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Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis

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SUMMARY

Background
Tumour necrosis factor alpha (TNFα)-antagonism effectively treats ulcerative colitis (UC). The golimumab clinical programme evaluated subcutaneous (SC) and intravenous (IV) induction, and SC maintenance regimens, in TNFα-antagonist-naïve patients with moderate-to-severe active UC despite conventional treatment.

Aim
To evaluate dose–response relationship, select IV golimumab induction doses for continued development, and evaluate the safety and efficacy of selected doses.

Methods
Adults with Mayo scores of 6–12 and endoscopic subscores ≥2 were enrolled into this multicentre, randomised, double-blind, placebo-controlled, integrated Phase 2/3 dose-finding/dose-confirming study. In Phase 2, 176 patients were randomised (1:1:1:1) to a single IV infusion of placebo, 1-, 2- or 4-mg/kg golimumab. While Phase 2 data were analysed to select doses for continued development, 71 additional patients were randomised. Phase 3 enrolment stopped after 44 additional patients were randomised (1:1:1) to placebo, 2- or 4-mg/kg golimumab. Due to insufficient power for the Phase 3 primary endpoint analysis (clinical response at week 6), efficacy analyses are considered exploratory and include all randomised patients.

Results
No dose–response was observed in Phase 2; however, higher serum golimumab exposure was associated with greater proportions of patients achieving more favourable clinical outcomes, clinical response and greater improvement in Mayo scores compared with placebo-treated patients and those with lower serum concentrations. Among all randomised patients, numerically greater proportions were in clinical response at week 6 in the 2- and 4-mg/kg golimumab groups compared with placebo [44.0% (33/75) and 41.6% (32/77) vs. 30.1% (22/73)].

Conclusions
Efficacy with single-dose golimumab IV induction was lower than expected and less than observed in the SC induction study. No new safety findings were observed. ClinicalTrials.gov Number, NCT00488774.

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INTRODUCTION

Over the past decade, the tumour necrosis factor alpha (TNFα)-antagonists, infliximab and adalimumab, have effectively treated patients with moderate-to-severe ulcerative colitis (UC) and an inadequate response to conventional therapy.[1, 2]

Golimumab, a fully human IgG1 monoclonal antibody against TNFα is approved[3] for the subcutaneous (SC) and intravenous (IV) treatment of rheumatoid arthritis (RA)[4–8] and SC treatment of ankylosing spondylitis,[9] psoriatic arthritis[10] and UC.[3, 8] The clinical development plan for golimumab in UC, known as Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT) included PURSUIT-IV (NCT00488774) which evaluated single-dose IV induction therapy in patients with moderate-to-severe UC activity. The programme also included induction and maintenance trials of the golimumab subcutaneous (SC) formulation [PURSUIT-SC, NCT00487539 and PURSUIT-Maintenance (PURSUIT-M), NCT00488631, respectively]. Patients who achieved response following the IV or SC induction were subsequently randomised into the primary analysis population of PURSUIT-M.

MATERIALS AND METHODS

Patients

The PURSUIT-IV induction study was conducted globally between August 2007 and May 2009. The institutional review board or ethics committee at each study site approved the protocol; all patients provided written informed consent. All authors had access to study data and reviewed and approved the final manuscript.

Eligibility criteria were the same as reported for the SC golimumab induction study, PURSUIT-SC (NCT00487539).[11] Briefly, eligible patients had confirmed diagnoses of UC and moderate-to-severe disease activity (Mayo score of 6–12, including an endoscopic subscore ≥2).[11–13] Patients had an inadequate response to, or failed to tolerate, ≥1 conventional therapy [i.e. oral 5-aminosalicylates (5-ASAs), oral corticosteroids, azathioprine (AZA) and/or mercaptopurine (MP)]; or were corticosteroid-dependent (i.e. unable to taper corticosteroids without UC symptom recurrence). Concomitant UC medication use and exclusion criteria were previously described; patients who had previously received anti-TNF therapy (including infliximab and adalimumab) were excluded from the study.[11]

Study design

This 6-week study comprised a Phase 2 dose-finding portion to evaluate the dose–response relationship and select IV golimumab induction regimens for continued development, and a Phase 3 dose-confirming portion to evaluate safety and efficacy of selected regimens. Both phases were multicentre, randomised, double-blind and placebo-controlled with parallel groups.

In Phase 2, 176 eligible patients (Figure S1A) were randomly assigned equally to receive a single IV infusion of one of three golimumab (SIMPONI; Janssen Biotech, Inc., Horsham, PA, USA) induction doses (1, 2 or 4 mg/kg) or placebo using adaptive randomisation stratified by investigative site.

After 176 patients were randomised in Phase 2, a planned interim analysis was conducted to evaluate the dose response and select doses for continued development during Phase 3.

While Phase 2 data were analysed, 71 additional patients were enrolled (Figure S1B). Following dose selection, 44 patients (Figure S1C) were randomised equally to receive single-dose IV infusions of 2-mg/kg or 4-mg/kg golimumab or placebo at baseline of Phase 3 using permuted block randomisation. A central randomisation centre using an interactive voice response system was employed.

Enrolled patients were eligible for subsequent participation in the 1-year golimumab SC maintenance study, PURSUIT–M (NCT00488631).[14] Patients not participating in PURSUIT–M were followed for safety through 16 weeks after the study infusion.

Study evaluations

Mayo scores were calculated at weeks 0 (baseline) and 6 as described previously.[11–13] Partial Mayo scores were assessed at screening and weeks 2 and 4.

Clinical response was defined by a decrease from baseline in the Mayo score ≥30% and ≥3 points, accompanied by a rectal bleeding subscore of 0 or 1 or a decrease from baseline in the rectal bleeding subscore ≥1.[11–13] Clinical remission was defined by a Mayo score ≤2 points, with no individual subscore >1. Mucosal healing was defined by a Mayo endoscopy subscore of 0 or 1[2, 11, 13] as assessed by a local endoscopist.

Health-related quality of life was assessed at baseline and week 6 using the Inflammatory Bowel Disease Questionnaire (IBDQ).[11, 15]

Blood samples were collected at baseline (before infusion and 1 h postinfusion) and weeks 2, 4 and 6 for determination of serum golimumab concentrations

(lowest quantifiable concentration in a sample is 0.039 μg/mL),[16] and at baseline and week 6 for antibodies to golimumab.[17] Serum samples collected at baseline and weeks 2, 4 and 6 were assessed for C-reactive protein (CRP) concentrations.

Concomitant medication use and adverse events (AEs) were recorded throughout the study.

Statistical methods

Descriptive statistics were used to summarise continuous variables and categorical data were described using counts and percentages. Cochran-Mantel-Haenszel or χ^2-tests, as appropriate, were used to compare the proportions of patients with selected endpoints (e.g. clinical response). Continuous response parameters were compared using analysis of variance/covariance (ANOVA/ANCOVA) on the van der Waerden normal scores.

Dose-confirming analyses were to be based on data collected during Phase 3. However, since study enrolment was stopped after 44 patients were randomised in Phase 3 after dose selection, there was insufficient statistical power for the primary endpoint analysis. Therefore, the efficacy analyses are considered exploratory and the analysis population was changed to include all randomised (n = 291) patients from Phases 2 and 3. Data for all randomised patients were included in the demographical analyses. Data from 286 of 291 randomised patients were included in the efficacy analyses; five patients (1.7%) were prospectively excluded from these analyses because of noncompliance with good clinical practice (i.e. source documentation) at one study site. Data for 290 patients who received ≥1 dose of study agent were included in the safety and pharmacokinetic (PK) analyses.

For all efficacy endpoints, treatment failure rules were applied unless otherwise specified. Patients were considered to have failed treatment if they had protocol-prohibited changes in concomitant UC medications, including corticosteroids, or had a colectomy (partial or total) or an ostomy before week 6. For dichotomous endpoints, patients meeting treatment failure criteria were considered as not achieving the respective endpoints. For continuous endpoints, patients considered to be treatment failures had their baseline (week 0) values carried forward from the time of failure. For patients who had at least one missing Mayo subscore at week 6, Mayo score was calculated by carrying forward the last available subscore(s). Patients with missing data for a dichotomous endpoint were considered not to have achieved the respective endpoint. Patients with missing data for a continuous endpoint had the last observation carried forward. Treatment failure rules superseded other data-handling rules. All statistical testing was performed at a significance level of 0.05 (two-sided) unless otherwise specified. Nominal P values are displayed for all analyses.

Golimumab concentrations over time and change from baseline in CRP concentrations were summarised. AEs were summarised by treatment group.

RESULTS

Baseline demographics, disease characteristics, concomitant medications and disposition

The PURSUIT-IV study was conducted at sites in Eastern Europe (111 patients; 38%), North America (92 patients; 32%), Asia Pacific (58 patients; 20%) and Western Europe (30 patients; 10%). Following review of data from both SC and IV induction studies [i.e. analyses of data from the dose–response analysis of the Phase 2 portion of this study (Appendix S2) and the subsequent analyses from the Phase 2 portion of the companion PURSUIT-SC induction study[11]], enrolment in the Phase 3 portion of PURSUIT-IV was stopped on 30 January 2009 because efficacy was lower than expected; there were no safety concerns.

Among 291 patients assigned, 214 received golimumab (1 mg/kg, N = 62; 2 mg/kg, N = 75; and 4 mg/kg, N = 77) and 77 received placebo. Overall, 290 patients received a single infusion of study agent (Figure S1D). One patient randomised to golimumab 4 mg/kg received 0.4 mg/kg and was included in the golimumab 1 mg/kg group for safety analyses. Among randomised patients, 270 (92.8%) completed study participation, including 259 who completed the week-6 visit and entered PURSUIT-M (66 of 69 patients receiving placebo, 55 of 57 patients receiving golimumab 1 mg/kg, 65 of 70 patients receiving golimumab 2 mg/kg and 73 of 74 patients receiving golimumab 4 mg/kg) and 11 who completed the safety follow-up visit, 16 weeks after last dose of study agent.

Demographical and baseline disease characteristics and concomitant medications were generally similar across the randomised groups (Table 1). Men comprised 59.8% of the randomised study population, the median age of which was 40.0 years. Randomised patients had UC for a median of 4.6 years and a median baseline Mayo score of 8.0 with extensive disease in approximately 45%. Concomitant UC medications at baseline included aminosalicylates (81.8%), corticosteroids (53.3%) and immunosuppressive agents (31.3%).

Table 1 | Baseline demographics, disease characteristics and concomitant medications: All randomised patients

		Golimumab				
	Placebo (*N* = 77)	1 mg/kg (*N* = 62)	2 mg/kg (*N* = 75)	4 mg/kg (*N* = 77)	All (*N* = 214)	Total (*N* = 291)
Male patients, *n* (%)	47 (61.0)	41 (66.1)	36 (48.0)	50 (64.9)	127 (59.3)	174 (59.8)
Race, *n* (%)						
Caucasian	62 (80.5)	50 (80.6)	64 (85.3)	63 (81.8)	177 (82.7)	239 (82.1)
Black	4 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)
Asian	9 (11.7)	10 (16.1)	11 (14.7)	14 (18.2)	35 (16.4)	44 (15.1)
Other	2 (2.6)	2 (3.2)	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.4)
Age (years)						
Mean ± s.d.	40.9 ± 12.58	40.7 ± 15.51	42.3 ± 13.14	39.9 ± 14.07	41.0 ± 14.16	41.0 ± 13.74
Median (IQR)	41.0 (30.0 to 50.0)	38.5 (27.0 to 49.0)	43.0 (30.0 to 51.0)	37.0 (29.0 to 48.0)	40.0 (29.0 to 50.0)	40.0 (29.0 to 50.0)
UC disease duration (years)						
Mean ± s.d.	6.8 ± 6.59	6.2 ± 5.07	7.6 ± 8.04	6.5 ± 6.54	6.8 ± 6.75	6.8 ± 6.69
Median (IQR)	4.3 (2.2 to 9.1)	5.3 (1.9 to 9.0)	4.2 (2.7 to 10.2)	4.9 (2.1 to 8.3)	4.6 (2.3 to 9.0)	4.6 (2.2 to 9.1)
Extent of disease, *n* (%)						
Limited to left side of colon	43 (55.8)	32 (51.6)	45 (60.0)	41 (53.2)	118 (55.1)	161 (55.3)
Extensive	34 (44.2)	30 (48.4)	30 (40.0)	36 (46.8)	96 (44.9)	130 (44.7)
Mayo score (0–12)						
Mean ± s.d.	8.1 ± 1.63	8.3 ± 1.46	8.4 ± 1.37	8.2 ± 1.47	8.3 ± 1.43	8.3 ± 1.48
Median (IQR)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)
CRP (mg/L), *n*	72	60	72	70	202	274
Mean ± s.d.	10.8 ± 17.43	16.2 ± 29.49	12.3 ± 19.11	8.9 ± 12.11	12.3 ± 21.05	11.9 ± 20.14
Median (IQR)	4.6 (1.8 to 11.8)	5.3 (1.9 to 19.0)	5.2 (1.5 to 13.6)	4.0 (0.9 to 11.2)	4.6 (1.2 to 14.0)	4.6 (1.3 to 13.3)
Patients receiving any UC medication, *n* (%)	71 (92.2)	61 (98.4)	70 (93.3)	72 (93.5)	203 (94.9)	274 (94.2)
Corticosteroids (excluding budesonide)	40 (51.9)	36 (58.1)	39 (52.0)	40 (51.9)	115 (53.7)	155 (53.3)
≥20 mg/day P.Eq.	22 (28.6)	26 (41.9)	30 (40.0)	27 (35.1)	83 (38.8)	105 (36.1)
< 20 mg/day P.Eq.	18 (23.4)	10 (16.1)	9 (12.0)	13 (16.9)	32 (15.0)	50 (17.2)
Budesonide	1 (1.3)	3 (4.8)	2 (2.7)	2 (2.6)	7 (3.3)	8 (2.7)
Immunomodulatory drugs	26 (33.8)	19 (30.6)	23 (30.7)	23 (29.9)	65 (30.4)	91 (31.3)
Mercaptopurine/ Azathioprine	23 (29.9)	19 (30.6)	23 (30.7)	23 (29.9)	65 (30.4)	88 (30.2)
Methotrexate	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Aminosalicylates	62 (80.5)	50 (80.6)	61 (81.3)	65 (84.4)	176 (82.2)	238 (81.8)

CRP, C-reactive protein; IQR, interquartile range; P.Eq., prednisone equivalent; s.d., standard deviation; UC, ulcerative colitis.

Efficacy

Study enrolment was stopped due to the lower than expected efficacy in Phase 2. Because of insufficient power for the planned Phase 3 primary endpoint analysis, the efficacy analysis population was redefined to include data for all randomised patients excluding those enrolled at the noncompliant site. The results of these analyses are considered exploratory.

Among all randomised patients, greater proportions were in clinical response in the 2-mg/kg and 4-mg/kg golimumab IV groups vs. placebo [44.0% (33/75) and 41.6% (32/77) vs. 30.1%, (22/73); $P = 0.081$ and 0.145 respectively]. The proportions of patients in clinical remission or with mucosal healing who received golimumab did not differentiate from placebo (Table 2). In contrast, numerically greater improvement in IBDQ was observed at week 6 among golimumab-treated patients, particularly those receiving a single 2-mg/kg (mean change of 23.0; $P = 0.031$) or 4-mg/kg (mean change of 24.4; $P = 0.016$) infusion vs. placebo (mean change of 12.9; Table 2).

Table 2 | Efficacy findings: All randomised patients (excluding noncompliant site)

Variable	Placebo (*N* = 73)	Golimumab 1 mg/kg (*N* = 61)	Golimumab 2 mg/kg (*N* = 75)	Golimumab 4 mg/kg (*N* = 77)	Golimumab Combined (*N* = 213)
Clinical response at week 6, *n* (%)*,†	22 (30.1)	22 (36.1)	33 (44.0)	32 (41.6)	87 (40.8)
P value		0.467	0.081	0.145	0.104
Clinical remission at week 6, n (%)*,†	8 (11.0)	6 (9.8)	12 (16.0)	10 (13.0)	28 (13.1)
P value		0.832	0.370	0.702	0.627
Mucosal healing at week 6, *n* (%)*,†	24 (32.9)	17 (27.9)	26 (34.7)	29 (37.7)	72 (33.8)
P value		0.531	0.818	0.540	0.885
Mayo score change from baseline at week 6*,†					
Baseline					
Mean ± s.d.	8.1 ± 1.64	8.3 ± 1.47	8.4 ± 1.37	8.2 ± 1.47	8.3 ± 1.43
Median (IQR)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)
Week 6 change					
Mean ± s.d.	−1.7 ± 2.53	−1.9 ± 2.63	−2.4 ± 2.84	−2.5 ± 2.60	−2.3 ± 2.70
Median (IQR)	−1.0 (−3.0 to 0.0)	−1.0 (−4.0 to 0.0)	−2.0 (−4.0 to 0.0)	−2.0 (−5.0 to −1.0)	−2.0 (−4.0 to 0.0)
P value		0.694	0.102	0.059	0.096
Partial Mayo score change from baseline*,†					
Baseline					
Mean ± s.d.	5.8 ± 1.49	5.8 ± 1.28	5.9 ± 1.15	5.8 ± 1.22	5.9 ± 1.21
Median (IQR)	6.0 (5.0 to 7.0)	6.0 (5.0 to 6.0)	6.0 (5.0 to 7.0)	6.0 (5.0 to 7.0)	6.0 (5.0 to 7.0)
Week 2 change					
Mean ± s.d.	−1.0 ± 1.78	−1.8 ± 1.87	−2.0 ± 1.91	−1.7 ± 1.59	−1.9 ± 1.79
Median (IQR)	−1.0 (−2.0 to 0.0)	−2.0 (−3.0 to 0.0)	−2.0 (−3.0 to −1.0)	−2.0 (−3.0 to −1.0)	−2.0 (−3.0 to −1.0)
Week 4 change					
Mean ± s.d.	−1.2 ± 1.90	−2.1 ± 2.24	−1.9 ± 1.94	−1.9 ± 1.84	−1.9 ± 1.99
Median (IQR)	−1.0 (−2.0 to 0.0)	−2.0 (−4.0 to 0.0)	−2.0 (−3.0 to 0.0)	−2.0 (−3.0 to 0.0)	−2.0 (−3.0 to 0.0)
Week 6 change					
Mean ± s.d.	−1.2 ± 2.04	−1.4 ± 2.13	−1.7 ± 2.22	−1.8 ± 2.06	−1.6 ± 2.14
Median (IQR)	−1.0 (−2.0 to 0.0)	−1.0 (−3.0 to 0.0)	−1.0 (−3.0 to 0.0)	−2.0 (−3.0 to 0.0)	−1.0 (−3.0 to 0.0)
IBDQ change from baseline, *n**,†	70	60	72	74	206
Baseline					
Mean ± s.d.	135.1 ± 40.56	134.0 ± 32.44	124.3 ± 32.33	131.9 ± 30.71	129.9 ± 31.91
Median (IQR)	132.0 (109.0, 170.0)	136.5 (110.5, 159.5)	125.0 (102.5, 148.5)	133.5 (111.0, 153.0)	130.5 (109.0, 154.0)
Week 6 change					
Mean ± s.d.	12.9 ± 29.07	22.0 ± 32.82	23.0 ± 30.99	24.4 ± 31.77	23.2 ± 31.67
Median (IQR)	9.5 (−4.0 to 27.0)	13.0 (−1.0 to 42.5)	21.0 (0.0 to 39.5)	18.5 (2.0 to 39.0)	18.0 (0.0 to 40.0)
P value		0.114	0.031	0.016	0.011
CRP (mg/L) change from baseline, *n**,†	69	59	72	70	201
Baseline					
Mean ± s.d.	11.1 ± 17.76	16.0 ± 29.67	12.3 ± 19.11	8.9 ± 12.11	12.2 ± 21.06
Median (IQR)	4.6 (1.6 to 12.1)	5.0 (1.6 to 17.4)	5.2 (1.5 to 13.6)	4.0 (0.9 to 11.2)	4.6 (1.2 to 13.8)
Week 2 change					
Mean ± s.d.	−3.3 ± 13.74	−6.5 ± 26.59	−4.6 ± 11.68	−5.0 ± 11.75	−5.3 ± 17.37
Median (IQR)	−0.4 (−2.5 to 0.2)	−2.1 (−7.8 to −0.1)	−1.4 (−6.1 to −0.1)	−1.0 (−5.7 to −0.2)	−1.6 (−6.1 to −0.2)
P value		0.054	0.093	0.058	0.024
Week 4 change					
Mean ± s.d.	−3.3 ± 12.26	−7.3 ± 24.54	−2.6 ± 15.27	−4.7 ± 12.04	−4.7 ± 17.63
Median (IQR)	−0.2 (−3.5 to 1.1)	−0.9 (−8.1 to 0.0)	−1.2 (−5.6 to −0.1)	−0.8 (−4.4 to 0.3)	−0.9 (−5.6 to 0.0)
P value		0.088	0.108	0.256	0.066

Table 2 | (Continued)

Variable	Placebo (*N* = 73)	Golimumab 1 mg/kg (*N* = 61)	Golimumab 2 mg/kg (*N* = 75)	Golimumab 4 mg/kg (*N* = 77)	Golimumab Combined (*N* = 213)
Week 6 change					
Mean ± s.d.	−0.8 ± 20.90	−6.2 ± 22.82	−2.8 ± 12.88	−2.3 ± 13.27	−3.7 ± 16.54
Median (IQR)	0.0 (−3.9 to 1.8)	−0.8 (−8.8 to 0.6)	−0.7 (−5.0 to 0.2)	−0.3 (−3.0 to 1.1)	−0.5 (−3.7 to 0.6)
P value		0.241	0.193	0.735	0.243

CRP, C-reactive protein; IBDQ, inflammatory bowel disease questionnaire; IQR, interquartile range; s.d., standard deviation.

The Mayo score is the sum of 4 subscores each ranging from 0 to 3, (i.e. stool frequency [each patient serves as his/her own control to establish the degree of abnormality], rectal bleeding [scored as the most severe bleeding of the day], endoscopic findings and a physician's global assessment) with values ranging from 0 to 12. Higher scores indicate greater disease activity for both the total score and the subscales. Both stool frequency and rectal bleeding subscores are an average of a 3-day period prior to the visit. Partial Mayo scores (i.e. Mayo score excluding the endoscopy subscore with values ranging from 0 to 9). The IBDQ is a 32-item questionnaire with item responses ranging from 7 ('not a problem at all') to 1 ('a very severe problem'). The total IBDQ score ranges from 32 to 224, with higher scores indicating better quality of life.

* Patients who had a prohibited change in medication or had an ostomy or colectomy before the designated analysis timepoint were considered not to be in clinical response or clinical remission and not to have mucosal healing; for Mayo and partial Mayo scores, IBDQ score and CRP, the respective baseline value was carried forward from the time of the event onward.

† Patients who had all 4 mayo subscores missing at the designated analysis timepoint were considered not to be in clinical response or clinical remission and had their last available Mayo subscores carried forward to impute the missing Mayo score or partial Mayo scores. Patients who had missing endoscopy subscore at the designated analysis timepoint were considered not to have mucosal healing. Patients who had a missing partial Mayo score, IBDQ score and CRP at the designated analysis timepoint had the last available value carried forward.

Median CRP changes from baseline at week 2 were greater in all golimumab groups than placebo. Only the effects of 2-mg/kg and 4-mg/kg golimumab on median CRP levels were still evident at week 6 (Table 2).

PK for all golimumab-treated patients

Following single IV infusions of 1-, 2- or 4-mg/kg golimumab, median serum golimumab concentrations were approximately proportional to dose through week 6 (Figure 1). Median serum golimumab concentrations at week 6 were 0.16 μg/mL, 0.56 μg/mL and 1.40 μg/mL for the 1-, 2- and 4-mg/kg groups, respectively (Figure 1).

To evaluate the relationship between serum golimumab concentrations and efficacy, golimumab concentrations at week 6 were grouped into quartiles and compared with efficacy at week 6 (Table 3). Patients in the two highest concentration quartiles (≥0.61 μg/mL to <1.35 μg/mL; ≥1.35 μg/mL) had numerically greater mean improvement in Mayo scores compared with patients in the placebo group and those in the two lowest concentration quartiles (<0.18 μg/mL; ≥0.18 μg/mL to <0.61 μg/mL). Likewise, proportions of patients achieving clinical response were greater in the two highest concentration quartiles compared with those in the placebo group and those in the lowest concentration quartiles. This pattern, although not as robust owing to the small sample size, was observed for clinical remission at week 6.

Comparison of IV and SC golimumab PK in UC patients

After correction for the absolute bioavailability of SC golimumab (approximately 51%), the 1-, 2- and 4-mg/kg IV golimumab single infusion induction regimens were

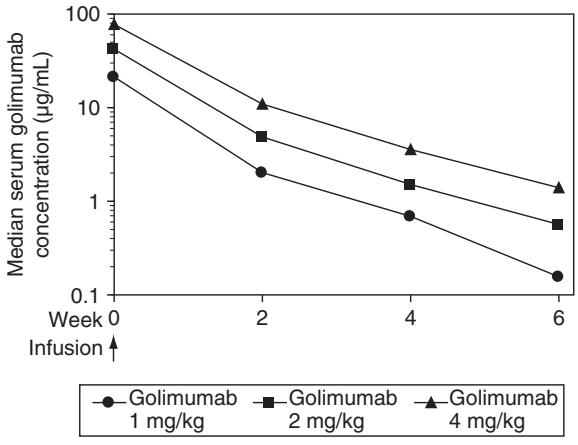

Figure 1 | Median serum golimumab concentration (μg/mL) through Week 6; all treated patients.

expected to provide comparable systemic drug exposure (area under the concentration-time curve) as the three SC golimumab induction regimens assessed in PURSUIT-SC (i.e. 100/50 mg, 200/100 mg and 400/200 mg golimumab SC injections at weeks 0 and 2).

However, at each corresponding IV and SC dose level (i.e. 1 mg/kg – 100/50 mg, 2 mg/kg – 200/100 mg and 4 mg/kg – 400/200 mg), serum golimumab concentrations for the SC dose were higher than those for the IV dose at weeks 2, 4 and 6 (Figure S1).

Safety

Approximately 37% of golimumab-treated and 31% of placebo-treated UC patients reported AEs through week 6 (Table 4). The most commonly observed AEs in golimumab-treated patients included UC exacerbation, cough and headache; those among placebo-treated patients included pruritus, UC exacerbation, anaemia, nausea, fatigue and decreased haematocrit/haemoglobin. No evidence of a golimumab dose response was observed for the occurrence of any AE, including infections. The overall proportions of patients with infections (10.8% vs. 6.5%, respectively) and infections requiring antimicrobial therapy (6.1% vs. 1.3%, respectively) were higher among golimumab-treated than placebo-treated patients.

Proportions of golimumab-treated (3.8%) and placebo-treated (2.6%) patients with serious AEs through week 6 were generally low and comparable (Table 4). Ulcerative colitis was the only serious AE occurring in more than one patient in either group (four golimumab-treated vs. 0 placebo-treated patients). Four golimumab-treated patients had serious infections through week 6, including one each with cellulitis (4 mg/kg) and sepsis (4 mg/kg), and two with UC exacerbation (2 mg/kg and 1 mg/kg). Each case resolved with treatment. Two patients experienced serious AEs after week 6: one in the 1-mg/kg group (UC and malnutrition) and one in the placebo group (UC and subileus).

No deaths, cases of tuberculosis, or opportunistic infections were reported. One case of cutaneous *in situ* squamous cell carcinoma (left scalp) was reported in a patient who received a single infusion of golimumab 4 mg/kg; the lesion was excised and no residual or invasive carcinoma was identified.

The proportions of patients with an infusion reaction were low [5 (2.3%) combined golimumab, 0 placebo]; reactions were mild-to-moderate, and none was serious.

Of 206 golimumab-treated patients with appropriate samples for antibody determination, none was positive for antibodies to golimumab through the final safety visit.

DISCUSSION

The PURSUIT programme was designed to evaluate both IV and SC induction regimens assuming the availability of both with a transition to SC maintenance therapy would afford better treatment options to patients with UC. Evidence-based medicine and clinical experience with infliximab were used to create a clinical development plan and dosing scheme for IV golimumab. With respect to induction dosing, results of infliximab studies in inflammatory bowel disease suggested that induction treatment with anti-TNFα agents was necessary to establish clinical efficacy and may be achieved with a single IV dose.[18] Single-induction infusion was considered sufficient as prior infliximab data had demonstrated substantial improvement by week 2 and IV golimumab (q12 week) was under evaluation in RA at the time this trial was initiated. Accordingly, the IV golimumab induction doses were selected on the basis of estimates of golimumab potency relative to infliximab from *in vitro*, pre-clinical and clinical study data in RA and IV infliximab (Crohn's disease and UC[2] studies). Subsequently, a two-dose induction regimen was identified to be effective in RA.[19]

In Phase 2 of this study, no dose–response was observed across golimumab groups, but greater efficacy was observed with higher golimumab serum concentrations, which was expected to correspond with the higher golimumab doses. Therefore, 2-mg/kg and 4-mg/kg golimumab were selected for further evaluation in the dose-confirmation portion of the study, potentially providing a more favourable exposure-response profile. Following review of the totality of data from both induction studies (i.e. results from the dose–response analysis of PURSUIT-IV Phase 2 and subsequent results from PURSUIT-SC Phase 2[11]), enrolment in the PURSUIT-IV Phase 3 was stopped. While data are limited because the study was stopped, single IV administration of 1-, 2- or 4-mg/kg golimumab did not demonstrate a substantially higher clinical response rate (36.1%, 44.0% or 41.6%, respectively) compared with placebo (30.1%). A similar pattern of results was seen for clinical remission and mucosal healing. The overall benefit from a single golimumab infusion was lower than expected across all efficacy measures and in comparison with PURSUIT SC.[11] While there were trends towards greater efficacy in patients with higher serum golimumab concentrations, this result must be interpreted with caution as it is possible that high golimumab levels may be a surrogate marker for patients who respond to treatment rather than the cause of clinical response.

Following IV administration, golimumab rapidly reached peak serum concentrations in a few hours in

Table 3 | Summary of clinical efficacy based on the Mayo score at week 6 by golimumab concentrations: All randomised patients (excluding noncompliant site)

		Golimumab combined			
	Placebo (*N* = 54)	<1st Quartile* (*N* = 44)	>1st and <2nd Quartile* (*N* = 45)	≥2nd and <3rd Quartile* (*N* = 45)	≥3rd Quartile* (*N* = 45)
Clinical efficacy at week 6					
Clinical response, *n* (%)†‡	18 (33.3)	13 (29.5)	18 (40.0)	30 (66.7)	20 (44.4)
Clinical remission, *n* (%)†‡	7 (13.0)	5 (11.4)	6 (13.3)	7 (15.6)	7 (15.6)
Mayo score change from baseline at week 6					
Baseline					
Mean ± s.d.	7.9 ± 1.46	8.2 ± 1.37	8.2 ± 1.43	8.4 ± 1.37	8.1 ± 1.44
Median (IQR)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (7.0 to 9.0)	8.0 (8.0 to 9.0)	8.0 (7.0 to 9.0)
Week 6 change†‡					
Mean ± s.d.	−1.9 ± 2.56	−1.8 ± 2.80	−2.1 ± 2.82	−3.4 ± 2.43	−2.7 ± 2.65
Median (IQR)	−2.0 (−3.0 to 0.0)	−1.0 (−3.0 to 0.0)	−2.0 (−4.0 to 0.0)	−4.0 (−5.0 to −2.0)	−2.0 (−5.0 to −1.0)

IQR, interquartile range; s.d., standard deviation.

The Mayo score is the sum of 4 subscores each ranging from 0 to 3, (i.e. stool frequency [each patient serves as his/her own control to establish the degree of abnormality], rectal bleeding [scored as the most severe bleeding of the day], endoscopic findings and a physician's global assessment) with values ranging from 0 to 12. Higher scores indicate greater disease activity for both the total score and the subscales. Both stool frequency and rectal bleeding subscores are an average of a 3-day period prior to the visit.

* The 1st, 2nd and 3rd quartiles of golimumab concentrations at week 6 are <0.1779 μg/mL; ≥0.1779 μg/mL to <0.6127 μg/mL; ≥0.6127 μg/mL to <1.3535 μg/mL; and ≥1.3535 μg/mL, respectively.

† Patients who had a prohibited change in medication or had an ostomy or colectomy before Week 6 are considered not to be in clinical response or clinical remission; for Mayo score, their baseline Mayo score was carried forward to week 6.

‡ Patients who had with all 4 mayo subscores missing at week 6 are considered not to be in clinical response or clinical remission and had their last available Mayo subscore carried forward to impute the missing Mayo score.

contrast to the kinetics following SC administration where the absorption process leads to relatively lower and delayed peak concentrations. Nevertheless, the elimination kinetics of golimumab following SC or IV administration were similar, as evidenced by similar half-lives from either route of administration (data on file). These results suggest that peak serum golimumab concentration is not a dominant driver of efficacy. A comparison of serum golimumab exposure across the PURSUIT-IV and -SC[11] studies indicate that the SC induction regimen was associated with more sustained serum golimumab concentrations over the 6-week induction period compared with the single IV induction regimens. The profile following two SC administrations of golimumab thus appeared more favourable for clinical efficacy than that following IV administration of a single golimumab dose. Together with the fact that SC induction regimens led to more robust efficacy than the IV dose regimen,[11, 20] these findings suggest that the maintenance of higher golimumab exposure at later time points by the SC induction regimens was required to elicit the levels of clinical efficacy achieved with the SC route of administration. This is further supported by the lower efficacy in PURSUIT-IV with a single-dose induction regimen compared with the ACT studies where a more intensive infliximab induction regimen was employed.[2]

Demographics, baseline disease characteristics and medication histories of patients enrolled in this IV golimumab study and those of patients receiving infliximab in the ACT studies were comparable. The proportions of patients achieving clinical response with the three-dose IV induction regimen of infliximab 5 mg/kg in ACT 1 and 2 were 69.4% and 64.5% respectively. In addition, the lower treatment effect in the PURSUIT-IV study cannot be attributed to a high placebo response rate. The proportion of placebo-treated patients who were in clinical response was 30.1% in PURSUIT-IV which is similar to that seen in both ACT 1 and ACT 2 (37.2%

Table 4 | Adverse events through week 6: All treated patients

		Golimumab			
	Placebo (*N* = 77)	1 mg/kg (*N* = 63)	2 mg/kg (*N* = 74)	4 mg/kg (*N* = 76)	Combined (*N* = 213)
Mean duration of follow-up, weeks	5.94	6.13	6.06	6.10	6.09
≥1 adverse event, *n* (%)	24 (31.2)	26 (41.3)	22 (29.7)	30 (39.5)	78 (36.6)
Common AEs (≥2% golimumab pts)	126 (38.2)	34 (47.9)	124 (37.5)	129 (38.9)	253 (382)
Ulcerative colitis (exacerbation)	2 (2.6)	3 (4.8)	5 (6.8)	0 (0.0)	8 (3.8)
Cough	0 (0.0)	2 (3.2)	3 (4.1)	1 (1.3)	6 (2.8)
Headache	1 (1.3)	1 (1.6)	3 (4.1)	2 (2.6)	6 (2.8)
Pharyngitis	0 (0.0)	1 (1.6)	3 (4.1)	0 (0.0)	4 (1.9)
≥1 serious adverse event, *n* (%)	2 (2.6)	2 (3.2)	3 (4.1)	3 (3.9)	8 (3.8)
≥1 infections, *n* (%)	5 (6.5)	9 (14.3)	6 (8.1)	8 (10.5)	23 (10.8)
≥1 infections requiring treatment	1 (1.3)	4 (6.3)	4 (5.4)	5 (6.6)	13 (6.1)
≥1 or more serious infections	0 (0.0)	1 (1.6)	1 (0.3)	2 (2.6)	4 (0.6)
Infusion reactions, *n* (%)	0 (0.0)	1 (1.6)	1 (1.4)	3 (3.9)	5 (2.3)

AEs, adverse events; pts, patients.

and 29.3%, respectively).[2] Similar results were observed for the proportions of placebo-treated patients who were in clinical remission across ACT 1, ACT 2 and PURSUIT-IV.

The proportion of patients with adverse events was slightly higher in the combined golimumab group compared with placebo; however, no dose–response was observed. Infection rates were numerically higher among golimumab- than placebo-treated patients, including infections requiring antibiotic therapy. No cases of tuberculosis or other opportunistic infections were reported. Serious AEs were uncommon and comparable among groups. One cutaneous *in situ* squamous cell carcinoma was reported in the 4-mg/kg golimumab group.

In summary, single-dose IV administration of golimumab in patients with moderate-to-severe UC did not lead to significant improvement in clinical outcome; however, those patients who did achieve clinical response entered the maintenance trial (PURSUIT-M) and therefore contributed to the overall evaluation of the efficacy and safety of continued treatment with golimumab through 1 year.

Based on the PK and numerically greater efficacy of golimumab at higher doses in achieving clinical response and improvement in IBDQ, an increase in the single IV dose or the addition of a second IV induction dose at weeks 2 or 4 may have been needed to maintain adequate drug exposure through week 6 to elicit robust response in this population. The limited safety findings of single-dose IV golimumab in UC were comparable to the safety profiles for other TNFα-antagonists and golimumab in other indications.

AUTHORSHIP

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PURSUIT-IV study group.

Appendix S2. Phase 2 analysis.

Figure S1. Patient disposition through Week 6 among patients randomized (A) in Phase 2, (B) while Phase 2 data were being analyzed, (C) in Phase 3, and (D) all randomized patients.

Figure S2. Median serum golimumab concentration by study visit (week) and by induction dose and regimen.

Table S1. Summary of baseline demographics and disease characteristics; all randomized patients in Phase 2.

Table S2. Efficacy findings in Phase 2.

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