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EXTENDED REPORT

Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study

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ABSTRACT

Objectives To evaluate the efficacy and safety of subcutaneous golimumab as add-on therapy in patients with active rheumatoid arthritis (RA) despite disease-modifying antirheumatic drug (DMARD) treatment. To evaluate an intravenous plus subcutaneous (IV+SC) golimumab strategy in patients who had not attained remission.

Methods GO-MORE was an open-label, multinational, prospective study in patients with active RA in typical clinical practice settings. In part 1, patients received add-on monthly 50-mg subcutaneous golimumab for 6 months. The percentage of patients with good/moderate European League Against Rheumatism (EULAR) 28-joint disease activity score (DAS28)–erythrocyte sedimentation rate (ESR) response was compared in patient subgroups with various concurrent or previous DMARD treatments. In part 2, patients with EULAR responses but not remission were randomly assigned to receive IV+SC or subcutaneous golimumab to month 12; DAS28–ESR remission was measured.

Results 3366 patients were enrolled. At baseline of part 1, 3280 efficacy-evaluable patients had mean disease duration of 7.6 years and mean DAS28–ESR of 5.97 (SD=1.095). At month 6, 82.1% achieved good/moderate EULAR responses and 23.9% attained remission. When EULAR responses were analysed by the number of previously failed DMARD or the concomitant methotrexate dose, DMARD type, or corticosteroid use, no statistically significant differences were observed. Part 2 patients (N=490) who received IV+SC or subcutaneous golimumab achieved similar remission rates (~25%). Adverse events were consistent with previous reports of golimumab and other tumour necrosis antagonists in this population.

Conclusions Add-on monthly subcutaneous golimumab resulted in good/moderate EULAR response in most patients; 25% achieved remission after 6 more months of golimumab, but an IV+SC regimen provided no additional efficacy over the subcutaneous regimen.

INTRODUCTION

Evidence-based clinical practice guidelines and consensus statements on the use of biological agents in rheumatoid arthritis (RA) recommend the use of tumour necrosis factor (TNF) α inhibitors for patients with RA in whom therapy with

conventional disease-modifying antirheumatic drugs (DMARD), including methotrexate, has failed.^{1 2} International guidelines also recommend that the primary target of RA management should be to achieve and maintain clinical remission or at least a state of low disease activity, thereby preventing progression of joint damage and disability.^{1 3 4}

In placebo-controlled clinical trials of RA, golimumab, an anti-TNF α monoclonal antibody, has demonstrated clinical efficacy in methotrexate-naïve patients, patients with previous inadequate methotrexate response, and patients with previous experience with at least one other TNF inhibitor.^{5–10} In the placebo-controlled GO-FORWARD trial, patients with active RA despite methotrexate treatment improved on multiple outcome measures after receiving subcutaneous golimumab.⁶ In GO-FURTHER, also a study of patients with active RA despite methotrexate treatment, intravenous golimumab plus methotrexate led to better outcomes than placebo plus methotrexate as early as week 2.¹¹ Golimumab has also been shown to inhibit radiographic progression in methotrexate-naïve patients.¹²

Limited information is available regarding the efficacy of golimumab in broad, heterogeneous patient populations outside the clinical trial setting, particularly as add-on therapy to various conventional DMARD and to low doses of methotrexate (<15 mg/week). Gaining information about TNF inhibitor responses among RA patients with a range of concomitant medications and treatment histories has the potential to improve treatment strategies, especially as the use of TNF inhibitors becomes more widespread and treatment goals evolve. In addition, no studies have evaluated the potential benefit of using a complementary intravenous plus subcutaneous (IV+SC) strategy to increase the chances of achieving remission. Strategies that target remission as the goal of therapy have shown improved overall disease control,¹³ and the higher drug exposure and weight-based dosing of an intravenous regimen may make it useful for attaining remission.^{14–16}

Here we report the results of the GO-MORE trial, a two-part study that investigated the use of golimumab as add-on therapy for RA patients who

Clinical and epidemiological research

were receiving a variety of concomitant DMARD in typical clinical practice settings. Part 2 evaluated whether an IV+SC golimumab treatment strategy might boost the efficacy of the initial subcutaneous regimen in patients who achieved response but not remission in part 1.

METHODS

Design and procedures

GO-MORE was an open-label, multinational (40 countries, 475 centres), prospective trial (protocol P06129; NCT00975130) composed of two parts (figure 1). The study received approval

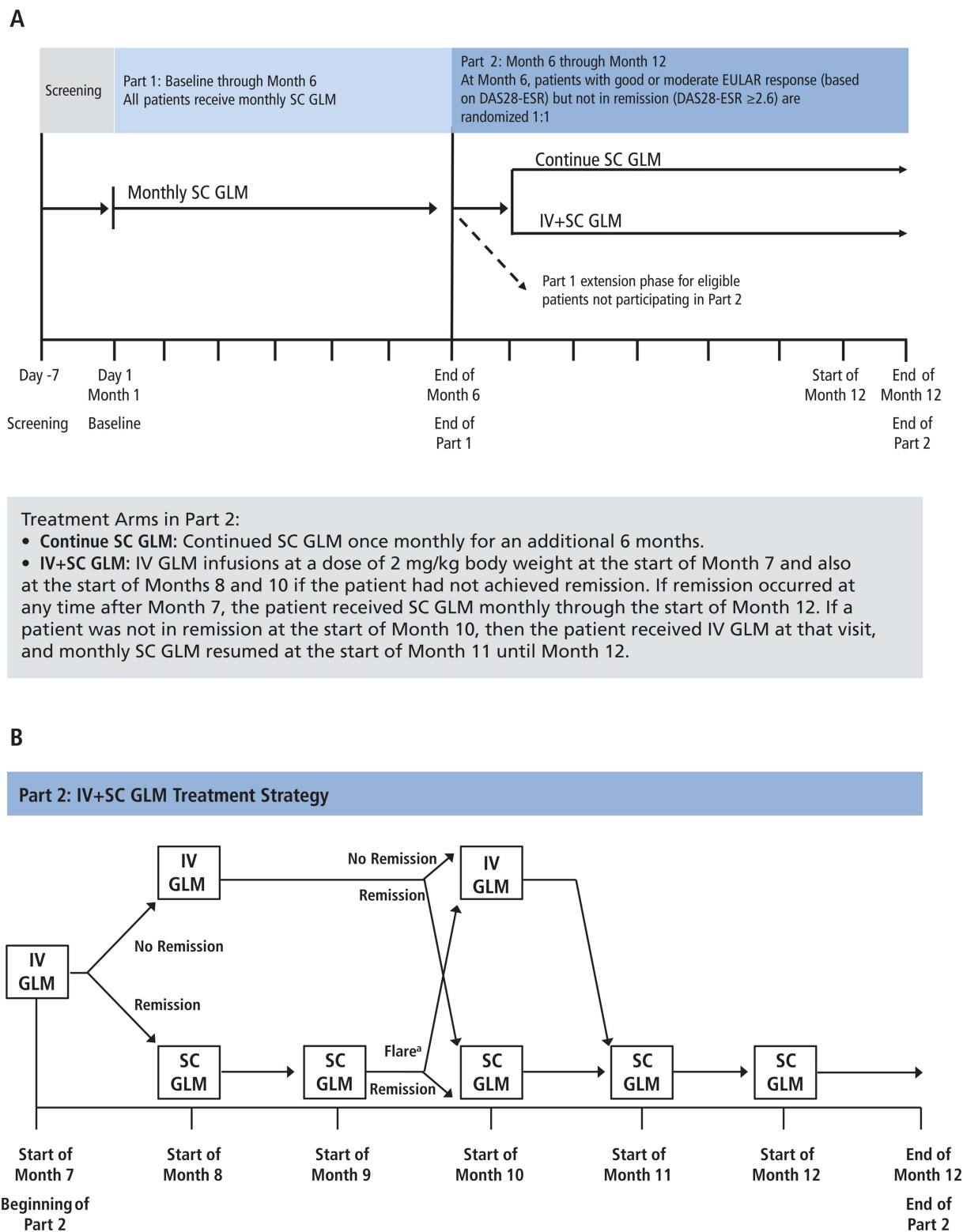


Figure 1 Study design of GO-MORE parts 1 and 2 (A) and details of part 2 (B). DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GLM, golimumab; IV, intravenous; IV golimumab2, IV golimumab 2 mg/kg; SC, subcutaneous. ^aA flare was defined as DAS28-ESR of 2.6 or greater (not retaining remission).

from appropriate research ethics committees and was conducted in accordance with the Declaration of Helsinki and standards of good clinical research practice. Data were collected from 29 October 2009 to 21 July 2011. Enrolled patients received subcutaneous golimumab 50 mg administered by autoinjector on the same day every month for 6 months. Patients continued their current DMARD regimen and oral corticosteroid regimens (if applicable) at stable doses. Assessments were performed at scheduled visits (screening; baseline; start of month 2; start of month 4; and end of month 6). Golimumab doses were administered after efficacy assessments.

In part 2, patients who had achieved a good or moderate European League Against Rheumatism (EULAR) response, calculated using the 28-joint disease activity score (DAS28) based on erythrocyte sedimentation rate (ESR), but who were not in remission (defined as DAS28-ESR < 2.6) at the end of month 6 were randomly assigned (1:1) to one of two treatment arms: combination regimen of intravenous golimumab 2 mg/kg plus subcutaneous golimumab 50 mg or continued subcutaneous golimumab 50 mg. Details of the treatment regimens are shown in figure 1. After eligibility was confirmed, treatment assignment was made by a central randomisation system. Randomisation was stratified by concomitant DMARD regimen (including the use of methotrexate or not) and disease activity at the start of part 2 (DAS28-ESR < 3.2 or DAS28-ESR ≥ 3.2).

Patients

Patients were biological agent naive and had active RA despite DMARD therapy. Key part 1 inclusion criteria included: age 18 years or older; an RA diagnosis according to the 1987 revised American College of Rheumatology criteria; active disease (DAS28-ESR ≥ 3.2) despite DMARD treatment; the use of at least one allowable DMARD (methotrexate, sulfasalazine, hydroxychloroquine, chloroquine, chloroquine phosphate, leflunomide, gold salts, azathioprine and cyclosporine) at a stable dose for at least 1 month before trial entry; and eligibility for TNF inhibitor use according to local guidelines and the investigator's opinion.

Patients were excluded for: evidence of active tuberculosis or untreated latent tuberculosis; a history of moderate to severe heart failure; a history of lymphoproliferative disease or malignancy within the past 5 years (except non-melanoma skin cancer treated without recurrence); or any contraindication for TNF inhibitor use. To be included in part 2, there must have been no safety concerns that precluded additional exposure to golimumab.

Efficacy and safety measures

The primary efficacy variable in part 1 was the proportion of patients who achieved good/moderate EULAR response (defined as DAS28-ESR improvement of > 1.2 from any baseline score or an improvement of 0.6–1.2 from a baseline score of ≤ 5.1) at the end of month 6. Key secondary efficacy variables included several composite measures of disease activity and their components: DAS28 calculated with C-reactive protein (CRP), DAS28-ESR and the simplified disease activity index (SDAI).¹⁷ Low disease activity (DAS28-ESR and DAS28-CRP ≤ 3.2, SDAI ≤ 11), remission (DAS28-ESR and DAS28-CRP < 2.6, SDAI ≤ 3.3), and achievement of minimal or no functional impairment (health assessment questionnaire-disability index (HAQ-DI) ≤ 0.5) were also assessed.

In part 2, the co-primary efficacy measures were the proportion of patients who were in DAS28-ESR remission at the start of month 11 and the end of month 12. Key secondary

endpoints include normalised area under the curve (AUC) for DAS28-ESR between the end of month 6 and the end of month 12 (AUC divided by the duration of time over which AUC is calculated); time to DAS28-ESR remission; DAS28-ESR remission rates; and proportion of patients achieving low disease activity (DAS28-ESR and SDAI criteria).

Safety was assessed by collection of treatment-emergent adverse events (TEAE).

Statistical methods

In part 1, enrolment of 3150 patients was planned for the detection of small differences in EULAR response between treatment subgroups. In part 2, a sample size of 500 with a 10% dropout rate provided 90% power for a χ^2 test to detect a 15% treatment group difference in DAS28-ESR remission rate at months 11 or 12 at an α level of 2.5% for each test.

The efficacy-evaluable populations for part 1 and part 2 included patients who received one or more dose of golimumab and had DAS28-ESR scores at baseline and at one or more post-baseline visit in part 1 and part 2, respectively. The safety populations for part 1 and part 2 included all patients who received one or more dose of study medication in part 1 and part 2, respectively.

In part 1, the primary outcome of good/moderate EULAR response at month 6 was evaluated by several treatment variables: concomitant methotrexate dose (low (< 10 mg/week), medium (≥ 10 and < 15 mg/week), high (≥ 15 mg/week)), concomitant corticosteroid use (yes or no), number of failed DMARD (one, two, or three or more), and type of concomitant DMARD (as shown in table 1). Cochran-Mantel-Haenszel (CMH) χ^2 tests were used to evaluate effects of treatment variables, controlling for baseline disease activity, with α of 0.05. For response variables, missing values were treated as non-response; other values were not imputed. For key secondary efficacy outcomes, analysis of covariance (ANCOVA) or logistic ANCOVA was used, with baseline scores as covariates.

Some analyses were also performed post-hoc for the subset of patients who received concomitant methotrexate and those who received leflunomide.

In part 2, the co-primary efficacy measures were analysed with χ^2 tests with α of 0.025. Treatment group differences in normalised AUC for DAS28-ESR and other continuous secondary endpoints were analysed using ANCOVA, adjusting for part 2 baseline scores. Time to remission was analysed using the Kaplan-Meier method with log-rank tests.

RESULTS

Patient disposition and baseline characteristics

Figure 2 shows the disposition of patients in parts 1 and 2 of the study. Characteristics of the efficacy-evaluable population (N=3280) are shown in table 1. In part 1, 90.9% (2981/3280) of efficacy-evaluable patients completed six golimumab doses and 95.9% of those patients received doses on average every 28–33 days.

In part 2, baseline characteristics were similar in the IV+SC golimumab and subcutaneous golimumab groups (table 1).

Efficacy results

Part 1

After 6 months of golimumab treatment, 82.07% (2692/3280) of patients had achieved a good/moderate EULAR response (figure 3): 35.98% (1180/3280) achieved good response and 46.10% (1512/3280) achieved moderate response. When EULAR responses were analysed by the number of previously failed DMARD or the concomitant treatment variables of

Table 1 Demographics and baseline characteristics

| Patient characteristics: part 1 | Subcutaneous golimumab (N=3280) |
|--|---------------------------------|
| Demographic characteristics | |
| Female, n (%) | 2716 (82.8%) |
| Age, years | |
| Mean (SD) | 52.3 (12.8) |
| Median (min, max) | 53.0 (18, 88) |
| Race, n (%) | |
| White | 2283 (69.6) |
| Multiracial | 444 (13.5) |
| Other | 211 (6.4) |
| Asian | 167 (5.1) |
| Not allowed to collect these data | 97 (3.0) |
| Black or African American | 57 (1.7) |
| American Indian or Alaska Native | 21 (0.6) |
| BMI (kg/m ²), median (min, max) | 26.2 (14.0, 54.5) |
| Treatment history | |
| Concomitant methotrexate dose | |
| Any dose, n (%) | n=3280 2663 (81.2) |
| Low (<10 mg/week), n (%) | 142 (4.3) |
| Medium (≥10 and <15 mg/week), n (%) | 526 (16.0) |
| High (≥15 mg/week), n (%) | 1995 (60.8) |
| Concomitant corticosteroid use | |
| Received corticosteroids, n (%) | n=3280 2078 (63.4) |
| DMARD combinations | |
| Methotrexate only, n (%) | n=3270 1681 (51.4) |
| Methotrexate+hydroxychloroquine, chloroquine, chloroquine phosphate, n (%) | 433 (13.2) |
| Methotrexate+leflunomide, n (%) | 216 (6.6) |
| Methotrexate+sulfasalazine, n (%) | 150 (4.6) |
| Methotrexate+hydroxychloroquine, chloroquine, chloroquine phosphate+sulfasalazine, n (%) | 106 (3.2) |
| Leflunomide only, n (%) | 303 (9.3) |
| Other DMARD combinations,* n (%) | 381 (11.7) |
| No of DMARD failed | |
| 1, n (%) | n=3279 1129 (34.4) |
| 2, n (%) | 1176 (35.9) |
| ≥3, n (%) | 974 (29.7) |
| Disease characteristics | |
| Disease duration, years | |
| Mean (SD) | n=3279 7.6 (7.9) |
| Median (min, max) | 4.9 (0.01, 56.6) |
| TJC28, mean (SD) | 13.0 (6.81) |
| SJC28, mean (SD) | 9.6 (5.56) |
| DAS28–ESR | |
| Moderate disease activity (3.2–5.1), n (%) | n=3270 698 (21.3) |
| High disease activity (>5.1), n (%) | 2572 (78.7) |
| Mean (SD) | 5.97 (1.095) |
| DAS28–CRP | |
| Mean (SD) | n=3236 5.41 (0.998) |
| CRP (mg/l) | |
| Mean (SD) | n=3236 14.48 (20.376) |
| ESR (mm/h) | |
| Mean (SD) | n=3280 34.9 (24.64) |
| Anti-CCP | n=3225 |

Continued

methotrexate dose, DMARD type, or corticosteroid use, no statistically significant pairwise differences were observed. Good/moderate EULAR responses were achieved by approximately 80% of the patients across all subgroups (figure 3 and see supplementary figure S1, available online only). Similarly, in analyses of effects of the treatment variables on DAS28–ESR,

DAS28–CRP and SDAI response rates (both changes from baseline and mean values across visits), no clinically or statistically significant differences were found across the treatment subgroups (data not shown).

Good/moderate EULAR response and DAS–ESR low disease activity and remission rates increased steadily over the 6-month

Table 1 Continued

| Patient characteristics: part 1 | | Subcutaneous golimumab (N=3280) | | |
|---|-----------------|---------------------------------|--------------------------------|------------------|
| Positive, (≥ 20 U/ml), n (%) | | 2318 (71.9) | | |
| Rheumatoid factor | | n=3234 | | |
| Positive (≥ 15 IU/ml), n (%) | | 2344 (72.5) | | |
| HAQ-DI, mean (SD) | | 1.44 (0.67) | | |
| | | N=490 | | |
| Patient characteristics: part 2 | | IV+SC golimumab (N=242) | Subcutaneous golimumab (N=248) | |
| Demographic characteristics | | | | |
| Female, n (%) | | 211 (87.2) | 211 (85.1) | |
| Age, years | | | | |
| Mean (SD) | | 53.4 (12.65) | 52.7 (12.77) | |
| Race, n (%) | | | | |
| White | | 184 (76.0) | 182 (73.4) | |
| Multiracial | | 37 (15.3) | 45 (18.1) | |
| Other | | 7 (2.9) | 9 (3.6) | |
| Asian | | 5 (2.1) | 6 (2.4) | |
| Black or African American | | 3 (1.2) | 2 (0.8) | |
| American Indian or Alaska Native | | 1 (0.4) | 0 | |
| Not allowed to collect data | | 5 (2.1) | 4 (1.6) | |
| BMI (kg/m^2), median (min, max) | | 26.57 (16.6, 54.5) | 26.76 (16.9, 52.3) | |
| Disease characteristics | Part 1 baseline | Part 2 baseline† | Part 1 baseline | Part 2 baseline† |
| DAS28-ESR, mean (SD) | 6.23 (1.008) | 4.00 (0.810) | 6.27 (1.003) | 3.98 (0.834) |
| DAS28-CRP, mean (SD) | 5.59 (0.956) | 3.46 (0.822) | 5.68 (0.963) | 3.50 (0.837) |
| TJC28, mean (SD) | 14.4 (6.66) | 4.6 (3.89) | 14.3 (6.97) | 4.6 (4.08) |
| SJC28, mean (SD) | 10.6 (5.31) | 2.9 (2.93) | 11.3 (5.78) | 3.3 (3.06) |
| CRP (mg/l), mean (SD) | 14.69 (19.591) | 7.6 (13.371) | 15.49 (23.622) | 8.14 (18.048) |
| ESR (mm/h), mean (SD) | 36.5 (24.17) | 24.5 (18.30) | 35.2 (22.97) | 22.6 (17.02) |
| HAQ-DI, mean (SD) | 1.52 (0.574) | 0.92 (0.629) | 1.57 (0.643) | 0.96 (0.617) |

*Each additional combination used by less than 3% of patients.

†Part 2 baseline measurements were those taken at the start of study month 7 (visit 6).

BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, 28-joint disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index; IV+SC, intravenous plus subcutaneous; max, maximum; min, minimum; SJC28, swollen joint count 28; TJC28, tender joint count 28.

treatment period (figure 3). At months 2, 4 and 6, patterns similar to those observed with EULAR and DAS28-ESR responses were seen for the percentage of patients with DAS28-CRP low disease activity (24.54%, 38.66% and 49.51%, respectively), DAS28-CRP remission (11.59%, 23.32% and 32.47%, respectively), SDAI low disease activity (20.46%, 36.74% and 48.32%, respectively), and SDAI remission (2.68%, 8.69% and 14.15%, respectively).

HAQ-DI also improved throughout the 6 months of golimumab treatment, with minimal or no functional impairment (HAQ-DI ≤ 0.5) achieved in 26.37%, 33.14% and 37.38% of patients at months 2, 4 and 6, respectively. Mean HAQ-DI improved from 1.44 at baseline to 1.07, 0.94 and 0.88 at months 2, 4 and 6, respectively.

Patients who had high disease activity at baseline were less likely to achieve remission than patients who had moderate disease activity at baseline (see supplementary figure S2, available online only), whether remission was measured by DAS28-ESR, DAS28-CRP, or SDAI criteria. Patients with shorter disease duration were somewhat more likely to attain remission. Month 6 DAS-ESR remission rates were 27.81%, 24.48%, 22.11% and 21.00% in patients with disease durations of less than 2 years, 2 to less than 5 years, 5-10 years and over 10 years, respectively (the only comparison that was statistically

significant was the comparison between the shortest and the longest duration groups, $p=0.0339$).

Patterns of EULAR response and DAS28-ESR remission were very similar in patients who received only concomitant leflunomide (the largest subgroup of patients who did not receive concomitant methotrexate; 9% of the population), and patients who received any combination of concomitant DMARD that included methotrexate (81% of the population). The response patterns in both of these groups were similar to those of the overall population (see supplementary figure S3, available online only; baseline characteristics and safety data are shown in supplementary tables S1 and S2, available online only).

Part 2

At the primary endpoints and all other time points in part 2, the percentages of patients who achieved DAS28-ESR remission did not differ between the IV+SC and subcutaneous golimumab groups (figure 4). Overall, approximately 25% of patients achieved remission after the additional 6 months of treatment.

The normalised AUC for DAS28-ESR between the end of month 6 and end of month 12 was similar for the IV+SC group (mean 3.67; SD 0.992) and the subcutaneous group (mean 3.67; SD 0.924, $p=0.931$); differences in DAS28-ESR

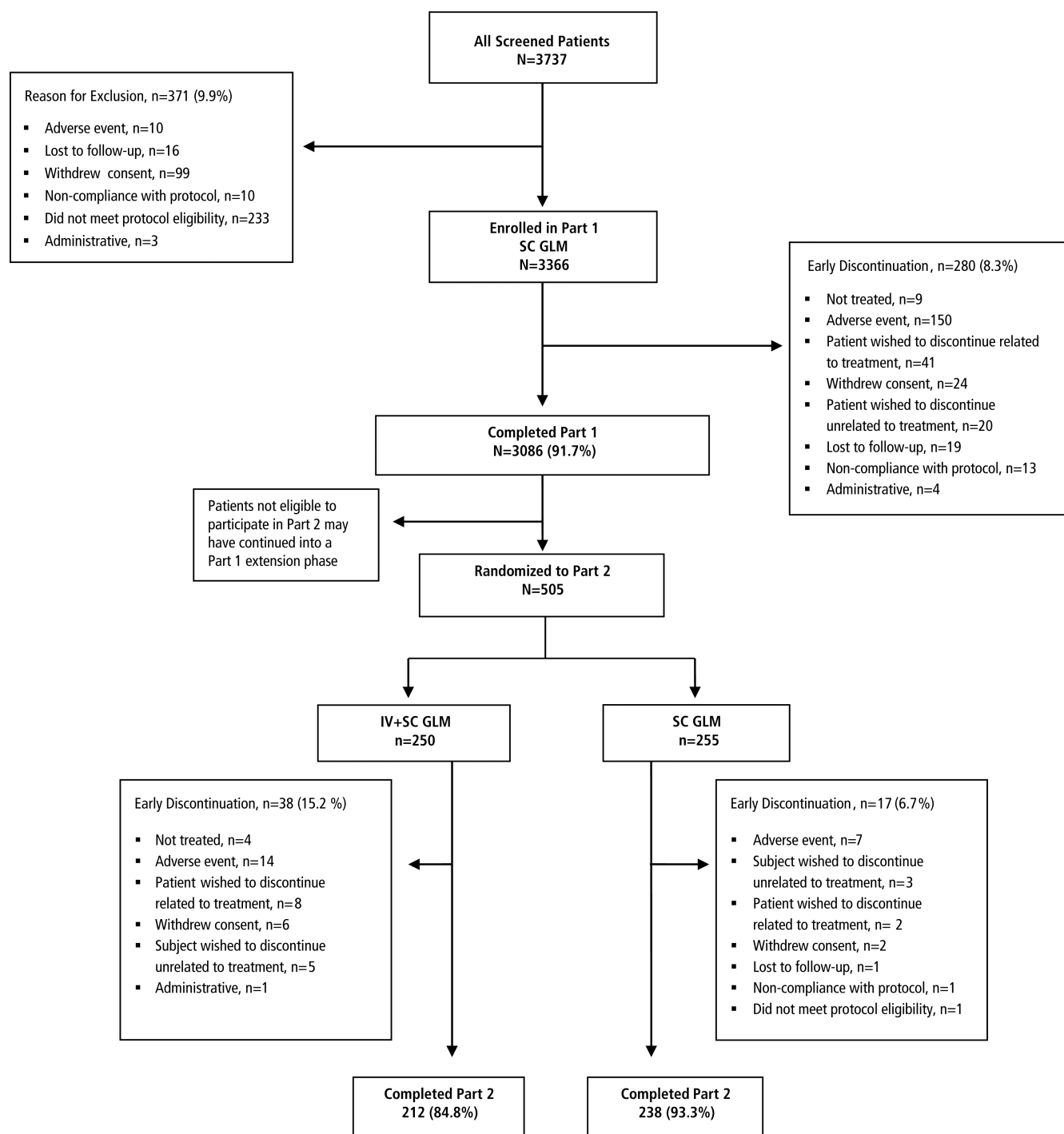


Figure 2 Patient disposition. GLM, golimumab; IV, intravenous; SC, subcutaneous.

were non-significant at each time point during part 2 (all $p > 0.113$). The treatment groups did not differ in the time to first DAS-ESR remission; Kaplan-Meier estimates of the percentage of patients in remission at month 12 were 44.31% and 45.10% of patients for the IV+SC and subcutaneous golimumab groups, respectively ($p = 0.791$). Changes from baseline in DAS28-ESR score, DAS28-CRP score, SDAI score and subcomponents of these indices were similar across treatment regimens. As observed in part 1, the responses of patients who received concomitant methotrexate (77.1% of the part 2 population) were similar to those of the full population (see supplementary figure S4, available online only).

Safety results

Part 1

The most frequently reported TEAE in the safety population in part 1 were nasopharyngitis (4.8%), urinary tract infection (3.3%), headache (3.2%), diarrhoea (2.7%) and bronchitis (2.4%). TEAE leading to early withdrawal occurred in 4.3% (145/3357) of patients (upper section of table 2).

Serious TEAE occurred in 5.7% (190/3357) of patients in part 1. The most common serious TEAE system organ class was infections and infestations (58/3357, 1.7%), most commonly pneumonia (0.27%), bacterial arthritis (0.15%), sepsis (0.12%) and tuberculosis (0.12%).

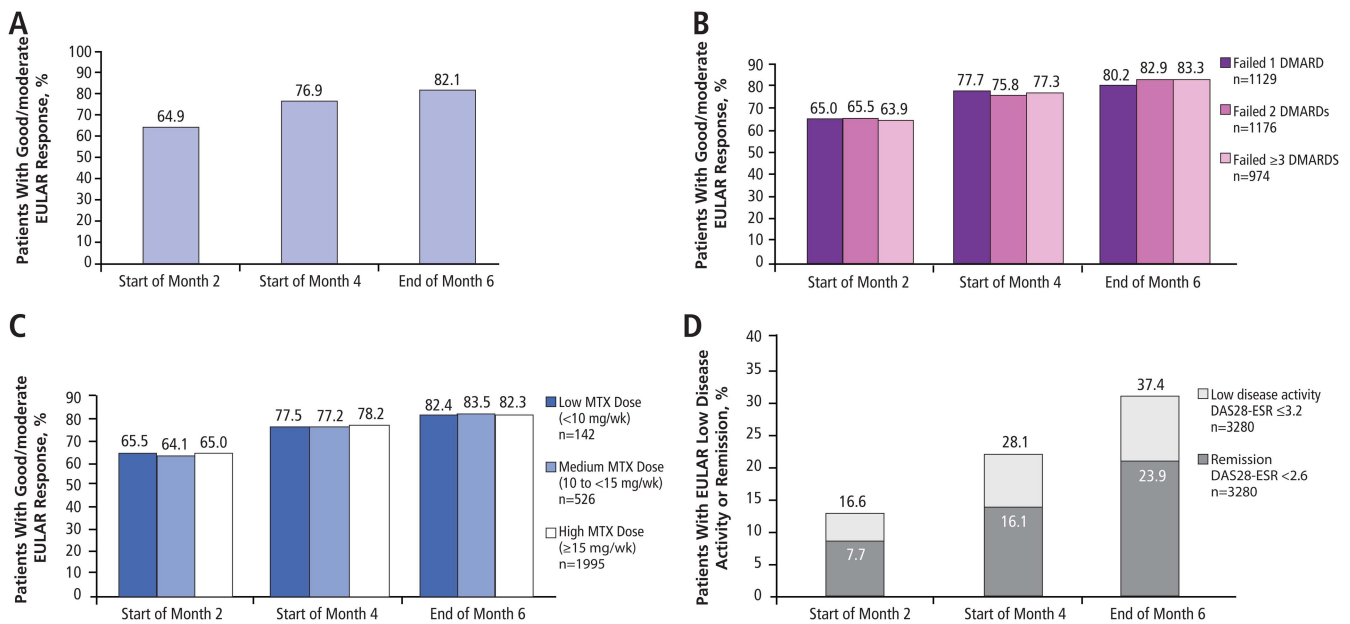


Figure 3 Response to golimumab treatment over 6 months in part 1: percentage of patients with good or moderate EULAR response (A),^a percentage of patients who achieved good or moderate EULAR DAS28 response by the number of previously failed DMARDs (B), percentage of patients who achieved good or moderate EULAR DAS28 response by concomitant methotrexate dose (C), and percentage of patients who achieved low disease activity or remission (D).^b DAS28, 28-joint disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GLM, golimumab; MTX, methotrexate. ^aA good or moderate response was defined as DAS28–ESR improvement of more than 1.2 from any baseline score or an improvement of 0.6–1.2 from a baseline score of 5.1 or less. ^bLow disease activity was defined as DAS28–ESR of ≤3.2. Remission was defined as DAS28–ESR of less than 2.6.

Six deaths occurred during part 1, and four additional events that led to death occurred in patients more than 30 days after their last dose of study medication. Of the 10 deaths, five were considered by the investigators to be potentially treatment related (gastrointestinal haemorrhage, septic shock, multiple myeloma, multiorgan failure, respiratory failure), and five were classified as unrelated (cardiopulmonary failure, pancreatic carcinoma, cervix carcinoma, squamous cell carcinoma, metastatic gastric cancer).

The incidence of clinically significant abnormal laboratory events was 4.9%, with the most common being elevation of liver transaminases and anaemia. Injection site reactions occurred in 0.7% of patients.

The subgroups of patients who received concomitant methotrexate (N=2656) or leflunomide only (N=309) had similar percentages of patients with TEAE (54.93% vs 56.96%, respectively), serious TEAE (5.12% vs 6.80%) and TEAE leading to

withdrawal (3.77% vs 6.80%) (see supplementary table S2, available online only).

Part 2

The overall incidence of TEAE in part 2 was similar to that in part 1 and similar across treatment groups (lower section of table 2). The most frequently reported TEAE in the IV+SC golimumab group were upper respiratory tract infection (6.1% of patients), nasopharyngitis (5.3%) and diarrhoea (2.9%). In the subcutaneous golimumab group, the most frequently reported TEAE were nasopharyngitis (7.1%), urinary tract infection (3.9%), bronchitis (3.1%) and headache (3.1%). TEAE leading to early withdrawal occurred in 4.9% and 2.4% of patients in the IV+SC golimumab and subcutaneous golimumab treatment arms, respectively. In the IV+SC golimumab group, injection site pain occurred in one (0.4%) patient. No other injection site or infusion reactions occurred in part 2.

Although the incidence of serious TEAE in part 2 was numerically greater in the IV+SC golimumab group (6.9%; 17/245) than in the subcutaneous golimumab group (2.4%; 6/255; lower section of table 2), it was similar to that observed in part 1 (5.7%). The serious TEAE in the IV+SC group had no identifiable pattern of system organ class distribution. The serious TEAE that occurred in at least two patients in this group were pneumonia and overdose (two each; 0.8%). The corresponding rates for these events in the subcutaneous golimumab group were 0.4% (one patient) for pneumonia and 0.4% (one patient) for overdose. All other serious TEAE occurred in one patient each.

Serious infections and infestations occurred in 2.0% (5/245) and 0.8% (2/255) of patients in the IV+SC golimumab and subcutaneous golimumab groups, with pneumonia occurring in two (0.8%) and one (0.4%) patient, respectively. One death (0.4% of patients) occurred in the IV+SC golimumab arm

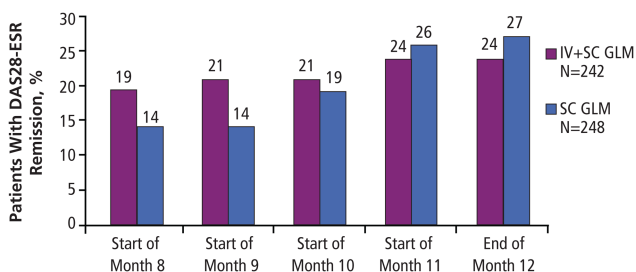


Figure 4 Percentage of patients with DAS28–ESR remission by treatment group in part 2. DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; GLM, golimumab; IV, intravenous; SC, subcutaneous.

Table 2 Summary of patients with TEAE

| Patients with TEAE* in part 1 | Subcutaneous golimumab (N=3357), n (%) | |
|--|--|--------------------------------------|
| One or more TEAE | 1881 (56.0) | |
| TEAE possibly or probably related to study medication | 943 (28.1) | |
| TEAE leading to early withdrawal | 145 (4.3) | |
| Deaths | 6 (0.2)† | |
| Injection site reactions | 23 (0.7) | |
| Clinically significant abnormal lab values | 163 (4.9) | |
| Serious TEAE | 190 (5.7) | |
| Infections and infestations | 58 (1.7) | |
| Injury, poisoning and procedural complications | 26 (0.8) | |
| Musculoskeletal and connective tissue disorders | 25 (0.7) | |
| Cardiac disorders | 15 (0.4) | |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 15 (0.4) | |
| Respiratory, thoracic and mediastinal disorders | 15 (0.4) | |
| Gastrointestinal disorders | 14 (0.4) | |
| Nervous system disorders | 11 (0.3) | |
| General disorders and administration site conditions | 10 (0.3) | |
| Vascular disorders | 9 (0.3) | |
| Renal and urinary disorders | 7 (0.2) | |
| Metabolism and nutrition disorders | 6 (0.2) | |
| Hepatobiliary disorders | 4 (0.1) | |
| Skin and subcutaneous tissue disorders | 4 (0.1) | |
| Surgical and medical procedures | 4 (0.1) | |
| Blood and lymphatic system disorders | 3 (0.1) | |
| Immune system disorders | 3 (0.1) | |
| Investigations | 3 (0.1) | |
| Psychiatric disorders | 3 (0.1) | |
| Reproductive system and breast disorders | 3 (0.1) | |
| Eye disorders | 2 (0.1) | |
| Ear and labyrinth disorders | 1 (0.03) | |
| Patients with TEAE in part 2 | IV+SC golimumab (N=245) n (%) | Subcutaneous golimumab (N=255) n (%) |
| One or more TEAE | 133 (54.3) | 127 (49.8) |
| TEAE possibly or probably related to study medication | 65 (26.5) | 57 (22.4) |
| TEAE leading to early withdrawal | 12 (4.9) | 6 (2.4) |
| Deaths | 1 (0.4) | 0 |
| Injection site reactions | 1 (0.4) | 0 |
| Clinically significant abnormal lab values | 13 (5.3) | 16 (6.3) |
| Serious TEAE | 17 (6.9) | 6 (2.4) |
| Infections and infestations | 5 (2.0) | 2 (0.8) |
| Musculoskeletal and connective tissue disorders | 3 (1.2) | 0 |
| Injury, poisoning, and procedural complications | 3 (1.2) | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 2 (0.8) | 0 |
| Gastrointestinal disorders | 2 (0.8) | 0 |
| Hepatobiliary disorders | 1 (0.4) | 0 |
| General disorders and administration site conditions | 1 (0.4) | 0 |
| Cardiac disorders | 1 (0.4) | 0 |
| Neoplasms benign, malignant and unspecified | 1 (0.4) | 2 (0.8) |
| Nervous system disorders | 1 (0.4) | 0 |
| Skin and subcutaneous tissue disorders | 0 | 1 (0.4) |
| Investigations | 0 | 1 (0.4) |

*A TEAE was defined as an adverse event occurring during the treatment period if it started on or after the first dose of study medication, and up to 30 days after the last dose of study medication, or if it was present before the first dose of study medication, but increased in severity during the treatment period.

†Four additional events that led to death occurred in patients more than 30 days after their last dose of study medication.

IV+SC, intravenous plus subcutaneous; TEAE, treatment-emergent adverse event.

(cerebrovascular accident, considered by the investigator as unlikely to have been treatment related).

Clinically significant abnormal laboratory events occurred in 5.3% and 6.3% of patients in the IV+SC and subcutaneous

golimumab arms, respectively; the most common events were elevation of liver transaminases and anaemia. No infusion-related reactions occurred, and few injection-site reactions occurred (IV+SC golimumab, 0.4%; subcutaneous golimumab, 0).

DISCUSSION

Of the 3280 efficacy-evaluable patients in the GO-MORE study, 82.1% achieved good or moderate EULAR DAS28-ESR response following 6 months of golimumab add-on treatment, and 23.9% achieved DAS28-ESR remission. This remission rate is similar to the rates reported in other observational studies of TNF inhibitors (etanercept, infliximab and adalimumab) in patients with RA, which ranged from 8% to 28%.^{18–21} The remission rate is also comparable to the ReAct study, which investigated the efficacy of adalimumab with or without concomitant DMARD (16% vs 20% at 3 months, respectively).²²

The study population was typical of clinical practice settings, and confirms the benefit of adding golimumab to conventional DMARD therapy. Patients showed response to treatment as early as the start of month 2 (after only one injection of subcutaneous golimumab) and had steady improvement in several measures of disease control over 6 months of treatment. EULAR response was consistently achieved, regardless of the concomitant methotrexate dose, concomitant DMARD background, concomitant corticosteroid use, or the number of previously failed DMARD. Previous pivotal RA trials did not study the efficacy and safety of golimumab when used with background treatments other than methotrexate.^{5–6} In the current study, patients had similar response patterns whether they received golimumab with concomitant methotrexate or leflunomide. In addition, golimumab efficacy was not affected by the dose of concomitant methotrexate. Similar results have been reported for certolizumab pegol with concomitant methotrexate²³ and adalimumab with concomitant methotrexate or with other DMARD.²²

In part 2, to evaluate possible continuation treatment strategies with golimumab, patients who responded but did not achieve remission after 6 months of subcutaneous golimumab treatment were eligible to receive an additional 6 months of treatment with either a subcutaneous-only regimen or switch to a short-term intravenous golimumab regimen to induce remission, followed by subcutaneous golimumab. Both strategies were equally effective; each had a DAS28-ESR remission rate of approximately 25%. The reason for the similar responses between the treatment groups remains unclear. The loss of the numerical difference between the two treatment arms observed early in part 2 may indicate that small improvements achieved with intravenous golimumab should be maintained with intravenous golimumab instead of resumed subcutaneous golimumab. This study did not test this possibility. Another uninvestigated potential explanation is that a plateau effect prevents increased intravenous golimumab efficacy despite greater peak concentrations.

In general, golimumab was well tolerated. The pattern of TEAE was consistent with previous reports on golimumab and other TNF antagonists in this population,^{10–11, 24} with no new signals identified. In this study, serious adverse event occurred in a lower percentage of patients (5%) than previously observed in a large, similarly designed study with the TNF antagonist adalimumab (13%); however, the three system organ classes with the greatest number of serious TEAE (infections and infestations; injury, poisoning and procedural complications; musculoskeletal and connective tissue disorders) were the same between the studies.²² In part 1, 0.7% of patients (26 patients) had a TEAE in the 'neoplasms benign, malignant, and unspecified' category and 0.4% of patients (15 patients) had a serious TEAE in this category; in part 2, four of these events occurred, three of which were serious. These rates are comparable to those reported in a meta-analysis of randomised, controlled trials in patients with RA; malignancies were reported in 0.7% (123/15 989) of patients who received biological agents with

methotrexate and 0.6% (65/9,819) of patients who received either placebo and/or any non-biological DMARD.²⁵

In part 2, the percentage of patients with serious TEAE was numerically greater in the IV+SC golimumab group (6.9%) than the subcutaneous golimumab group (2.4%); however, the percentage in the IV+SC group was comparable to the percentage for patients who had subcutaneous golimumab treatment in part 1 (5.7%). This percentage is also similar to that observed in the GO-FURTHER trial, in which patients with RA received a combination of intravenous golimumab and methotrexate, and 4.1% of patients reported serious adverse events over 24 weeks.¹¹ With other TNF inhibitors, serious infection risk has been shown to decrease after 6 months of treatment.²⁶ In the current study, serious infections occurred in 1.7% of patients at month 6. At month 12, the rate had increased to 2.0% in the IV+SC golimumab group and decreased to 0.8% in the subcutaneous golimumab group.

One strength of the GO-MORE study is that the number of enrolled patients was large enough to allow for comparison of responses among various patient subpopulations and collection of safety data on a broad sample of patients with RA. Although the open-label, observational, non-randomised design of part 1 makes the study subject to certain biases, it is also beneficial because the data are likely to be representative of that obtained in clinical practice.

Overall, the results from the GO-MORE study suggest that adding golimumab to several different non-biological DMARD has a favourable benefit-to-risk profile in a broader RA patient population than was studied in previous clinical trials. In this typical clinical practice population, approximately 80% of patients achieved good or moderate EULAR response, and approximately 25% achieved remission at month 6, regardless of concomitant or previous DMARD treatment.

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Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study

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