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Efficacy and safety of subcutaneous golimumab in methotrexate-naïve patients with rheumatoid arthritis: 5-year results of the GO-BEFORE trial

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ABSTRACT

Objective: Evaluate the safety and efficacy of golimumab through 5 years in adults with active RA who had not previously received methotrexate (MTX).

Methods: In GO-BEFORE, 637 MTX-naïve adult patients with active RA were randomized (1:1:1:1) to placebo+MTX (Group 1), golimumab 100mg+placebo (Group 2), golimumab 50mg+MTX (Group 3), or golimumab 100mg+MTX (Group 4). Inadequate responders in Groups 1, 2, and 3 entered early escape at week28 to golimumab 50mg+MTX, golimumab 100mg+MTX, or golimumab 100mg +MTX, respectively; remaining patients in Group 1 could crossover to golimumab 50mg+MTX at week52. Assessments included ACR20/50/70 response, DAS28-CRP scores, and vdH-mTSS. Efficacy was analyzed using an intent-to-treat analysis. Pharmacokinetics and immunogenicity were evaluated at selected visits.

Results: A total of 422 patients completed golimumab treatment through week256. At week256, 72.8%, 54.6%, and 38.0% of all patients in the full ITT population (n=637) had an ACR20/50/70 response, respectively, 84.1% had a good or moderate DAS28-CRP response, and 72.7% had a clinically meaningful improvement in physical function. Radiographic progression was minimal in all treatment groups through week256, and the overall mean change from baseline in vdH-mTSS was 1.36. Serum trough golimumab concentrations were approximately dose proportional and maintained through week256. Antibodies to golimumab occurred in 9.6% of patients through week256. Infections were the most common type of AE; 204/616 patients (33.1%) had ≥1 serious AE.

Conclusions: Clinical efficacy with golimumab treatment was maintained through week256 of the GO-BEFORE trial of MTX-naïve RA patients. No unexpected AEs occurred; safety results through 5 years are consistent with earlier reports.

Significance and Innovations

- Clinical response to golimumab (50 mg and 100 mg) + methotrexate (MTX) was maintained through 5 years in adult patients with moderate to severe rheumatoid arthritis who had not previously received MTX.
- Safety findings were consistent with previous golimumab studies and other anti-tumor necrosis factor agents; no unexpected adverse events occurred.
- The incidence of antibodies to golimumab was low and the presence of antibodies to golimumab was not associated with adverse events.

INTRODUCTION

Golimumab, a fully human anti-tumor necrosis factor (TNF) antibody, has been shown to improve the signs and symptoms of rheumatoid arthritis (RA) in adults in large, randomized, placebo-controlled phase 3 trials.(1-3) The GO-BEFORE trial evaluated the safety and efficacy of subcutaneous (SC) golimumab in adult patients with RA who had not previously received methotrexate (MTX) therapy, and results through 2 years have been reported.(1, 4) In the GO-BEFORE trial, patients treated with golimumab (50mg or 100mg)+MTX had significantly greater improvements in the signs and symptoms of RA than did those treated with MTX monotherapy. These improvements were observed at week24(1) and were maintained through 2 years.(4) In addition, golimumab+MTX-treated patients also had significantly less radiographic progression through 1 year when compared with those who received MTX monotherapy.(5) Here we report the final efficacy and safety results of the GO-BEFORE trial through 5 years.

PATIENTS AND METHODS

Patients and study design. The detailed eligibility criteria and study design of the GO-BEFORE trial have been previously described.(1) Briefly, adult patients with active RA who had not been previously treated with MTX were randomly assigned to receive SC injections of placebo+MTX (Group 1), golimumab 100mg+placebo (Group 2), golimumab 50mg+MTX (Group 3), or golimumab 100mg+MTX (Group 4); injections were administered at baseline and every 4 weeks. Active RA was defined as ≥4 swollen joints, ≥4 tender joints, and at least two of the following criteria: C-reactive protein (CRP) level of ≥1.5 mg/dL or ESR ≥28 mm/h using the Westergren method; morning stiffness lasting ≥30 minutes; or evidence of bone erosion radiographs or magnetic resonance imaging.(1) Eligible patients also could not have a history of latent tuberculosis (TB) prior to screening and could not have any signs or symptoms of active TB. Patients were screened for TB by chest radiographs (both posterior-anterior and lateral views) within 3 months before the first study drug administration and diagnostic testing (tuberculin and QuantiFERON-TB Gold tests) within 6 weeks before the first study drug administration. Patients with a newly identified positive result (tuberculin or QuantiFERON-TB Gold testing) could participate in the trial if they initiated appropriate treatment for latent TB.

Patients were stratified by investigational site and baseline CRP level (<1.5 mg/dL or ≥ 1.5 mg/dL). Placebo and golimumab injections were administered at baseline and every 4 weeks. At week28, patients in Groups 1-3 with an inadequate response to treatment entered blinded early escape such that patients in Group 1 switched from placebo to golimumab 50mg injections, patients in Group 2 initiated concomitant MTX therapy while continuing golimumab 100mg injections, and patients in Group 3 increased their golimumab dose to 100mg; patients in Groups 1 and 3 continued concomitant MTX. Patients in Group 4 did not have any changes in treatment

regimen, regardless of their early escape status. The active-control period continued through week52.

The long-term extension began with the week52 visit and continued through week268 (5 years). At week52, patients in Group 1 who did not have any swollen or tender joints continued MTX monotherapy; patients with at least one swollen or tender joint were switched from placebo injections to golimumab 50mg. Patients in Groups 2, 3, and 4 continued the treatment they were receiving at week52. The blind was maintained until the week52 database was locked, after which treatment adjustments could be made at the investigator's discretion. Patients in Group 1 who were receiving MTX monotherapy could initiate treatment with golimumab 50mg, and a one-time golimumab dose increase to 100mg or decrease to 50mg was permitted (including patients who had dose-escalated to 100mg). Additionally, MTX therapy could be initiated or adjusted during the long-term extension period. Concomitant therapy with NSAIDs, corticosteroids, or other analgesics for RA could also be adjusted at the investigator's discretion. The final study golimumab injection was at week252. After week256, patients transitioned to standard-of-care treatment for RA, including commercially available biologics.

The GO-BEFORE trial was conducted according to the Declaration of Helsinki. The protocol was approved by the institutional review board or ethics committee at each site, and all patients gave written informed consent before any study-related procedures were performed.

Evaluations. During the long-term extension, clinical response was assessed every 12 weeks through week256, with an additional assessment at week104. Disease activity was assessed using the American College of Rheumatology (ACR) criteria(6) and the European League Against Rheumatism 28-joint count disease activity score using CRP (DAS28-CRP).(7) Post-hoc

efficacy assessments included the simplified disease activity index (SDAI)(8) and clinical disease activity index (CDAI).(9)

Physical function was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI).(10) Normal physical function was defined as a HAQ-DI score ≤0.5, and a minimal clinically important difference (MCID) was defined as an improvement ≥0.25.(11) Health-related quality of life (HRQol) was evaluated using the physical and mental component summary scores (PCS, MCS) of the 36-item short-form health survey (SF-36).(12) The impact of disease on productivity was assessed using a visual analogue scale (0-10 cm) at baseline and at week256.

Radiographs of the hands and feet were obtained at weeks 52, 104, 208, and 256 during the long-term extension; results through week104 have been previously reported.(1, 4) Data from patients with radiographs at baseline, week104, and at least one radiograph after week104 were included in the current analysis. As previously detailed,(5) radiographs were scored by two independent readers and an adjudicator using the van der Heijde-modified total Sharp score (vdH-mTSS).(13)

Patients were monitored through week268 for adverse events (AEs). Routine laboratory analyses were performed through week256. The incidence of each AE was summarized according to actual treatment received at the time of the event. Blood samples were collected (prior to administration of study agents) at selected visits for the analysis of pharmacokinetics and evaluation for the presence of antibodies to golimumab using a validated immunoassay.(14)

Statistical analysis. Descriptive statistics (eg, counts and percentages and means/medians) were used to summarize the efficacy results of the long-term extension by randomized treatment

group. In the a priori analysis of clinical efficacy endpoints (ACR components and DAS28-CRP), observed data were determined through week256 with no imputation for missing values. A more stringent post hoc intent-to-treat (ITT) analysis including all randomized patients was performed on the clinical efficacy measures, and these results are reported herein. This ITT analysis used the following data imputation and treatment failure rules: 1) missing baseline values for continuous variables were replaced with the median value of the corresponding baseline CRP stratum (<1.5 mg/dL or ≥1.5 mg/dL), and the last observation carried forward methodology was applied to missing post-baseline values, and 2) patients who discontinued the study agent due to unsatisfactory therapeutic effect were imputed as nonresponders. The proportions of patients achieving at least a 20%, 50%, or 70% improvement in the ACR criteria(6) (ACR20/50/70 response), a moderate or good DAS28-CRP response,(7, 15) a DAS28-CRP score <2.6, a DAS28-CRP score ≤3.2, an MCID in HAQ-DI score, and a HAQ-DI score ≤0.5 were determined. SF-36 and productivity outcomes were analyzed using observed data, with no missing data imputation, and included improvements from baseline in SF-36 PCS and MCS scores and the impact of disease on productivity at week256, as well as the proportions of patients with normal SF-36 PCS or MCS scores (score ≥50). In the post-hoc analysis, the proportions of patients who achieved remission, as defined by an SDAI score ≤3.3,(16) a CDAI score ≤2.8,(16) or Boolean definition(17) were also determined.

Radiographic data through week256 were summarized by randomized treatment group and included all patients who had radiographs at weeks 0, 104, and at least one post-week104. Changes from baseline to week208 and week256 in the vdH-mTSS are reported; missing post-baseline values were replaced using the LOCF methodology. Among patients with a vdH-mTSS at baseline and week256, annual rates of progression at baseline and 5 years were determined

using the vdH-mTSS divided by RA duration for each patient at baseline and the change in vdH-mTSS over 5 years.

Cumulative safety data are reported for all patients who received at least one administration of golimumab through week268. AEs and SAEs were summarized according to the treatment received at the time of the event. As a result of early escape, placebo crossover, and golimumab dose adjustments allowed during the long-term extension, patients could be included in more than one treatment group. AEs were summarized through week268, with the exception of those that occurred after receipt of any commercial biologic (including commercial golimumab). Patients who received commercially available biologic treatment after discontinuing study golimumab, but who remained in the study, had AEs reported through week268, but these AEs were excluded from the safety summaries. The rates per 100 patient-years and 95% confidence intervals (CIs) for the total numbers of serious infections, malignancies (including nonmelanoma skin cancers), and death are also reported. In addition, standardized incidence ratios (SIRs) for malignancies were determined using the Surveillance, Epidemiology and End Results (SEER) database; nonmelanoma skin cancers were excluded from this comparison because they are not reported in the SEER database.

RESULTS

Data for this report were collected from December 2005 to June 2012. As previously reported, patient demographics and disease characteristics at baseline were well balanced among the treatment groups.(1) A total of 637 patients were randomly assigned to Group 1 (n=160), Group 2 (n=159), Group 3 (n=159), and Group 4 (n=159) (Supplemental Table 1). Eighty-nine patients (Group 1, n=28; Group 2, n=22; Group 3, n=20; Group 4, n=19) met the early escape

criteria at week28. (4) Through week104, 140 patients discontinued the SC study agent, with AEs being the most common reason.(4) A total of 215 (33.9%) patients discontinued the study agent through week252; 111 (17.5%) discontinued due to an AE, including worsening of RA (n=4; 0.6%), and 23 (3.6%) patients discontinued due to unsatisfactory therapeutic effect (Table 1). Four hundred two (63.4%) patients completed the safety follow-up through week268.

Through week256, 616 patients received at least one administration of golimumab. Of these, 172 received only the 50mg dose, 243 received only the 100mg dose, and 201 received at least one administration of each dose during the trial.

Clinical efficacy and patient-reported outcomes.

Clinical efficacy results from the ITT analysis that included all randomized patients are shown in Table 2. At week256, 72.8% of all patients had an ACR20 response, 54.6% had an ACR50 response, and 38.0% had an ACR70 response. After the placebo crossover at week52, ACR20 and ACR50 response rates were maintained for all treatment groups through week256 (Figure 1). Additionally, 84.1% of all patients had either a good or moderate DAS28-CRP response at week256, and 43.3% of patients had a DAS28-CRP score <2.6. Approximately 28% of all patients were in remission at week256 according to the SDAI and CDAI remission criteria, and 21.2% met the Boolean remission criteria (Table 2). Meaningful improvements in physical function were observed, with an overall mean improvement in HAQ-DI score of 0.57 at week256. Additionally, at week256, 72.7% of all patients had an improvement from baseline ≥0.25, and 43.0% achieved normal physical function (HAQ-DI ≤0.5; Table 2) compared with 9.1% (58/637) who had a normal HAQ-DI score at baseline. The results of the protocol-specified

efficacy analysis were consistent with this modified intent-to-treat analysis (Supplemental Table 2).

A total of 101 patients had an increase in golimumab dose from 50mg to 100mg during the long-term extension (after week52), and of these, 100 patients had ≥12 weeks of follow-up available. Among these patients, 84 did not have a DAS28-CRP score <2.6 immediately prior to dose escalation, and 68 did not have a score ≤3.2 prior to dose escalation. Both of these subgroups had a mean (standard deviation [SD]) improvement in DAS28-CRP score of 1.0 (1.1) at 12 weeks after dose escalation.

Improvements from baseline to week256 in patient-reported outcomes were generally similar among the treatment groups (Table 3). Mean improvements in SF-36 PCS and MCS scores ranged from 11.3-11.9 and 4.5-7.6, respectively. Among patients with evaluable SF-36 data at baseline and week256, 27.9% had a normal (score ≥50) SF-36 PCS score, and 46.9% had a normal SF-36 MCS score at week256 (Table 3) compared with 1.4% and 28.8% who had normal baseline SF-36 PCS and MCS scores, respectively. Mean improvements from baseline to week256 in the impact of disease on productivity ranged from 3.2 - 4.3 among the treatment groups.

At week256, 41.0% (n=261/637) of all patients were receiving concomitant oral corticosteroids (mean dose: 6.1 mg/day prednisone or equivalent) as compared to 52.0% (n=331/637) at baseline (mean dose: of 7.4 mg/day). Likewise, 67.8% (n=432) used concomitant NSAIDs at week256 in comparison with 82.9% (n=528) of patients at baseline.

Radiographic progression.

A total of 465 patients (Group 1, n=120; Group 2, n=113; Group 3, n=120; Group 4, n=112) had radiographic data available at baseline, week104, and at least one post-week104 time point and were therefore included in the analysis for reading session 3. At week256, radiographic progression was low, with a mean change from baseline in vdH-mTSS for all patients of 1.36; mean changes among the treatment groups ranged from 0.60 to 2.28 (Table 2). Furthermore, approximately 60% of all patients had a change in vdH-mTSS ≤0 at week256, and 73% of patients had a change from baseline ≤0.5.

At baseline, the mean estimated annual rates of radiographic progression for Groups 1, 2, 3, and 4 were 8.44, 8.32, 9.75, and 6.76, respectively (mean duration of RA: Group 1, 2.9 years; Group 2, 4.1 years; Group 3, 3.5 years, Group 4, 3.6 years). Over the 5-year study, the mean annual rate of progression was 0.27 for all patients, and 0.46, 0.36, 0.14, and 0.12 for Groups 1, 2, 3, and 4, respectively.

Adverse events.

Six hundred sixteen patients received at least one dose of golimumab 50mg or 100mg and were included in the safety analysis. A total of 402 patients completed the safety follow-up through week268. The mean duration of follow-up for all golimumab-treated patients was 205 weeks, and the mean number of golimumab administrations was 46.9 (Table 4). The most common types of AEs by MedDRA classification were infections and infestations (n=463, 75.2%), gastrointestinal disorders (n=323, 52.4%), and musculoskeletal and connective tissue disorders (n=258, 41.9%). Commonly reported AEs are listed in Table 4 and include upper respiratory tract infection (n=181, 29.4%), nausea (n=121, 19.6%), bronchitis (n=102, 16.6%),

and increased alanine aminotransferase (n=99, 16.1%). Among all golimumab-treated patients, 73 (11.9%) had at least one injection site reaction through week268; none of these reactions were considered to be severe. Of the 28,866 golimumab injections administered, 258 (0.9%) were associated with an injection-site reaction.

Through week268, 204 patients (33.1%) had at least one SAE. Seventy-five patients (12.2%) had a serious infection the most common being pneumonia (n=14; 2.3%) (Table 4). Among all golimumab-treated patients, the incidence (95% CI) of serious infections per 100 patient-years of was 4.61 (3.80, 5.55). At baseline, 106 patients (16.6%) required treatment for latent TB. Through week268, 13 patients were diagnosed with active TB (golimumab 50mg: n=2; 100mg: n=11). The majority of these cases were in endemic countries (eg, Philippines, Chile, and Thailand). Ten of these patients had negative tuberculin and QuantiFERON testing at screening; the remaining patients were identified as having latent TB, completed the required treatment as specified in the protocol, and developed active TB several months after completing the treatment for latent TB. Eleven TB cases occurred before week104 and have been previously described.(4) The two cases that occurred after week104 were TB pleurisy and intestinal TB. There were no cases of disseminated TB or deaths resulting from TB in this study. Five opportunistic infections were reported through week268. Two were classified as serious infections (pneumonia legionella, n=1; *Pneumocystitis jiroveci* pneumonia, n=1), and three were classified as nonserious infections (esophageal candidiasis, n=2; aspergillosis, n=1).

Two patients experienced demyelination AEs (demyelination of the central nervous system and autoimmune demyelination); both patients were receiving golimumab 100mg+MTX. Both AEs were considered to be serious, and the patients discontinued study treatment. No cases of systemic lupus erythematosus were reported.

Among all patients who received golimumab, 21 reported a malignancy through week268. The incidence (95% CI) of all malignancies per 100 patients-years was 0.87 (0.54, 1.33) (Table 4). Two cases of lymphoma were reported among golimumab-treated patients (both patients received the 100mg dose); the incidence (95% CI) per 100 patient-years for lymphoma was 0.08 (0.01, 0.30).

Eight deaths occurred prior to week104 and have been previously described.(1, 4) An additional four deaths occurred after week104: two patients receiving golimumab 50mg+MTX (a 71-year-old woman, with a history of cigarette smoking, died from myocardial infarction, and a 50-year-old woman, with a history of chronic lung disease, hypertension, and cigarette smoking, died from unknown causes), one patient receiving golimumab 100mg+placebo (a 68-year-old woman died from hematemesis), and one patient receiving golimumab 100mg+MTX (a 61-year-old woman, with a history of hyperlipidemia, hypertension, and cigarette smoking, died of sepsis). Through week268, the incidence (95% CI) of death per 100 patient-years for all golimumab-treated patients was 0.49 (0.26, 0.86).

After discontinuing the study golimumab injections, a total of 47 patients received a commercial biologic (including commercial golimumab) after week 256. Six of these patients had an AE after receiving commercial golimumab; most AEs were similar to those reported during receipt of study drug during the trial. One of these six patients had an SAE (cellulitis).

Golimumab pharmacokinetics and immunogenicity. Serum trough golimumab concentrations were approximately dose proportional and were generally maintained through week256 for patients who did not have any changes in golimumab dose. Through week256, 57 (9.6%) golimumab-treated patients tested positive for antibodies to golimumab, and of these, 46 patients

(92.0%) were positive for neutralizing antibodies. Eight patients (14.0%) who were positive for antibodies to golimumab also had an injection site reaction; one reaction of moderate injection site erythema was classified as serious and led to discontinuation of study agent. Among the 538 patients who tested negative for antibodies to golimumab, 78 (14.5%) had an injection site reaction; none were serious or led to study discontinuation.

DISCUSSION

The GO-BEFORE trial evaluated the safety and efficacy of golimumab with and without MTX in MTX-naïve patients with active RA. Through 24 weeks, patients treated with golimumab 50mg or 100mg+MTX had substantial improvements in disease activity,(1) and these improvements were sustained through weeks 52 and 104.(4) Through 1 year, patients treated with golimumab+MTX had significantly less radiographic progression than did patients who received MTX monotherapy,(5) and progression was minimal in all treatment groups at week104, when all patients had been receiving golimumab.(4) Here we report the final clinical efficacy, radiographic, and safety findings through 5 years of the GO-BEFORE trial.

Approximately 66% of patients who were randomized at baseline continued study treatment through week252. Long-term completion rates through 5 years were approximately 46% - 49% in previous trials of other SC anti-TNF therapies in patients with RA who were MTX-naive.(18, 19) Among all randomized patients in the GO-BEFORE trial, 72.8% of patients had an ACR20 response, 54.6% had an ACR50 response, and 38.0% had an ACR70 response at week256 (when all patients were receiving golimumab), with no appreciable differences among the treatment groups. Additionally, over 80% of golimumab-treated patients had either a good or moderate DAS28-CRP response at week256. Golimumab-treated patients also had clinically

meaningful improvements in physical function as demonstrated by an overall mean improvement from baseline in HAQ-DI score of 0.57, and 72.7% of patients having an improvement ≥ 0.25. Radiographic progression was low through 5 years; the mean change in vdH-mTSS was 0.72 and 0.60 over 5 years in patients randomized to golimumab 50mg+MTX and 100mg+MTX, respectively, with nearly three-quarters of all patients having no progression (change in vdH-mTSS of ≤ 0.5).

The proportion of patients using oral corticosteroids and the median dose received decreased from baseline to week256. The proportion of patients using NSAIDs also decreased during the trial. These observations may suggest that reduced use of these concomitant medications could be achieved with golimumab treatment. However, it should be noted that the use of these medications was solely at the discretion of the investigator.

Safety findings through week268 were generally consistent with those reported through week104,(1, 4) The majority of cases of active TB occurred in patients receiving the 100-mg dose; however, it is difficult to compare the two doses (50 and 100mg) due to the treatment changes allowed through early escape and adjustments to golimumab and concomitant medications during the long-term extension. The incidences of serious infections, lymphoma, and deaths adjusted for patient-years of exposure for both golimumab doses were generally consistent with long-term data reported for other biologic anti-TNF agents from both randomized clinical trials(18-20) and observational studies.(21, 22)

Throughout the trial, infections were the most common type of AE and SAE; pneumonia was the most common type of serious infection (n=14; 2.3%). There were a total of 13 cases of active TB. All patients were screened for TB prior to study entry and had to either have negative

TB test results or initiate treatment for latent TB. The 13 cases of TB in the GO-BEFORE trial were considered to be new active infections and most were in areas with a high background rate of TB (eg, Philippines, Chile, and Thailand). Given the substantial number of patients who were enrolled from regions with a high TB incidence rate, the comprehensive screening procedures utilized in this trial may have contributed to a lower than expected rate of TB.(23) However, physicians should remain vigilant regarding the development of new TB infections. Five opportunistic infections were reported, including pneumonia legionella, *Pneumocystitis jiroveci* pneumonia, and esophageal candidiasis. A total of 12 deaths occurred through week268; no predominant cause of death was identified.

Among golimumab-treated patients, 21 malignancies were reported. Two cases of lymphoma occurred through week268, both in patients receiving golimumab 100mg, which corresponded to a SIR (95%CI) of 9.54 (1.16, 34.48). A previous registry analysis of more than 6,000 patients with RA did not show an increase in lymphoma risk with increasing duration of anti-TNF therapy.(24)

Throughout the trial, less than 1% of all golimumab injections were associated with an injection site reaction. The incidence of injection site reactions through week256 was similar between patients who tested positive for antibodies to golimumab (14.0%) and those who tested negative for antibodies to golimumab (14.5%).

A substantial portion (66%) of the patients who were enrolled and treated in the GO-BEFORE trial completed treatment with golimumab through week252. Interpretation of the long-term efficacy and safety results is limited by selection bias over time, although our use of an ITT analysis including all randomized patients may have mitigated this effect. The results

through 5 years of this study are also limited by the lack of a control group after week52, as well as possible confounding effects of concomitant medications and golimumab dose changes that were permitted during the long-term extension. The overall findings of the GO-BEFORE trial indicate that the majority of patients remained in the trial through 5 years and had sustained improvements in clinical and radiographic outcomes with long-term safety results consistent with other anti-TNF therapies.

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Drs. Zhou, Leu, and Hsia are employees of Janssen Research & Development, LLC, and own stock in Johnson & Johnson, of which Janssen Research & Development, LLC, is a wholly-owned subsidiary. Dr. Han is an employee of Janssen Global Services, LLC, and owns stock in Johnson & Johnson. Mr. Gathany was an employee of Janssen Global Services, LLC, at the time this work was performed and owns stock in Johnson & Johnson.

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FIGURE LEGENDS

Figure 1. The proportions of patients with an ACR20 (A) or ACR50 (B) response through week 256. ACR20/50, ≥ 20%/50% improvement in the American College of Rheumatology criteria; MTX, methotrexate

Table 1. Patients who discontinued study agent through Week 252.

	Placebo + MTX	Golimumab 100mg+Placebo	Golimumab + MTX 50 mg	Golimumab + MTX 100 mg	Golimumab + MTX Combined	Total
Patients randomized, n	160	159	159	159	318	637
Patients treated, n	160	157	158	159	317	634
Patients who discontinued study agent	50 (31.3)	56 (35.7)	49 (31.0)	60 (37.7)	109 (34.4)	215 (33.9)
Reason for discontinuation						
Initiated protocol prohibited medication(s)	0	0	0	0	0	0
Adverse event	21 (13.1)	32 (20.4)	24 (15.2)	34 (21.4)	58 (18.3)	111 (17.5)
Worsening of RA	0	3 (1.9)	0	1 (0.6)	1 (0.3)	4 (0.6)
Unsatisfactory therapeutic effect	5 (3.1)	6 (3.8)	5 (3.2)	7 (4.4)	12 (3.8)	23 (3.6)
Lost to follow-up	3 (1.9)	4 (2.5)	7 (4.4)	6 (3.8)	13 (4.1)	20 (3.2)
Death	0	3 (1.9)	3 (1.9)	2 (1.3)	5 (1.6)	8 (1.3)
Other	21 (13.1)	11 (7.0)	10 (6.3)	11 (6.9)	21 (6.6)	53 (8.4)

Data presented as n (%) unless otherwise noted. MTX, methotrexate; RA, rheumatoid arthritis

Table 2. Clinical efficacy, patient-reported outcomes, and radiographic results at week 256 using the ITT analysis.

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX 50 mg	Golimumab + MTX 100 mg	Golimumab + MTX Combined	Total
Clinical efficacy[a]						
Patients randomized, n	160	159	159	159	318	637
ACR20	109 (68.1)	117 (73.6)	114 (71.7)	124 (78.0)	238 (74.8)	464 (72.8)
ACR50	80 (50.0)	83 (52.2)	88 (55.3)	97 (61.0)	185 (58.2)	348 (54.6)
ACR70	61 (38.1)	59 (37.1)	57 (35.8)	65 (40.9)	122 (38.4)	242 (38.0)
DAS28-CRP response[b]	128 (80.0)	138 (86.8)	131 (82.4)	139 (87.4)	270 (84.9)	536 (84.1)
DAS28-CRP < 2.6	67 (41.9)	65 (40.9)	70 (44.0)	74 (46.5)	144 (45.3)	276 (43.3)
DAS28-CRP ≤3.2	86 (53.8)	90 (56.6)	91 (57.2)	94 (59.1)	185 (58.2)	361 (56.7)
SDAI ≤3.3	47 (29.4)	40 (25.2)	42 (26.4)	46 (28.9)	88 (27.7)	175 (27.5)
CDAI ≤2.8	51 (31.9)	40 (25.2)	44 (27.7)	49 (30.8)	93 (29.2)	184 (28.9)
Boolean remission	30 (18.8)	32 (20.1)	38 (23.9)	35 (22.0)	73 (23.0)	135 (21.2)
Improvement from baseline in HAQ-DI, mean± SD	0.68 ± 0.69	0.70 ± 0.74	0.65 ± 0.70	0.80 ± 0.72	0.72 ± 0.71	0.70 ± 0.71
Patients with improvement in HAQ-DI ≥0.25	120 (75.0)	111 (69.8)	110 (69.2)	122 (76.7)	232 (73.0)	463 (72.7)
Patients with HAQ-DI score ≤0.5, n (%)	61 (38.1)	62 (39.0)	72 (45.3)	79 (49.7)	151 (47.5)	274 (43.0)
Radiographic results						
Change from baseline, mean ± SD[c]						
At week 208	2.18 ± 6.53	1.74 ± 6.71	0.68 ± 3.59	0.54 ± 2.72	0.61 ± 3.19	1.29 ± 5.23
At week 256	2.28 ± 6.65	1.81 ± 6.82	0.72 ± 3.67	0.60 ± 2.86	0.66 ± 3.30	1.36 ± 5.34
Change from week 104, mean ± SD[c]						
At week 208	0.68 ± 3.19	0.79 ± 4.39	0.43 ± 1.82	0.57 ± 2.36	0.50 ± 2.10	0.62 ± 3.08
At week 256	0.78 ± 3.40	0.87 ± 4.64	0.47 ± 2.05	0.64 ± 2.64	0.55 ± 2.35	0.69 ± 3.31
Patients with change in total vdH-mTSS ≤0 at week256	65 (54.2)	64 (56.6)	75 (62.5)	73 (65.2)	148 (63.8)	277 (59.6)
Patients with change in total vdH-mTSS ≤ 0.5 at week256	78 (65.0)	82 (72.6)	92 (76.7)	89 (79.5)	181 (78.0)	341 (73.3)
Estimated annual rate of progression at baseline, mean ± SD	8.44 ± 19.37	8.32 ± 27.49	9.75 ± 24.86	6.76 ± 14.73	8.31 ± 20.61	8.34 ± 22.14
Estimated annual rate of progression at week 256, mean ± SD	0.46 ± 1.34	0.36 ± 1.36	0.14 ± 0.74	0.12 ± 0.57	0.13 ± 0.66	0.27 ± 1.07

Data presented as n (%) unless otherwise noted. [a]Modified intent-to-treat (ITT) analysis in which the following rules were applied: 1) missing baseline values for continuous variables were replaced with the median value, and last-observation-carried-forward methodology was applied to missing post-baseline values, and 2) patients who discontinued study agent due to unsatisfactory therapeutic effect were considered to be nonresponders. [b]Good or moderate response as defined by the European League Against Rheumatism.(14) [c]Includes patients who had vdH-mTSS at weeks 0 and 104 and at least one score post-week 104.

MTX, methotrexate; ACR20, ≥ 20% improvement in the American College of Rheumatology criteria; DAS28-CRP, 28-joint count disease activity score using C-reactive protein; SDAI, simplified disease activity index; CDAI, clinical disease activity index; HAQ-DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation; vdH-mTSS, van der Heijde modification of the total Sharp score

Table 3. Improvements in health-related quality of life and productivity at week 256.

			Golimumab + MTX			
	Placebo + MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Total
SF-36 PCS Score						
Improvement from baseline, mean ± SD	11.3 ± 10.5	11.6 ± 11.0	11.9 ± 11.1	11.9 ± 10.0	11.9 ± 10.6	11.7 ± 10.7
Patients with score ≥ 50, n (%)	28 (25.7)	28 (26.9)	33 (30.6)	28 (28.3)	61 (29.5)	117 (27.9)
SF-36 MCS Score						
Improvement from baseline, mean ± SD	4.5 ± 12.6	7.6 ± 12.0	5.7 ± 12.1	6.4 ± 11.9	6.1 ± 12.0	6.0 ± 12.2
Patients with score ≥ 50, n (%)	47 (43.1)	51 (49.0)	55 (50.9)	44 (44.4)	99 (47.8)	197 (46.9)
Improvement in the impact of disease on productivity, mean ± SD	3.2 ± 3.1	4.3 ± 4.3	3.9 ± 2.7	4.2 ± 2.8	4.0 ± 2.8	3.9 ± 3.3

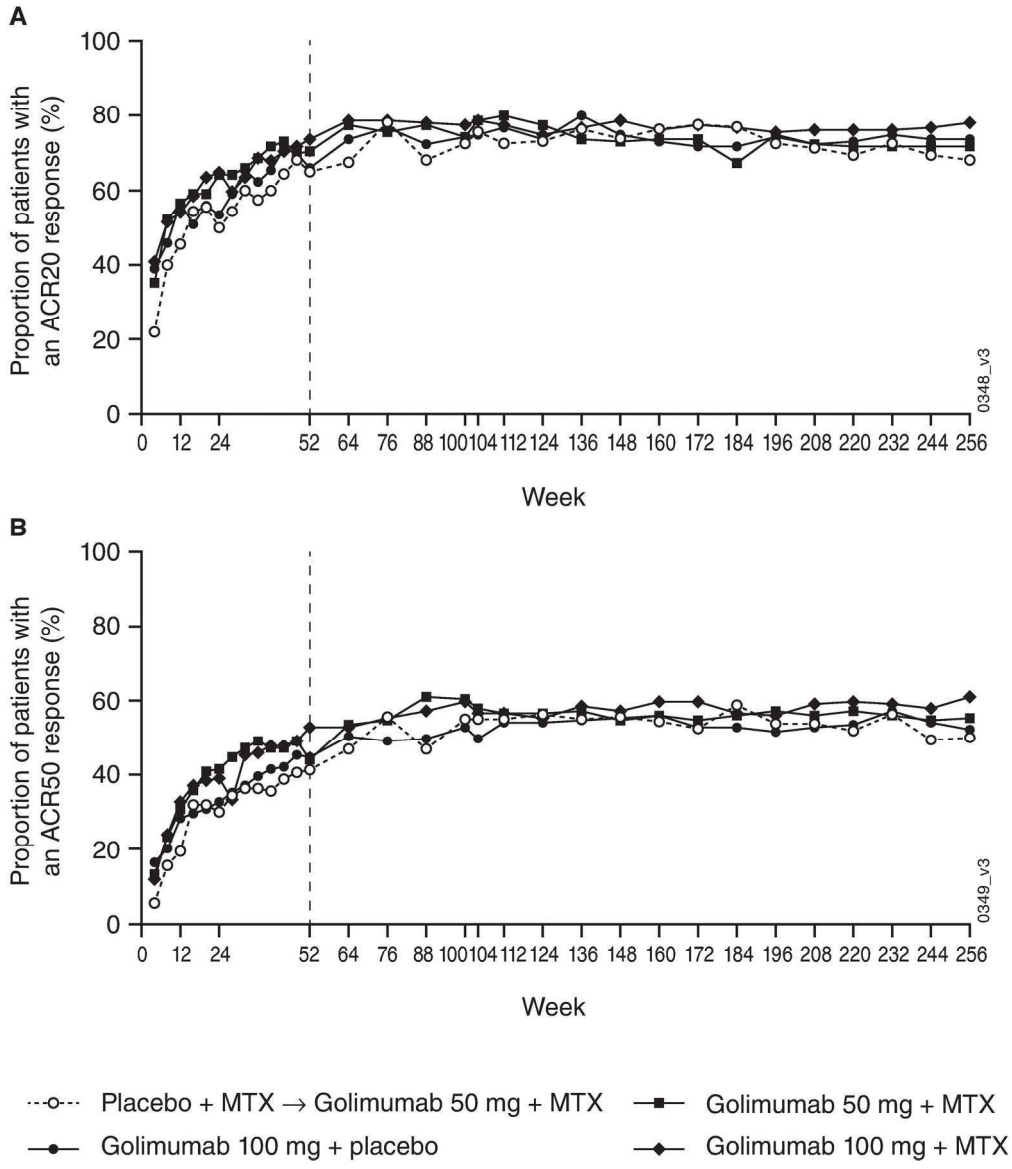
MTX, methotrexate; SF-36 PCS/MCS; 36-item short form health survey physical/mental component summary; SD, standard deviation

Table 4. Adverse events through week 268.

	50 mg + MTX only	50 mg and 100 mg + Placebo or MTX	Golimumab 100 mg + Placebo or MTX	Total Golimumab
Treated patients, n	172	201	243	616
Mean duration of follow-up, weeks	182.9	238.7	192.7	205.0
Mean number of administrations	41.5	54.9	44.0	46.9
Patients with ≥1 AE	161 (93.6)	187 (93.0)	234 (96.3)	582 (94.5)
Patients who discontinued due to AEs	30 (17.4)	14 (7.0)	67 (27.6)	111 (18.0)
Common AEs (≥10%)				
Upper respiratory tract infection	46 (26.7)	72 (35.8)	63 (25.9)	181 (29.4)
Nausea	22 (12.8)	44 (21.9)	55 (22.6)	121 (19.6)
Bronchitis	27 (15.7)	34 (16.9)	41 (16.9)	102 (16.6)
Alanine aminotransferase increased	31 (18.0)	32 (15.9)	36 (14.8)	99 (16.1)
Cough	19 (11.0)	29 (14.4)	37 (15.2)	85 (13.8)
Patients with ≥1 injection site reaction	15 (8.7)	19 (9.5)	39 (16.0)	73 (11.9)
Patients with ≥1 SAE	55 (32.0)	55 (27.4)	94 (38.7)	204 (33.1)
Pneumonia	5 (2.9)	5 (2.5)	4 (1.6)	14 (2.3)
Pulmonary tuberculosis	1 (0.6)	1 (0.5)	4 (1.6)	6 (1.0)
Breast cancer	1 (0.6)	0	3 (1.2)	4 (0.6)
Uterine leiomyoma	1 (0.6)	2 (1.0)	1 (0.4)	4 (0.6)
Basal cell carcinoma	0	2 (1.0)	1 (0.4)	3 (0.5)
Hodgkin's disease	0	0	2 (0.8)	2 (0.3)
Non-small cell lung cancer	2 (1.2)	0	0	2 (0.3)
Patients with ≥1 serious infection	17 (9.9)	25 (12.4)	33 (13.6)	75 (12.2)
Incidence/100 patient-years	3.97	3.68	6.00	4.61
(95%CI)	(2.54, 5.90)	(2.55, 5.15)	(4.50, 7.82)	(3.80, 5.55)
Pneumonia	5 (2.9)	5 (2.5)	4 (1.6)	14 (2.3)
Herpes zoster	0	3 (1.5)	2 (0.8)	5 (0.8)
Pulmonary tuberculosis	1 (0.6)	1 (0.5)	3 (1.2)	5 (0.8)
Sepsis	0	1 (0.5)	3 (1.2)	4 (0.6)
Urinary tract infection	1 (0.6)	2 (1.0)	1 (0.4)	4 (0.6)
Appendicitis	0	2 (1.0)	1 (0.4)	3 (0.5)
Upper respiratory tract infection	1 (0.6)	0	2 (0.8)	3 (0.5)
Malignancies				
Lymphoma	0	0	2 (0.8)	2 (0.3)
Incidence/100 patient-years	0.00	0.00	0.22	0.08
(95% CI)	(0.00, 0.50)	(0.00, 0.32)	(0.03, 0.80)	(0.01, 0.30)
SIR (95%CI)	0.00 (0.00, 18.91)	0.00 (0.00, 12.15)	9.54 (1.16, 34.48)	3.26 (0.39, 11.76)
Nonmelanoma skin cancers	0	3 (1.5)	2 (0.8)	5 (0.8)
Incidence/100 patient-years	0.00	0.33	0.22	0.21
(95% CI)	(0.00, 0.50)	(0.07, 0.95)	(0.03, 0.80)	(0.07, 0.48)
Other malignancies	8 (4.7)	2 (1.0)	4 (1.6)	14 (2.3)
Incidence/100 patient-years	1.33	0.22	0.44	0.58
(95% CI)	(0.57, 2.62)	(0.03, 0.78)	(0.12, 1.14)	(0.32, 0.97)
SIR (95%CI)*	2.21 (0.95, 4.35)	0.36 (0.04, 1.28)	0.85 (0.23, 2.18)	1.00 (0.55, 1.68)
Total Malignancies	8 (4.7)	5 (2.5)	8 (3.3)	21 (3.4)
Incidence/100 patient-years	1.33	0.54	0.89	0.87
(95% CI)	(0.57, 2.62)	(0.18, 1.27)	(0.38, 1.75)	(0.54, 1.33)
SIR (95%CI)*	2.12 (0.91, 4.18)	0.34 (0.04, 1.23)	1.23 (0.45, 2.67)	1.10 (0.63, 1.79)
Deaths	6 (3.5)	0 (0.0)	6 (2.5)	12 (1.9)
Incidence/100 patient-years	0.99	0.00	0.67	0.49
(95% CI)	(0.36, 2.16)	(0.00, 0.32)	(0.24, 1.45)	(0.26, 0.86)

Data presented as n (%) unless otherwise noted. MTX, methotrexate; AE, adverse event; CI, confidence interval; SAE, serious adverse event, SIR, standardized incidence ratio.

*The SIR is in comparison with the expected number of events in the SEER database (2004), which does not include nonmelanoma skin cancers.



The proportions of patients with an ACR20 (A) or ACR50 (B) response through week 256. ACR20/50, ≥ 20%/50% improvement in the American College of Rheumatology criteria; MTX, methotrexate
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Supplemental Table 1. Actual treatment received through week 256

			Golimumab + MTX			
	Placebo + MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Total
Patients randomized	160	159	159	159	318	637
Patients treated	160	157	158	159	317	634
Treatment received						
Placebo + MTX	160 (100.0%)	0	0	0	0	160 (25.2%)
Placebo + MTX → golimumab 50 mg + MTX (early escaped at Week 28)	28 (17.5%)	0	0	0	0	28 (4.4%)
Dose escalated to 100 mg + MTX (LTE)[a]	15 (9.4%)	0	0	0	0	15 (2.4%)
Dose decreased to 50 mg + MTX (LTE)[b]	1 (0.6%)	0	0	0	0	1 (0.2%)
Placebo + MTX → golimumab 50 mg + MTX (crossover (Week 52-252))	113 (70.6%)	0	0	0	0	113 (17.8%)
Dose escalated to 100 mg + MTX (LTE)[a]	49 (30.6%)	0	0	0	0	49 (7.7%)
Dose decreased to 50 mg + MTX (LTE)[b]	20 (12.5%)	0	0	0	0	20 (3.2%)
Golimumab 100 mg + Placebo	0	157 (100.0%)	0	0	0	157 (24.8%)
Golimumab 100 mg + Placebo → golimumab 100 mg + MTX (early escaped at Week 28)	0	22 (14.0%)	0	0	0	22 (3.5%)
Dose decreased to 50 mg + MTX (LTE)[b]	0	9 (5.7%)	0	0	0	9 (1.4%)
Golimumab 100mg + Placebo did not early escape at Week 28	0	135 (86.0%)	0	0	0	135 (21.3%)
Dose decreased to 50 mg + Placebo (LTE)[b]	0	29 (18.5%)	0	0	0	29 (4.6%)
Golimumab 50 mg + MTX	0	0	158 (100.0%)	0	158 (49.8%)	158 (24.9%)
Golimumab 50 mg + MTX did not early escape at Week 28	0	0	138 (87.3%)	0	138 (43.5%)	138 (21.8%)

Dose escalated to 100 mg + MTX (LTE)[a]	0	0	42 (26.6%)	0	42 (13.2%)	42 (6.6%)
Dose decreased to 50 mg + MTX (LTE)[b]	0	0	12 (7.6%)	0	12 (3.8%)	12 (1.9%)
Golimumab 50 mg + MTX → 100 mg + MTX (early escaped at Week 28)	0	0	20 (12.7%)	0	20 (6.3%)	20 (3.2%)
Dose decreased to 50 mg + MTX (LTE)[b]	0	0	4 (2.5%)	0	4 (1.3%)	4 (0.6%)
Golimumab 100 mg + MTX	0	0	0	159 (100.0%)	159 (50.2%)	159 (25.1%)
Dose decreased to 50 mg + MTX (LTE)[b]	0	0	0	35 (22.0%)	35 (11.0%)	35 (5.5%)

[a] Per protocol, after the week 52 database lock and unblinding the sites to treatment (June 4, 2008), the golimumab dose could increase from 50 mg to 100 mg at the discretion of the investigator.

[b] Based on protocol amendment 4, all patients receiving golimumab 100 mg as of April 16, 2010 could decrease from 100 mg to 50 mg at the discretion of the investigator.

MTX, methotrexate; LTE, long-term extension

Supplemental Table 2. Clinical efficacy results at week 256 (observed data analysis).

			Golimumab + MTX			
	Placebo + MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined	Total
Clinical efficacy						
ACR20	87 (79.1)	89 (84.8)	92 (85.2)	87 (88.8)	179 (86.9)	355 (84.3)
ACR50	68 (61.8)	68 (64.8)	72 (66.7)	73 (74.5)	145 (70.4)	281 (66.7)
ACR70	53 (48.2)	47 (44.8)	47 (43.5)	52 (53.1)	99 (48.1)	199 (47.3)
DAS28-CRP response[a]	96 (90.6)	98 (95.1)	99 (93.4)	94 (96.9)	193 (95.1)	387 (93.9)
DAS28-CRP < 2.6	56 (52.8)	50 (48.5)	59 (55.7)	60 (61.9)	119 (58.6)	225 (54.6)
SDAI ≤3.3	42 (39.6)	33 (32.0)	35 (33.0)	38 (38.8)	73 (35.8)	148 (35.8)
CDAI ≤2.8	45 (41.3)	33 (31.1)	37 (34.3)	39 (39.8)	76 (36.9)	154 (36.6)
DAS28-CRP ≤3.2	70 (66.0)	69 (67.0)	76 (71.0)	70 (71.4)	146 (71.2)	285 (68.8)
Improvement from baseline in HAQ-DI, mean ± SD	0.76 ± 0.64	0.82 ± 0.67	0.73 ± 0.69	0.91 ± 0.68	0.82 ± 0.69	0.80 ± 0.67
Patients with improvement in HAQ-DI ≥0.25	90 (82.6)	86 (82.7)	78 (73.6)	83 (83.8)	161 (78.5)	337 (80.6)

Data presented as n (%). [a] Good or moderate response as defined by the European League Against Rheumatism. MTX, methotrexate; ACR20/50/70, ≥ 20%/50%/70% improvement in American College of Rheumatology criteria; DAS28-CRP, 28-joint count disease activity score using C-reactive protein; SDAI, simplified disease activity index CDAI, clinical disease activity index; HAQ-DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation