Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for golimumab (rmc)

Proprietary Product Name: Simponi

Sponsor: Janssen-Cilag Pty Ltd

Date of CER: 26 November 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
CRP	C-reactive protein

1. Clinical rationale

The purpose of this submission is to support a new therapeutic indication for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder of unknown aetiology. The overall estimate of the prevalence of ulcerative colitis is approximately 730,000 people in North America and 1 million people in Europe.

The sponsor argues:

> *'There is unmet therapeutic need for patients with ulcerative colitis, since many do not respond to or are intolerant of conventional therapies, or demonstrate corticosteroid dependence. Among patients with ulcerative colitis who respond to corticosteroids, long-term use is not recommended due to its toxicity'.*

And further that, since the biologic anti-TNF agents infliximab and adalimumab are globally approved for use in patients with moderately to severely active ulcerative colitis. Golimumab:

> *'provides a convenient, alternative treatment option for patients with ulcerative colitis who have not responded to conventional therapy.'*

1.1. Guidance

- CHMP/EWP/18463/2006 Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis Effective: 8 April 2009.
- CPMP/BPWG/283/00 Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use Effective: 12 March 2003.

1.2. Regulatory background

Date of inclusion on the ARTG: 13 November 2009.

The international birth date of Simponi is 07 April 2009 based on first approval in Canada.

At the time of this submission similar ulcerative colitis applications have been made in EU, USA,Canada & Switzerland.

The 100 mg data set package has been prepared specifically for Australia (separate dossier not required elsewhere).

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One Phase I PK Study CNTO148NAP1001, of single SC 200 mg and 400 mg doses in healthy volunteers.
- 2 clinical studies (C0524T16 & C0524T17) that provided PK and PD data.
- 1 population pharmacokinetic analysis.
- 3 pivotal efficacy/safety studies in subjects with moderately to severely active ulcerative colitis:
  - C0524T16 intravenous 6 week induction study double-blind, placebo controlled, parallel-group study.
  - C0524T17 subcutaneous (SC) 6 week induction study double-blind, placebo controlled, parallel-group study.

    These studies, to evaluate efficacy and safety, were designed with 2 parts, a Phase II dose-finding portion (Part 1) and a Phase III dose-confirming portion (Part 2). The Part 1 analyses gave better results for the SC induction regimens than observed with the IV induction regimens, so the enrolment into the IV induction Study C0524T16 was stopped.
- Long term (54 week) maintenance study (C0524T18) of efficacy and safety. Subjects who enrolled in C0524T16 and C0524T17 and who completed the Week 6 visit were eligible to enter the maintenance study, C0524T18.
- A population PK model of golimumab in subjects with moderately to severely active ulcerative colitis was developed, using PK samples obtained from the induction and maintenance studies.
- The submission also referred to old studies for updating the clinical pharmacology information in the Product Information or for cross-study comparisons with PK data from the golimumab ulcerative colitis studies:
  - C0524T23- Phase I, single blind, partially randomized, two-dose study of Japanese and Caucasians to assess the PK profiles of golimumab following a single SC injection of 50 and 100 mg golimumab.
  - C0524T14 - Phase I randomised, open label outpatient study to assess the PKs & PDs of golimumab following multiple IV or SC administrations of golimumab in subjects with rheumatoid arthritis.
  - C0524T15 - Phase I randomised, open label parallel study to assess the absolute bioavailability of a single subcutaneous administration of golimumab in healthy subjects.
- PSUR: 7 October 2011 to 6 April 2012.
- Literature references.
- The sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

2.2. Paediatric data

The submission included no paediatric data.

2.3. Good clinical practice

All newly submitted studies were conducted in compliance with Good Clinical Practice.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose 200 & 400 mg	Study CNTO148NAP1001	*
PK in special populations	Target population§ - Multi-dose	Study C0524T16 Study C0524T17 Study C0524T18	
Population PK analyses	Target population	POPPK-CNTO148-UC	*

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 2. Previously submitted & evaluated PK studies referred to in this submission

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose 50 mg and 100 mg	Study C0524T23	*
	Bioavailability	Study C0524T15	*
	- Multi-dose	Study C0524T14	*

* Indicates the primary aim of the study.

None of the PK studies had deficiencies that excluded their results from consideration.

Due to findings of investigator misconduct at site 6706 and site 7257, subject data from these 2 sites were excluded from all efficacy analyses but were included in the demography, PK, immunogenicity, and safety analyses.

3.2. Population PK study

This was developed using PK samples from Phase II/III induction studies (C0524T16 and C0524T17) and a Phase III maintenance study (C0524T18) in adult subjects with moderately to severely active ulcerative colitis. Of the 11,280 serum golimumab concentration samples in the final population PK analysis dataset, 590 samples (5.2%) were BLQ. These samples were

associated with the first BLQ samples within a dosing interval and were set to half of the LLOQ value for the population PK analysis; however, trailing BLQ samples (n = 572) were excluded from the analysis data set. There were ten outlier samples excluded from the analysis.

The objectives were:

- To develop a population PK model and quantify population PK parameters including typical values and random variability estimates for golimumab using pooled PK data from three studies in adult subjects with ulcerative colitis.
- To identify covariates which significantly influence golimumab PKs in subjects with ulcerative colitis.
- To evaluate the performance of the final PK model developed for golimumab.

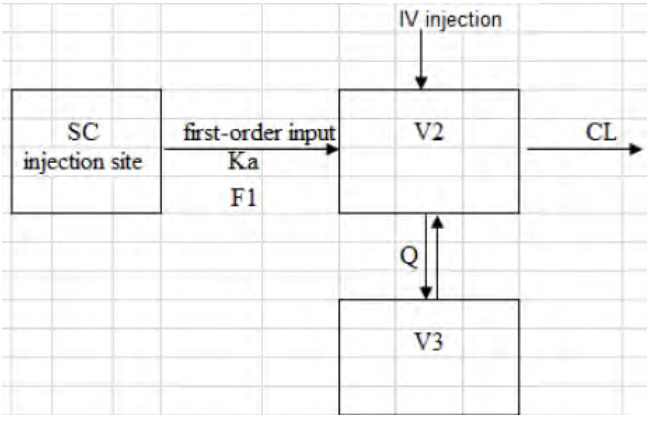
3.2.1. Deviations from the data analysis plan

Covariates found to be significant at the 0.005 level (> 7.88 change in objective function [OFV]) were considered for inclusion in the "full model" instead of a 0.05 level as initially planned. Similarly, for the covariate model reduction procedure, covariates found to be significant at the 0.001 level (> 10.83 change in OFV) were considered for inclusion in the "final model" instead of the 0.005 level as initially planned.

The covariates that were assessed for influence on the PK variability of golimumab included all significant covariates identified in previous PopPK analyses of golimumab including body weight, C-reactive protein, antibody to golimumab status, smoking status, and subject's sex; additional covariates assessed were: body surface area, lean body mass, age, albumin, white blood cell count, estimated creatinine clearance, hepatic enzymes, Mayo score, disease duration, race (Caucasians versus non-Caucasians, and Japanese versus non- Japanese), and concomitant use of immunomodulators (azathioprine/6-mercaptopurine/ or methotrexate, AZA/6-MP or MTX). Subjects with missing covariate data represented less than 3% of the 1227 subjects, and the missing covariates were imputed in the population PK analysis.

A two-compartment model was assumed to be a more appropriate structural model. Since IV data was included in analyses, however, a one compartment model was tested to confirm that the current data supported this assumption. The objective function value for the two compartment model (1,107) was 820 points lower than that of the one-compartment model (1,927). Furthermore, the residual error for the two-compartment model (21.4%) was much smaller than that of the one-compartment model (42.6%).

Figure 1. A Two-Compartment PK Model with a First-Order Absorption Following SC Administration and IV Administration



CL = clearance, V2 = volume of distribution of the central compartment, Q = inter-compartmental flow rate, V3 = volume of distribution of the peripheral compartment, Ka = absorption rate constant, F1 = bioavailability
Source: Scheme 1

3.2.1.1. Covariate model building

Initially, covariate-parameter relationships were explored graphically and any correlations between covariates were noted. Scatter plots of individual PK parameters and random effects were plotted against continuous covariates of interest with a non-parametric trend line overlaid on the plots to help identify functional relationships. For categorical covariates, box and whisker plots of the PK parameters were used to identify differences between groups. A trend between a covariate and a PK parameter led to direct assessment in NONMEM.

Final covariate model selection was conducted using a stepwise backward elimination procedure starting with the "full" covariate model which was carefully constructed to avoid inclusion of collinear or strongly correlated covariates.

A model reduction procedure was performed by deleting one covariate at a time while retaining all other covariates in the model and then comparing the objective functions of the NONMEM runs.

In lieu of using the likelihood ratio test for formal hypothesis testing, inferences about clinical relevance of parameters were based on the resulting parameter estimates and measures of estimation precision (standard errors or 95% confidence intervals). Covariates were also evaluated based on the magnitude of the expected effect given the range of covariate values in the dataset. A covariate resulting in a less than 20% change in parameter values was not generally considered clinically relevant within the specified covariate range.

Model selection was data driven and was based on various goodness of fit measures, including comparisons based on change in OFV, diagnostic plots, and evaluation of the population estimates of the fixed and random effect parameters. At least 1000 bootstrap replicates were generated by randomly re-sampling the original dataset with replacement.

Apart from the effects of body weight on V3 and Q, covariates were tested only on CL and V2 since they were the primary PK parameters of interest. The full model had 10 covariates on CL and 8 covariates on V2 with a condition number of 156.9.

Each of the covariate factors was removed from the full model in order to rank their changes in OFV. When a covariate was removed and the increase in OFV was < 10.83, the covariate factor was not considered statistically significant ($p > 0.001$). The Between-Subject Variability of CL and V2 were reduced by 7.2% and 4.5%, respectively, in the final model. Body weight accounted for the majority (4.5%) of the total decrease in the Between-Subject Variability while serum albumin, immune response, CRP, and alkaline phosphatase accounted for 2.9%, 0.8%, 0.5%, and 0.4% of the decrease in Between-Subject Variability of CL, respectively.

In the following Table are listed covariates statistically significant ($p<0.001$) in influencing golimumab PK parameters along with the population PK parameter estimates of golimumab from the final population PK model. None of the other factors evaluated were found to be statistically significant.

Between-subject random effects of CL, V2, V3, Ka and F1 are approximately normally distributed around zero.

Both the CL and V2 values exhibited approximately lognormal distribution in the final model. The median terminal elimination half-life of golimumab was estimated to be 10.5 days.

Table 3. Population PK Parameters of Golimumab from the Final PK Model

Parameters [a]	Estimate [b]	Median (95% CI) [c]	Magnitude of Change
CL (L/day)	0.544 (2.3)	0.538 (0.511 - 0.567)	-
WGT on CL [d]	0.812 (6.4)	0.791 (0.694 - 0.890)	-11.8% to 16.0% [h]
ALB on CL [d]	-1.150 (7.3)	-1.060 (-1.250 - -0.864)	-7.6% to 8.9% [h]
IRP on CL [d]	0.243 (26.2)	0.262 (0.149 - 0.385)	24.3% increase in CL for a subject positive for antibodies to golimumab
ALK on CL [d]	0.069 (38.9)	0.085 (0.040 - 0.134)	-1.2% to 1.4% [h]
CRP on CL [d]	0.033 (17.8)	0.030 (0.018 - 0.043)	-3.6% to 3.3% [h]
V2 (L)	3.43 (4)	3.44 (3.29 - 3.58)	-
WGT on V2 [e]	0.873 (13.4)	0.856 (0.663 - 1.050)	-12.6% to 17.3% [h]
V3 (L)	2.27 (4.3)	2.31 (2.13 - 2.52)	-
WGT on V3 [f]	0.900 (15.9)	0.907 (0.736 - 1.090)	-13.0% to 17.8% [h]
Q (L/day)	0.291 (6.9)	0.297 (0.257 - 0.355)	-
WGT on Q [g]	1.220 (19.1)	1.240 (0.826 - 1.700)	-17.1% to 24.9% [h]
Ka (1/day)	0.213 (3.3)	0.213 (0.200 - 0.230)	-
F1	0.522 (2.4)	0.527 (0.499 - 0.559)	-
BSV of CL (%)	26.7 (8.2)	25.7 (22.5 - 29.1)	-
BSV of V2 (%)	24.0 (12.4)	23.7 (11.3 - 33.8)	-
BSV of V3 (%)	35.4 (6.3)	35.2 (26.5 - 42.5)	-
BSV of Q (%)	0.0 (fixed)	0.0 (fixed)	-
BSV of Ka (%)	44.6 (9.8)	43.9 (37.8 - 49.3)	-
BSV of F1 (%)	47.4 (8.7)	48.8 (35.6 - 59.6)	-
Correlation between BSV of CL and V2	0.768	0.732 (0.576 - 0.858)	-
Correlation between BSV of CL and V3	-0.641	-0.655 (-0.812 - -0.491)	-
Proportional residual error (CV%)	32.2 (0.4)	32.3 (30.1 - 34.4)	-
Additive residual error (µg/mL)	0.040 (1.0)	0.039 (0.016 - 0.075)	-

a CL = clearance; V2 = volume of distribution of the central compartment; V3 = volume of distribution of the peripheral compartment; Q = inter-compartment clearance; Ka = absorption rate constant; F1 = bioavailability after SC administration; WGT = body weight; ALB = albumin; IRP = immune response; ALK = alkaline phosphatase; CRP = C-reactive protein; BSV = between-subject variability, calculated as (variance)1/2*100%

b Mean [RSE%] estimates by NONMEM of the original PK dataset

c Median [95% CI]: median value and 95% confidence interval calculated from 1035 replicates of re-sampled and successfully converged bootstrapping runs.

d $$CL\,(L/day) = 0.544 \times \left(\frac{WGT}{70}\right)^{0.812} \times \left(\frac{ALB}{4.2}\right)^{-1.15} \times \left(\frac{ALK}{68}\right)^{0.069} \times \left(\frac{CRP}{4.8}\right)^{0.033} \times (1 + IRP \times 0.243)$$

e $$V2\,(L) = 3.43 \times \left(\frac{WGT}{70}\right)^{0.873}$$

f $$V3\,(L) = 2.27 \times \left(\frac{WGT}{70}\right)^{0.90}$$

g $$Q\,(L/day) = 0.291 \times \left(\frac{WGT}{70}\right)^{1.22}$$

h The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, that is, % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population. Source: Table 1.

Due to body weight increase from the 25th percentile (60 kg) to the 75th percentile (84 kg), the change in CL ranged from -11.8% to +16% of the median CL estimate, while the change in V2 ranged from −12.6% to 17.3% of the median V2 estimate.

Simulation showed that at steady-state after 100 mg golimumab SC every four weeks, the median AUC in ulcerative colitis subjects weight > 100kg was approximately 33% lower than that in those weighing ≤ 100kg.

The effect of Age, Sex, Race & Renal Function (Baseline CrCL) on CL and V2 was not significant.

In the 34 subjects (2.8%) who developed immunogenicity against golimumab the model-predicted mean CL value for golimumab was 24.3% higher.

The majority of the subjects appeared to have relatively normal hepatic function. Of baseline alanine aminotransferase, aspartate aminotransferase, total bilirubin and alkaline phosphatase, none had a significant effect on the V2 of golimumab and only alkaline phosphatase had an effect on CL golimumab. The change in CL of golimumab due to alkaline phosphatase was negligible ranging from - 1.2% to + 1.4% of the median CL estimate when alkaline phosphatase increased from the 25th percentile (57 IU/L) to the 75th percentile (83 IU/L), respectively.

The change in CL due to albumin ranged from - 7.6% to + 8.9% of the median CL estimate when albumin decreased from the 75th percentile (4.5g/dL) to the 25th percentile (3.9g/dL), respectively, in this patient population. No significant effect on V2 of golimumab was found.

The change in CL due to C-reactive protein was minor and ranged from - 3.6% to + 3.3% of the median CL estimate when C-reactive protein increased from the 25th percentile (1.59mg/L) to the 75th percentile (12.8mg/L), respectively, in this patient population. There was no significant effect on V2.

The concomitant use of immunomodulators had no significant effect on CL and V2 of golimumab.

PK simulation to assess the carry over effect of different induction doses on serum golimumab concentrations during maintenance showed that although systemic golimumab exposure during the induction studies (C0524T16 or C0524T17) varied due to differences in induction dose and route of administration, subjects in the maintenance study (C0524T18) reached the same steady state maintenance level within about 8 weeks (approximately 5 half-lives) from when they began receiving the same maintenance dose regimens.

3.3. Comparisons of pharmacokinetics

3.3.1. Ulcerative colitis pharmacokinetics versus healthy subjects

From Study C0524T15 using non-compartmental analysis (NCA) with rich data provided the basic PK parameters of golimumab following either IV or SC administration in healthy subjects.

In ulcerative colitis subjects, golimumab CL was estimated to be 0.544 L/day for a 70 kg subject. This estimate is within about 10% of the mean value of golimumab CL estimated in C0524T15 following a single IV administration of 100 mg golimumab (6.86 mL/day/kg or approximately 0.480 L/day for a 70 kg subject).

The median terminal elimination half-life of golimumab was estimated to be 10.5 days in ulcerative colitis subjects while the median half-life values for golimumab in C0524T15 was 10.9 days and 11.8 days following SC administration and IV administration respectively.

The bioavailability of golimumab following SC administration in ulcerative colitis subjects was estimated to be 52.2% while the bioavailability estimate in C0524T15 was 51.1%.

3.3.2. Ulcerative colitis pharmacokinetics versus Rheumatoid arthritis

Study C0524T14 using non-compartmental analysis derived PK parameters the basic PK parameter of golimumab and the magnitude of drug-drug interaction between methotrexate and golimumab following repeated IV and SC administration.

Following the first IV administration of golimumab 100 mg to subjects with Rheumatoid arthritis in C0524T14, the mean systemic CL of golimumab was estimated to be 7.64 mL/kg/day (approximately 0.535L/day for a 70kg subject) which is comparable to the typical value of CL in ulcerative colitis subjects (0.544 L/day).

Golimumab $t_{1/2}$ was estimated to be 13.72 ± 3.78 days and 13.11 ± 5.01 days following IV and SC administration in Rheumatoid arthritis subjects, respectively, compared to a median half-life of 10.5 days in subjects with ulcerative colitis. Of note, the median t1/2 in Rheumatoid arthritis subjects who did not receive methotrexate was 11.0 days, which was similar to that observed in the ulcerative colitis population.

The bioavailability estimate of golimumab following SC administration in ulcerative colitis subjects (52.2 %) while in Rheumatoid arthritis subjects it was 53.0%.

3.4. Evaluator's overall conclusions on pharmacokinetics

Overall, the PK characteristics of golimumab were not greatly different between ulcerative colitis and healthy subjects. The data suggest that the PKs of golimumab in ulcerative colitis is generally comparable to those in Rheumatoid arthritis subjects. In particular, the median $t_{1/2}$ for Rheumatoid arthritis subjects who did not receive methotrexate was similar to that observed in the ulcerative colitis population.

4. Pharmacodynamics

5. Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 4. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on inflammatory markers (serum amyloid A [SAA] and plasminogen activator inhibitor-1 [PAI-1]), extracellular matrix remodelling proteins (metalloproteinase -9 [MMP-9]) and growth factors (hepatocyte growth factor [HGF]), as well as soluble signalling proteins (soluble glycoprotein 130 [sgp130]; interleukin-2 receptor-alpha [IL-2Rα], interleukin-6 receptor 1 [IL-6R1], and soluble tumour necrosis factor receptor 1 [TNFR1]).	C0524T16
	Microarray analysis of the gene transcript levels in ulcerative colitis colonic biopsies	C0524T17

PD Topic	Subtopic	Study ID
	Antibodies to Golimumab	C0524T16
	Antibodies to Golimumab	C0524T17
	Antibodies to Golimumab Neutralizing Antibodies to Golimumab	C0524T18

* Indicates the primary aim of the study.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Due to findings of investigator misconduct at site 6706 and site 7257, subject data from these 2 sites were excluded from all efficacy analyses but were included in the demography, PK, immunogenicity, and safety analyses.

6. Dosage selection for the pivotal studies

The IV and SC golimumab induction doses studied in C0524T16 and C0524T17, along with the SC maintenance dosage studied in C0524T18 were selected based on clinical data of IV infliximab in Crohn's disease and ulcerative colitis estimates of the potency of golimumab relative to infliximab using clinical data in Rheumatoid arthritis subjects, and data from the use of biologic anti-TNFα agents in Crohn's disease.

7. Clinical efficacy

7.1. For: The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy

7.1.1. Pivotal efficacy studies

There was essentially a single pivotal efficacy Study C0524T18 of 54 weeks that was fed by 2 preceding 6 week induction studies (C0524T16 & C0524T17).

7.1.1.1. Study C0524T18 (PURSUIT - Maintenance)

Due to findings of investigator misconduct at site 6706 and site 7257, subject data from these 2 sites were excluded from all efficacy analyses.

7.1.1.2. Study design, objectives, locations and dates

A Phase III, multicentre, placebo-controlled, double-blind, parallel-group, randomized-withdrawal study to evaluate the safety and efficacy of golimumab maintenance therapy, administered subcutaneously, in subjects with moderately to severely active ulcerative colitis.

From 28 Sep 2007 to 24 Oct 2011;

- The 464 subjects in the target population were from 172 sites as follows:
- 46.1% (214 subjects) from Eastern Europe (Bulgaria, Hungary, Poland, Romania, Serbia, Slovakia [Slovak Republic], Ukraine, Latvia, Russia, and the Czech Republic)
- 23.9% (111 subjects) from North America (United States and Canada)

- 14.2% (66 subjects) from Asia Pacific (Japan, Australia, India, and New Zealand) and South Africa
- 15.7% (73 subjects) subjects from Western Europe (Austria, Belgium, France, Netherlands, Denmark, Sweden, Germany, and Israel).

7.1.1.2.1. Primary objectives

- To evaluate the efficacy of 2 SC maintenance dose regimens of golimumab in maintaining clinical response through Week 54 in subjects with moderately to severely active ulcerative colitis who achieved clinical response with golimumab in 1 of the induction studies, C0524T16 or C0524T17.
- To evaluate the safety of 2 SC maintenance dose regimens of golimumab in subjects with moderately to severely active ulcerative colitis.

7.1.1.2.2. Secondary objectives

- To evaluate the efficacy of golimumab maintenance dose regimens in maintaining clinical remission at Week 30 and Week 54.
- To evaluate the efficacy of golimumab maintenance dose regimens in maintaining mucosal healing at Week 30 and Week 54.
- To evaluate the efficacy of golimumab maintenance dose regimens in maintaining clinical remission at Week 30 and Week 54 for subjects in clinical remission at Week 0 of this study.
- To evaluate the efficacy of golimumab maintenance dose regimens in achieving clinical remission and eliminating corticosteroid use at Week 54 among subjects receiving concomitant corticosteroids at Week 0 of this study.

7.1.1.3. Inclusion criteria

- Have received all study agent administrations and completed the Week 6 Mayo score evaluation in one of the induction studies of golimumab for ulcerative colitis (that is., C0524T16 or C0524T17).
- Are able to complete the Week 0 visit on the same day as the Week 6 visit of the induction Study C0524T16 or C0524T17.

7.1.1.4. Exclusion criteria

- Had any of the following changes to their concomitant ulcerative colitis medications (that is, oral 5-ASA compounds, oral corticosteroids [including budesonide], 6-MP, AZA, methotrexate [MTX]) since Week 0 of an induction study (C0524T16 or C0524T17):
  - an increased dose
  - initiation of a concomitant ulcerative colitis medication except for dose equivalent substitutions.
- Have received any of the following therapies since Week 0 of the induction study:
  - rectal corticosteroid therapy (that is, corticosteroids [including budesonide], administered to the rectum or sigmoid colon via foam, enema, or suppository)
  - rectal 5-ASA compounds (that is, 5-ASA compounds administered to the rectum or sigmoid colon via foam, enema, or suppository)
  - parenteral corticosteroids
  - pentoxifylline
  - total parental nutrition (TPN)

- antibiotics for the treatment of ulcerative colitis (including but not limited to ciprofloxacin, metronidazole, or rifaximin)
- immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-thioguanine [6 TG], cyclosporine, mycophenolate mofetil [MMF], tacrolimus, and sirolimus)
- immunomodulatory biologic agents (including but not limited to infliximab, anakinra, etanercept, adalimumab, rituximab, natalizumab, visilizumab)
- thalidomide or related agents
- investigational drugs
- apheresis (for example, Adacolumn apheresis).
- Have signs and symptoms of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis.
- Have signs and symptoms of non-tuberculous mycobacterial infection or opportunistic infection (for example, cytomegalovirus, Pneumocystis carinii, aspergillosis).
- Have had a clinically significant infection (for example, hepatitis, pneumonia, or pyelonephritis) or have received parenteral antibiotics for an infection since Week 0 of an induction study. Less serious infections (for example, acute upper respiratory tract infection, simple urinary tract infection, or infections requiring a short course of empiric parenteral antibiotic for less than or equal to 3 days) need not be considered exclusionary at the discretion of the investigator.
- Have signs and symptoms of infection with HIV, hepatitis B, or hepatitis C.
- Have signs and symptoms of any malignancy.
- Have signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphoma or lymphadenopathy of unusual size or location (for example, nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or clinically significant hepatomegally or splenomegally.
- Have undergone a colectomy (partial or total) or an ostomy (that is, temporary colostomy, permanent colostomy, ileostomy, or other enterostomy) since Week 0 of the induction studies (C0524T16 or C0524T17).

7.1.1.5. Study treatments

- Subjects who were in clinical response to golimumab at Week 6 in C0524T16 or C0524T17 (that is, the target population) were randomized in a 1:1:1 ratio at Week 0 of this study to receive 1 of the following maintenance treatment regimens administered subcutaneously (SC) every 4 weeks:
- placebo, (if subsequent loss of clinical response given golimumab 100 mg q4w)
- golimumab 50 mg, (if subsequent loss of clinical response randomly given 50 or 100 mg q4w)
- golimumab 100 mg. (if subsequent loss of clinical response some given 200 mg q4w)
- If no response at 26 weeks golimumab discontinued.

Subjects who were in clinical response to placebo and subjects who were not in clinical response to golimumab or placebo at Week 6 in C0524T16 or C0524T17 were not randomized but were eligible to be enrolled in the study (that is, the nonrandomized group) and received the following treatment regimens, but if unimproved by 16 weeks golimumab discontinued:

- placebo induction responders - placebo q4w (if subsequent loss of clinical response given golimumab 100 mg q4w)
- placebo induction nonresponders - golimumab 100 mg q4w
- golimumab induction nonresponders - golimumab 100 mg q4w

Subjects in clinical response to golimumab or placebo who were receiving oral corticosteroids on entry into this study were to begin tapering the daily dose of corticosteroids beginning at Week 0 of this study. The maximum rate of corticosteroid taper was not to exceed:

- Dose > 20 mg/day prednisone or equivalent: taper dose by 5mg/week.
- Dose less than or equal to 20 mg/day prednisone or equivalent: taper dose by 2.5mg/week.

7.1.1.6. Efficacy variables and outcomes

The primary endpoint was clinical response[1] through Week 54 as assessed by the Mayo score or partial score.[2]

The major secondary efficacy endpoints are:

- The proportion of subjects in clinical remission at both Week 30 and Week 54.
- The proportion of subjects who demonstrate mucosal healing at both Week 30 and Week 54.
- Among the subjects who had achieved clinical remission at baseline, the proportion of subjects in clinical remission at both Week 30 and Week 54.
- Among the subjects receiving concomitant corticosteroids at baseline, the proportion of subjects at Week 54 who are in clinical remission and are not receiving concomitant corticosteroids.

There were multiple other secondary endpoints.

7.1.1.7. Randomisation and blinding methods

Subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (placebo, golimumab 50 mg, or golimumab 100 mg) using an adaptive randomization procedure 11 with 3 stratification variables:

- Investigative site
- A 4-level cross-classification of clinical remission status at Week 0 (yes or no) of this study and Week 0 corticosteroid use (yes or no)
- A 6-level induction dose factor (IV golimumab 1mg/kg, IV golimumab 2mg/kg, IV golimumab 4mg/kg, SC golimumab 100 mg → 50 mg, SC golimumab 200 mg →100 mg, and SC golimumab 400 mg → 200 mg).

The adaptive randomization method was a minimization procedure with a biased-coin assignment.

[1] Clinical response was defined as a decrease from Week 0 of C0524T16 or C0524T17 in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. Subjects who lost clinical response at any time prior to Week 54 were considered not to be in clinical response for the primary endpoint analysis.

[2] The Mayo score is calculated as the sum of 4 subscores of stool frequency, rectal bleeding, physician's global assessment, and findings of endoscopy and ranges from 0 to 12 points; a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. The partial Mayo score is the Mayo score excluding the endoscopy subscore and ranges from 0 to 9 points.

7.1.1.8. Analysis populations

The primary efficacy analysis population was subjects randomized at Week 0 of this maintenance study (that is, subjects in clinical response to golimumab induction at Week 0 of this maintenance study), excluding those from sites 6706 and 7257.

7.1.1.9. Sample size

Because a fixed sequence testing procedure was used to control the Type I error rate at the 0.05 level (2-sided) for the comparisons of the 2 golimumab maintenance regimens with the placebo maintenance regimen for the primary endpoint, the sample size/power calculations were based on the comparison between subjects receiving the higher golimumab dose (100 mg) and those receiving placebo.

At the time of initiation of this study, no data were available for golimumab in the treatment of ulcerative colitis. The estimate of the proportion of subjects in clinical response through Week 54 in the golimumab 100 mg group was obtained using data from the ACT 1 study of infliximab in subjects with ulcerative colitis, and the estimate for the placebo group was obtained using data from the ACCENT 1 study of infliximab in subjects with Crohn's disease.

Assuming a 35% clinical response rate in the placebo group and 55% in the golimumab 100 mg group, approximately 128 subjects in each randomized treatment group (384 subjects in total) would provide an overall power of 90% with respect to the primary endpoint at a significance level of 0.05 (based on a 2-sided chi-square test).

At a designated time point near the completion of planned enrolment of C0524T17, the interactive voice response system projected, based on the available data and a predefined algorithm, whether or not the target number of subjects for the primary analysis population of this study would be reached, and, if not, how many more subjects from C0524T17 would need to be enrolled to reach the target.

7.1.1.10. Statistical methods

The major secondary efficacy analyses would only be considered if the test between the high maintenance dose (100 mg) and placebo was positive for the primary endpoint of clinical response through Week 54.

- The following are the major secondary endpoint analyses, which are presented in the order in which they were to be tested:
- The proportion of subjects in clinical remission at both Week 30 and Week 54 to be summarized and compared between treatment groups.
- The proportion of subjects who demonstrated mucosal healing at both Week 30 and Week 54 to be summarized and compared between treatment groups.
- Among the subjects who had achieved clinical remission at baseline, the proportion of subjects in clinical remission at both Week 30 and Week 54 to be summarized and compared between treatment groups.
- Among the subjects receiving concomitant corticosteroids at baseline, the proportion of subjects at Week 54 who are in clinical remission and are not receiving concomitant corticosteroids to be summarized and compared between treatment groups.

A fixed-sequence testing procedure was to be employed to control the Type 1 error rate at the 0.05 (2-sided) significance level within each of the 4 major secondary efficacy analyses; with the exception that the low dose for a major secondary endpoint could not be tested unless the low dose tested positive for the previous major secondary endpoint (or the primary endpoint if the endpoint being tested was the 1st major secondary endpoint).

That is, for each major secondary endpoint, the high maintenance dose (100 mg) was to first be compared with the placebo maintenance dose at the two sided 0.05 level of significance. Only if this test was positive would the low maintenance dose (50 mg) be compared with the placebo maintenance dose at the two-sided 0.05 level of significance.

Except for the third major secondary endpoint, analyses of major secondary endpoints were to use the CMH chi-square test stratified by clinical remission status at baseline (yes or no) and induction dose factor. For the third major secondary endpoint, a CMH chi-square test stratified by induction dose factor was to be used.

7.1.1.11. Participant flow

464 subjects were enrolled in the target population[3] and randomized:

- 154 subjects to golimumab 50 mg, discontinued 45, 109 received study drug to Week 52
- 154 subjects to golimumab 100 mg, discontinued 43, 111 received study drug to Week 52
- 156 subjects to placebo, discontinued 43, 112 received study drug to Week 52.[4]

A further 764 subjects[5] were enrolled but not randomized.

Table 5. Number of subjects who discontinued study agent prior to Week 52 by reason for discontinuation; enrolled subjects

	Randomized Subjects					Nonrandomized Subjects			
		Golimumab					Golimumab 100 mg		
	Placebo[a]	50 mg	100 mg	Combined	Total	Placebo[b]	Placebo Nonresponders (Induction)	Golimumab Nonresponders (Induction)	Total
Subjects enrolled	156	154	154	308	464	129	230	405	1228
Subjects who discontinued study agent	43 (27.6%)	43 (27.9%)	45 (29.2%)	88 (28.6%)	131 (28.2%)	41 (31.8%)	103 (44.8%)	216 (53.3%)	491 (40.0%)
Reason for discontinuation									
Adverse event	17 (10.9%)	12 (7.8%)	12 (7.8%)	24 (7.8%)	41 (8.8%)	12 (9.3%)	30 (13.0%)	50 (12.3%)	133 (10.8%)
Unsatisfactory therapeutic effect	19 (12.2%)	17 (11.0%)	22 (14.3%)	39 (12.7%)	58 (12.5%)	18 (14.0%)	56 (24.3%)	124 (30.6%)	256 (20.8%)
Lost to follow-up	1 (0.6%)	2 (1.3%)	1 (0.6%)	3 (1.0%)	4 (0.9%)	0 (0.0%)	3 (1.3%)	7 (1.7%)	14 (1.1%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Other	6 (3.8%)	12 (7.8%)	10 (6.5%)	22 (7.1%)	28 (6.0%)	11 (8.5%)	14 (6.1%)	34 (8.4%)	87 (7.1%)

a Subjects who were in clinical response to golimumab induction dosing and were randomized to placebo on entry into this maintenance study Source: Table 1, b Subjects who were in clinical response to placebo induction dosing and received placebo on entry into this maintenance study.

[3] that is were in clinical response to golimumab at Week 6 of an induction study;
[4] Doesn't add up – sources Table 1.
[5] Golimumab and placebo induction nonresponders and placebo induction responders.

Table 6. Summary of demographics at Week 0 of an induction study; enrolled subjects

	Randomized Subjects					Nonrandomized Subjects			
		Golimumab					Golimumab 100 mg		
	Placebo[a]	50 mg	100 mg	Combined	Total	Placebo[b]	Placebo Nonresponders (Induction)	Golimumab Nonresponders (Induction)	Total
Subjects enrolled	156	154	154	308	464	129	230	405	1228
Sex									
n	156	154	154	308	464	129	230	405	1228
Male	75 (48.1%)	77 (50.0%)	89 (57.8%)	166 (53.9%)	241 (51.9%)	61 (47.3%)	131 (57.0%)	267 (65.9%)	700 (57.0%)
Female	81 (51.9%)	77 (50.0%)	65 (42.2%)	142 (46.1%)	223 (48.1%)	68 (52.7%)	99 (43.0%)	138 (34.1%)	528 (43.0%)
p-value					0.194				
Age (yrs)									
n	156	154	154	308	464	129	230	405	1228
Mean ± SD	40.2 ± 14.05	41.4 ± 13.84	39.1 ± 13.11	40.2 ± 13.51	40.2 ± 13.68	38.0 ± 13.27	40.3 ± 12.67	41.2 ± 13.60	40.3 ± 13.44
Median	38.0	41.0	37.0	39.0	39.0	35.0	39.5	40.0	39.0
IQ range	(29.0, 49.5)	(30.0, 53.0)	(28.0, 49.0)	(29.0, 50.5)	(29.0, 50.0)	(27.0, 49.0)	(30.0, 48.0)	(30.0, 51.0)	(29.0, 50.0)
Range	(18, 77)	(18, 79)	(18, 72)	(18, 79)	(18, 79)	(18, 72)	(19, 71)	(18, 78)	(18, 79)
p-value					0.330				
Weight (kg)									
n	156	154	154	308	464	128	230	405	1227
Mean ± SD	72.18 ± 19.120	72.43 ± 17.571	74.18 ± 17.211	73.30 ± 17.386	72.93 ± 17.975	72.51 ± 19.195	72.74 ± 16.795	75.03 ± 18.605	73.54 ± 18.112
Median	70.00	71.75	72.15	72.05	71.95	70.95	71.00	74.00	72.00
IQ range	(57.15, 83.45)	(60.00, 81.80)	(62.10, 85.00)	(60.00, 83.95)	(59.55, 83.75)	(58.00, 83.25)	(60.00, 83.00)	(61.00, 85.50)	(60.00, 84.40)
Range	(40.0, 136.1)	(35.0, 137.0)	(37.4, 137.8)	(35.0, 137.8)	(35.0, 137.8)	(37.9, 133.6)	(40.0, 140.0)	(33.0, 150.0)	(33.0, 150.0)
p-value					0.568				

[a] Subjects who were in clinical response to golimumab induction dosing and were randomized to placebo on entry into this maintenance study. Source: Attachment 1.8

[b] Subjects who were in clinical response to placebo induction dosing and received placebo on entry into this maintenance study.

7.1.1.1. Major protocol violations/deviations

6 subjects in the target population did not meet study selection criteria. Overall, these deviations resulted in the exclusion of data from 2 subjects in the per-protocol sensitivity analysis. Among subjects in the target population, 30.4% (141 subjects) had a deviation in study agent administration. There were no major differences in the proportions of subjects who had a deviation in study agent administration across the 50 mg, 100 mg, and the placebo groups. The most frequent deviation was administrations received outside the protocol-specified window (25.0% [116 subjects]). A total of 6.3% (29 subjects) missed an administration, 1.7% (8 subjects) received an incorrect study agent or dose, and 0.2% (1 subject) received an incorrect number of injections. These deviations were equally distributed across treatment groups, and did not result in AEs related to study agent administration. Among subjects in the target population, a total of 39 (8.4%) had a deviation in the use of concomitant medications during study participation - all subjects were considered treatment failures No subjects from site 6706 and 1 subject from site 7257 were in the target population and were prospectively excluded from all efficacy analyses.

7.1.1.2. Results for the primary efficacy outcome

50.6% of those on 100 mg and 47.1% of those on 50 mg maintained clinical response through Week 54, compared to 31.4% of those on placebo ($p < 0.001$ and $p = 0.010$ and respectively).

7.1.1.3. Results for major secondary efficacy outcomes

The 100 mg group for a major secondary endpoint was tested if the test between the 100 mg group and the placebo group tested positive for the preceding endpoint, regardless of the result of the test between the 50 mg group and the placebo group for the preceding endpoint. The 50 mg group for a major secondary endpoint could not be tested unless the 100 mg group tested positive for the same endpoint and the 50 mg group was positive for the preceding endpoint.[6]

[6] Clinical Study Report page 15

Accordingly none other than the first listed p-value for the 50 mg group was considered and the final major secondary endpoint (Among the subjects receiving concomitant corticosteroids at baseline, the proportion of subjects at Week 54 who are in clinical remission and are not receiving concomitant corticosteroids) was not of any statistical relevance.

7.1.1.4. Study C0524T17 (PURSUIT – Subcutaneous)

7.1.1.4.1. Study design, objectives, locations and dates

A multicentre randomized, placebo-controlled, parallel-group, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered subcutaneously, in subjects with moderately to severely active ulcerative colitis.

In Japan, Australia, India, New Zealand, South Africa, Bulgaria, Hungary, Poland, Romania, Serbia, Slovakia [Slovak Republic], Ukraine, Lithuania, Russia, Czech Republic, United States, Canada, Austria, Belgium, France, Israel, Denmark, Sweden, Germany and Netherlands.

Initially the study was dose-ranging with 169 subjects randomised in a 1:1:1:1 ratio at Week 0 to administration subcutaneously of golimumab weeks 0 & 2 (100 mg → 50 mg, 200 mg → 100 mg or 400 mg → 200 mg) or placebo.

An interim analysis to help determine optimal SC induction doses of golimumab was conducted after all subjects in Part 1 either completed the Week 6 visit or terminated study participation prior to Week 6.

From this the induction dose regimens of golimumab for Part 2 were decided (200 mg → 100 mg and 400 mg → 200 mg). There was no break in enrolment. The 170th subject was randomised in, and approximately 500 subjects were to be randomised in Part 2, the dose-confirming portion. However, due to the termination of the C0524T16 induction study on 30 Jan 2009,[7] which together with this study was to provide the required number of subjects to power the maintenance study, the number of subjects in Part 2 of this study was increased to 875.

At Week 6, subjects were evaluated for clinical response. All subjects were eligible to enrol in the maintenance study (C0524T18). Those not doing so were evaluated for safety 16 weeks (after Week 0).

7.1.1.4.2. Study objectives [8]

Part 1: Dose-ranging

- To evaluate the dose response of SC golimumab induction regimens in subjects with moderately to severely active ulcerative colitis.
- To select SC induction regimen(s) of golimumab, based on safety and efficacy, for continued development in Part 2.
- To provide the target study population to be evaluated in the 1-year golimumab maintenance study (C0524T18).

Part 2: Dose-confirming

7.1.1.4.2.1. Primary objectives

- To evaluate the efficacy of SC induction regimens of golimumab in inducing clinical response in subjects with moderately to severely active ulcerative colitis.
- To evaluate the safety of SC induction regimens of golimumab in subjects with moderately to severely active ulcerative colitis.

[7] Following the dose response analysis for this SC induction Study C0524T17 and a review of the totality of the data from both studies.
[8] Revised Protocol Page 15

7.1.1.4.2.2. Secondary objectives

- To evaluate the efficacy of SC induction regimens of golimumab in inducing clinical remission.
- To evaluate the efficacy of SC induction regimens of golimumab in inducing mucosal healing.
- To evaluate the efficacy of SC induction regimens of golimumab in improving disease-specific health-related quality of life.
- To provide the target study population to be evaluated in the 1-year golimumab maintenance study (C0524T18).

7.1.1.4.3. Protocol amendments

First amendment 08 May 2008:

- Since an appropriate re-randomization test was not developed and validated in the time frame necessary for this study, the randomization for Part 2 was changed to a permuted block randomization.
- Inclusion of subjects who are corticosteroid dependent.
- Inclusion of subjects who are refractory to or intolerant of oral 5-ASAs.

Second amendment 20 August 2009:

- Increased the number of subjects enrolled in Part 2 to approximately 875 and the number of study sites to approximately 275.
- The primary analysis population was changed to include only subjects randomised to Part 2 after the dose selection.

7.1.1.4.4. Inclusion criteria

- Had ulcerative colitis diagnosed prior to screening.
- Prior or current medication for ulcerative colitis must include at least 1 of the following:
  - Current treatment with at least 1 of the following therapies: oral 5-ASAs, oral corticosteroids, 6-MP, or AZA OR
  - Have a history of failure to respond to, or tolerate, at least 1 of the following therapies: oral 5-ASAs, oral corticosteroids, 6-MP, or AZA OR
  - Currently have or have had a history of corticosteroid dependency (that is, an inability to successfully taper corticosteroids without a return of the symptoms of ulcerative colitis).
- Prior to the screening endoscopy or the earliest entry in the Mayo diary card that will be used to calculate the baseline Mayo score, whichever of these 2 events comes first, the following conditions must be met:
  - If receiving 6-MP, AZA, or MTX, must have been receiving it for at least 12 weeks. The class of agent (6-MP/AZA versus MTX) prescribed may not have changed during those 12 weeks, and the dose must be stable for at least4 weeks.
  - If 6-MP, AZA, or MTX have been recently discontinued, they must have been stopped for at least 4 weeks.
  - If receiving oral 5-ASA compounds or oral corticosteroids, the dose must have been stable for at least 2 weeks.
  - If oral 5-ASA compounds or oral corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks.

- The following medications/therapies must have been discontinued for at least 2 weeks:
  - rectal corticosteroids (that is, corticosteroids administered to the rectum or sigmoid colon via foam or enema or suppository)
  - rectal 5-ASA compounds (that is, 5-ASAs administered to the rectum or sigmoid colon via foam or enema or suppository)
  - parenteral corticosteroids
  - total parenteral nutrition (TPN)
  - pentoxifylline
  - thalidomide or related agents
  - antibiotics for the treatment of ulcerative colitis (that is, ciprofloxacin, metronidazole, or rifaximin).
  - 6-thioguanine (6-TG) must have been discontinued for at least 4 weeks.

· Must be ambulatory and have moderately to severely active ulcerative colitis confirmed during the screening sigmoidoscopy by a ≥ 2 endoscopy subscore of the Mayo score.

· Must have results from a biopsy collected at the screening endoscopy procedure or have a previous biopsy result obtained within the last year that is consistent with the diagnosis of ulcerative colitis.

· Have moderately to severely active ulcerative colitis, defined as a baseline (Week 0) Mayo score of 6 to 12, inclusive.

· All subjects ≥ 45 years of age, must either have had a colonoscopy to assess for the presence of adenomatous polyps within 5 years of the first administration of study agent or a colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed prior to the first administration of study agent.

· All subjects who have had extensive colitis for ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years, must either have had a colonoscopy to assess the presence of dysplasia within 1 year prior to the first administration of study agent or a colonoscopy to assess for the presence of malignancy at the screening visit.

· Are considered eligible according to the TB screening criteria.

· Have negative stool results for enteric pathogens.

7.1.1.4.5. Exclusion criteria

· Have severe extensive colitis as evidenced by:
  - Investigator judgment that the subject is likely to require a colectomy within 12 weeks of baseline OR
  - Symptom complex at screening or baseline visits that includes at least 4 of the following:
    - diarrhoea with ≥ 6 bowel movements/day with macroscopic blood in stool
    - focal severe or rebound abdominal tenderness
    - persistent fever (≥ 37.5°C)
    - tachycardia (> 90 beats/minute)
    - anaemia (haemoglobin < 8.5 g/dL).

· Have ulcerative colitis limited to the rectum only or to < 20 cm of the colon.

· Presence of a stoma.

- Presence or history of a fistula.
- Require, or required within the 2 months prior to screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study agent treatment.
- Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).
- History of extensive colonic resection (for example, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity.
- History of colonic mucosal dysplasia.
- Presence on screening endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed.
- Have ever received biologic therapy targeted at TNFα (for example, infliximab, etanercept, certolizumab, adalimumab).
- Have received natalizumab within 12 months of first study agent administration.
- Have received agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of first study agent administration, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.
- Are receiving oral corticosteroids at a dose of greater than 40 mg of prednisone or its equivalent per day.
- Have received cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 8 weeks prior to first administration of study agent.
- Have used apheresis (that is, Adacolumn apheresis) within 2 weeks prior to first administration of study agent.
- Have a history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to screening.
- Have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (for example, bronchiectasis), sinusitis, recurrent urinary tract infection (for example, recurrent pyelonephritis, chronic cystitis), an open, draining, or infected skin wound, or an ulcer.
- Presence or history of lymphoproliferative disease.
- Concomitant diagnosis or history of CHF.
- History of systemic lupus erythematosis.
- History of demyelinating disease.

7.1.1.4.6. Study treatments

Initially the study was dose-ranging with 169 subjects randomised in a 1:1:1:1 ratio at Week 0 to:

- Placebo at Week 0 and placebo at Week 2 (placebo)
- Golimumab 100 mg at Week 0 and 50 mg at Week 2 (100 mg → 50 mg)

- Golimumab 200 mg at Week 0 and 100 mg at Week 2 (200 mg → 100 mg)
- Golimumab 400 mg at Week 0 and 200 mg at Week 2 (400 mg → 200 mg).

While the data from Part 1 were being evaluated, newly enrolled subjects in Part 2 were equally randomised to the same SC doses of golimumab or placebo as in Part 1.

After the interim analysis, the Dose Selection Committee selected the 200 mg → 100 mg and 400 mg → 200 mg SC golimumab doses for the dose-confirming portion in Part 2. Patients were then randomised equally to 200 mg → 100 mg and 400 mg → 200 mg golimumab or placebo.

7.1.1.4.7. Efficacy variables and outcomes

Part 1: Dose-ranging

- Change from baseline in the Mayo score at Week 6.[9]

Part 2: Dose-confirming

- Primary Endpoint: Clinical response at Week 6.[10]
- Major Secondary Endpoints:
  - Clinical remission at Week 6.
  - Mucosal healing at Week 6.
  - Change from baseline in the Inflammatory Bowel Disease Questionnaire IBDQ score at Week 6.

7.1.1.4.8. Randomisation and blinding methods

An interactive voice response system was used to randomly assign subjects to study treatment and dispense study agent. In Part 1, subjects were randomly assigned to receive placebo or 1 of 3 dose regimens of golimumab (100 mg → 50 mg, 200 mg → 100 mg, or 400 mg → 200 mg at Week 0 and 2, respectively) using an adaptive randomization procedure, with investigative site as the stratification variable. The randomization method was a minimization procedure with a biased-coin assignment. In Part 2, eligible subjects were allocated to a treatment regimen using a permuted block randomization.

There were no visual differences in appearance between the syringes of placebo and golimumab. The designated pharmacists, or other appropriately licensed and authorized personnel who dispensed the study agent, and independent drug monitors were unblinded to study agent. The subjects, site monitors, principal investigator, and all the investigator site staff were blinded to study agent assignment. The results of laboratory tests that could potentially unblind the treatment assignment were only available to data management staff and, if applicable, QA representatives.

7.1.1.4.9. Analysis populations

Part 1

The efficacy analyses included all subjects randomized in Part 1.

Part 2

The primary population will be used for the primary endpoint analysis. The primary population consists of subjects randomized to Part 2 after the dose selection excluding those from site 7257.

[9] Revised Protocol page 19 this is not in the Revised Statistical Analysis Plan
[10] defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 at Week 6.

Other analysis populations are (excluding those from site 7257):

- All subjects randomized in Part 1
- All subjects randomized in Part 2
- All subjects randomized in Part 2 before the dose selection
- The first 450 subjects randomized in Part 2 after the dose selection
- All subjects randomized in the study (Part 1 and Part 2 combined.)[11]

7.1.1.4.10. Sample size

Sample size/power calculations were based on a chi-square test to detect a significant difference between subjects receiving the selected golimumab dose(s) and those receiving placebo.

No data existed for golimumab in the treatment of ulcerative colitis. Sample size and power calculations for the study were based on estimates obtained from studies of infliximab in subjects with moderately to severely active ulcerative colitis.

For the current study, if 1 active dose is selected from the analysis of the Part 1 data, the clinical response rate for the selected golimumab group is assumed to approximate the rate for infliximab and is set at 65%. If 2 active doses are selected, it is assumed that the clinical response rate for one dose follows the rate from infliximab and is set at 65%, and the clinical response rate for the other is 55%. In either situation, the placebo clinical response rate is estimated to be 45%.

To power the study at 90% with respect to the primary endpoint when 2 doses are selected, approximately 150 subjects per selected dose group and placebo group (total 450 subjects) would have to be enrolled after the dose selection.

To provide a sufficient number of subjects to enrol in, and adequately power, the 1-year golimumab maintenance study (C0524T18), approximately 500 subjects originally should have been enrolled in Part 2.

However, due to the termination of the C0524T16 induction study, which together with this study was to provide the required number of subjects to power the maintenance study, the number of subjects in Part 2 of this study was increased to 875 to provide a sufficient number of subjects to enrol in and adequately power C0524T18.

With 122 subjects enrolled in Part 2 of this study prior to the dose selection, 753 subjects were to be included in the primary analysis population (that is, subjects enrolled in Part 2 after the dose selection). The sample size of 753 subjects would provide statistical power of 99% and 96% for the primary endpoint at the $\alpha = 0.05$ and $\alpha = 0.01$ (2-sided) level, respectively, using a step-up testing procedure in a 3-arm study.

7.1.1.4.11. Statistical methods

Part 1

An interim analysis was conducted after all subjects in Part 1 (n = 169) had either completed the Week 6 visit or terminated study participation prior to Week 6. The purpose of the interim analysis was to evaluate the dose response of IV golimumab induction regimens, and select the SC induction regimens of golimumab for further evaluation in Part 2. The decision on which dose(s) to continue for further evaluation was made by a dose selection committee.[12]

Part 2

[11] Revised Statistical Analysis Plan
[12] Which consisted of management representative(s) from Centocor and Schering-Plough

7.1.1.4.12. Primary efficacy analysis

The proportions of subjects in clinical response at Week 6 were summarized and compared between the placebo and golimumab groups using a 2-sided chi-square test. A fixed sequence testing procedure was employed to control the Type 1 error rate at the 0.05 level. In this testing procedure, the comparison between the higher selected golimumab dose versus placebo was first tested at the two-sided 0.05 level of significance. Only if this test is positive, the lower selected golimumab dose will be compared with placebo at the two sided 0.05 level of significance. The study was to be considered positive if the test involving the higher selected golimumab dose was positive, regardless of the result of the test for the lower selected golimumab dose.

7.1.1.4.13. Major secondary efficacy analyses

- The proportions of subjects in clinical remission at Week 6 were summarized and compared between the golimumab and placebo treatment groups.
- The proportions of subjects with mucosal healing at Week 6 were summarized and compared between the golimumab and placebo treatment groups.
- The change from baseline in the IBDQ scores at Week 6 were summarized and compared between the golimumab and placebo treatment groups.

The same multiple testing procedure (that is fixed sequence testing procedure) was used to control the Type 1 error rate within each of the 3 major secondary efficacy analyses at the 0.05 (2-sided) significance level.

In addition, a fixed-sequence testing procedure was used to control the Type 1 error rate across the 3 major secondary endpoints. The first major secondary hypothesis (clinical remission) was tested if the primary hypothesis had been met. Only if the first test for clinical remission was positive, will the second hypothesis for mucosal healing to be tested. The third hypothesis for IBDQ was to be tested only if the second test for mucosal healing was positive.

Analyses of clinical remission and mucosal healing endpoints were conducted using a 2-sided chi-square test. Analysis of the change from baseline in the IBDQ score was conducted using an analysis of variance on the van der Waerden normal scores.

Among all randomized subjects:

- 92.1% were receiving ulcerative colitis medications;
- 43.2% were receiving corticosteroids (excluding budesonide), with 25.1% receiving ≥ 20 mg/day (PEq);
- 2.1% were receiving budesonide;
- 29.8% were receiving immunomodulators, with 28.3% receiving 6-MP/AZA and 1.6% receiving MTX;
- 81.4% were receiving aminosalicylates (protocol amendment). [13]
- 68.9% were refractory to, dependent on, or intolerant of corticosteroids;
- 49.6% were refractory to or intolerant of 6-MP/AZA;
- 95.7% were refractory to or intolerant of 5-ASAs.
- 91.7% had used corticosteroids (excluding budesonide);

[13] Prior to amendment 1, subjects were required to be at least refractory to or intolerant of corticosteroids and/or the immunomodulators 6-MP or AZA. With amendment 1, entry criteria were modified to allow subjects who were only refractory to or intolerant of oral 5-ASAs to be considered eligible to enter the study.

- 55.4% had used immunomodulatory agents;
- 99.5% had used aminosalicylates;
- 33.3% had used antibiotics.

7.1.1.4.14. Major protocol violations/deviations

Study Entry Criteria Deviations were categorized as ulcerative colitis disease criteria (24 subjects),[14] medication criteria (14 subjects),[15] laboratory criteria (41 subjects),[16] medical history criteria (66 subjects),[17] and other (9 subjects). The absence of documentation confirming a subject's eligibility at randomization was considered a deviation even if subsequent follow-up supported that the subject would have met the specific entry criterion.

There were no major differences in the proportions of subjects who did not meet study selection criteria across the selected golimumab dose groups and the placebo group.

Study Agent Administration Deviations were received incorrect study agent or dose (3 (0.3%) subjects), and received an administration outside the protocol-specified window (48 [4.5%] subjects).

Deviations in the use of concomitant medications were by 26 subjects who initiated or increased the use of concomitant ulcerative colitis medications (corticosteroids - 20 subjects).

A manual update to the interactive voice response system of a field that determined to which part of the study subjects were to be randomized (Part 1 or Part 2) prematurely triggered randomization to Part 2. As a result, only 169 subjects were randomized to Part 1.

Due to findings of inappropriate completion of Informed Consent Forms and Mayo diary cards at site 7257, subject data from this site were excluded from all efficacy analyses but were included in PK and safety analyses. In total, 7 subjects were randomized at site 7257 (1 subject from Part 1, and 3 subjects each from Part 2 before the dose selection and Part 2 after the dose selection.

7.1.1.4.15. Results for the primary efficacy outcome

The proportions of subjects in the primary analysis population in clinical response at Week 6 were significantly greater for each golimumab group compared with the placebo group. The sensitivity analyses support this.

The majority of subjects had complete Mayo score data at Week 6 (93.8% and 96.3% in the placebo and golimumab combined groups, respectively). Few subjects were missing 1 to 3 Mayo subscores: 2 (0.8%) subjects each in the placebo and 200 mg → 100 mg groups and no subjects in the 400 mg → 200 mg group were missing 1 subscore. No subjects in any group were missing 2 or 3 subscores. In the placebo and golimumab combined groups, 5.5% and 3.3% of subjects, respectively, were missing all 4 Mayo subscores. Among subjects missing all 4 Mayo subscores, the majority terminated study participation prior to Week 6.

[14] In 21 subjects it was the absence of a biopsy collected at the screening endoscopy procedure or the availability of a biopsy result obtained within the last year that was consistent with the diagnosis of ulcerative colitis.
[15] 13 subjects were related to a failure to maintain stable doses of concomitant medications before randomization for the intervals specified
[16] In 35 subjects it was the absence at randomization of negative stool culture results for enteric pathogens
[17] majority (57 subjects) were TB screening requirements.

7.1.1.4.16. Results for other efficacy outcomes

Table 7. Major Secondary Efficacy Outcomes (excluding sites 6706 and 7257)

	Placebo	Golimumab		
		200mg→100mg	400mg→200mg	Combined
Proportion in clinical remission at Week 6				
Week 6 n	256	257	258	515
Subjects in clinical remission[a,b]	16 (6.3%)	48 (18.7%)	46 (17.8%)	94 (18.3%)
p-value		<0.0001	<0.0001	<0.0001
Proportion with mucosal healing at Week 6				
Week 6 n	256	257	258	515
Subjects with mucosal healing[a,c]	73 (28.5%)	111 (43.2%)	117 (45.3%)	228 (44.3%)
p-value		0.0005	<0.0001	<0.0001
Change from baseline in the IBDQ score at Week 6.				
Week 6[d,e] n	255	256	256	512
Mean ± SD	14.6 ± 31.37	27.4 ± 33.68	27.0 ± 34.23	27.2 ± 33.92
Median	11.0	23.0	21.5	22.0
IQ range	(-3.0, 29.0)	(1.0, 50.0)	(0.0, 50.0)	(0.0, 50.0)
Range	(-80, 115)	(-49, 131)	(-60, 187)	(-60, 187)
p-value		<0.0001	<0.0001	<0.0001

[a] Subjects who had a prohibited change in concomitant ulcerative colitis medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect prior to the Week 6 visit are considered not to be in clinical remission or have mucosal healing

[b] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical remission.

[c] Subjects who had a missing endoscopy subscore at Week 6 are considered not to have mucosal healing.

[d] Subjects who had a prohibited change in concomitant ulcerative colitis medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect prior to the Week 6 visit had their baseline value carried forward to Week 6.

[e] Subjects who had a missing IBDQ score at Week 6 had the last available value carried forward.

Source: Table 10, Attachments 3.23 & 3.25

7.1.2. Study C0524T16 (PURSUIT – Intravenous)

Comment: This was a 2 phase study. The protocol and Statistical analysis plan make it clear that the objectives and endpoints differed between the 2 phases. The study was closed prematurely before the intended population of its second phase was achieved. However the resulting smaller population meant that there was not sufficient power for the primary endpoint analysis, which was based on the population of subjects from Part 2. For this reason, all analyses based on the population of subjects in Part 2, which includes the primary and major secondary endpoints, was not performed. The revised plan was to analyse all efficacy (including the endpoints originally designated as the primary and major secondary endpoints), safety, and PK endpoints using the combined population of subjects from Part 1 and Part 2.[18]

Following the dose response analysis for the companion golimumab SC induction study C0524T17 and a review of the totality of the data from both studies, enrolment was terminated on 30 January 2009 after 115 subjects were randomised.

Thus the size of the population enrolled in Part 2 was not known until after the unblinding of those in Part 1 for review, that is a decision was made to alter the primary and secondary variables and endpoints with part of the population already unblinded.

[18] Ulcerative Colitis Revised Statistical Analysis Plan page 9

7.1.2.1.1. Study design, objectives, locations and dates

A multicentre randomized, placebo-controlled, parallel-group, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered intravenously, in subjects with moderately to severely active ulcerative colitis. From 2 August 2007 to 18 May 2009. In Australia, India, New Zealand, Bulgaria, Hungary, Latvia, Poland, Romania, Serbia, Slovakia [Slovak Republic], Ukraine, United States, Canada, Austria, Belgium, France, Israel, and Netherlands.

Initially the study was dose-ranging with 176 subjects randomised in a 1:1:1:1 ratio at Week 0 to a single IV administration of golimumab (1mg/kg, 2mg/kg, or 4mg/kg) or placebo.

An interim analysis to help determine optimal IV induction doses of golimumab was conducted after all subjects in Part 1 either completed the Week 6 visit or terminated study participation prior to Week 6. From this the induction dose regimens of golimumab for Part 2 were decided (2mg/kg and 4mg/kg). There was no break in enrolment. The 177th subject was randomised in, and approximately 500 subjects were to be randomised in Part 2, the dose-confirming portion, enrolment into the study was terminated on 30 Jan 2009 after 115 subjects were randomised.[19]

At Week 6, subjects were evaluated for clinical response. All subjects were eligible to enrol in the maintenance study C0524T18. Those not doing so were evaluated for safety 16 weeks after Week 0.

7.1.2.1.2. Study objectives [20]

Part 1: Dose-ranging

- To evaluate the dose response of IV golimumab induction regimens in subjects with moderately to severely active ulcerative colitis.
- To select IV induction regimen(s) of golimumab, based on safety and efficacy, for continued development in Part 2.
- To provide the target study population to be evaluated in the 1-year golimumab maintenance study (C0524T18).

Part 2: Dose-confirming

Primary Objectives

- To evaluate the efficacy of IV induction regimens of golimumab in inducing clinical response in subjects with moderately to severely active ulcerative colitis.
- To evaluate the safety of IV induction regimens of golimumab in subjects with moderately to severely active ulcerative colitis.

Secondary Objectives

- To evaluate the efficacy of IV induction regimens of golimumab in inducing clinical remission.
- To evaluate the efficacy of IV induction regimens of golimumab in inducing mucosal healing.
- To evaluate the efficacy of IV induction regimens of golimumab in improving disease-specific health-related quality of life.
- To provide the target study population to be evaluated in the 1-year golimumab maintenance study (C0524T18).

[19] Following the subsequent dose response analysis for the companion golimumab SC induction Study C0524T17 and a review of the totality of the data from both studies.
[20] Revised Protocol Page 15

7.1.2.1.3. Inclusion & exclusion criteria

Were the same as for Study C0524T17.

7.1.2.1.4. Study treatments

Initially the study was dose-ranging with 176 subjects randomised in a 1:1:1:1 ratio at Week 0 to a single IV administration of golimumab (1mg/kg, 2mg/kg, or 4mg/kg) or placebo.

While the data from Part 1 were being evaluated, newly enrolled subjects in Part 2 were equally randomised to the same IV doses of golimumab or placebo as in Part 1.

After the interim analysis, the Dose Selection Committee selected the 2mg/kg and 4mg/kg IV golimumab doses for the dose-confirming portion in Part 2. Patients were then randomised equally to 2mg/kg, or 4mg/kg golimumab or placebo.

7.1.2.1.5. Efficacy variables and outcomes

Part 1: Dose-ranging

- Change from baseline in the Mayo score at Week 6.

Part 2: Dose-confirming

- Primary Endpoint: Clinical response at Week 6.
- Major Secondary Endpoints:
  - Clinical remission at Week 6.
  - Mucosal healing at Week 6.
  - Change from baseline in the IBDQ score at Week 6.

However the smaller population than planned for Part 2 meant that there was not sufficient power for the primary endpoint analysis, which was based on the population of subjects from Part 2. For this reason, all analyses based on the population of subjects in Part 2, which includes the primary and major secondary endpoints, was not performed.[21,22]

The revised plan was to analyse all efficacy (including the endpoints originally designated as the primary and major secondary endpoints), safety, and PK endpoints using the combined population of subjects from Part 1 and Part 2.

7.1.2.1.6. Randomisation and blinding methods

Were the same as for Study C0524T17.

7.1.2.1.7. Analysis populations

There will be no primary endpoint analysis since the study was terminated. However, clinical response at Week 6 will be analysed using all randomized subjects in Part 1 and Part 2 combined, and also all randomized subjects in Part 1.[23]

Analysis populations include:

- All subjects randomized in Part 1.
- All subjects randomized in the study (Part 1 and Part 2 combined).

[22] Ulcerative Colitis Revised Statistical Analysis Plan page 9

[23] Revised Statistical Analysis Plan page 16 This differs from the statement in the Clinical Study Report page 42 The primary analysis population was subjects randomized in Part 2 after the dose selection, excluding those from site 7257.

Analyses will be performed for Part 1 and Part 2 combined. In addition, selected efficacy endpoints were to be analysed using only the subjects in Part 1.

7.1.2.1.8. Sample size

Calculations the same as initially for Study C0524T17.

To power the study at 90% with respect to the primary endpoint when 2 doses are selected, approximately 150 subjects per selected dose group and placebo group (total 450 subjects) would have to be enrolled after the dose selection.

To provide a sufficient number of subjects to enrol in, and adequately power, the 1-year golimumab maintenance study (C0524T18), approximately 500 subjects should be enrolled in Part 2.

7.1.2.1.9. Statistical methods

An interim analysis was conducted after all subjects in Part 1 (n = 176) had either completed the Week 6 visit or terminated study participation prior to Week 6. The purpose of the interim analysis was to evaluate the dose response of IV golimumab induction regimens, and select the IV induction regimens of golimumab for further evaluation in Part 2. The decision on which dose(s) to continue for further evaluation was made by a dose selection committee.[24]

Following the dose response analysis for the companion golimumab SC induction study C0524T17 and a review of the totality of the data from both studies, enrolment was terminated on 30 Jan 2009 after 115 subjects were randomised. Hence, there was not sufficient power for the primary endpoint analysis, which was based on the population of subjects from Part 2. For this reason, all analyses based on the population of subjects in Part 2, which includes the primary and major secondary endpoints, were not performed.

A revised plan was to analyse all efficacy (including the endpoints originally designated as the primary and major secondary endpoints), safety, and PK endpoints using the combined population of subjects from Part 1 and Part 2. In addition, selected efficacy, safety, and PK endpoints were to be analysed using all subjects in Part 1.

7.1.2.1.10. Major protocol violations/deviations

10 (3.4%) subjects who did not meet study selection criteria were randomized.

One subject had a deviation in study agent administration - the infusion was stopped due to an AE.

Investigator misconduct at Site 6706 meant subject data from this site were excluded from all efficacy analyses but were included in the safety and PK analyses.

7.1.2.1.11. Results for the efficacy outcome

For the Part 1 and Part 2 combined populations, 44.0% of those on 2mg/kg and 41.6% of those on 4mg/kg at Week 6 achieved clinical response compared with 30.1% in the placebo group, although the differences were not significant.

7.1.3. Evaluator's conclusions on clinical efficacy

Entering the maintenance study were almost all subjects (464/467) in clinical response on golimumab at Week 6 of studies C0524T16 (87 [40.8%] versus 22 [30%] on placebo) and parts 1 & 2 of C0524T17 (380 [52.1%] versus 104 [31.7%] on placebo).

Of these in the maintenance study (C0524T18) on placebo 49 (31.4%) stayed in clinical response on placebo and 150 (48.9%) did so on golimumab (57.7% and 38.8% respectively met

[24] Which consisted of management representative(s) from Centocor and Schering-Plough

treatment failure criteria). While the difference was statistically significant, it should also be remembered that the "placebo" group had received 1 IV or 2 SC doses of golimumab initially.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

- IV induction study (C0524T16),
- SC induction study (C0524T17),
- SC maintenance study (C0524T18).

8.2. Patient exposure

Table 8. Golimumab exposure in clinical studies in subjects with moderately to severely active UC

Study Number\Phase	Duration of Follow-up for this Submission	Doses Administered (Treated Subjects)
C0524T16, Phase 2/3	6 weeks for subjects entering C0524T18 16 weeks following the last study agent administration for subjects not entering C0524T18	**IV administration at Week 0:** Placebo 77 1 mg/kg 63 2 mg/kg 74 4 mg/kg 76
C0524T17, Phase 2/3	6 weeks for subjects entering C0524T18 16 weeks following the last study agent administration for subjects not entering C0524T18	**SC administration at Week 0 and at Week 2:** Placebo → placebo 330 100 mg → 50 mg 71 200 mg → 100 mg 331 400 mg → 200 mg 332
C0524T18, Phase 3	54 weeks	**SC administration every 4 weeks:** **Subjects in response to golimumab induction (Randomized Subjects)** Placebo 156 50 mg 154 100 mg 154 **Other populations (Nonrandomized Subjects)** Placebo (pbo induction responders) 129 100 mg (pbo induction nonresponders) 230 100 mg (gol induction nonresponders) 405

In C0524T18 Study, 1075 subjects were treated with golimumab with 741 (68.9%) exposed to golimumab for at least 6 months and 536 (49.9%) exposed for at least 1 year. Gol = golimumab; pbo = placebo. Source: Table 1.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

The proportions of subjects with an AE through Week 54 of the maintenance study were similar among the placebo, 50 mg, and 100 mg maintenance treatment groups (73.2%, 77.9%, and

78.6%, respectively, with 39.0, 50.4, and 45.1 average weeks of follow-up, respectively. The overall proportion of AEs was 74.1% in those subjects who received placebo induction who subsequently received 100 mg maintenance, with an average follow-up of 39.2 weeks.

The pattern of AEs among treated subjects from the SC induction study C0524T17 was similar to that observed for subjects enrolled from both induction studies. This is not an unexpected observation since 78.7% (970/1233) of subjects enrolled in C0524T18 were from C0524T17.

The most common AE in all treatment groups was colitis ulcerative occurring in 18.6%, 17.5%, and 15.6% of subjects in the placebo, 50 mg, and 100 mg treatment groups, respectively. AEs of nasopharyngitis, upper respiratory tract infection, abdominal pain, rash, and cough were more frequent in the 50 mg and 100 mg groups than in the placebo group.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal study C0524T18

Among randomized subjects, the proportions of subjects with reasonably related AEs through Week 54 were 28.2%, 25.3%, and 35.7% in the placebo, golimumab 50 mg, and golimumab 100 mg groups, respectively. The SOCs with the most frequently reported AEs that were considered to be reasonably related were Infections and infestations and Skin and subcutaneous tissue disorders. Nasopharyngitis was the most frequently reported AE that was considered to be reasonably related, in 1.9%, 3.2%, and 3.9% of subjects in the placebo, golimumab 50 mg, and golimumab 100 mg groups, respectively.

Similarly, among all treated subjects, the proportions of subjects with reasonably related AEs through Week 54 were 24.9%, 25.3%, and 29.0% in the placebo, golimumab 50 mg, and golimumab 100 mg groups, respectively, and the SOCs with the most frequently reported AEs that were considered to be reasonably related were also Infections and infestations and Skin and subcutaneous tissue disorders.

8.3.2.2. Other studies

8.3.2.2.1. Study C0524T17

Through Week 6, the proportions of treated subjects with reasonably related AEs were low overall (15.5% and 16.8% in the placebo and all golimumab groups, respectively) and similar in the 200 mg → 100 mg and 400 mg → 200 mg groups (16.3% and 17.5%, respectively).

The most frequently reported reasonably related AEs (≥ 1%) by preferred term in any of the placebo, 200 mg → 100 mg, or 400 mg → 200 mg groups were as follows (ordered by decreasing frequency in the 400 mg → 200 mg group):

- Headache: 2.1%, 0.3%, and 1.8%, respectively;
- Nausea: 0.6%, 0.0%, and 1.8%, respectively;
- Arthralgia: 0.6%, 0.3%, and 1.5%, respectively;
- Injection site erythema: 0.0%, 1.5%, and 1.2%, respectively;
- Pyrexia: 1.2%, 0.6%, and 1.2%, respectively;
- Cough: 1.5%, 0.6%, and 0.6%, respectively;
- Nasopharyngitis: 1.8%, 1.8%, and 0.3%, respectively.

8.3.2.2.2. Study C0524T16

Through Week 6, the proportions of subjects with reasonably related AEs were generally comparable in the golimumab combined and placebo groups (13.1% and 11.7%, respectively; Attachment 4.7). Reasonably related AEs that occurred in more than 1 golimumab-treated subject were pharyngitis and headache (3 subjects each), and pruritis, pyrexia, ALT increased,

AST increased, and cough (2 subjects each). Reasonably related AEs that occurred in more than 1 placebo-treated subject were pruritis and nausea (2 subjects each).

8.3.2.2.3. Deaths

8.3.2.2.3.1. Pivotal study C0524T18

In C0524T18, 3 deaths occurred through Week 54.

A 66-year-old man in, died from cardiac failure on Study Day 335 (golimumab 100 mg maintenance; golimumab 400 → 200 mg SC induction). This subject had a history of thrombosis but no history of heart disease or arterial hypertension. The subject died 82 days after the last study agent administration.

A 60-year-old woman (golimumab 100 mg maintenance; golimumab 2mg/kg IV induction), died of septic shock on Study Day 364. The subject was hospitalized on Study Day 362 with high-grade fever, hypotension, tachycardia, tachypnoea, and oliguria and appeared emaciated and malnourished. She died 2 days later. No source for the sepsis was identified. The subject died 26 days after the last study agent administration.

A 58-year-old man (golimumab 100 mg maintenance; golimumab 200 → 100 mg SC induction), died of disseminated TB on Study Day 206. The subject entered the induction study with a positive QuantiFERON-TB Gold test result and was receiving isoniazid treatment during the maintenance study under the supervision of a pulmonologist. The subject died 37 days after the last study agent administration.

8.3.2.2.3.2. Other studies

In C0524T17, 1 death (golimumab 400 mg → 200 mg) due to an SAE of ischiorectal abscess on Study Day 94, 79 days after the last dose of study agent.

No deaths occurred in Study C0524T16.

8.3.2.2.4. Serious adverse events

8.3.2.2.4.1. Pivotal Study C0524T18

The proportions of randomised subjects who discontinued study agent due to an AE were 6.4%, 5.2%, and 9.1% in the placebo, 50 mg, and 100 mg groups, respectively, with 32.7, 44.3, and 46.3 average weeks of follow-up, respectively. When adjusted for follow-up, the incidences per 100 subject-years of follow-up of AEs leading to discontinuation were 10.43, 6.16, and 10.44 in the placebo, 50 mg, and 100 mg groups, respectively.

The most frequently reported AEs leading to discontinuation of study agent were in the Gastrointestinal disorders SOC. Colitis ulcerative was the most common AE that resulted in discontinuation of study agent among randomized subjects and occurred among 1.9%, 3.9%, and 4.5% of subjects in the placebo, 50 mg, and 100 mg groups, respectively.

8.3.2.2.4.2. Other studies

Through Week 6 in C0524T16, the proportion of subjects with SAEs was in the overall placebo and combined IV golimumab groups (2.6% and 3.8%, respectively; C0524T16). The only SAE that occurred in more than 1 subject was colitis ulcerative, occurring in 4 (1.9%) golimumab-treated subjects and no placebo-treated subjects.

Through Week 6 in C0524T17, the proportions of subjects with SAEs were 6.1%, 2.7%, and 3.3% in the placebo, 200 mg → 100 mg and 400 mg → 200 mg groups, respectively.

The most common SAE in the placebo, 200 mg → 100 mg, and 400 mg → 200 mg groups was ulcerative colitis (2.4%, 0.9%, and 1.2%, respectively). Anaemia was the only other SAE occurring in more than 1 subject receiving golimumab, occurring in 0.6%, 0.6%, and 0.0% of subjects in the placebo, 200 mg → 100 mg and 400 mg → 200 mg groups, respectively.

8.3.2.2.5. Discontinuation due to adverse events

8.3.2.2.5.1. Pivotal study C0524T18

The proportions of randomised subjects who discontinued study agent due to an AE were 6.4%, 5.2%, and 9.1% in the placebo, 50 mg, and 100 mg groups, respectively, with 32.7, 44.3, and 46.3 average weeks of follow-up, respectively. When adjusted for follow-up, the incidences per 100 subject-years of follow-up of AEs leading to discontinuation were 10.43, 6.16, and 10.44 in the placebo, 50 mg, and 100 mg groups, respectively.

The most frequently reported AEs leading to discontinuation of study agent were in the Gastrointestinal disorders SOC. Colitis ulcerative was the most common AE that resulted in discontinuation of study agent among randomized subjects and occurred among 1.9%, 3.9%, and 4.5% of subjects in the placebo, 50 mg, and 100 mg groups, respectively.

8.3.2.2.5.2. Other studies

In Study C0524T16 no discontinuations were possible.

Through Week 6 in C0524T17, the proportions of subjects with an AE leading to study agent discontinuation were 0.9%, 0.3%, and 0.3% in the placebo, 200 mg → 100 mg, and 400 mg → 200 mg groups, respectively. No AE (by preferred term) leading to discontinuation of study agent was reported in more than 1 subject in any treatment group.

8.3.2.2.6. Laboratory tests

8.3.2.2.6.1. Antibodies to Golimumab

During the induction studies, only 3 subjects were positive for antibodies to golimumab all in the SC Study C0524T17 only 1 of whom continued into this maintenance study.

In Study C0524T18 of 455 randomized subjects, 20 (4.4%) were positive for antibodies to golimumab - the majority (16/20) exhibited low titres (under 1:640).

- 11 of 155 (7.1%) in the placebo group (they had received golimumab induction),
- 4 of 152 (2.6%) in the golimumab 50 mg group,
- 5 of 148 (3.4%) in the golimumab 100 mg group.

Of 1,103 treated subjects 32 subjects (2.9%) were positive for antibodies to golimumab - the majority (21/32) had low titters (under 1:640):

- 11 of 155 (7.1%) in the randomized placebo group (they had received golimumab induction),
- 2 of 56 (3.6%) in the nonrandomized placebo golimumab 100 mg group,
- 4 of 152 (2.6%) in the golimumab 50 mg group, and
- 15 of 740 (2.0%) subjects in the combined golimumab 100 mg group.

In Study C0524T18 although the incidence of anti-golimumab antibodies was low overall (2.9%), the proportions of subjects who were positive for golimumab antibodies appeared to be higher in subjects randomized to placebo (7.1%) compared with the proportions in the other treatment groups (2.0% - 3.6%). The reason for this apparent difference is not known.

Of 932 golimumab-treated subjects who did not increase their dose and had appropriate samples for antibodies, 24 (2.6%) were positive for antibodies to golimumab The proportion of subjects who developed antibodies to golimumab was similar between subjects who received golimumab 50 mg (2/127 [1.6%]) and those who received golimumab 100 mg (15/726 [2.1%]).

2 of 25 subjects (8.0%) in the golimumab 50 mg → 100 mg treatment group were positive for antibodies to golimumab, in comparison, none (0/14) of the subjects in the golimumab 100 mg → 200 mg group were. Median serum golimumab concentrations (mcg/mL) over time by

antibody to golimumab status during this maintenance study through Week 54; treated subjects who were randomized to placebo, golimumab 50 mg, or golimumab 100 mg treatment group

8.3.2.2.6.2. Effect on clearance (PopPK study)

In the 34 subjects (2.8%) who developed immunogenicity against golimumab the model-predicted mean CL value for golimumab was 24.3% higher.

8.3.2.2.6.3. Neutralizing antibodies to Golimumab

Of 19 randomized subjects who were positive for antibodies to golimumab and were evaluated for Neutralizing Antibodies to Golimumab, 11 (57.9%) were positive. Among those who increased their maintenance dose 4/6 [66.7%] were positive.

Of 31 treated subjects (including both randomized and nonrandomized subjects) who were positive for antibodies to golimumab, and were evaluated for Neutralizing Antibodies to Golimumab, 21 (67.7%) were positive.

Median serum golimumab concentrations were lower in subjects who were positive for antibodies to golimumab compared with levels in subjects who were negative for antibodies to golimumab.

8.3.2.2.6.4. Haematology

Among all treated subjects, the most common markedly abnormal post baseline haematology laboratory value was a decrease in lymphocytes, reported in 34.9%, 25.3%, and 23.6% of subjects in the placebo, 50 mg, and 100 mg groups, respectively with 19.2%, 14.9%, and 11.1%, respectively, having more than 1 markedly abnormal decrease. Any markedly abnormal decrease in absolute neutrophils was observed in 3.2%, 3.9%, and 5.8% of subjects in the placebo, 50 mg, and 100 mg groups, respectively, with 1.1%, 1.3%, and 1.8%, respectively, having a markedly abnormal decrease in neutrophils on more than 1 occasion. Among these subjects, 8 subjects presented with a transient decrease in absolute neutrophils to levels below 1.0 x 103 cells/mcL. Two additional subjects had a decrease in absolute neutrophils to levels below 1.0 x 103 cells/mcL on 2 occasions.

Among all treated subjects, the maximum toxicity grades for post baseline haematology laboratory values were generally consistent across treatment groups and most were Grade 0 through Grade 2. Post baseline Grade 4 haematology values were generally transient events.

8.3.2.2.6.5. Liver function

In C0524T18 3 subjects had a concurrent elevations in ALT > 3x ULN and total bilirubin > 2x ULN (2 in the 50 mg group and 1 in the placebo group). None of the subjects had evidence of drug-induced liver injury as all events were transient and the subjects continued to receive study agent.

In C0524T17 3 subjects in the placebo and 2 in the golimumab treatment groups had ALT and AST measurements both of which were ≥ 3 x ULN. Two subjects (100 mg → 50 mg and 400 mg → 200 mg) presented with a maximum post baseline total bilirubin > 2 x ULN that was not accompanied by clinically significant changes in ALT or AST.

In C0524T16 only 1 subject treated with golimumab had a single, transient maximum post baseline ALT of ≥ 5 to < 8 times the ULN and a single, transient maximum post baseline AST of ≥ 5 to < 8 times the ULN. Total bilirubin was normal.

Overall during the combined controlled and uncontrolled periods from Week 0 of an induction study through Week 54 of the maintenance study for all treated subjects with maximum post baseline ALT, measurements that were ≥ 3x ULN were 1.5% and 2.0% in the placebo and golimumab groups, respectively.

8.3.2.2.6.6. Kidney function

There were no persistently abnormal urea results and only 1 creatinine in each of placebo and 100 mg maintenance groups.

8.3.2.2.6.7. Other clinical chemistry

Subjects reporting more than 1 markedly abnormal post baseline clinical chemistry value were relatively rare but did occur among all treatment groups for markedly abnormal value of elevated potassium, with even less frequent hyponaetraemia on 1 occasion in 2 patients on maintenance 100 mg.

8.3.2.2.7. Vital signs

Not recorded.

8.3.2.2.8. Post-marketing experience

Nil submitted for this indication.

8.3.2.2.9. Safety issues with the potential for major regulatory impact

Based on the PI included sepsis, pneumonia, TB, opportunistic infections, cellulitis, demyelination, CHF, hypersensitivity reactions, serum sickness-like and anaphylactic reactions, and hepatobiliary events.

8.3.2.2.10. Infections

Rates of AEs of an infection among subjects who received golimumab in C0524T16 and C0524T17 and who were randomized in C0524T18, were: 35.3%, 43.5%, and 42.9%in the placebo, 50 mg, and 100 mg groups, respectively. Nasopharyngitis was reported in 7.7%, 10.4%, and 11.7% of subjects in the placebo, 50 mg, and 100 mg groups, respectively.

When adjusted for follow-up, the incidence per 100 subject-years among subjects who received golimumab induction was 95.21 (CI: 78.39, 114.56), 100.41 (CI: 84.98, 117.82), and 85.76 (CI: 78.34, 93.69) in the placebo, 50 mg, and 100 mg groups, respectively.

The most common infections requiring treatment were pharyngitis (2.6%, 3.2%, and 3.2%) and sinusitis (1.9%, 3.2%, and 3.2%), in the placebo, 50 mg, and 100 mg groups, respectively.

Among subjects who received golimumab induction and were randomized in C0524T18 the proportion with an infection requiring oral or parenteral antimicrobial treatment was 18.6%, 26.6%, and 32.5% of subjects in the placebo, 50 mg, and 100 mg groups, respectively.

Among subjects who received golimumab in C0524T16 and C0524T17 who were randomized in C0524T18, the proportions of subjects with a serious infection were 2.6%, 3.2%, and 3.2%, respectively among the placebo, 50 mg, and 100 mg maintenance treatment groups. The most common serious infection was appendicitis, which was reported in 0.0%, 0.0%, and 1.9% of subjects in the placebo, 50 mg, and 100 mg groups.

During the placebo-controlled period across disease populations, the incidence of sepsis per 100 subject-years of follow-up was 0.16 (CI: 0.00, 0.89) in the placebo group and 0.86 (CI: 0.49, 1.40) in the golimumab group with the 95% CI for the golimumab group overlapping the placebo group. Two cases of septic shock were reported among subjects with ulcerative colitis treated with golimumab during the placebo-controlled period with an incidence of 0.19 (CI: 0.02, 0.67) per 100 subject-years of follow-up, which was similar to the incidence across disease populations of 0.08 (CI: 0.03, 0.17).

Among ulcerative colitis subjects treated with golimumab, from Week 0 of an induction study through Week 54 of the maintenance study, 17 (1.4%) subjects had pneumonia with an incidence of 1.76 (CI: 1.06, 2.75) per 100 subject-years of follow-up compared with the incidence across disease populations of 3.03 (CI: 2.67, 3.42.)

Four cases of active TB were reported from Week 0 of an induction study through Week 54 of the maintenance study, including 3 cases of disseminated TB. All 4 cases occurred in regions with endemic TB (India and Poland: 2 cases each). All subjects with TB were on concomitant immunosuppressives including high dose corticosteroids. The incidence of TB was 0.37 (CI: 0.10, 0.95) per 100 subject-years of follow-up), compared with the incidence across disease populations of 0.31 (CI: 0.21, 0.46).

Opportunistic infections were reported in 4 subjects, 3 of whom were in the 100 mg maintenance group (2 with oesophageal Candida and 1 with multiple brain abscesses) and 1 in the placebo induction group who never received golimumab (candidiasis). The incidence of opportunistic infections was 0.28 (CI: 0.06, 0.81) per 100 subject-years of follow-up, compared with the incidence across disease populations of 0.23 (CI: 0.14, 0.36).

Among ulcerative colitis subjects treated with golimumab, from Week 0 of an induction study through Week 54 of the maintenance study, 11 (0.9%) subjects had cellulitis with an incidence of 1.48 (CI: 0.85, 2.41) per 100 subject-years of follow-up, compared with the incidence across disease populations of 2.29 (CI: 1.98, 2.63).

8.3.2.2.11. Congestive heart failure

Congestive heart failure was reported for a single ulcerative colitis subject (2 events) who received SC golimumab 400 mg → 200 mg induction and was randomized into the 100 mg maintenance group; this incident had a fatal outcome.

8.3.2.2.12. Demyelination

Demyelination was reported on Study Day 160 for one ulcerative colitis subject who received SC golimumab (400 mg → 200 mg) induction followed by placebo maintenance. The subject's symptoms improved after discontinuation of study drug without further treatment.

8.3.2.2.13. Hypersensitivity reactions

Among ulcerative colitis subjects treated with golimumab, from Week 0 of an induction study through Week 54 of the maintenance study, 22 (1.8%) subjects had a hypersensitivity reaction with an incidence of 2.13 (CI: 1.35, 3.20), which was similar to the incidence across disease populations of 2.72 (CI: 2.38, 3.09). the highest incidence was on 200 mg (7.1%) with an incidence per 100 subject-years of 13.50 (CI 0.34, 75.20).

8.3.2.2.14. Serum sickness-like and anaphylactic reactions

Among ulcerative colitis subjects treated with golimumab from Week 0 of an induction study through Week 54 of the maintenance study, a single subject had a non-serious serum sickness-like reaction with an incidence of 0.09 (CI: 0.00, 0.52) per 100 subject-years of follow-up, compared with the incidence across disease populations of 0.07 (CI: 0.03, 0.15).

8.3.2.2.15. Malignancies

In C0524T18 the sole malignancy on golimumab was lung adenocarcinoma in a patient with a 40-year history of smoking. there were 4 malignancies on placebo thyroid, rectal, colon and breast.

8.3.2.3. Safety related to drug-drug interactions and other interactions

8.3.2.3.1. Interaction with immunomodulators

For randomized subjects in C0524T18, no trends were observed with regard to subjects' baseline immunomodulator (6-MP/AZA/MTX) status (that is, receiving or not receiving them) and the proportion of subjects who died, discontinued study agent because of an AE, or who had an AE, SAE, infection, serious infection, malignant neoplasm, or injection site reaction. Because of the small number of subjects in each of the immunomodulator groups, any comparison between groups is limited and should be interpreted with caution.

8.4. Evaluator's overall conclusions on clinical safety

There was an association of formation of antibodies to golimumab and median serum golimumab concentrations.

There appear to be no new signals compared with the risks shown to be associated with long term golimumab treatment of other disorders.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of golimumab in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are:

- Compared to placebo inducing and maintaining lower disease severity as assessed by signs and symptoms using the Mayo score.

9.2. First round assessment of risks

The risks of golimumab in the proposed usage are:

- The proposed dosage is double that for other Indications.
- Antibody formation was 3% (9/300) on golimumab and & 7.1% (11/155) after an initial 1 IV or 2 SC doses. 25. There was an association of formation of antibodies to golimumab and median serum golimumab concentrations.
- 5 (3.2%) of the "placebo" and 11 (3.6%) of the golimumab groups discontinued study agent due to lack of therapeutic effect
- Ulcerative colitis was the most common AE leading to discontinuation of study agent.
- The main AEs associated with the use of anti - TNFα agents is infections (including TB and opportunistic infections). Others include hepatotoxicity, congestive heart failure, hematologic toxicity, neurologic or demyelinating events, malignancies, autoimmune disorders, administration reactions, anaphylactic reactions, and delayed hypersensitivity reactions.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of golimumab, given the proposed usage, in patients who have had an inadequate response to conventional therapy is marginally favourable.

10. First round recommendation regarding authorisation

It is recommended that delegate approve the proposed Indication of:

> *The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy.*

[25] The "Placebo" maintenance group

11. Clinical questions

Please provide maintenance of response and remission rates that is response and remission at both Week 30 and Week 54 for subjects in Study C0524T18 (PURSUIT- Maintenance) who had antibodies to golimumab during the study. The total number of subjects who had antibodies to golimumab during the study should also be stated.

12. Second round evaluation of clinical data submitted in response to questions

The sponsor has attempted to answer, however the question cannot be accurately answered because there were 5 sub-populations treated with golimumab studied in one of the two preceding studies or in the subsequent Study C0524T18.

- those on placebo in the preceding studies and who were considered nonresponders who were treated with golimumab in Study C0524T18
- those on golimumab in the preceding studies and who were considered nonresponders who were treated with golimumab in Study C0524T18.

These groups were not randomised in the study and only continued beyond Week 16 if they became responders.

The primary analysis population was subjects randomized at Week 0 of maintenance Study C0524T18 which included.

- those responders to golimumab in the initial studies who were randomised to treatment with placebo in Study C0524T18
- those responders in the initial studies who were randomised to treatment with golimumab who were randomised to treatment with golimumab in Study C0524T18.

Thus only those responders on placebo in the initial studies did not received golimumab initially in Study C0524T18, however if they lost response they were given golimumab. This accounts for the differences in the numbers in the reply and in this evaluation.

The sponsor in the section 31 response reiterates that the limited number of subjects who were positive for antibodies to golimumab in C0524T18 precludes a definitive conclusion regarding the impact of the presence of antibodies to golimumab on efficacy.

13. Second round benefit-risk assessment

As before: The benefit-risk balance of golimumab, given the proposed usage, in patients who have had an inadequate response to conventional therapy is marginally favourable.

14. Second round recommendation regarding authorisation

As before: It is recommended that delegate approve the proposed Indication of:

> *The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy.*

15. References

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use
- CPMP/EWP/2330/99 Points to Consider on Application with
  - Meta-Analyses;
  - One Pivotal Study

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