

# Efficacy and Safety of Subcutaneous Golimumab in Methotrexate-Naive Patients With Rheumatoid Arthritis: Five-Year Results of a Randomized Clinical Trial

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**Objective.** To evaluate the safety and efficacy of golimumab through 5 years in adults with active rheumatoid arthritis (RA) who had not previously received methotrexate (MTX).

**Methods.** In the GO-BEFORE study, 637 MTX-naive adult patients with active RA were randomized (1:1:1:1) to placebo + MTX (group 1), golimumab 100 mg + placebo (group 2), golimumab 50 mg + MTX (group 3), or golimumab 100 mg + MTX (group 4). Inadequate responders in groups 1, 2, and 3 entered early escape at week 28 to golimumab 50 mg + MTX, golimumab 100 mg + MTX, or golimumab 100 mg + MTX, respectively; remaining patients in group 1 could cross over to golimumab 50 mg + MTX at week 52. Assessments included the American College of Rheumatology 20%/50%/70% improvement criteria (ACR20/50/70) response, the Disease Activity Score in 28 joints (DAS28) using C-reactive protein (CRP) level, and the modified Sharp/van der Heijde score (SHS). Efficacy was analyzed using an intent-to-treat (ITT) analysis. Pharmacokinetics and immunogenicity were evaluated at selected visits.

**Results.** A total of 422 patients completed golimumab treatment through week 256. At week 256, 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 week 256, and the overall mean change from baseline in SHS was 1.36. Serum trough golimumab concentrations were approximately dose proportional and maintained through week 256. Antibodies to golimumab occurred in 9.6% of patients through week 256. Infections were the most common type of adverse event (AE); 204 of 616 patients (33.1%) had  $\geq 1$  serious AE.

**Conclusion.** Clinical efficacy with golimumab treatment was maintained through week 256 of the GO-BEFORE trial of MTX-naive RA patients. No unexpected AEs occurred; safety results through 5 years are consistent with earlier reports.

## 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

Supported by Janssen Research & Development, LLC, a Johnson & Johnson pharmaceutical company, and Merck/Schering-Plough.

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## Significance & 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.

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 (50 mg or 100 mg) + MTX had significantly greater improvements in the signs and symptoms of RA than those treated with MTX monotherapy. These improvements were observed at week 24 (1) and were maintained through 2 years (4). In addition, golimumab + MTX-treated patients 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.

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Dr. Emery has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from AbbVie, Bristol Myers-Squibb, Janssen Research & Development, MSD, Novartis, Pfizer, Roche, Samsung, and UCB. Dr. Fleischmann has received consulting fees and grant support from Janssen Research & Development (less than \$10,000). Dr. Strusberg has received speaking fees from AstraZeneca, Bristol Myers-Squibb, and Janssen Research & Development (less than \$10,000 each). Dr. Nash has received consulting fees from Janssen Research & Development (less than \$10,000). Dr. Amante has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from AstraZeneca, Janssen Research & Development, MSD, Novartis, Pfizer, Roche, and United Laboratories. Dr. Park has received consulting fees from Celltrion (more than \$10,000). Dr. Pons-Estel has served on advisory boards for GlaxoSmithKline and Wyeth. Dr. Han, Mr. Gathany, Mr. Xu, and Drs. Zhou, Leu, and Hsia own stock in Johnson & Johnson, of which Janssen Research & Development is a wholly owned subsidiary.

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Submitted for publication May 22, 2015; accepted in revised form October 6, 2015.

## 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 100 mg + placebo (group 2), golimumab 50 mg + MTX (group 3), or golimumab 100 mg + MTX (group 4); injections were administered at baseline and every 4 weeks. Active RA was defined as  $\geq 4$  swollen joints,  $\geq 4$  tender joints, and at least 2 of the following criteria: C-reactive protein (CRP) level of  $\geq 1.5$  mg/dl or erythrocyte sedimentation rate  $\geq 28$  mm/hour using the Westergren method; morning stiffness lasting  $\geq 30$  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 posteroanterior 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  $\geq 1.5$  mg/dl). Placebo and golimumab injections were administered at baseline and every 4 weeks. At week 28, 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 50-mg injections, patients in group 2 initiated concomitant MTX therapy while continuing golimumab 100-mg injections, and patients in group 3 increased their golimumab dose to 100 mg; 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 week 52.

The long-term extension began with the week-52 visit and continued through week 268 (5 years). At week 52, patients in group 1 who did not have any swollen or tender joints continued MTX monotherapy; patients with at least 1 swollen or tender joint were switched from placebo injections to golimumab 50 mg. Patients in groups 2, 3, and 4 continued the treatment they were receiving at week 52. The blind was maintained until the week-52 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 50 mg, and a 1-time golimumab dose increase to 100 mg or decrease to 50 mg was permitted (including patients who had dose-escalated to 100 mg). Additionally, MTX therapy could be initiated or adjusted during the long-term extension period. Concomitant therapy with nonsteroidal antirheumatic drugs (NSAIDs), corticosteroids, or other analgesics for RA could also be adjusted at the investigator's discretion. The final study golimumab injection was at week 252. After week 256, patients transitioned to

Table 1. Patients who discontinued study agent through week 252\*

	Placebo + MTX	Golimumab 100 mg + placebo	Golimumab + MTX			Total
			50 mg	100 mg	Combined	
Patients randomized, no.	160	159	159	159	318	637
Patients treated, no.	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 followup	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)

\* Values are the number (percentage) unless indicated otherwise. MTX = methotrexate; RA = rheumatoid arthritis.

standard-of-care treatment for RA, including commercially available biologic agents.

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 week 256, with an additional assessment at week 104. Disease activity was assessed using the American College of Rheumatology (ACR) criteria (6) and the European League Against Rheumatism Disease Activity Score in 28 joints (DAS28) using CRP level (7). Post hoc efficacy assessments included the Simplified Disease Activity Index (SDAI) (8) and the Clinical Disease Activity Index (CDAI) (9).

Physical function was evaluated using the Health Assessment Questionnaire (HAQ) disability index (DI) (10). Normal physical function was defined as a HAQ DI score  $\leq 0.5$ , and a minimal clinically important difference (MCID) was defined as an improvement  $\geq 0.25$  (11). Health-related quality of life was evaluated using the physical component summary (PCS) and mental component summary (MCS) scores of the Short Form 36-item (SF-36) health survey (12). The impact of disease on productivity was assessed using a visual analog scale (0–10 cm) at baseline and at week 256.

Radiographs of the hands and feet were obtained at weeks 52, 104, 208, and 256 during the long-term extension; results through week 104 have been previously reported (1,4). Data from patients with radiographs at baseline, week 104, and at least 1 radiograph after week 104 were included in the current analysis. As previously detailed (5), radiographs were scored by 2 independent readers and an adjudicator using the modified Sharp/van der Heijde score (SHS) (13).

Patients were monitored through week 268 for adverse events (AEs). Routine laboratory analyses were performed through week 256. 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 validated immunoassays (14).

**Statistical analysis.** Descriptive statistics (e.g., 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 end points (ACR components and DAS28-CRP), observed data were used through week 256 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 level stratum ( $< 1.5$  mg/dl or  $\geq 1.5$  mg/dl), and the last observation carried forward (LOCF) methodology was applied to missing postbaseline 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 (ACR20/50/70 response) (6), a moderate or good DAS28-CRP response (7,15), a DAS28-CRP  $< 2.6$ , a DAS28-CRP  $\leq 3.2$ , an MCID in HAQ DI score, and a HAQ DI score  $\leq 0.5$  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 week 256, as well as the proportions of patients with normal SF-36 PCS or MCS scores (score  $\geq 50$ ). In the post hoc analysis, the proportions of patients who achieved remission, as defined by an SDAI score  $\leq 3.3$  (16), a CDAI score  $\leq 2.8$  (16), or Boolean definition (17) were also determined.

Radiographic data through week 256 were summarized by randomized treatment group and included all patients who had radiographs at weeks 0, 104, and at least 1 radiograph

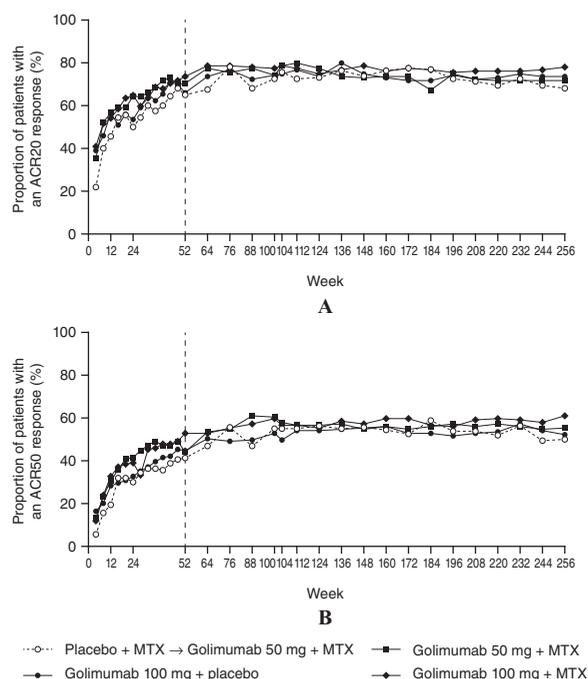
**Table 2. Clinical efficacy, patient-reported outcomes, and radiographic results at week 256 using the ITT analysis\***

	Placebo + MTX	Golimumab 100 mg + placebo	Golimumab + MTX			Total
			50 mg	100 mg	Combined	
Clinical efficacy†						
Patients randomized, no.	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‡	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 ≤0.5	61 (38.1)	62 (39.0)	72 (45.3)	79 (49.7)	151 (47.5)	274 (43.0)
Radiographic results						
SHS change from baseline, mean ± SD§						
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
SHS change from week 104, mean ± SD§						
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 SHS ≤0 at week 256	65 (54.2)	64 (56.6)	75 (62.5)	73 (65.2)	148 (63.8)	277 (59.6)
Patients with change in total SHS ≤0.5 at week 256	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
* Values are the number (percentage) unless indicated otherwise. ITT = intent-to-treat; MTX = methotrexate; ACR20/50/70 = American College of Rheumatology criteria for 20%/50%/70% improvement; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; DI = disability index; SHS = modified Sharp/van der Heijde score.						
† Modified 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 postbaseline values, and 2) patients who discontinued study agent due to unsatisfactory therapeutic effect were considered to be nonresponders.						
‡ Good or moderate response as defined by the European League Against Rheumatism (14).						
§ Includes patients who had an SHS at weeks 0 and 104 and at least 1 score after week 104.						

after week 104. Changes from baseline to week 208 and week 256 in the SHS are reported; missing postbaseline values were replaced using the LOCF methodology. Among patients with an SHS score at baseline and week 256, annual rates of progression at baseline and 5 years were determined using the SHS score divided by RA duration for each patient at baseline and the change in SHS over 5 years.

Cumulative safety data are reported for all patients who received at least 1 administration of golimumab through week 268. AEs and serious AEs 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 1 treatment group. AEs were summarized through week 268, with the

exception of those that occurred after receipt of any commercial biologic agent (including commercial golimumab). Patients who received commercially available biologic treatment after discontinuing study golimumab, yet who remained in the study, had AEs reported through week 268, but these AEs were excluded from the safety summaries. The rates per 100 patient-years and 95% confidence intervals (95% 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.



**Figure 1.** The proportions of patients with A) American College of Rheumatology 20% improvement criteria (ACR20) response or B) ACR50 response through week 256. MTX = methotrexate.

## 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 ( $n = 159$ ; see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22759/abstract>). Eighty-nine patients (group 1,  $n = 28$ ; group 2,  $n = 22$ ; group 3,  $n = 20$ ; and group 4,  $n = 19$ ) met the early escape criteria at week 28 (4). Through week 104, 140 patients discontinued the SC study agent, with AEs being the most common reason (4). A total of 215 patients (33.9%) discontinued the study agent through week 252; 111 (17.5%) discontinued due to an AE, including worsening of RA ( $n = 4$ , 0.6%), and 23 patients (3.6%) discontinued due to unsatisfactory therapeutic effect (Table 1). A total of 402 patients (63.4%) completed the safety followup through week 268.

Through week 256, a total of 616 patients received at least 1 administration of golimumab. Of these, 172 received only the 50-mg dose, 243 received only the 100-mg dose, and 201 received at least 1 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 week 256, 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 week 52, ACR20 and ACR50 response rates

were maintained for all treatment groups through week 256 (Figure 1). Additionally, 84.1% of all patients had either a good or moderate DAS28-CRP response at week 256, and 43.3% of patients had a DAS28-CRP  $< 2.6$ . Approximately 28% of all patients were in remission at week 256 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 week 256. Additionally, at week 256, 72.7% of all patients had an improvement from baseline  $\geq 0.25$ , and 43.0% achieved normal physical function (HAQ DI  $\leq 0.5$ ) (Table 2) compared with 9.1% (58 of 637) who had a normal HAQ DI score at baseline. The results of the protocol-specified efficacy analysis were consistent with this modified ITT analysis (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22759/abstract>).

A total of 101 patients had an increase in golimumab dose from 50 mg to 100 mg during the long-term extension (after week 52), and of these, 100 patients had  $\geq 12$  weeks of followup available. Among these patients, 84 did not have a DAS28-CRP  $< 2.6$  immediately prior to dose escalation, and 68 did not have a score  $\leq 3.2$  prior to dose escalation. Both of these subgroups had a mean  $\pm$  SD improvement in DAS28-CRP of  $1.0 \pm 1.1$  at 12 weeks after dose escalation.

Improvements from baseline to week 256 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 week 256, 27.9% had a normal (score  $\geq 50$ ) SF-36 PCS score, and 46.9% had a normal SF-36 MCS score at week 256 (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 week 256 in the impact of disease on productivity ranged from 3.2–4.3 among the treatment groups.

At week 256, 41.0% ( $n = 261$  of 637) of all patients were receiving concomitant oral corticosteroids (mean dosage: 6.1 mg/day prednisone or equivalent) compared with 52.0% ( $n = 331$  of 637) at baseline (mean dose: 7.4 mg/day). Likewise, 67.8% ( $n = 432$ ) used concomitant NSAIDs at week 256 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,  $n = 120$ ; and group 4,  $n = 112$ ) had radiographic data available at baseline, week 104, and at least 1 radiograph after the week-104 time point and were therefore included in the analysis for reading session 3. At week 256, radiographic progression was low, with a mean change from baseline in SHS 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 SHS  $\leq 0$  at week 256, and 73% of patients had a change from baseline  $\leq 0.5$ .

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, and group 4,

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

	Placebo + MTX	Golimumab 100 mg + placebo	Golimumab + MTX			Total
			50 mg	100 mg	Combined	
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, no. (%)	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, no. (%)	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 = Short Form 36 health survey; PCS = physical component summary; MCS = mental component summary.

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.

**AEs.** A total of 616 patients received at least 1 dose of golimumab 50 mg or 100 mg and were included in the safety analysis, and 402 patients completed the safety followup through week 268. The mean duration of followup 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 the Medical Dictionary for Regulatory Activities 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 1 injection site reaction through week 268; 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 week 268, 204 patients (33.1%) had at least 1 serious AE. 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 was 4.61 (3.80–5.55). At baseline, 106 patients (16.6%) required treatment for latent TB. Through week 268, 13 patients were diagnosed with active TB (golimumab 50 mg: n = 2; 100 mg: n = 11). The majority of these cases were in endemic countries (e.g., 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 week 104 and have been previously described (4). The 2 cases that occurred after week 104 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 week 268. Two were classified as serious infections (pneumonia legionella, n = 1; *Pneumocystis jiroveci* pneumonia, n = 1), and 3 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 100 mg + 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 week 268. The incidence (95% CI) of all malignancies per 100 patient-years was 0.87 (0.54–1.33) (Table 4). Two cases of lymphoma were reported among golimumab-treated patients (both patients received the 100-mg dose); the incidence (95% CI) per 100 patient-years for lymphoma was 0.08 (0.01–0.30).

Eight deaths occurred prior to week 104 and have been previously described (1,4). An additional 4 deaths occurred after week 104: two patients receiving golimumab 50 mg + 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), 1 patient receiving golimumab 100 mg + placebo (a 68-year-old woman died from hematemesis), and 1 patient receiving golimumab 100 mg + MTX (a 61-year-old woman, with a history of hyperlipidemia, hypertension, and cigarette smoking, died of sepsis). Through week 268, 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 agent (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 6 patients had a serious AE (cellulitis).

#### Golimumab pharmacokinetics and immunogenicity.

Serum trough golimumab concentrations were approximately dose proportional and were generally maintained through week 256 for patients who did not have any changes in goli-

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, no.	172	201	243	616
Mean duration of followup, weeks	182.9	238.7	192.7	205.0
Mean number of administrations	41.5	54.9	44.0	46.9
Patients with $\geq 1$ 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 ( $\geq 10\%$ )				
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 $\geq 1$ injection site reaction	15 (8.7)	19 (9.5)	39 (16.0)	73 (11.9)
Patients with $\geq 1$ 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 $\geq 1$ serious infection	17 (9.9)	25 (12.4)	33 (13.6)	75 (12.2)
Incidence per 100 patient-years (95% CI)	3.97 (2.54–5.90)	3.68 (2.55–5.15)	6.00 (4.50–7.82)	4.61 (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 per 100 patient-years (95% CI)	0.00 (0.00–0.50)	0.00 (0.00–0.32)	0.22 (0.03–0.80)	0.08 (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 per 100 patient-years (95% CI)	0.00 (0.00–0.50)	0.33 (0.07–0.95)	0.22 (0.03–0.80)	0.21 (0.07–0.48)
Other malignancies	8 (4.7)	2 (1.0)	4 (1.6)	14 (2.3)
Incidence per 100 patient-years (95% CI)	1.33 (0.57–2.62)	0.22 (0.03–0.78)	0.44 (0.12–1.14)	0.58 (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 per 100 patient-years (95% CI)	1.33 (0.57–2.62)	0.54 (0.18–1.27)	0.89 (0.38–1.75)	0.87 (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	6 (2.5)	12 (1.9)
Incidence per 100 patient-years (95% CI)	0.99 (0.36–2.16)	0.00 (0.00–0.32)	0.67 (0.24–1.45)	0.49 (0.26–0.86)

\* Data presented as number (percentage) unless indicated otherwise. MTX = methotrexate; AE = adverse event; SAE = serious AE; 95% CI = 95% confidence interval; SIR = standardized incidence ratio.

† The SIR is in comparison with the expected number of events in the Surveillance, Epidemiology, and End Results database (2004), which does not include nonmelanoma skin cancers.

mumab dose. Through week 256, a total of 57 golimumab-treated patients (9.6%) 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; 1 reaction of moderate injection site erythema was classified as serious and led to discontinuation of the 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-naive patients with active RA. Through 24 weeks, patients treated with golimumab 50 mg or 100 mg + 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 week 104, 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 week 252. 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 week 256 (when all patients were receiving golimumab), with no appreciable differences among the treatment groups. Additionally, more than 80% of golimumab-treated patients had either a good or moderate DAS28-CRP response at week 256. 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 by 72.7% of patients having an improvement  $\geq 0.25$ . Radiographic progression was low through 5 years; the mean change in SHS was 0.72 and 0.60 over 5 years in patients randomized to golimumab 50 mg + MTX and 100 mg + MTX, respectively, with nearly three-quarters of all patients having no progression (change in SHS of  $\leq 0.5$ ).

The proportion of patients using oral corticosteroids and the median dose received decreased from baseline to week 256. 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 week 268 were generally consistent with those reported through week 104 (1,4). The majority of cases of active TB occurred in patients receiving the 100-mg dose; however, it is difficult to compare the 2 doses (50 and 100 mg) 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 serious AE; 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 (e.g., 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, *P jiroveci* pneumonia, and esophageal candidiasis. A total of 12 deaths occurred through week 268; no predominant cause of death was identified.

Among golimumab-treated patients, 21 malignancies were reported. Two cases of lymphoma occurred through week 268, both in patients receiving golimumab 100 mg, which corresponded to an 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 week 256 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 of the patients (66%) who were enrolled and treated in the GO-BEFORE trial completed treatment with golimumab through week 252. 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 week 52, 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.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Emery had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Emery, Fleischmann, Park, Han, Leu, Hsia.

**Acquisition of data.** Emery, Fleischmann, Strusberg, Durez, Nash, Amante, Churchill, Park, Pons-Estel, Han, Zhou, Hsia.

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## ROLE OF THE STUDY SPONSOR

Authors who are or were employees of Janssen Research & Development, LLC were involved in the study design and in the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. All authors approved the manuscript for submission. Rebecca Clemente, PhD, and Mary Whitman, PhD, of Janssen Scientific Affairs provided writing support.

## REFERENCES

- Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor  $\alpha$  monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60:2272–83.
- Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor  $\alpha$  given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789–96.
- Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor  $\alpha$  inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374:210–21.
- Emery P, Fleischmann RM, Doyle MK, Strusberg I, Durez P, Nash P, et al. Golimumab, a human anti-tumor necrosis factor monoclonal antibody, injected subcutaneously every 4 weeks in patients with active rheumatoid arthritis who had never taken methotrexate: 1-year and 2-year clinical, radiologic, and physical function findings of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Care Res (Hoboken)* 2013;65:1732–42.
- Emery P, Fleischmann R, van der Heijde D, Keystone EC, Genovese MC, Conaghan PG, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;63:1200–10.
- Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
- Van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the Preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;39:34–40.
- Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003;42:244–57.
- Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796–806.
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
- Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. *Pharmacoeconomics* 2004;22:27–38.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- Van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992;35:26–34.
- Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, et al. Pharmacokinetics and safety of golimumab, a fully human anti-TNF- $\alpha$  monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007;47:383–96.
- Van Riel PL, van Gestel AM, Scott DL. *EULAR handbook of clinical assessments in rheumatoid arthritis*. Alphen Aan Den Rijn (The Netherlands): Van Zuiden Communications; 2000.
- Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. *Best Pract Res Clin Rheumatol* 2007;21:663–75.
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;63:573–86.
- Genovese MC, Bathon JM, Fleischmann RM, Moreland LW, Martin RW, Whitmore JB, et al. Long-term safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005;32:1232–42.
- Van der Heijde D, Breedveld FC, Kavanaugh A, Keystone EC, Landewe R, Patra K, et al. Disease activity, physical function, and radiographic progression after long-term therapy with adalimumab plus methotrexate: 5-year results of PREMIER. *J Rheumatol* 2010;37:2237–46.
- Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001;28:1238–44.
- Burmester GR, Matucci-Cerinic M, Mariette X, Navarro-Blasco F, Kary S, Unnebrink K, et al. Safety and effectiveness of adalimumab in patients with rheumatoid arthritis over 5 years of therapy in a phase 3b and subsequent post-marketing observational study. *Arthritis Res Ther* 2014;16:R24.
- Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;50:124–31.
- Hsia EC, Cush JJ, Matteson EL, Beutler A, Doyle MK, Hsu B, et al. Comprehensive tuberculosis screening program in patients with inflammatory arthritides treated with golimumab, a human anti-tumor necrosis factor antibody, in phase III clinical trials. *Arthritis Care Res (Hoboken)* 2013;65:309–13.
- Asklung J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor  $\alpha$  therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009;60:3180–9.