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## EXTENDED REPORT

# Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis

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## ABSTRACT

**Objective** To assess pooled golimumab safety up to year 3 of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) trials.

**Methods** Golimumab 50 and 100 mg, administered subcutaneously (SC) every 4 weeks (q4wk), were assessed in patients with active RA (methotrexate-naïve, methotrexate-experienced and anti-TNF (tumour necrosis factor)-experienced), PsA or AS, despite conventional therapy. Placebo control continued up to week (wk) 24 (wk 52, methotrexate-naïve), with early escape at wk 16 (wk 28, methotrexate-naïve); subsequently, all patients received golimumab 50 or 100 mg q4wk. After the blinded controlled period, golimumab doses could be adjusted per investigator discretion. Pooled safety analyses reported herein include data from placebo-controlled and uncontrolled study periods up to wk 160. Determinations of incidences/100 patient-years (pt-yrs) for rare events also included RA patients from a phase IIb trial.

**Results** Across five phase III trials of SC golimumab, 639 patients received placebo and 2226 received golimumab 50 mg (n=1249) and/or 100 mg (n=1501) up to wk 160 (patients may be included in more than one group because non-responders were allowed early escape); 1179 patients were treated for  $\geq 156$  weeks. For placebo, golimumab 50 mg and golimumab 100 mg, respective adverse event incidences/100 pt-yrs (95% CIs) up to wk 160 were: 0.28 (0.01 to 1.56), 0.30 (0.12 to 0.62), 0.41 (0.23 to 0.69) for death; 5.31 (3.20 to 8.30), 3.03 (2.36 to 3.82), 5.09 (4.36 to 5.90) for serious infection; 0.00 (0.00 to 0.84), 0.17 (0.05 to 0.44), 0.35 (0.18 to 0.62) for tuberculosis; 0.00 (0.00 to 0.84), 0.13 (0.03 to 0.38), 0.24 (0.10 to 0.46) for opportunistic infection; 0.00 (0.00 to 0.84), 0.00 (0.00 to 0.13), 0.12 (0.03 to 0.30) for demyelination; and 0.00 (0.00 to 0.84), 0.04 (0.00 to 0.24), 0.18 (0.06 to 0.38) for lymphoma.

**Conclusions** SC golimumab safety up to 3 years remained consistent with that of other TNF antagonists. Golimumab 100 mg showed numerically higher incidences of serious infections, demyelinating events and lymphoma than 50 mg; safety follow-up up to year 5 continues.

## INTRODUCTION

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are disorders characterised by excessive production of proinflammatory

cytokines, including tumour necrosis factor- $\alpha$  (TNF), and patients with these chronic diseases receive treatment for a protracted time. After approximately 12–15 years of clinical use, the safety profile of anti-TNF agents is generally well characterised and consistent across agents, including adalimumab,<sup>1</sup> certolizumab,<sup>2</sup> etanercept<sup>3</sup> and infliximab.<sup>4</sup>

As a more recently developed TNF antagonist, the human monoclonal antibody, golimumab, has not been studied as extensively. To date, however, golimumab safety appears to be consistent with that of older agents.<sup>5–7</sup> The pivotal phase III trials of subcutaneous (SC) golimumab in patients with RA, PsA and AS comprised randomised, double-blind, placebo-controlled periods, followed by long-term extensions designed to evaluate safety up to 5 years. Herein, we report the safety findings up to 3 years of golimumab treatment pooled across these clinical trials.

## PATIENTS AND METHODS

### Study patients and designs

All clinical trials contributing data to this pooled analysis were conducted according to the Declaration of Helsinki and the International Committee on Harmonisation of Good Clinical Practices. Study protocols were approved by either central or individual site institutional review boards/ethics committees; all patients provided written informed consent before study participation. Details of patient selection criteria and study designs for each trial have been reported.<sup>8–20</sup>

Data from a phase IIb trial in RA were included in these pooled analyses for determining the incidences of rare but important events, as four patients in this smaller trial had a malignancy (three with non-melanoma skin cancers (NMSCs) and one with lung cancer). The duration of the phase IIb trial was 6 months, rather than the 3 years of follow-up for the phase III trials. The phase IIb trial was therefore not included in the analyses of more common adverse events (AEs). See table 1 and online supplementary text for further details of patients/trial designs.

### Data collection and analyses

All AEs were systematically captured and categorised by the site investigator for seriousness,

**Table 1** Golimumab clinical trials contributing data to 3-year pooled safety analyses

Trial phase/identifier	Indication	Study design	Study treatment	Patients randomised/ treated
Phase IIb <sup>8</sup> (for rare events only)	RA, inadequate response to MTX	Multicentre, randomised (1:1:1:1:1), double-blind, placebo-controlled, 5-arm, dose-ranging study	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo+MTX: wk 0 and q2w to wk 18 with crossover to IV infliximab (3 mg/kg) at wks 20, 22, and 28, and then q8w to wk 44</li> <li>▶ Golimumab 50 mg+MTX: wk 0 and q4w to wk 0 and wk 48</li> <li>▶ Golimumab 50 mg+MTX: wk 0 and q2w to wk 18, then q4w wks 20–48</li> <li>▶ Golimumab 100 mg+MTX: wk 0 and q4w to wk 48</li> <li>▶ Golimumab 100 mg+MTX: wk 0 and q2w to wk 18, then q4w for wks 20–48</li> </ul>	Placebo: 35/34 Golimumab: 137/137 Total: 172/171
Phase III, GO-BEFORE <sup>9 10</sup>	RA, MTX-naïve	Multicenter, randomised (1:1:1:1), double-blind, placebo-controlled to wk 52 with early escape* at wk 28, followed by open-label golimumab from wk 52 DBL forward	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo+MTX q4w</li> <li>▶ Golimumab 100 mg q4w+placebo</li> <li>▶ Golimumab 50 mg q4w+MTX</li> <li>▶ Golimumab 100 mg q4w+MTX; All to wk 52 with early escape at wk 28*</li> </ul> Beginning at wk 52, placebo+MTX-treated pts crossed over to golimumab 50 mg+MTX, During the OLE, the investigator could escalate open-label golimumab to 100 mg and/or adjust the MTX dose	Placebo: 160/160 Golimumab: 477/474 Total: 637/633
Phase III, GO-FORWARD <sup>11–13</sup>	RA, inadequate response to MTX	Multicentre, randomised (3:3:2:2), double-blind, placebo-controlled to wk 24 with early escape* at wk 16, followed by blinded golimumab to wk 52 and then open-label golimumab from wk 52 DBL forward	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo+MTX q4w</li> <li>▶ Golimumab 100 mg q4w+placebo</li> <li>▶ Golimumab 50 mg q4w+MTX</li> <li>▶ Golimumab 100 mg q4w+MTX; All to wk 24 with early escape at wk 16*</li> </ul> Beginning at wk 24, placebo+MTX-treated pts crossed over to double-blind golimumab 50mg+MTX During the OLE, the investigator could escalate open-label golimumab to 100 mg and/or adjust the MTX dose	Placebo: 133/133 Golimumab: 311/311 Total: 444/444
Phase III, GO-AFTER <sup>14 15</sup>	RA, inadequate response to anti-TNF	Multicentre, randomised (1:1:1), double-blind, placebo-controlled to wk 24 with early escape* at wk 16, followed by open-label golimumab after wk 24 DBL	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo q4w</li> <li>▶ Golimumab 50 mg 4w</li> <li>▶ Golimumab 100 mg q4w; All to wk 24 with early escape at wk 16*</li> </ul> Beginning at wk 24, placebo-treated pts crossed over to golimumab 50 mg During the OLE, the investigator could escalate open-label golimumab to 100 mg	Placebo: 155/155 Golimumab: 306/306 Total: 461/461
Phase III, GO-REVEAL <sup>16–18</sup>	PsA, inadequate response to DMARDs/NSAIDs	Multicentre, randomised (1:1.3:1.3), double-blind, placebo-controlled to wk 24 with early escape* at wk 16, followed by blinded golimumab from wk 24 forward. Blinded therapy continued to wk 52 DBL, after which the long-term OLE began	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo</li> <li>▶ Golimumab 50 mg q4w</li> <li>▶ Golimumab 100 mg q4w; All to wk 24 with early escape at wk 16*</li> </ul> Beginning at wk 24, placebo-treated pts crossed over to golimumab 50 mg During the OLE, the investigator could escalate the golimumab dose to 100 mg	Placebo: 113/113 Golimumab: 292/292 Total: 405/405
Phase III, GO-RAISE <sup>19 20</sup>	AS, inadequate response to DMARDs/NSAIDs	Multicentre, randomised (1:1.8:1.8), double-blind, placebo-controlled to wk 24 with early escape* at wk 16, followed by dose-blinded golimumab from wk 24 forward. Blinded therapy continued to wk 104 DBL, after which the long-term OLE began	Fixed SC doses of placebo or golimumab <ul style="list-style-type: none"> <li>▶ Placebo</li> <li>▶ Golimumab 50 mg q4w</li> <li>▶ Golimumab 100 mg q4w; All to wk 24 with early escape at wk 16*</li> </ul> Beginning at wk 24, placebo-treated pts crossed over to golimumab 50 mg During the OLE, the investigator could escalate the golimumab dose to 100 mg	Placebo: 78/78 Golimumab: 278/277 Total: 356/355

\*For patients meeting the early escape criteria (ie, <20% improvement in tender and swollen joint counts for RA, <10% improvement in tender and swollen joint counts for PsA, <20% improvement in total back and morning stiffness for AS), those receiving placebo escaped to golimumab 50 mg, those receiving golimumab 100 mg+placebo added MTX, those receiving golimumab 50 mg increased the golimumab dose to 100 mg, and those receiving golimumab 100 mg had no change in study medication. AS, ankylosing spondylitis; DBL, database lock; DMARD, disease-modifying antirheumatic drug; IV, intravenous; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; OLE, open-label extension; PsA, psoriatic arthritis; pt, patient; RA, rheumatoid arthritis; SC, subcutaneous; TNF, tumour necrosis factor; q2/4/8w, every 2/4/8 weeks; wk, week.

intensity, causality and action taken. Investigators were also required to document whether or not each AE represented an infection or injection-site reaction (ISR). AEs were summarised and categorised by system-organ class using the *Medical dictionary for regulatory activities*, V12.1.

Aggregate AE-reporting rates were analysed across the trials based on treatment received (placebo/golimumab dose) before the AE. Safety events from the first golimumab exposure to the end of the 16-week placebo-controlled period and 3-year reporting period common to the phase III trials were included. See the online supplement for further details of data collection/analyses.

## RESULTS

### Extent of exposure

Across these five phase III trials evaluating SC golimumab, 639 patients received placebo, 1249 received golimumab 50 mg, and 1501 received golimumab 100 mg (table 2). Some patients are counted in more than one treatment group because they escaped early, crossed over between treatment arms, and/or escalated the golimumab dose.

### Baseline patient characteristics

The baseline patient demographics have been reported for each phase III RA,<sup>9 11 14</sup> PsA<sup>16</sup> and AS<sup>19</sup> trial. Of the 2303 patients, 356 (15.5%) had AS, 405 (17.6%) had PsA, and 1542 (67.0%) had RA. Baseline disease characteristics of mean C-reactive protein level (2.0 mg/dL) and Health Assessment Questionnaire-Disability Index score (1.4) confirm that the overall pooled safety population entered the trials with inflammation and moderate functional impairment (table 3).

### Adverse events

During the 16-week placebo-controlled period, similar proportions of patients in the placebo (64.2%), golimumab 50 mg (67.9%) and golimumab 100 mg (65.7%) groups experienced  $\geq 1$  AE. Infection was the most common AE; only upper respiratory tract infection, nasopharyngitis and nausea occurred in  $>5\%$  of patients in either golimumab group. Up to week (wk) 16 in the placebo, 50 mg and 100 mg groups, 4.9%, 4.4% and 3.6%, respectively, of patients experienced  $\geq 1$  serious AE (SAE), and 2.8%, 2.6% and 1.8% of patients, respectively, discontinued the study agent because of  $\geq 1$  AE (table 4). Infection was also the most commonly occurring SAE.

Up to wk 160,  $\geq 1$  AE was reported by 73.6%, 85.6% and 86.7% of patients receiving placebo (average length of follow-up 28.1 weeks), golimumab 50 mg (93.4 weeks) and golimumab 100 mg (115.1 weeks), respectively (table 4). Overall

AEs were generally evenly distributed across disease states, as were the most commonly occurring types of AEs (see online supplementary table S1).

The AEs occurring in  $>5\%$  of patients in any treatment group up to wk 160 were similar to those observed during the placebo-controlled period. Across all treatment groups, infections were again the most common (placebo, 34.6%; 50 mg, 60.4%; 100 mg, 64.3%). Although the proportion of patients with infection in each golimumab group was nearly twice as high as that in the placebo group, the duration of golimumab follow-up was  $\geq 3$  times longer than that for placebo. The time-adjusted incidence of serious infection was higher for golimumab 100 mg (5.09/100 pt-yrs) than for golimumab 50 mg (3.03/100 pt-yrs); however, the incidence observed with placebo (5.31/100 pt-yrs) was the highest among the three groups up to 160 weeks; a similar pattern was observed during the placebo-controlled period (table 5). Serious infections appeared to be more common among golimumab-treated patients with RA (147/1616, 9.1%) than among golimumab-treated patients with PsA (10/394, 2.5%) or AS (17/353, 4.8%). Within each indication, the 95% CIs surrounding serious infection incidence rates for golimumab 50 mg and 100 mg were contained within those for placebo (see online supplementary table S1). Serious infections, but not all infections or opportunistic infections, also appeared to occur more commonly among golimumab-treated patients with baseline oral corticosteroid use versus patients not using corticosteroids at baseline, although the 95% CIs did overlap, at both wk 24 and wk 160 (see online supplementary table S2).

Higher incidences of tuberculosis (0.35 vs 0.17/100 pt-yrs) and opportunistic infection (0.24 vs 0.13/100 pt-yrs) were observed with golimumab 100 mg than with golimumab 50 mg; the 95% CIs for both golimumab doses, however, were contained within those for placebo for both of these AEs up to 160 weeks (table 5). Of the patients with tuberculosis, 15 had RA and one had AS (see online supplementary table S1). Pulmonary tuberculosis was the most common presentation, and all patients were located outside of North America (Asia, Europe and South America).

Up to wk 160, with a far longer period of follow-up for golimumab than for placebo treatment, 57 (8.9%), 192 (15.4%) and 325 (21.7%) patients in the placebo, golimumab 50 mg and golimumab 100 mg groups, respectively, had  $\geq 1$  SAE, and 31 (4.9%), 92 (7.4%) and 158 (10.5%) patients, respectively, discontinued the study agent because of an AE (table 4). Up to wk 160, 22 patients died, including one (0.1%), seven (0.5%) and 14 (0.9%) patients in the placebo, golimumab 50 mg and golimumab 100 mg groups, respectively. The time-adjusted

**Table 2** Extent of exposure: pooled data from five phase III studies of SC golimumab in RA, PsA and AS

	Placebo $\pm$ MTX	Golimumab 50 mg $\pm$ MTX	Golimumab 100 mg $\pm$ MTX
Number of treated patients*	639	1249	1501
Number of SC injections (mean/median)	6.6/6.0	22.4/22.0	27.5/35.0
Weeks of follow-up (mean/median)	28.1/24.0	93.4/100.0	115.1/144.6
Cumulative golimumab dose (mean/median), mg	N/A	1118.6/1100.0	2739.9/3500.0
Number (%) of patients by length of golimumab exposure			
<104 weeks	N/A	663 (53.1)	604 (40.2)
104 to <156 weeks	N/A	323 (25.9)	200 (13.3)
$\geq 156$ weeks	N/A	263 (21.1)	697 (46.4)

\*Patients may appear in  $\geq 1$  treatment column.

AS, ankylosing spondylitis; MTX, methotrexate; N/A, not applicable; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous.

**Table 3** Baseline patient demographic and disease characteristics: pooled data from five phase III trials of SC golimumab in RA, PsA and AS

Characteristic	Placebo±MTX	Golimumab 50 mg±MTX	Golimumab 100 mg±MTX	Total
Randomised patients, N	639	685	979	2303
Women, n (%)	442 (69.2)	413 (60.3)	660 (67.4)	1515 (65.8)
Race, n (%)				
Asian	67 (10.5)	83 (12.1)	135 (13.8)	285 (12.4)
Black	18 (2.8)	12 (1.8)	17 (1.7)	47 (2.0)
White	515 (80.6)	563 (82.2)	781 (79.8)	1859 (80.7)
Other	39 (6.1)	27 (3.9)	46 (4.7)	112 (4.9)
Age, years				
Mean±SD	49.4±13.03	48.0±12.52	48.4±12.50	48.6±12.66
Median (IQR)	50.0 (41.0, 58.0)	48.0 (40.0, 57.0)	49.0 (40.0, 57.0)	49.0 (40.0, 57.0)
Disease duration, years				
Mean±SD	8.2±8.73	7.7±8.12	7.2±7.75	7.6±8.15
Median (IQR)	4.8 (1.6, 11.6)	4.9 (1.4, 11.1)	4.5 (1.4, 10.1)	4.7 (1.4, 10.9)
CRP, mg/dL				
Mean±SD	1.9±2.73	2.0±2.62	2.1±2.86	2.0±2.76
Median (IQR)	1.0 (0.3, 2.3)	0.9 (0.3, 2.4)	0.9 (0.3, 2.6)	0.9 (0.3, 2.4)
HAQ-DI in RA and PsA, 0–3*, N	559	542	831	1932
Mean±SD	1.4±0.67	1.4±0.70	1.4±0.68	1.4±0.68
Median (IQR)	1.4 (1.0, 1.9)	1.4 (0.9, 1.9)	1.4 (0.9, 1.9)	1.4 (0.9, 1.9)
DAS28-CRP in RA pts only, N	448	398	688	1534
Mean±SD	5.6±1.04	5.8±1.09	5.6±1.03	5.7±1.05
Median (IQR)	5.6 (4.8, 6.3)	5.8 (5.0, 6.5)	5.6 (4.9, 6.4)	5.7 (4.9, 6.4)
BASDAI >4 in AS pts, n/N (%)	75/78 (96.2)	130/138 (94.2)	135/140 (96.4)	340/356 (95.5)
MTX use in RA and PsA†				
Number of MTX-treated patients	156	174	169	499
Mean dose±SD (mg)	16.0±5.01	16.0±5.30	16.3±5.33	16.1±5.21
Median dose (IQR) (mg)	15.0 (12.5, 20.0)	15.0 (12.5, 20.0)	15.0 (12.5, 20.0)	15.0 (12.5, 20.0)
Oral corticosteroid use in RA and PsA†				
Number of corticosteroid-treated patients	270	260	413	943
Mean dose±SD (mg)	6.6±2.59	6.8±2.70	6.8±2.60	6.8±2.62
Median dose (IQR) (mg)	5.0 (5.0, 10.0)	6.0 (5.0, 10.0)	5.0 (5.0, 10.0)	5.0 (5.0, 10.0)

\*HAQ-DI data were not collected in the GO-RAISE golimumab trial conducted in patients with AS.

†MTX use at baseline was not allowed in the GO-BEFORE golimumab trial in MTX-naïve patients with RA; MTX and oral corticosteroid use was very limited in patients with AS and are thus summarised only for patients with RA and PsA.

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DAS28-CRP, 28-joint Disease Activity Score using CRP; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous.

incidence of death was 0.52/100 pt-yrs for the placebo-controlled period and 0.41/100 pt-yrs up to wk 160 for patients who received golimumab 100 mg, which was numerically higher than for patients who received golimumab 50 mg (0.27 and 0.30/100 pt-yrs, respectively); the 95% CIs for the 100 mg group, however, were contained within that for placebo at both time points (table 5). Fourteen of the 22 deaths occurred between wk 52 and wk 160. Causes of death were cerebrovascular/cardiovascular event in six patients, malignancy in five patients, infection in three patients, hypoglycaemic coma in one patient, hepatitis in one patient, an unrelated accident in one patient, and an overdose in one patient; the cause of death was unknown for four patients. More golimumab-treated patients with RA (19/1616, 1.2%) died than did golimumab-treated patients with PsA (2/394, 0.5%) or AS (0/353, 0.0%). Within each indication, the 95% CIs surrounding death incidence rates for golimumab 50 mg and 100 mg were contained within those for placebo (see online supplementary table S1).

The overall incidence of malignancy up to wk 160 did not appear to be elevated with golimumab vs placebo treatment, with golimumab 100 mg vs 50 mg, or when compared with rates expected in the general US population. Similar findings were observed for NMSC. A higher incidence of lymphoma was

observed up to wk 160 with golimumab 100 mg (0.18/100 pt-yrs) than with golimumab 50 mg (0.04/100 pt-yrs) or placebo (0.00/100 pt-yrs), and also relative to the general US population (standardised incidence ratio (SIR) of 6.69 and surrounding 95% CI of (2.45 to 14.56), which was not inclusive of 1; table 5). The higher incidence of lymphoma in golimumab-treated patients was driven by that in patients with RA (SIR (95% CI) of 5.70 (2.09 to 12.42)) (see online supplementary table S1).<sup>21–25</sup> No predominant time point at which the lymphomas occurred was observed: two cases of lymphoma occurred during year 1, two occurred during year 2, one occurred during year 3, and two occurred during year 4.

Up to wk 160, the number of golimumab-treated patients who experienced ≥1 AE associated with the following selected autoimmune disorders were: lupus-like syndrome, one (0.0%); systemic lupus erythematosus, one (0.0%); pustular psoriasis, 11 (0.5%); vasculitic rash, four (0.2%); and anti-neutrophil cytoplasmic antibody-positive vasculitis, one (0.0%). No patient in the placebo group experienced any such event. No anaphylactic events or serum sickness-like reactions were reported up to wk 160.

Up to wk 160, four demyelination events were identified in three patients randomised to golimumab 100 mg, all of whom had RA, with none occurring among patients randomised to either

**Table 4** Safety findings up to week 16 and week 160: pooled data from five phase III studies of SC golimumab in rheumatological indications (RA, PsA and AS)

	Week 16 (placebo-controlled)			Week 160		
	Placebo±MTX	Golimumab 50 mg±MTX	Golimumab 100 mg±MTX	Placebo±MTX	Golimumab 50 mg±MTX	Golimumab 100 mg±MTX
Number of treated patients*	639	683	977	639	1249	1501
Patients with ≥1 AE	410 (64.2)	464 (67.9)	642 (65.7)	470 (73.6)	1069 (85.6)	1302 (86.7)
Most common AE†						
Upper respiratory tract infection	37 (5.8)	51 (7.5)	69 (7.1)	56 (8.8)	263 (21.1)	346 (23.1)
Nasopharyngitis	31 (4.9)	37 (5.4)	54 (5.5)	42 (6.6)	167 (13.4)	219 (14.6)
Nausea	28 (4.4)	35 (5.1)	51 (5.2)	51 (8.0)	104 (8.3)	159 (10.6)
Cough	–	–	–	38 (5.9)	124 (9.9)	149 (9.9)
Headache	–	–	–	38 (5.9)	114 (9.1)	149 (9.9)
Back pain	–	–	–	22 (3.4)	110 (8.8)	146 (9.7)
Bronchitis	–	–	–	24 (3.8)	113 (9.0)	145 (9.7)
Sinusitis	–	–	–	16 (2.5)	101 (8.1)	142 (9.5)
Hypertension	–	–	–	16 (2.5)	84 (6.7)	135 (9.0)
Diarrhoea	–	–	–	37 (5.8)	92 (7.4)	123 (8.2)
Injection-site erythema	–	–	–	7 (1.1)	56 (4.5)	113 (7.5)
Urinary tract infection	–	–	–	19 (3.0)	70 (5.6)	109 (7.3)
ALT increased	–	–	–	33 (5.2)	108 (8.6)	107 (7.1)
RA	–	–	–	25 (3.9)	58 (4.6)	107 (7.1)
Fatigue	–	–	–	25 (3.9)	66 (5.3)	101 (6.7)
Rash	–	–	–	23 (3.6)	62 (5.0)	88 (5.9)
Pharyngitis	–	–	–	16 (2.5)	57 (4.6)	80 (5.3)
Influenza	–	–	–	15 (2.3)	47 (3.8)	77 (5.1)
AST increased	–	–	–	23 (3.6)	76 (6.1)	72 (4.8)
Patients with ≥1 SAE	31 (4.9)	30 (4.4)	35 (3.6)	57 (8.9)	192 (15.4)	325 (21.7)
Treatment discontinued due to ≥1 AE	18 (2.8)	18 (2.6)	18 (1.8)	31 (4.9)	92 (7.4)	158 (10.5)
Injection-site reactions						
Patients with reactions‡	14 (2.2)	32 (4.7)	65 (6.7)	18 (2.8)	107 (8.6)	174 (11.6)
Mild	14 (2.2)	32 (4.7)	64 (6.6)	18 (2.8)	102 (8.2)	169 (11.3)
Moderate	0 (0.0)	1 (0.1)	3 (0.3)	0 (0.0)	11 (0.9)	18 (1.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Patients with ≥1 hepatobiliary AEs§	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.2)	5 (0.3)
ALT ≥3×ULN and bilirubin ≥2×ULN	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
ALT ≥3×ULN and serious hepatobiliary AE	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	3 (0.2)

Data shown are number (%) of patients.

\*Patients may appear in ≥1 treatment column.

†Defined as AE occurring in ≥5% of patients in any treatment group up to week 16 or week 160. Common AEs are presented in decreasing order of frequency in the golimumab 100 mg group up to week 160. AEs with ‘–’ did not meet the criterion for ‘common’ at that time point.

‡Patients may have reported ≥1 injection-site reaction.

§Hepatobiliary AE defined as ALT ≥3×ULN in combination with either bilirubin ≥2×ULN or the occurrence of an AE within the hepatobiliary system-organ class of the *Medical dictionary for regulatory activities* that was classified as serious by the investigator in accordance with regulatory guidelines. For the latter criterion, two patients (one RA, one AS) had cholelithiasis, one RA patient had hepatitis leading to acute hepatic failure of unknown cause and ultimately death, one AS patient had hepatic stenosis, and one AS patient had hepatitis.

AE, adverse event; ALT, alanine aminotransferase; AS, ankylosing spondylitis; AST, aspartate aminotransferase; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SAE, serious adverse event; SC, subcutaneous; ULN, upper limit of normal.

placebo or golimumab 50 mg. The incidence (95% CI) of demyelination for golimumab 100 mg was 0.12 (0.03 to 0.30)/100 pt-yrs; this 95% CI was contained within that for placebo (table 5).

There were few hepatobiliary AEs up to wk 16 (table 4). Up to wk 160, five patients developed a hepatobiliary SAE with alanine aminotransferase (ALT) ≥3 × the upper limit of normal (ULN). Two patients (one with RA and one with AS) had cholelithiasis, one AS patient had hepatic steatosis, one AS patient (with concomitant methotrexate (MTX) and indomethacin use and recent alcohol use) had asymptomatic ALT and aspartate aminotransferase elevations >5 × ULN after the first two doses of golimumab 100 mg that resolved after golimumab discontinuation, and one RA patient had investigator-reported hepatitis that resulted in acute hepatic failure (with both events reported as being of unknown cause by the investigator). This patient

experienced bleeding after liver biopsy and subsequently died. Possible confounding factors included recent initiation of methimazole and history of herbal medicine use.

Although a higher proportion of patients (6.7%) and injections (1.4%) had an ISR associated with golimumab 100 mg than with placebo (2.2% and 0.5%, respectively) or golimumab 50 mg (4.7% and 0.8%, respectively), no ISR was severe, serious, or led to permanent discontinuation of the study agent up to wk 16. Similar findings were observed up to wk 160, with only one patient/injection (golimumab 100 mg) having a severe ISR (table 4). An additional patient (golimumab 100 mg +MTX) developed a serious ISR (moderate injection-site erythema) that resulted in discontinuation of the study agent 1 day after the 52-week visit. This patient had detectable antibodies to golimumab.

**Table 5** Incidences of rare safety events during the placebo-controlled period and up to week 160: pooled data from phase IIb and phase III studies of SC golimumab in rheumatological indications (RA, PsA and AS)

	Placebo-controlled period*			Week 160		
	Placebo±MTX	Golimumab 50 mg±MTX	Golimumab 100 mg±MTX	Placebo±MTX	Golimumab 50 mg±MTX	Golimumab 100 mg±MTX
Number of treated patients†	674	750	1044	674	1317	1571
Death, n (%)	1 (0.1)	1 (0.1)	3 (0.3)	1 (0.1)	7 (0.5)	14 (0.9)
Incidence per 100 pt-yrs (95% CI)	0.32 (0.01 to 1.79)	0.27 (0.01 to 1.53)	0.52 (0.11 to 1.53)	0.28 (0.01 to 1.56)	0.30 (0.12 to 0.62)	0.41 (0.23 to 0.69)
Serious infection, n (%)	17 (2.5)	12 (1.6)	27 (2.6)	17 (2.5)	57 (4.3)	117 (7.4)
Incidence per 100 pt-yrs (95% CI)	5.50 (3.21 to 8.81)	3.31 (1.71 to 5.78)	4.76 (3.14 to 6.92)	5.31 (3.20 to 8.30)	3.03 (2.36 to 3.82)	5.09 (4.36 to 5.90)
Tuberculosis, n (%)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	4 (0.3)	12 (0.8)
Incidence per 100 pt-yrs (95% CI)	0.00 (0.00 to 0.96)	0.55 (0.07 to 1.98)	0.00 (0.00 to 0.52)	0.00 (0.00 to 0.84)	0.17 (0.05 to 0.44)	0.35 (0.18 to 0.62)
Opportunistic infection, n (%)‡	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.2)	8 (0.5)
Incidence per 100 pt-yrs (95% CI)	0.00 (0.00 to 0.96)	0.00 (0.00 to 0.82)	0.17 (0.00 to 0.97)	0.00 (0.00 to 0.84)	0.13 (0.03 to 0.38)	0.24 (0.10 to 0.46)
Malignancy						
All malignancies, n (%)	6 (0.9)	3 (0.4)	10 (1.0)	7 (1.0)	29 (2.2)	38 (2.4)
Incidence per 100 pt-yrs (95% CI)	1.93 (0.71 to 4.21)	0.82 (0.17 to 2.41)	1.75 (0.84 to 3.21)	1.97 (0.79 to 4.05)	1.26 (0.84 to 1.81)	1.13 (0.80 to 1.55)
SIR (95% CI)§ vs SEER database	1.07 (0.13 to 3.87)	0.97 (0.12 to 3.49)	1.25 (0.34 to 3.21)	0.94 (0.11 to 3.38)	1.48 (0.89 to 2.31)	0.99 (0.61 to 1.53)
Non-melanoma skin cancer, n (%)	4 (0.6)	1 (0.1)	6 (0.6)	5 (0.7)	10 (0.8)	18 (1.1)
Incidence per 100 pt-yrs (95% CI)	1.29 (0.35 to 3.30)	0.27 (0.01 to 1.53)	1.05 (0.38 to 2.28)	1.40 (0.46 to 3.28)	0.43 (0.21 to 0.80)	0.53 (0.32 to 0.84)
Lymphoma, n (%)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.08)¶	6 (0.4)**
Incidence per 100 pt-yrs (95% CI)	0.00 (0.00 to 0.96)	0.00 (0.00 to 0.82)	0.35 (0.04 to 1.26)	0.00 (0.00 to 0.84)	0.04 (0.00 to 0.24)	0.18 (0.06 to 0.38)
SIR (95% CI)§ vs SEER database	0.00 (0.00 to 36.43)	0.00 (0.00 to 32.66)	<b>14.13 (1.71 to 51.03)</b>	0.00 (0.00 to 31.98)	1.71 (0.04 to 9.55)	<b>6.69 (2.45 to 14.56)</b>
Demyelinating disorder, n (%)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)
Incidence per 100 pt-yrs (95% CI)	0.00 (0.00 to 0.96)	0.00 (0.00 to 0.82)	0.17 (0.00 to 0.97)	0.00 (0.00 to 0.84)	0.00 (0.00 to 0.13)	0.12 (0.03 to 0.30)

\*The controlled study period could extend up to week 52 per trial design.

†Patients may appear in ≥1 treatment column.

‡Identified events included histoplasmosis, listeria sepsis, oesophageal candidiasis, pneumonia legionella, coccidioidomycosis, eye infection toxoplasmal, *Pneumocystis jiroveci* pneumonia and *Mycobacterium kansasii* infection.

§95% CIs not containing 1 (in bold) indicate a significant difference from the SEER database.

¶This patient had AS.

\*\*All six patients had RA. Two patients were diagnosed with lymphoma during the placebo-controlled period; the other four were diagnosed with lymphoma after the placebo-controlled period and by week 160.

AS, ankylosing spondylitis; MTX, methotrexate; PsA, psoriatic arthritis; pt-yrs, patient-years; RA, rheumatoid arthritis; SC, subcutaneous; SEER, Surveillance, Epidemiology and End Results; SIR, standardised incidence ratio.

## DISCUSSION

We assessed SC golimumab safety up to 3 years by pooling data from five pivotal phase III trials in patients with active RA, PsA or AS. Each study included a placebo-controlled period, followed by uncontrolled study periods up to wk 160, during which all patients received golimumab 50 or 100 mg every 4 weeks; the golimumab dose could be adjusted at the investigator's discretion during the trials' long-term extensions. In several studies, background MTX use was continued. Results of these pooled safety analyses indicate that the overall SC golimumab safety profile remains consistent with those of other TNF antagonists used in the treatment of patients with RA and other immune-mediated inflammatory disorders,<sup>1-4 26 27</sup> although the incidence of lymphoma associated with the 100 mg golimumab dose requires continued monitoring (see below). We also evaluated AE incidences by indication and found that RA patients, who comprised approximately two-thirds of this safety population, largely drove the overall AE incidences.

The increased risk of serious and opportunistic infections associated with TNF antagonist therapy has been well characterised. The rates of serious infection among patients with RA treated with biological agents in clinical trials and observational studies typically range from 3 to 8/100 pt-yrs, and the rate of infection associated with anti-TNF therapy is approximately 1.5–2.0-fold higher than that associated with non-biological disease-modifying antirheumatic drug treatment.<sup>28-34</sup> In this pooled analysis, the incidence of serious infection was generally consistent across the treatment groups, although the incidence observed for golimumab 100 mg was numerically higher than for golimumab 50 mg, but not for placebo, during the placebo-controlled study periods. Serious infections also appeared to be somewhat more common among patients for whom oral corticosteroid use was documented at baseline. The incidences of tuberculosis and opportunistic infection were each numerically higher with golimumab 100 mg than with golimumab 50 mg at wk 160; the 95% CIs for both golimumab doses, however, fell below or were contained within those for placebo.

The possible increased risk of serious infection with golimumab 100 mg is consistent with that calculated in a meta-analysis of 18 randomised, controlled, clinical trials of anti-TNF agents, which included 8808 patients with RA who received recommended doses of adalimumab (20 mg/week), etanercept (50 mg/week) or infliximab (0.375 mg/kg/week), or doses lower or higher than recommended. While the odds of developing a serious infection were not increased among patients who received recommended anti-TNF doses, doses two to three times higher than recommended by product labelling were associated with an increased risk of serious infection.<sup>35</sup>

TNF is essential for the host defence against mycobacterial infection, and patients receiving TNF antagonists are at increased risk of tuberculosis re-activation.<sup>36</sup> While the current analysis did not definitively show an increase in tuberculosis with up to 3 years of golimumab therapy, tuberculosis screening is required before initiation of a patient on TNF antagonist therapy. Details of tuberculosis screening test results in this golimumab phase III programme have been published.<sup>37 38</sup> Patients identified as having latent tuberculosis must start isoniazid treatment before beginning anti-TNF therapy. Even with treatment for latent tuberculosis, however, patients should be observed carefully for active tuberculosis.

The incidence of opportunistic infection was not significantly increased during up to 3 years of golimumab treatment. However, histoplasmosis, coccidioidomycosis and pneumocystis pneumonia are the most common opportunistic infections

observed with TNF antagonist treatment, and caution must be exercised when initiating anti-TNF therapy for patients who have lived in or travelled to regions with endemic infecting organisms.

The mortality incidences observed in the pooled analysis of golimumab safety data up to wk 160 (0.28–0.41/100 pt-yrs) are somewhat lower than those of 1.1 and 1.6/100 pt-yrs derived from observation of patients treated with TNF inhibitors in national registries of Swedish RA patients.<sup>39 40</sup> Nonetheless, the generalisability of our results may be limited by exclusion of patients with numerous comorbidities from the clinical trials that contributed data to the pooled analyses.

Although the malignancy risk with anti-TNF therapy has been a concern because of the role of TNF in inhibiting tumour growth, this has not been borne out in studies of patients with RA.<sup>41-43</sup> There is, however, considerable evidence that long-standing chronic inflammation in the very patients who receive anti-TNF agents is itself related to an increased lymphoma risk.<sup>44</sup> Although the overall malignancy risk was not increased with golimumab therapy, there was a higher incidence of lymphoma with golimumab 100 mg than with either golimumab 50 mg or placebo. However, the 95% CIs for both golimumab doses were fully contained within those for placebo. Six of the seven lymphoma cases observed in these golimumab studies developed in patients with RA. Of the seven cases of lymphoma, four occurred in the GO-AFTER study, which enrolled RA patients who had previously received other TNF inhibitors and had substantial disease activity at baseline.<sup>15</sup> This is not unexpected, since the risk of developing lymphoma is higher among RA patients with active inflammation for longer time periods<sup>44</sup> and who are more likely to have previously received a TNF antagonist, but is not associated with TNF inhibitor therapy itself.<sup>45</sup> Although the majority of lymphomas developed in patients who received golimumab 100 mg, this may not be unexpected given the possibility of escalating the dose from 50 to 100 mg in patients with persistently active disease and the longer exposure of a greater number of patients to the 100 mg dose. Golimumab treatment did not appear to increase the incidence of NMSC, although such a risk has been identified with other anti-TNF agents,<sup>42 46</sup> and continued assessment is warranted. The Surveillance, Epidemiology, and End Results (SEER) database is the standard source for general population-based cancer data in the USA; however, although patients from North America (USA, N=622; Canada, N=340) comprised the largest patient group from a single continent in the golimumab trials, comparison of patients with rheumatic diseases from other geographic regions with those in the SEER database may limit the interpretation of such findings.

TNF antagonism may be associated with demyelinating disease,<sup>47</sup> but the incidence is low among patients with rheumatic diseases.<sup>48</sup> Demyelinating disorders were reported infrequently, with three cases observed among patients treated with golimumab 100 mg (incidence 0.12 per 100 pt-yrs (95% CI 0.03 to 0.30)) and none among patients in other treatment groups. Retrospective medical history revealed two of these patients had symptoms before initiating golimumab therapy, one of whom had no improvement of symptoms after cessation of golimumab. The remaining two patients reported improvement after stopping golimumab.

In addition to analytical limitations discussed, the duration of placebo control in trials contributing data to these analyses was relatively short. Thus, comparisons between the golimumab- and placebo-treated groups beyond the placebo-controlled phase must take into account that 'placebo-treated' patients may

actually have received golimumab for most of the time. Results may also be confounded by study design differences among the phase III trials and different durations of follow-up across treatment groups, as well as by the small number of events observed, particularly of death, opportunistic infection, demyelination and lymphoma. Between-dose comparisons are limited by the longer duration of exposure to golimumab 100 mg and possible selection bias, whereby more patients with severe disease/inflammation might have had their golimumab dose escalated to the 100 mg limit.

In conclusion, the safety profile of SC golimumab up to 3 years has remained largely consistent with those of other TNF antagonists. Golimumab 100 mg, vs 50 mg, was possibly associated with an increased incidence of lymphoma and other infrequently occurring safety events. Pharmacovigilance continues up to 5 years in the large phase III clinical trials of golimumab in rheumatological indications.

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