METHODS

The study was conducted according to the Declaration of Helsinki, the protocol was reviewed and approved by the institutional review board/independent ethics committee governing each site, and all patients provided written informed consent.

Patients had ankylosing spondylitis (AS), classified per the 1984 modified New York Criteria,[8] for ≥3 months before the first administration of study agent and an inadequate response to current or previous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or disease-modifying antirheumatic drugs (DMARDs). Patients were randomly assigned (1:1.8:1.8) using an interactive voice/web response system to receive subcutaneous injections of placebo (Group 1), golimumab 50mg (Group 2), or golimumab 100mg (Group 3) every 4 weeks (q4wk; Figure 1). Concomitant methotrexate sulfasalazine, hydroxychloroquine, corticosteroid, and NSAID use was permitted as previously described.[1]

Patients with <20% improvement from wk0→wk16 in both total back pain and morning stiffness entered early escape, with patients in Group 1 initiating treatment with golimumab 50mg instead of placebo and patients in Group 2 increasing their golimumab dose from 50mg→100mg; patients in Group 3 had no change.

Group-1 patients still receiving placebo began receiving golimumab 50mg at wk24; all other patients continued to receive assigned treatment (resulting from randomization/subsequent early escape). Subcutaneous injections continued q4wk through wk252, with final efficacy/safety assessments at wk256/wk268, respectively. Although the placebo-controlled period ended at wk24, participants and investigators remained blinded to golimumab dose through wk100. The study's long-term extension, during which the investigator could increase (from 50mg→100mg)

or decrease (from 100mg→50mg) the golimumab dose one time and/or adjust concomitant DMARD, corticosteroid, and/or NSAID treatment, started at wk104. After wk52, patients were allowed to administer study agent at home and were to attend visits q12wk. Following the last golimumab study injection, patients could transition to standard-of-care AS treatment, including commercially available biologics.

We evaluated clinical response by determining the proportions of patients with at least 20%/40% improvement in the Assessment in SpondyloArthritis international Society response criteria (ASAS20/ASAS40), ASAS partial remission (defined as value <2 in each of four ASAS domains), and ≥50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index [9] (i.e., BASDAI50 response). Note that components of the aforementioned composite scores were assessed using visual analog scales. ASAS20/40 responses were also assessed before and after dose escalation among patients who increased golimumab dose from 50mg→100mg at any time and received at least two consecutive 100mg doses. Only 11 patients reduced the dose from 100mg→50mg; hence, no analysis was undertaken to evaluate efficacy in this dosing cohort.

Changes from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI),[10] Bath Ankylosing Spondylitis Metrology Index (BASMI) defined as a linear score,[11,12] BASDAI,[9] and physical and mental component summary (PCS and MCS, respectively) scores of the 36-item Short-Form health survey (SF-36)[13] were used to assess physical function, range of motion, and health-related quality of life, respectively.

Adverse events (AEs) were documented and blood samples were collected for determination of antibodies to golimumab[14] throughout study participation. Results of magnetic resonance

imaging conducted through wk104 [15] and radiographic evaluations conducted through wk208[16] as part of GO-RAISE have been reported.

Because all patients were receiving golimumab after wk24, no statistical comparisons were made for efficacy results after that time. Efficacy summaries reported herein are based on both intent-to-treat (ITT) and observed data. In the ITT analyses based on randomized patients, missing baseline component data were replaced with the median of all non-missing baseline values for the same C-reactive protein stratification group and missing post-baseline data were replaced using last-observed-carried-forward methodology. For dichotomous response endpoints, treatment failure rules were applied such that patients who discontinued due to unsatisfactory therapeutic effect were considered nonresponders from the time of failure onward. For observed data, patients who did not discontinue study participation as of wk24 are included, no treatment failure rules were applied, and missing data were not imputed. Ninety-five percent confidence intervals (95% CIs) were determined for select outcomes.

Reported AEs were summarized through wk268, with the exception of those that occurred after receipt of any commercial biologic (including commercial golimumab). Individual AEs were attributed to treatment received at event onset. Patients who received commercially available biologic treatment after discontinuing study golimumab, but who remained in the study, had AEs reported up to wk268, but these AEs were excluded from the safety summaries. Individual AEs were attributed to treatment received at event onset. Standardized incidence ratios for malignancies (excluding nonmelanoma skin cancer) were determined using the Surveillance, Epidemiology and End Results database.[17]

RESULTS

ASAS response

Based on observed data, 52 patients continued in the trial through wk256 despite not having achieved an ASAS20 response. Among these patients, median percent improvements from baseline to wk256 were 12% for inflammation (per BASDAI assessment), 16% for patient assessment of total back pain, and 10% for patient global assessment of disease. Additionally, night back pain and sleep scale scores improved in a majority of nonresponding patients, with median percent improvements at the last visit assessed of 16% for night back pain (wk256) and 27% for sleep score (wk52). Thus, these patients may be deriving sufficient overall benefit from golimumab to continue therapy for 5 years despite not achieving an ASAS20 response.

Additional clinical findings

Based on ITT analyses, 161/356 (45.2%) and 199/356 (55.9%) were in BASDAI50 response at wk24 and wk256, respectively (Figure S2A). Mean changes in the BASDAI, BASFI, and BASMI scores from wk24 to wk256 indicate additional improvement in disease activity, function, and mobility, respectively, through up to 5 years of golimumab treatment (Fig S2B-D). Findings were consistent when assessed using observed data (Figure S3A-D).

Health-related quality of life

Table S1. Physical component summary (PCS) and mental component summary (MCS) scores of the 36-item Short-Form Health Survey – Intent-to-treat analyses.

	Placebo→GLM	GLM 50 mg	GLM 100 mg	All Pts
Randomized pts	78	138	140	356
PCS score				
Mean±SD change from baseline to:				
Week 24	6.6 ± 9.14	9.1 ± 10.42	8.9 ± 10.44	8.5 ± 10.18
Week 104	12.5 ± 9.66	11.0 ± 11.10	10.9 ± 10.06	11.3 ± 10.38
Week 160	11.5 ± 10.42	10.3 ± 10.88	9.9 ± 10.54	10.4 ± 10.63
Week 256	12.7 ± 11.24	10.5 ± 11.66	9.8 ± 10.50	10.7 ± 11.15
Number (%) of patients achieving score ≥ 50				
Week 0	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.3)
Week 24	6 (7.7)	31 (22.5)	32 (22.9)	69 (19.4)
Week 104	21 (26.9)	37 (26.8)	39 (27.9)	97 (27.2)
Week 160	23 (29.5)	33 (23.9)	38 (27.1)	94 (26.4)
Week 256	24 (30.8)	38 (27.5)	31 (22.1)	93 (26.1)
MCS score				
Mean±SD change from baseline to:				
Week 24	3.6 ± 9.24	2.0 ± 8.42	5.7 ± 10.17	3.8 ± 9.43
Week 104	3.2 ± 9.89	2.7 ± 9.43	6.4 ± 10.76	4.3 ± 10.19
Week 160	3.9 ± 10.30	3.2 ± 9.23	6.4 ± 11.92	4.6 ± 10.66
Week 256	3.3 ± 10.61	3.1 ± 10.10	5.3 ± 11.41	4.0 ± 10.77
Number (%) of patients achieving score ≥ 50				
Week 0	31 (39.7)	50 (36.2)	48 (34.3)	129 (36.2)
Week 24	42 (53.8)	69 (50.0)	72 (51.4)	183 (51.4)
Week 104	42 (53.8)	72 (52.2)	79 (56.4)	193 (54.2)
Week 160	40 (51.3)	73 (52.9)	80 (57.1)	193 (54.2)
Week 256	42 (53.8)	68 (49.3)	70 (50.0)	180 (50.6)

GLM, golimumab; SD, standard deviation

Antibodies to golimumab

Antibodies to golimumab were detected in 20 (6.4%; 95% CI: 3.7%, 9.1%) of 313 golimumab-treated patients who had samples appropriate for testing through wk256. Of these, 14 (70%) patients tested positive for neutralizing antibodies. The highest titer of 1:1280 was observed in one patient randomized to receive golimumab 50mg who was in ASAS20 response at wk24 and wk52 when the antibodies were detected, but who later withdrew from the study because of unsatisfactory therapeutic effect. There was no association between the presence of anti-

golimumab antibodies and lack of ASAS20 response, and in a number of patients antibodies to golimumab were detected at one time point but not at subsequent time points.

Safety

Through wk268, 97.5% (344/353) of golimumab-treated patients had ≥1AE, most commonly infections in 285 (80.7%) and musculoskeletal and connective tissue disorders in 210 (59.5%) patients. Also through wk268, 9.1% (32/353) of patients discontinued study agent due to an AE. The majority of AEs leading to discontinuation of study agent were infections (7 [2.0%]). Other common reasons for discontinuation of golimumab included AS (4 [1.1%] patients), increased alanine aminotransferase (2 [0.6%] patients), and increased aspartate aminotransferase (2 [0.6%] patients).

Few golimumab-treated patients had > 1 markedly abnormal postbaseline chemistry value through wk268. Those observed included 7/352 (2.0%) patients with > 1 markedly increased bilirubin level (≥100% increase + value >1.5 mg/dL); 6/352 (1.7%) patients with > 1 markedly elevated alanine aminotransferase level (≥100% increase + value >150 IU/L).

Injection-site reactions, most commonly erythema, swelling, and pain, were observed in 43 (12.2%) golimumab-treated patients through wk268, accounting for approximately 1.0% of administered injections (186/17,822). Approximately 17% of patients who escalated the golimumab dose from 50mg to 100mg had injection-site reactions, compared with approximately 11% of patients who received only one dose level (Table 1). Most injection-site reactions occurred within the first year of treatment (12.7% of patients), after which the occurrence appeared to gradually decline over time (i.e., 2.2%, 4.5%, 1.4%, and 1.1% of patients during

years 2, 3, 4, and 5, respectively) among the fairly stable numbers of patients continuing treatment (Table S2).

After discontinuation of study golimumab injections, 82 patients received commercially available biologics through wk268, six of whom had AEs. These events were similar to AEs observed during receipt of study medication in the overall trial, and none were serious.

Table S2. Incidences [95% confidence interval] per 100 patient-years of serious AEs, serious infections, and malignancies and occurrence of infusion reactions per year, all through week 268.

	GLM 50 mg only	GLM 50 and 100 mg	GLM 100 mg only	All GLM patients
Serious AEs				
Year 1 treated pts[1,2]	17.28 [10.83, 26.16]	11.34 [4.89, 22.34]	22.77 [14.87, 33.36]	17.94 [13.56, 23.30]
Year 2 treated pts[1,3]	4.52 [1.66, 9.84]	7.04 [2.29, 16.44]	7.95 [3.43, 15.67]	6.24 [3.76, 9.75]
Year 3 treated pts[1,4]	5.67 [2.28, 11.68]	26.23 [15.54, 41.45]	11.86 [5.92, 21.22]	12.64 [8.85, 17.49]
Year 4 treated pts[1,5]	8.25 [3.96, 15.18]	8.85 [3.25, 19.26]	9.16 [3.95, 18.04]	8.68 [5.56, 12.92]
Year 5 treated pts[1,6]	11.21 [6.13, 18.80]	20.09 [10.70, 34.36]	9.19 [3.97, 18.10]	12.65 [8.81, 17.59]
Serious infections				
Year 1 treated pts[1,2]	0.79 [0.02, 4.38]	2.83 [0.34, 10.24]	3.50 [0.95, 8.97]	2.24 [0.90, 4.62]
Year 2 treated pts[1,3]	0.75 [0.02, 4.20]	4.23 [0.87, 12.35]	0.00 [0.00, 2.98]	1.31 [0.36, 3.37]
Year 3 treated pts[1,4]	2.43 [0.50, 7.10]	4.37 [0.90, 12.77]	3.23 [0.67, 9.45]	3.16 [1.44, 6.00]
Year 4 treated pts[1,5]	0.00 [0.00, 2.47]	1.47 [0.04, 8.22]	0.00 [0.00, 3.43]	0.36 [0.01, 2.02]
Year 5 treated pts[1,6]	2.40 [0.50, 7.02]	3.09 [0.37, 11.17]	2.30 [0.28, 8.30]	2.53 [1.02, 5.21]
Malignancies				
Year 1 treated pts[1,2]	0.00 [0.00, 2.35]	0.00 [0.00, 4.25]	0.88 [0.02, 4.91]	0.32 [0.01, 1.79]
Year 2 treated pts[1,3]	0.00 [0.00, 2.26]	0.00 [0.00, 4.22]	0.00 [0.00, 3.01]	0.00 [0.00, 0.99]
Year 3 treated pts[1,4]	0.00 [0.00, 2.43]	0.00 [0.00, 4.37]	0.00 [0.00, 3.27]	0.00 [0.00, 1.06]
Year 4 treated pts[1,5]	0.83 [0.02, 4.62]	1.50 [0.04, 8.33]	0.00 [0.00, 3.47]	0.73 [0.09, 2.64]
Year 5 treated pts[1,6]	0.00 [0.00, 2.40]	0.00 [0.00, 4.68]	0.00 [0.00, 3.49]	0.00 [0.00, 1.09]
Infusion reactions, n/N (%)				
Year 1 treated pts	17/157 (10.8)	11/77 (14.3)	16/118 (13.6)	45/353 (12.7)
Year 2 treated pts	3/136 (2.2)	2/73 (2.7)	2/103 (1.9)	7/312 (2.2)
Year 3 treated pts	7/124 (5.6)	5/69 (7.2)	1/93 (1.1)	13/286 (4.5)

Year 4 treated pts	2/122 (1.6)	1/68 (1.5)	1/88 (1.1)	4/278 (1.4)
Year 5 treated pts	1/118 (0.8)	1/64 (1.6)	1/82 (1.2)	3/264 (1.1)

Data presented are incidence per 100 patient-years [95% confidence interval] unless indicated otherwise.
[1]Among treated patients continuing at the beginning of the treatment year.
[2]The numbers of patients for Year 1 = 158, 77, 118, and 353 across the golimumab groups shown above.
[3]The numbers of patients for Year 2 = 141, 73, 105/106, and 319/320 across the golimumab groups shown above.
[4]The numbers of patients for Year 3 = 126, 69, 93/94, and 288/289 across the golimumab groups shown above.
[5]The numbers of patients for Year 4 = 122, 68, 89, and 279 across the golimumab groups shown above.
[6]The numbers of patients for Year 5 = 118, 64, 81, and 263 across the golimumab groups shown above.
AE = adverse event, GLM = golimumab

SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

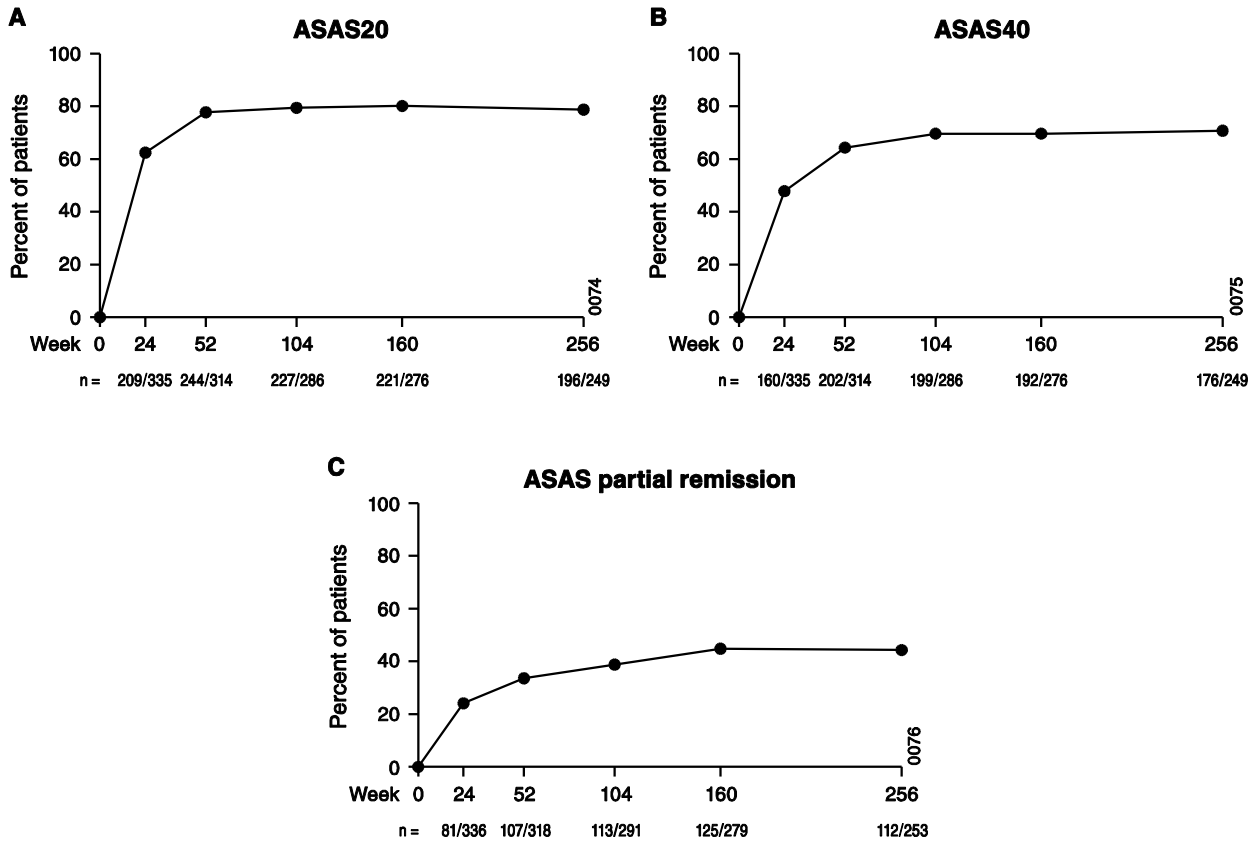

Figure S1: The proportions of patients in ASAS20 response (**A**), ASAS40 response (**B**), and/or ASAS partial remission (**C**) through week 256. Observed efficacy data (no imputation of missing data) are summarized for patients who did not discontinue from the study through week 24. The placebo-controlled study period ended at week 24, but study participants and investigators remained blinded to the golimumab dose (50 or 100 mg) through week 100. During the long-term extension, which started with the week-104 golimumab injection, the investigator could increase or decrease the golimumab dose. *ASAS20/40, ≥ 20%/40% improvement in the Assessment of SpondyloArthritis international Society (ASAS) criteria*

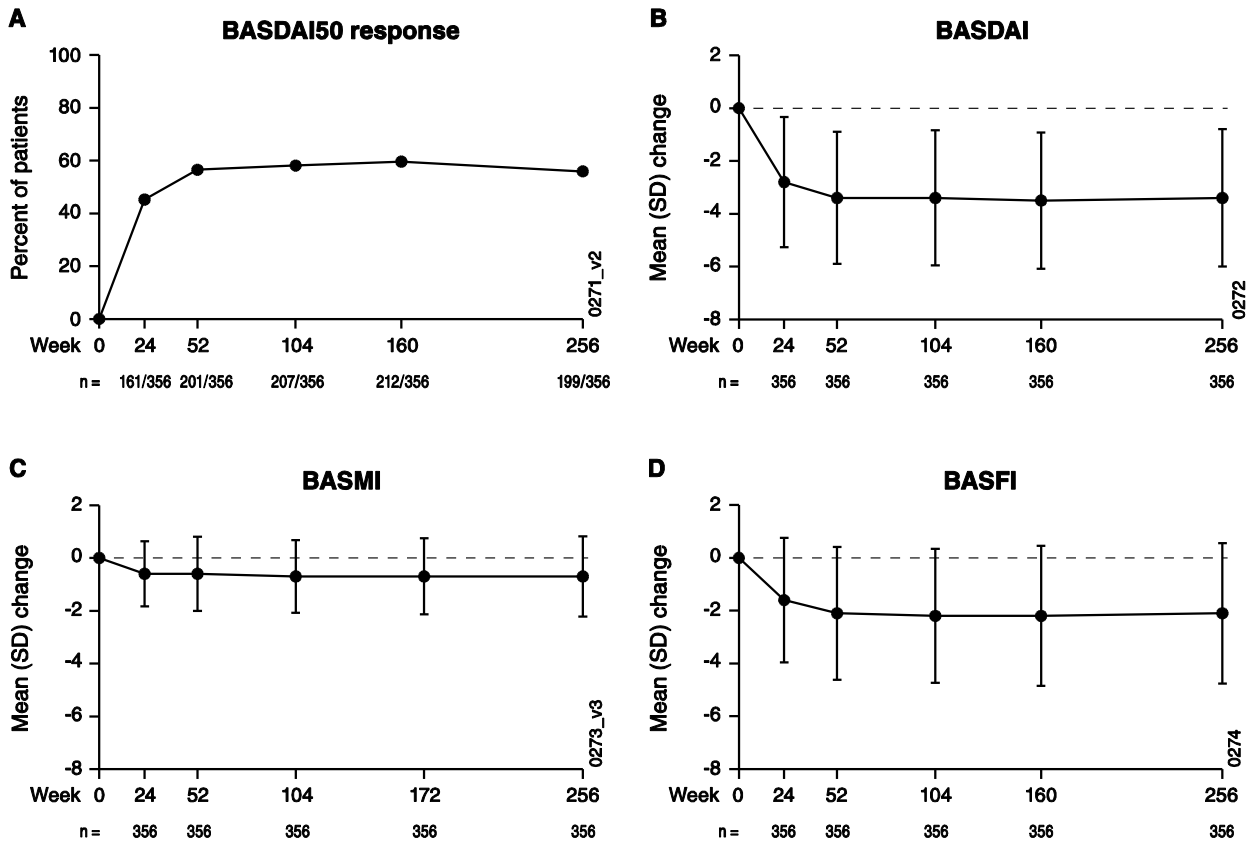

Figure S2: The proportions of patients in BASDAI50 response through week 256 (**A**) and mean (SD) changes from baseline to week 256 in BASDAI (**B**), BASMI (**C**), and BASFI (**D**) scores based on intent-to-treat analyses. The placebo-controlled study period ended at week 24, but study participants and investigators remained blinded to the golimumab dose (50 or 100 mg) through week 100. During the long-term extension, which started with the week-104 golimumab injection, the investigator could increase or decrease the golimumab dose. *BASDAI50, ≥50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation*

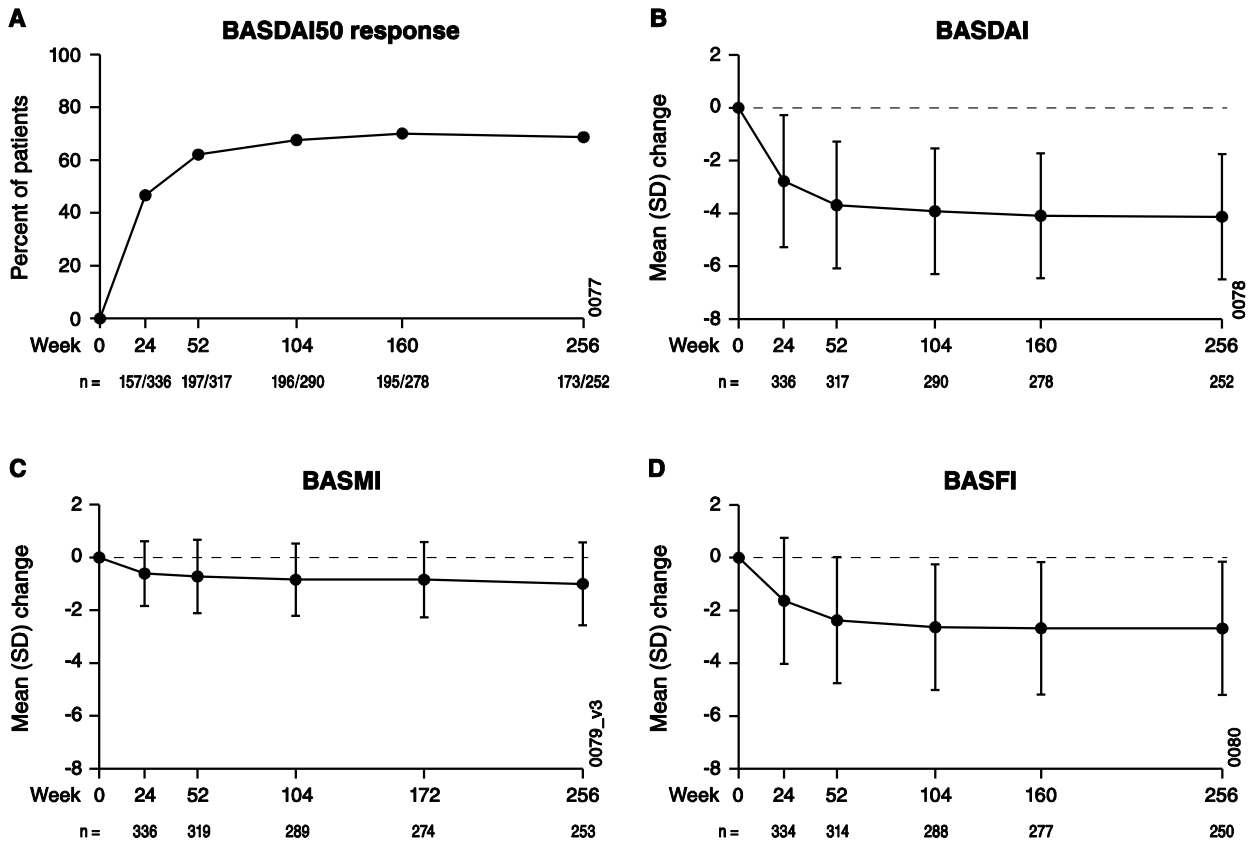

Figure S3: The proportions of patients in BASDAI50 response through week 256 (**A**) and mean (SD) changes from baseline to week 256 in BASDAI (**B**), BASMI (**C**), and BASFI (**D**) scores. Observed efficacy data (no imputation of missing data) are summarized for patients who did not discontinue from the study through week 24. The placebo-controlled study period ended at week 24, but study participants and investigators remained blinded to the golimumab dose (50 or 100 mg) through week 100. During the long-term extension, which started with the week-104 golimumab injection, the investigator could increase or decrease the golimumab dose.

BASDAI50, ≥50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation