR20 | Wk 14 | Wk 24 |
| Golimumab | 50 mg | 100 mg | Adalimumab | 32% | 34% |
| 34% | 44% | Etanercept | 41% | 44% |
| Placebo | 17% | Infliximab | 41% | 48% |

| References | 10, 11 |

100 mg golimumab plus MTX, respectively). The study conclusion was that golimumab plus MTX significantly reduced the signs and symptoms of RA and improved physical function in the time frame in which the patients were evaluated. The trial is scheduled to end in 2012.

A Phase 3 study (NCT00361335) of golimumab administered IV every 12 weeks was started in August 2006. A total of 643 patients were to receive 30 min IV infusions of either 2 mg/kg or 4 mg/kg golimumab or placebo at 0, 12, 24, 36 and 48 weeks with or without MTX. The primary outcome measure was a comparison of ACR50 response at week 14 between the groups
The study conclusion was that golimumab was well-tolerated and significantly reduced RA signs and symptoms, as well as improved physical function, in the patient population evaluated. Study data was also examined to assess whether the type, number or reason for discontinuation of other anti-TNF agents affected the efficacy and safety of golimumab. Subgroup analysis was thus performed so that comparisons could be made between the proportions of ACR20 responders at week 14 in the combined golimumab and placebo groups for patients who had received adalimumab only, etanercept only, infliximab only, and those who had received two of these anti-TNF α agents. For patients who had previously used one anti-TNF α agent, ACR20 response at week 14 was achieved in 39 and 20% of those receiving golimumab and placebo, respectively. For patients who had previously used two anti-TNF α agents, ACR20 response at week 14 was achieved in 38 and 16% of those receiving golimumab and placebo, respectively.

Specifically, for patients who had previously been treated with one anti-TNF α agent (either adalimumab, etanercept or infliximab), ACR20 response at week 14 was achieved in 32, 41 and 41% at week 14, respectively, and 34, 44 and 48% at week 24, respectively. Golimumab was found to be effective in patients who had discontinued other anti-TNF α agents due to lack of efficacy. At week 14, 39% of patients who were unresponsive to other TNFα agents and who received golimumab in the study achieved ACR20 responses compared to 18% of similar patients who received placebo. Concomitant use of DMARD was also examined. At week 14, 40% of patients receiving golimumab with concomitant use of DMARDs achieved ACR20 responses compared to 18% of those receiving placebo. In contrast, for those with no DMARD use, 29% of patients receiving golimumab achieved ACR20 responses compared to 19% of those receiving placebo.

Phase 3 studies in patients with active RA despite treatment with a DMARD. One Phase 2/3 study (NCT00771251) of golimumab monotherapy was initiated in May 2008. In this study, golimumab may be used in patients not receiving MTX therapy. Patients are administered golimumab SC at either 50 mg or 100 mg doses every four weeks from weeks 0–152. The primary outcome measure is the ACR20 response. The study is currently enrolling patients; an estimated 285 patients will participate.

Phase 3 study in patients previously treated with another TNFα agent. The Phase 3 GO-AFTER study (NCT00299546) was conducted to assess the efficiency and safety of golimumab in patients who had active RA although they had previously been treated with at least one biologic anti-TNFα agent (etanercept, adalimumab or infliximab). Patients received either SC placebo or golimumab at 50 or 100 mg doses. A total of 461 patients were assigned to treatment administered at 4 week intervals for 24 weeks. Post week 24, all patients were to receive golimumab at 4 week intervals for 4.5 years. At week 14, ACR20 was achieved by 35 and 38% of those administered golimumab at 50 or 100 mg, respectively, versus 18% of patients receiving placebo. At week 24, these values had increased to 34, 44 and 17% for those receiving 50 mg golimumab, 100 mg golimumab and placebo, respectively. The study conclusion was that golimumab was well-tolerated and significantly reduced RA signs and symptoms, as well as improved physical function, in the patient population evaluated.

Study data was also examined to assess whether the type, number or reason for discontinuation of other anti-TNF agents affected the efficacy and safety of golimumab. Subgroup analysis was thus performed so that comparisons could be made between the proportions of ACR20 responders at week 14 in the combined golimumab and placebo groups for patients who had received adalimumab only, etanercept only, infliximab only, and those who had received two of these anti-TNF α agents. For patients who had previously used one anti-TNF α agent, ACR20 response at week 14 was achieved in 39 and 20% of those receiving golimumab and placebo, respectively. For patients who had previously used two anti-TNF α agents, ACR20 response at week 14 was achieved in 38 and 16% of those receiving golimumab and placebo, respectively.

Specifically, for patients who had previously been treated with one anti-TNF α agent (either adalimumab, etanercept or infliximab), ACR20 response at week 14 was achieved in 32, 41 and 41% at week 14, respectively, and 34, 44 and 48% at week 24, respectively. Golimumab was found to be effective in patients who had discontinued other anti-TNF α agents due to lack of efficacy. At week 14, 39% of patients who were unresponsive to other TNFα agents and who received golimumab in the study achieved ACR20 responses compared to 18% of similar patients who received placebo. Concomitant use of DMARD was also examined. At week 14, 40% of patients receiving golimumab with concomitant use of DMARDs achieved ACR20 responses compared to 18% of those receiving placebo. In contrast, for those with no DMARD use, 29% of patients receiving golimumab achieved ACR20 responses compared to 19% of those receiving placebo.

Phase 3 studies in patients with no prior MTX treatment. The GO-BEFORE active-control Phase 3 trial (NCT00264537)
included 637 patients naïve to MTX in the evaluation of the efficacy of SC administration of golimumab alone or in conjunction with MTX. Patients received either 20 mg/wk MTX plus placebo, 100 mg golimumab plus placebo or 20 mg/wk MTX combined with either 50 or 100 mg golimumab. The test agents were administered every 4 weeks. At week 24, an ACR20 response was seen in 62% of patients receiving MTX and either the 50 or 100 mg doses of golimumab compared to 52 and 49% of those receiving either golimumab or MTX alone, respectively. At week 24, ACR50 responses were achieved by 40 and 37% of the patients receiving 50 or 100 mg of golimumab and MTX, respectively, and 33% and 29% of those receiving either golimumab or MTX alone, respectively (Table 1). The 100 mg golimumab only group was considered to be similar to the MTX only group according to a non-inferiority comparison. The primary endpoint (ACR50) was not achieved by intent-to-treat (ITT) analysis, but a modified ITT analysis indicated that the 50 mg golimumab plus MTX group had a statistically greater response compared to those receiving MTX alone. The study, which began in November 2005, is expected to be complete in March 2011.

Clinical Studies in Psoriatic Arthritis

During December 2005 to May 2007, the GO-REVEAL multicenter Phase 3 trial (NCT00265096) was conducted in 405 patients with active PsA despite therapy with DMARDs or NSAIDs. SC golimumab (50 or 100 mg) or placebo was given at week 0, then at intervals of 4 weeks. At week 16, patients demonstrating inadequate response (<10% improvement) after administration of placebo were switched to 50 mg golimumab, and unresponsive patients in the 50 mg golimumab group were switched to 100 mg.

At 14 weeks, patients receiving golimumab tolerated the drug well and reported improvements in physical conditions and quality of life. Through week 24, adverse events were reported for a majority of both the golimumab and placebo-treated patients (65 and 59%, respectively), although the safety profile of the mAb was considered to be consistent with those of other anti-TNFα therapeutics.

An ACR20 response was achieved by 51% of patients administered 50 mg golimumab and 45% of those who received 100 mg doses, compared with 9% of placebo patients. Additional improvements were observed with continued treatment. By week 24, the percentages had increased to 52 and 61% for patients receiving 50 and 100 mg golimumab, respectively, compared to 12% of placebo patients.

A psoriasis area and severity index (PASI) was also used to assess the effects of treatment with golimumab. Again, drug-treated cohorts fared significantly better than their placebo counterparts based on this assessment parameter at 14 weeks. Of a total of 217 patients affected by psoriasis over least 3% of their body surface area, 40% patients receiving 50 mg golimumab, and 50% of those administered 100 mg of the mAb, had at least 75% improvement in the PASI. Additionally, a PsA-modified Maastricht ankylosing spondylitis enthesitis score (MASES) index evaluation at both 14 and 24 weeks indicated that golimumab-treated patients improved compared to those given placebo. The median percentage change in PsA-modified MASAS was 50% for both the 50 and 100 mg mAb-treated groups at 14 weeks; this increased to 60 and 67% for the 50 and 100 mg golimumab-treated groups, respectively, at 24 weeks. In comparison, the median percentage change was 12% for patient who received placebo. Golimumab treated patients also showed improvement in nail psoriasis severity index (NAPSI) compared to placebo recipients (Table 2). Patients participating in this study are continuing to be evaluated; the study is scheduled for completion in 2012.

Clinical Studies in Ankylosing Spondylitis

The efficacy of golimumab in reducing signs and symptoms of AS was studied (GO-RAISE study; NCT00265083) in 356 patients with active disease that was unresponsive to DMARDs or NSAIDs. Study sites were located in North America, Europe and Asia; data were collected between December 2005 and May 2007. Patients were administered SC golimumab (50 or 100 mg) or placebo at week 0, and then at 4-week intervals. At week 16, placebo-treated patients or those receiving 50 mg golimumab who showed less than 20% improvement in total back pain and morning stiffness were switched to either 50 mg golimumab (patients previously receiving placebo) or 100 mg golimumab (patients previously receiving 50 mg golimumab). Patients were evaluated for a 20% improvement in the assessment in AS (ASAS20) criteria. At week 14, golimumab recipients showed improvement compared to placebo recipients; 59 and 60% of patients in the 50 mg and 100 mg groups achieved an ASAS20 response compared to 22% of those receiving placebo (Table 3). The results at week 24 were similar to those observed at week 14.

Bath AS disease activity (BASDAI) index scores were also used to assess efficacy. A 50% improvement in the score over baseline was observed in 51 and 48% of patients receiving 50 mg and 100 mg golimumab, respectively, compared to 15% of those administered placebo. Overall, the observed improvements seen in the golimumab-treated patients were considered to be significant and clinically-meaningful, but efficacy was similar to that of other anti-TNFα therapeutics such as etanercept, infliximab, and adalimumab.

Drug-induced affects on sleep patterns in AS patients were evaluated based on a Jenkins sleep evaluation questionnaire (JSEQ). Patients also self-reported effects of golimumab on health-related quality of life using the short form 36 (SF-36) health survey. Scores for the two golimumab-treated groups showed significant improvements at weeks 14 and 24 compared to the placebo group for both measures (Table 3). Patients are continuing to be evaluated; the GO-RAISE study is scheduled for completion in January 2012.

Clinical Studies in Additional Indications

Golimumab has also been studied as a treatment for UC and asthma. A total of three studies in patients with UC and one study in patients with asthma were conducted. As of May 2009, the product has not approved for these indications.
therapy administered SC to patients who participated in the Phase 2/3 studies. Patients will receive multiple SC injections for a total dose of 0, 50, 100 or 200 mg golimumab every 4 weeks through week 52.

### Ulcerative Colitis

Two on-going, placebo-controlled Phase 2/3 studies will assess the safety and effectiveness of golimumab administered either IV or SC to patients with moderately to severely active ulcerative colitis using different routes of administration (Table 4). The estimated enrollment is 676 patients for each study. The IV induction regimen (NCT00488774) involves a single infusion at week 0 of either placebo or golimumab at either 1, 2 or 4 mg/kg. In a similar study (NCT00487539), patients will be given multiple injections SC for a total dose of 0, 100, 200 or 400 mg golimumab at week 0. At week 2, additional total doses of 0, 50, 100 or 200 mg golimumab will be administered.

A placebo-controlled Phase 3 study (NCT00488631) will evaluate the safety and efficacy of golimumab maintenance therapy administered SC to patients who participated in the Phase 2/3 studies. Patients will receive multiple SC injections for a total dose of 0, 50, 100 or 200 mg golimumab every 4 weeks through week 52.

### Asthma

Golimumab was evaluated as a treatment for uncontrolled, severe persistent asthma in a proof-of-concept study (NCT00207740).\(^{15}\) Safety and efficacy were assessed in 309 patients with asthma despite use of high-dose inhaled corticosteroids and long-acting β₂ agonists (Table 5). Monthly SC injections of either placebo or golimumab at 50, 100 or 200 mg doses were administered throughout week 52. Efficacy was assessed from the change from baseline in the prebronchodilator percent-predicted forced

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**Table 2. Clinical studies in approved indications: Psoriatic arthritis**

| Study conditions and dosage: sc golimumab (50 or 100 mg) or placebo every 4 wks for ~5 yrs. Patients demonstrating inadequate arthritis response in placebo group were switched to 50 mg golimumab and unresponsive patients in the 50 mg group were switched to 100 mg golimumab at wk 16. |

| Results | Primary endpoint | Secondary endpoint |
|---------|-----------------|--------------------|
|         | ACR20 (wk 14)   | ACR20 (wk 24)      |
| Golimumab (50 mg) | 51% | Golimumab (50 mg) | 52% |
| Golimumab (100) | 45% | Golimumab (100) | 61% |
| Placebo | 9%  | Placebo | 12% |

| % patients achieving response based on PsA response criteria |
|-------------------------------------------------------------|
| Wk 14 | Wk 24 |
| Golimumab (50 mg) | 73% (p < 0.001) | Golimumab (50 mg) | 70% (p < 0.001) |
| Golimumab (100) | 72% (p < 0.001) | Golimumab (100) | 85% (p < 0.001) |
| Placebo | 21% | Placebo | 29% |

| MASES index (% change in PsA modified MASES) |
|--------------------------------------------|
| Wk 14 | Wk 24 |
| % change | % change |
| Golimumab (50 mg) | 50 (<0.001) | Golimumab (50 mg) | 60 (<0.001) |
| Golimumab (100) | 50 (<0.001) | Golimumab (100) | 67 (<0.001) |
| Placebo | 0 | Placebo | 12 |

| Effect of golimumab on improvement in psoriatic skin manifestations (PASI75 response) |
|----------------------------------------------------------------------------------|
| Wk 14 | Wk 24 |
| Golimumab (50 mg) | 40% | Golimumab (50 mg) | 56% |
| Golimumab (100) | 58% | Golimumab (100) | 66% |
| Placebo | 2.5% | Placebo | 1% |

| Effect of golimumab on nail psoriasis severity (NAPSI) |
|-------------------------------------------------------|
| Wk 14 | Wk 24 |
| Improvement: NAPSI median change % |
| Golimumab (50 mg) | 25 (0.015) | Golimumab (50 mg) | 33 (<0.001) |
| Golimumab (100) | 43 (<0.001) | Golimumab (100) | 54 (<0.001) |
| Placebo | 0 | Placebo | 0 |

| Reference |
|-----------|
| 13 |
therapeutic mAb marketed for treatment of Crohn disease, is now under investigation for treatment of RA.\textsuperscript{16} mAbs that target other antigens either are now or will be market competitors. These include anti-CD20 rituximab (Rituxan\textsuperscript{TM}), an intravenously administered chimeric mAb that has shown benefits in patients with severe refractory RA that do not respond to MTX and respond poorly to one or more anti-TNF\textsubscript{α} therapies,\textsuperscript{17} and tocilizumab (Actemra\textsuperscript{TM}), an anti-IL-6 receptor mAb, that is currently undergoing FDA review as a treatment for RA.\textsuperscript{18} However, the convenience of a once-monthly dosing schedule of golimumab is considered to be a major advantage for marketing of the product.

The carefully crafted reverse-merger between Merck and Schering-Plough was specifically intended to circumvent the legal and ultimately monetary ramifications of the licensing deal struck between Johnson and Johnson and Schering-Plough regarding the golimumab intellectual property. Estimated annual US sales of golimumab have been estimated to reach over $1 billion in the first year of its launch,\textsuperscript{16} and the company has set ambitious goals for its future growth.

### Future Prospects

The FDA has now approved golimumab (Simponi\textsuperscript{TM}) to treat RA, PsA and AS. It is the first patient-administered, once-monthly injectable anti-TNF\textsubscript{α} drug on the market, making it an attractive option for patients and physicians alike. Direct competitors for golimumab are other anti-TNF\textsubscript{α} agents that are FDA-approved for the same indications: infliximab (Remicade\textsuperscript{TM}), an intravenously administered chimeric mAb that has shown benefits in patients with severe refractory RA that do not respond to MTX and respond poorly to one or more anti-TNF\textsubscript{α} therapies,\textsuperscript{17} and tocilizumab (Actemra\textsuperscript{TM}), an anti-IL-6 receptor mAb, that is currently undergoing FDA review as a treatment for RA.\textsuperscript{18} However, the convenience of a once-monthly dosing schedule of golimumab is considered to be a major advantage for marketing of the product.

The carefully crafted reverse-merger between Merck and Schering-Plough was specifically intended to circumvent the legal and ultimately monetary ramifications of the licensing deal struck between Johnson and Johnson and Schering-Plough regarding the golimumab intellectual property. Estimated annual US sales of golimumab have been estimated to reach over $1 billion in the first year of its launch,\textsuperscript{16} and the company has set ambitious goals for its future growth.

### Table 3. Clinical studies in approved indications: Ankylosing spondylitis

| Study conditions and dosage: Sc golimumab (50 or 100 mg) or placebo was given every 4 wks for 20 wks. At wk 24, placebo patients were switched to golimumab (50 mg) up to a total of 5 years. At wk 16, placebo or golimumab-50 patients who showed <20% improvement in total back pain and morning stiffness were switched to either 50 mg golimumab (patients previously receiving placebo) or 100 mg golimumab (patients previously receiving 50 mg golimumab). |
|---|---|
| NCT00265083. | GO-RAISE: |
| Phase 3 trial in patients with active AS (n = 356) |

| RESULTS | PRIMARY ENDPOINT |
|---|---|
| ASAS20 (wk 14) | |
| Golimumab (50 mg) | 59% |
| Golimumab (100 mg) | 60% |
| Placebo | 22% |

| BASDAI50 (% reduction in disease activity) | |
|---|---|
| Golimumab (50 mg) | 51% |
| Golimumab (100 mg) | 48% |
| Placebo | 15% |

| EFFECT OF GOLIMUMAB ON SLEEP PATTERNS | JSEQ SCORE (SCALE 0–20) |
|---|---|
| Sc, subcutaneous; MTX, methotrexate; ACR20, 20% improvement based on American College of Rheumatology criteria; DAS28, disease activity score 28; RA, rheumatoid arthritis; wk, week; iv, intravenous; TNFα, tumor necrosis factor α; HAQ, health assessment questionnaire; MASES, Maastricht ankylosing spondylitis enthesitis score; PASI75, 75% improvement from baseline based on psoriasis area and severity index; NAPSI, nail psoriasis severity index; ASAS20, 20% improvement in the assessment in ankylosing spondylitis; BAFSI, Bath ankylosing spondylitis functional index; BASDAI, Bath ankylosing spondylitis disease activity index; JSEQ, Jenkins sleep evaluation questionnaire; UC, Ulcerative colitis. |

| Study conditions and dosage: Sc golimumab (50 or 100 mg) or placebo was given every 4 wks for 20 wks. At wk 24, placebo patients were switched to golimumab (50 mg) up to a total of 5 years. At wk 16, placebo or golimumab-50 patients who showed <20% improvement in total back pain and morning stiffness were switched to either 50 mg golimumab (patients previously receiving placebo) or 100 mg golimumab (patients previously receiving 50 mg golimumab). |

| Reference | 14 |

Sc, subcutaneous; MTX, methotrexate; ACR20, 20% improvement based on American College of Rheumatology criteria; DAS28, disease activity score 28; RA, rheumatoid arthritis; wk, week; iv, intravenous; TNFα, tumor necrosis factor α; HAQ, health assessment questionnaire; MASES, Maastricht ankylosing spondylitis enthesitis score; PASI75, 75% improvement from baseline based on psoriasis area and severity index; NAPSI, nail psoriasis severity index; ASAS20, 20% improvement in the assessment in ankylosing spondylitis; BAFSI, Bath ankylosing spondylitis functional index; BASDAI, Bath ankylosing spondylitis disease activity index; JSEQ, Jenkins sleep evaluation questionnaire; UC, Ulcerative colitis.
Table 4. Clinical studies in additional indications: Ulcerative colitis

| Study                                                                 | Description                                                                 |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|
| **NCT004887744.**                                                     | **Phase 2/3 trial in patients with moderate to severely active UC (n = 676)  |
| **Study conditions and dosage:** Single IV infusion of placebo or golimumab at either 1, 2 or 4 mg/kg at wk 0. | **Results**<br>Evaluation of dose response<br>Evaluation of safety and efficacy of IV regimens of golimumab in induction of clinical response. Was considered unsafe.<br>Evaluation of efficacy of IV regimens of golimumab in inducing clinical remission, mucosal healing, and improving disease-specific health-related quality of life.<br>**STUDY SUSPENDED** |
| **References**                                                        | No peer reviewed literature published as of May 2009                        |
| **NCT00487539.**                                                     | **Phase 2/3 trial in patients with moderate to severely active UC (n = 676)  |
| **Study conditions and dosage:** Multiple SC injections of golimumab at 0, 100, 200 or 400 mg of golimumab at wk 0. At wk 2, additional doses of 0, 50, 100 or 200 mg golimumab will be administered. | **Results**<br>Evaluation of dose response<br>Evaluation of safety and efficacy of SC regimens of golimumab in induction of clinical response.<br>Evaluation of efficacy of SC regimens of golimumab in inducing clinical remission, mucosal healing, and improving disease-specific health-related quality of life.<br>**STUDY ONGOING** |
| **References**                                                        | No peer reviewed literature published as of May 2009                        |
| **NCT00488631.**                                                     | **Phase 3 trial in patients with moderate to severely active UC (expected n = 1350)** |
| **Study conditions and dosage:** Multiple SC injections of golimumab at 0, 50, 100 or 200 mg will be administered every 4 wks up to wk 52. | **Results**<br>Safety and efficacy of SC golimumab will be tested in patients who participated in the phase 2/3 trials described above.<br>**STUDY ONGOING** |
| **References**                                                        | No peer reviewed literature published as of May 2009                        |

Table 5. Clinical studies in additional indications: Asthma

| Study                                                                 | Description                                                                 |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|
| **NCT00207740. Phase 2 trial in patients with moderate to severely persistent asthma (n = 309)** | **Results**<br>Changes in % predicted FEV<sub>1</sub><br>**Placebo**<br>**Golimumab, combined group (50 and 100 mg)**<br>2.44<br>2.91<br>**STUDY TERMINATED DUE TO UNFAVORABLE BENEFIT-RISK PROFILE** |
| **Reference**                                                         | 15                                                                          |
for golimumab total $30 MM (2,000 patients at $15,000 per year), and by 2013 golimumab is estimated to have sales exceeding $1.4B across all three indications. In an obvious move to protect what is thought to be a nascent blockbuster in the era of the drug patent expiry, golimumab has good reason to be fought over.

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