15 March 2012

EMA/217675/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

adalimumab

Procedure No.: EMEA/H/C/000481/II/0082

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Scientific discussion

1.1. Introduction

About the product

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. Adalimumab is approved for the treatment of inflammatory diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (Ps), and Crohn's disease (CD), the other primary form of inflammatory bowel disease (IBD).

Problem statement

Ulcerative colitis (UC) is the first of the two primary forms of idiopathic IBD. It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The clinical symptoms include inflammatory diarrhoea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission. The onset of UC can occur in all ages, but is most commonly diagnosed in late adolescence and early adulthood. The incidence in Europe is estimated at 1.5 to 20.3 cases per 100,000 person-years.

The diagnosis of UC is established after colonoscopy and histology of colonic mucosa. Clinical features can vary among individuals, and in general do not reflect the histological and endoscopic findings. Common symptoms can include inflammatory diarrhoea (rectal bleeding, presence of mucus) and sometimes abdominal pain. Disease of moderate or severe activity may be associated with anorexia, nausea, weight loss, and rarely fever.The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extraintestinal complications include arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (*pyoderma gangrenosum, erythema nodosum, aphthous stomatitis*), uveitis, and primary sclerosing cholangitis. Patients with UC are at an increased risk for colon cancer and more rarely lymphoma. UC can be considered an autoimmune disease, harbouring in genetically susceptible individuals. The inflammatory process plays a key role in the injury of colonic mucosa that characterises the UC. In this cascade, the tumor necrosis factor alfa (TNFα) appears to be critical to the amplification of mucosal inflammation.

The aim of medical treatment in UC is to induce and maintain remission. Conventional therapies often do not completely abate the inflammatory process and have significant side effects. Conventional therapies for the induction of remission have included anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. 5-ASA derivatives as well as immunomodulatory agents (azathioprine or 6-mercaptopurine [6-MP]) have been used for the maintenance of remission. Corticosteroids are not effective for the maintenance of remission. Infliximab, a chimeric monoclonal anti-TNFα antibody, has demonstrated efficacy in subjects with moderately to severely active UC and is approved for the treatment of adult patients with moderate to severe UC who have had an inadequate response to conventional therapy.

The main option of the surgical treatment consists of a total colectomy that is a curative approach. However, this radical procedure can be associated with significant decrease of the quality of life and transient morbidities.

Scope of the variation

In this submission the MAH applies for 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. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated accordingly as well as Annex II and IIIB.

The SmPC has been revised to incorporate all information relevant to the UC indication. Some editorial changes have also been made to make the text flow better, including a re-ordering of SmPC section 4.1 to group the indications by therapy area.

The initially applied wording for extension of indication reads as follows:

Ulcerative colitis

Humira is indicated for 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.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/85/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/85/2010 was not yet completed as some measures were deferred.

Development programme and compliance with CHMP guidance and scientific advice

The clinical development program for adalimumab in the sought UC indication includes 3 clinical studies:

- Two pivotal randomized, double-blind, placebo-controlled studies; both completed:
    - Study M06-826 (induction of remission study)
    - Study M06-827 (induction and maintenance of remission study)
- An ongoing supportive long-term open-label (OL) extension study: Study M10-223 (with a data cut-off of 31 December 2009 for the data included in this submission).

Pharmacokinetic (PK) data were collected only in Study M06-827. Study M06-826 compared the efficacy and safety of adalimumab 160/80/40 mg and adalimumab 80/40 mg to placebo and consisted of an 8- or 12-week double-blind (DB), placebo-controlled period followed by an OL period (duration depended on the version/amendment of the protocol) through 52 weeks. Study M06-827 compared the efficacy and safety of adalimumab 160/80/40 to placebo and consisted of a DB, placebo-controlled period of up to 52 weeks, with the option to switch to OL adalimumab in the event of a disease flare

starting at Week 12. In the OL extension study subjects received adalimumab 40 mg eow or ew, if required.

Compliance with scientific advice

The MAH received Scientific Advice from the CHMP in June 2006 (EMEA/CHMP/SAWP/233559/2006) before the start of the UC clinical development program. The Scientific Advice pertained to clinical aspects of the dossier. Based on this scientific advice, the maintenance Study M06-827 was designed so that the placebo-controlled portion of the study began at Week 0 and continued through Week 52, rather than having an open-label run-in phase up to Week 8. It was expected that this design would best provide information on the benefit of continuing adalimumab beyond 8 weeks in subjects who did or did not respond by Week 8. Overall, the pivotal studies submitted (the induction study of at least 8 weeks and a second induction and maintenance of at least 52 weeks) are consistent with the plan agreed by the SAWP in 2006.

Compliance with CHMP guideline

Applicable for this development is the Guideline on the development of medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006). In line with this regulatory guideline, one study was conducted to investigate induction of clinical remission at Week 8 (study M06-826) and a separate study provided data on the maintenance of clinical remission (study M06-827). Key design aspects are discussed in the Discussion on Clinical Efficacy.

General comments on compliance with GMP, GLP, GCP

The clinical trial submitted in support of this variation was performed in accordance with GCP as claimed by the applicant. The MAH has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.2. Clinical aspects

1.2.1. Clinical pharmacology

Pharmacokinetics

The PK of adalimumab has earlier been characterised in patients with RA, AS, JIA, Ps and CD. After subcutaneous (SC) administration of a single 40 mg dose, absorption and distribution of adalimumab is slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. Estimated apparent clearance (CL/F) and volume of distribution (Vss/F) values are fairly similar between indications. CL/F has been estimated on average from 11-18 mL/h and Vss/F around 10 L. The mean terminal phase half-life is approximately two weeks. CL/F increases with body weight and is approximately doubled in the presence of anti-adalimumab antibody. Furthermore, concomitant methotrexate treatment has been observed to decrease CL/F by 44%.

The adalimumab PK was evaluated in subjects with moderately to severely active UC in Study M06-827. The population PK of adalimumab was also evaluated for UC subjects using a non-linear mixed effects modeling (NONMEM) approach using data from PK Study M06-827. The impact of covariates on adalimumab PK was assessed. The PK results from M06-827 were compared with results from previous studies in subjects with CD in which subjects were administered a 4-week 160 mg/80 mg induction regimen (PK Study M02-403) and a 52-week 40 mg maintenance regimen (PK Study M02-433). The

PK of adalimumab following a 4-week induction regimen were also evaluated in subjects with moderate to severe CD who had lost response or were intolerant to infliximab in PK Study M04-691. The immunogenicity of adalimumab was examined in all aforementioned studies (M06-827, M02-403, M02-433 and M04-691).

Study M06-827

The PK of adalimumab following SC administration was evaluated in 487 subjects with moderately to severely active UC in study M06-827. Subjects were stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomized 1:1 to receive adalimumab or placebo by SC injection. Subjects assigned to the adalimumab treatment arm received 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week (eow) between Weeks 4 and 50. At or after Week 10, subjects were to be evaluated to determine if they met the criteria for inadequate response and then switched to open-label adalimumab 40 mg eow beginning at Week 12. Subjects who demonstrated inadequate response at two consecutive visits at least 14 days apart while on open-label adalimumab 40 mg eow were to dose escalate to adalimumab 40 mg weekly.

Blood samples were collected from all subjects immediately prior to dosing at Weeks 0 (Baseline), 2, 4, 8, 32, and 52 (or Early Termination Visits) for adalimumab assay and at Weeks 0 (Baseline), 8, 32, and 52 (or Early Termination Visits) for anti-adalimumab antibody (AAA) assay. Blood samples were also collected for infliximab and human anti-chimeric antibody (HACA) assays at Week 0 (Baseline) and measured by validated assay methods. Adalimumab serum concentrations were determined using an enzyme-linked immunosorbent assay (ELISA).

Trough serum concentrations of adalimumab were summarized by treatment group at each time point using descriptive statistics. The trough values from study M06-827 are presented in Table 1 and Figure 1.

Table 1 Summary of serum adalimumab trough concentrations (µg/mL) by dose in subjects with Ulcerative Colitis.

	Mean ± SD (Min-Max), N_{nmiss}					
	Week					
Treatment Groups	0	2	4	8	32	52
Double-blind 160/80/40 mg eow Subjects Who Stayed in 40 mg eow (N = 178)	0.178 ± 1.54 (0.000 – 18.8), 166	11.8 ± 3.95 (0.000 – 23.1), 167	12.3 ± 5.45 (0.000 – 26.2), 160	9.28 ±4.74 (0.000 – 22.8), 151	8.26 ± 4.94 (0.000 – 26.9), 109	7.97 ± 6.09 (0.000 – 39.3), 101
Double-blind 160/80/40 mg eow Subjects Who Dose Escalated to 40 mg Weekly (N = 67)	0.320 ± 2.09 (0.000 – 16.4), 62	11.4 ± 4.36 (0.923 – 25.7), 66	10.3 ± 5.41 (0.000 – 22.6), 64	7.28 ± 4.71 (0.000 – 18.5), 64	10.3 ± 8.54 (0.000 – 32.5), 47	15.0 ± 8.75 (0.000 – 38.0), 36
Double-blind Placebo Subjects Who Stayed in Placebo (N = 108)	0.035 ± 0.187 (0.000 – 1.60), 103	0.113 ± 0.713 (0.000 – 5.42), 98	0.024 ± 0.170 (0.000 – 1.52), 86	0.016 ± 0.134 (0.000 – 1.14), 72	0.000 ± 0.000 (0.000 – 0.000), 51	0.000 ± 0.000 (0.000 – 0.000), 47
Double-blind Placebo Subjects Who Switched to Open-Label 40 mg eow (N = 50)	0.139 ± 0.869 (0.000 – 6.01), 48	0.112 ± 0.736 (0.000 – 5.10), 48	0.076 ± 0.516 (0.000 – 3.61), 49	0.038 ± 0.263 (0.000 – 1.82), 48	4.58 ± 5.28 (0.000 – 20.2), 36	6.71 ± 5.29 (0.000 – 18.2), 31
Double-blind Placebo Subjects Who Switched to Open-Label 40 mg eow, Then Dose Escalated to 40 mg Weekly (N = 84)	0.071 ± 0.366 (0.000 – 2.92), 82	0.022 ± 0.145 (0.000 – 1.31), 84	0.007 ± 0.040 (0.000 – 0.320), 80	0.019 ± 0.158 (0.000 – 1.42), 81	10.3 ± 8.60 (0.000 – 27.3), 52	15.7 ± 9.19 (0.000 – 36.5), 42

N_{nmiss} = number of non-missing observations

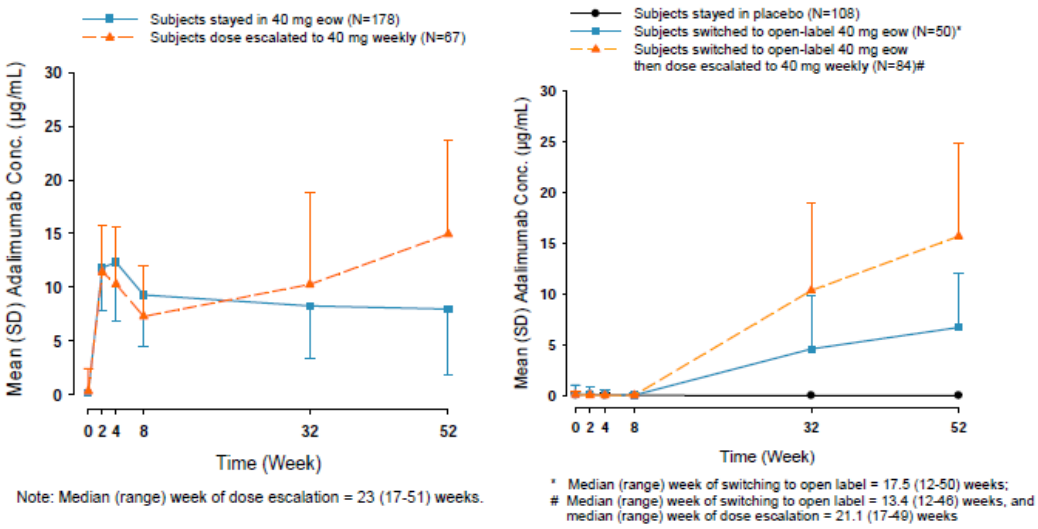

Figure 1 **Mean (SD) serum adalimumab trough concentrations versus time by dose in subjects with Ulcerative Colitis (Left panel: double-blind 160/80/40 mg group; Right panel: double-blind placebo group).**

A loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieved serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 8 µg/ml were observed in UC patients who received a maintenance dose of 40 mg adalimumab every other week. Adalimumab concentrations at Week 52 were approximately double in subjects who dose escalated to 40 mg weekly compared to those who received 40 mg eow. Among 245 subjects randomized to the adalimumab 160/80/40 mg eow treatment group, 110 were anti-TNF experienced. Among 242 subjects in the placebo treatment group, 108 were anti-TNF experienced. Data showed that the mean adalimumab trough concentrations were similar in anti-TNF-naïve and anti-TNF–experienced subjects.

PK in HACA+ vs. HACA- patients.

Among 245 subjects in the adalimumab 160/80/40 mg eow treatment group, 52 (21.2%) subjects had measurable HACA (HACA+) at Baseline. Among 242 subjects in the placebo treatment group, 44 (18.2%) subjects were HACA+.

Population PK analysis

Population PK analyses were performed to estimate the CL/F and apparent volume of distribution of central compartment (V2/F) of adalimumab in subjects with UC. All subjects with at least one measurable serum adalimumab concentration during the study (week 0-52) were included in a population PK analysis using nonlinear mixed effect modeling.

The data were described with a two-compartment model with first order absorption and elimination. Inter-individual variability was included solely for CL/F and residual error was described with a combination of additive and proportional terms. The typical Vss/F was 8.98 L. Body weight, occurrence of anti-adalimumab antibody (AAA), and plasma albumin were significant covariates on the CL/F. The CL/F for typical patient weighing 73 kg, having an albumin level of 4.2 g/dL and being AAA negative was 0.37 L/day (15.2 mL/h). The model predicted CL/F was 0.258 L/day and 0.504 L/day for typical patients weighing 50 and 100 kg, respectively. The presence of AAA would lead to approximately doubling of CL/F for the typical individual. Body weight and AAA have been known to impact

adalimumab PK parameters in a similar way as observed in Crohn's disease. Plasma albumin was tested as a covariate for the first time and an increase in plasma albumin concentration by 1 g/dL is expected to decrease CL/F of adalimumab by approximately 41%, and the predicted CL/F was 0.476 and 0.251 L/day for a typical subject with an albumin level of 3.5 and 5.0 g/dL, respectively.

Comparison to PK data in CD patients

Induction Regimen: PK during the first 4 weeks of the induction period were evaluated in 245 subjects (PK Study M06-827) with moderately to severely active UC, 159 subjects (Study M04-691) with moderately to severely active CD who had previously responded to infliximab but stopped responding or were intolerant to infliximab and in 71 infliximab-naïve subjects (PK Study M02-403). During the induction phase, the mean trough concentrations of adalimumab were similar between UC subjects (11.7 µg/mL at Week 4) and CD subjects (infliximab intolerant or naïve) (12.6 µg/mL at Week 4) following the induction dose of 160 mg/80 mg administered at Week 0/Week 2.

Maintenance Regimen: The PK of adalimumab were evaluated during Week 4 to Week 52 maintenance regimen in subjects with moderately to severely active UC (Study M06-827) and during a 52-week maintenance regimen in subjects with moderately to severely active CD (PK Study M02-433). Week 4 of Study M02-403 was the Baseline visit for Study M02-433. Serum concentrations of adalimumab were consistent between subjects with UC (mean ± SD, 7.97 ± 6.09 µg/mL at Week 52, Study M06-827 PK Report) and subjects with CD (mean ± SD, 7.22 ± 4.58 µg/mL at Week 56, Study M02-433) who remained on 40 mg eow SC for the duration of the maintenance studies. In subjects escalated to 40 mg weekly, trough concentrations appear to be slightly higher in UC than in CD patients.

Effects of concomitantly-administered immunosuppressants

The effects of concomitantly-administered immunosuppressants on the PK of adalimumab were also evaluated. For subjects with UC in PK Study M06-827, adalimumab clearance was approximately 17% lower in subjects on concomitant immunosuppressants including azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX). Following longer-term treatment with adalimumab in the maintenance PK Study M02-433, neither AZA nor 6-MP had effects on adalimumab CL/F ($p>0.09$). The numbers of subjects on MTX were too small to make conclusions regarding its effects on adalimumab clearance.

Immunogenicity

Immunogenicity of adalimumab in subjects with UC (Study M06-827) was assessed and compared to that observed in subjects with CD (Study M02-403, Study M04-691 and Study M02-433). AAA were measured by a double antigen sandwich ELISA method using adalimumab as capture and detector antigen.

Study M06-827

The overall AAA-positive rate in subjects with UC across the adalimumab and placebo treatment groups in study M06-827 was 3.9% (19/487). The AAA-positive rate was 3.7% (8/218) in subjects with previous anti-TNF use, and 4.1% (11/269) in the anti-TNF naïve subjects. By comparison, in the CD population, the immunogenicity rate was 2.6% (7 of 269 subjects) in subjects who received adalimumab treatment up to 56 weeks in Study M02-433.

For subjects who had measurable HACA at Week 0, 6 were AAA-positive (6/96, 6.5%), whereas, for subjects who were HACA-negative, 13 were AAA-positive (13/345, 3.80%). One AAA-positive subject (80616) received concomitant methotrexate (1/19, 5.3%) while the remaining 18 AAA-positive subjects did not receive concomitant immunosuppressants (18/19, 94.7%). The earliest time point at

which a subject was identified as AAA-positive was at Week 8. The majority of subjects (10/19, 52.6%) became AAA-positive at Week 32. Six (6/19, 31.6%) subjects were AAA-positive at the early termination visit. The disposition of AAA-positive subjects is summarized in Table 2.

Table 2 AAA positive subject disposition and information

Treatment	AAA+ (n)	Remitters at Week 8 (n)	Remitters at Week 52 (n)	Responder at Week 8 (n)	Responder at Week 52 (n)	Previous Infliximab Use (n)	HACA+ at Baseline (n)	Concomitant Use of Immuno-suppressants[a] (n)
40 mg eow	7	2[b]	2[b]	5[c]	4	2[d]	1	0
40 mg eow to Weekly	6	0	0	2	0	3	3	0
Placebo Stayed	0	0	0	0	0	0	0	0
Placebo to 40 mg eow	2	1	0	1	0	0	0	0
Placebo to 40 mg eow to Weekly	4	0	0	0	0	3	2	1
Total	19[e]	3	2	8	4	8	6[f]	1[g]

AAA = anti-adalimumab antibody; HACA = human anti-chimeric antibody; a. Methotrexate, 6-MP, and/or azathioprine. b. One subject was a remitter at Week 8 and Week 52. c. Three subjects achieved clinical response at Week 8 and Week 52. d. One subject was included as infliximab experienced since there was measurable baseline HACA result even though the subject was anti-TNF naïve in the clinical data base. e. One subject was excluded from the AAA analysis due to site non-compliance. f. One subject had no HACA result. g. One subject received concomitant methotrexate.

Overall, adalimumab concentrations appeared to decline rapidly in subjects who developed AAA. Three (3/19, 15.8%) AAA-positive subjects were in remission at Week 8 and 2 subjects (2/19, 10.5%) at Week 52. One subject (1/19, 5.3%) was in remission at both Week 8 and Week 52. AAA did not affect the tolerability to adalimumab and there were no indications of any clinically important differences in safety between subjects who developed AAA versus those who did not. The number of AAA-positive subjects in each treatment group are too small (N≤7) to conclude on the impact of immunogenicity on serum adalimumab concentrations and its efficacy.

Justification for an alternative induction dose regimen

The treatment for subjects with UC consists of an induction dose regimen of 160/80 mg adalimumab administered at Week 0/Week 2. The 160 mg dose requires four injections on a single day, which may be inconvenient and could lead to non-compliance in some patients. Therefore simulations were performed using the final population pharmacokinetic model to justify the administration of 160 mg dose given on 2 consecutive days. According to the MAH, a similar approach was also taken to support the initial dose of 160 mg administered over 2 days in CD patients.

Two induction regimens were simulated: (1) 160 mg on Day 0 and 80 mg on Day 14; and (2) 80 mg on Day 0, 80 mg on Day 1 and 80 mg on Day 14. A total of 2,500 subjects were simulated for each regimen; 100% compliance was assumed. The mean, median, 5th, 25th, 75th and 95th percentile concentration values at Weeks 2, 4, and 8 from the simulations were compared with those observed in Study M06-827.

The simulated serum adalimumab concentrations for the 4-week induction periods following 160 mg adalimumab given over 1 or 2 days was presented, along with the observed adalimumab concentrations following 160 mg adalimumab given over 1 day in Study M06-827. The results demonstrate that by Week 1 serum adalimumab concentrations are similar whether 160 mg adalimumab is given over 1 or 2 days. Therefore, it is considered that splitting the 160 mg induction dose to two 80 mg doses administered over 2 days would have minimal impact on efficacy.

Discussion on clinical pharmacology

The PK profile of adalimumab has been characterised in previous submissions. Adalimumab PK data were collected in the pivotal maintenance study M06-827. In the current application only trough levels were analysed in Study M06-827. The results were compared with results from previous studies in subjects with CD in which subjects were administered a 4-week 160 mg/80 mg induction regimen (Study M02-403) and a 52-week 40 mg maintenance regimen (Study M02-433). PK data from study M06-827 were also used for population PK analyses. As only clearance may theoretically vary due to the pathology, the aim of the PK study in UC patients was to confirm that, in these patients, the clearance is similar to that reported in patients with other pathologies (in particular CD patients). An additional aim of the PK study was to achieve data allowing defining a relationship between trough levels and efficacy. Therefore, the analysis of only trough levels is considered justified.

Data from Study M06-827 showed that mean serum adalimumab trough concentration have a good relationship to the administered dose. During the induction and maintenance period, the mean trough concentrations of adalimumab were similar between UC and CD subjects. Overall, the results were comparable to the adalimumab PK reported for CD patients.

Population PK analyses were performed to estimate the CL/F and apparent volume of distribution of central compartment (V2/F) of adalimumab in subjects with UC. Body weight, occurrence of AAA, and plasma concentration of albumin were determined as significant covariates on the apparent clearance. An increase of body weight by 10 kg is expected to increase CL/F by approximately 13%. The presence of AAA would lead to approximately double of CL/F. A similar impact of body weight and AAA on adalimumab PK parameters has been observed in subjects with RA, JIA, AS, Ps, and CD. Plasma albumin was tested as a covariate for the first time for adalimumab. The findings and the wide therapeutic window of adalimumab support the notion that dosing does not need to be adjusted by serum albumin concentrations and/or body weight. Therefore, dose adjustments should be made on the basis of clinical outcomes, i.e., those patients not achieving satisfactory response or experiencing flare should be considered for dose escalation to weekly adalimumab. Overall, based on these results, it is considered that no dosage adjustment of adalimumab based on covariates analysis is warranted.

Immunogenicity of adalimumab in subjects with UC in Study M06-827 was assessed and compared to that observed in subjects with CD (Study M02-403, M04-691 and M02-433).The overall AAA-positive rate in subjects with UC across the treatment groups was 3.9% (19/487). By comparison, in the CD population, the immunogenicity rate was 2.6% (7 of 269 subjects). The immunogenicity rates appear to be similar in both UC and CD patients.

Data from the simulations regarding the alternative induction dose regimen (160 mg on day 1 or 80 mg on days 1 and 2) have shown that splitting the first induction dose of 160 mg to 2 doses of 80 mg administered over 2 days has no significant impact on the PK of adalimumab.

Conclusion on clinical pharmacology

The PK data presented in this application showed that adalimumab PK parameters in UC patients are comparable with those previously observed in CD patients; a population for which adalimumab is approved. Also the data confirmed that trough serum levels increase in a rather proportional manner with the dose. Presence or absence of AAA is confirmed as the main factor influencing trough levels. The immunogenicity rates appear to be similar in both UC and CD patients.

Overall based on the data submitted it is agreed that adalimumab induction dose regimen for adult patients with moderate to severe UC is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg eow. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg ew. Additionally, the 160/80/40 mg and 80/40 mg dosing induction regimens are in accordance with the CD dosage recommendations in the current SmPC (80/40 mg or 160/80/40 mg if a rapid response is required).

1.2.2. Clinical efficacy

Main pivotal studies

Study M06-826

A multicenter, randomized, double-blind, placebo controlled study to assess the efficacy and safety of 2 dosing regimen of adalimumab for the induction of clinical remission in subjects with moderately to severely active UC.

Methods

Patients received a double-blind therapy (160/80/40 mg or 80/40 mg or placebo) from baseline until week 8 and the open-label adalimumab therapy from week 8 until the end of the study. The second treatment arm (80/40 mg) was introduced through a protocol amendment. Figure 2 displays the schematic design of the study. Patients that completed both the controlled and the open-label periods of the study were invited to participate in an open-label extension study (M10-223) and continue to receive adalimumab.

All patients underwent colonoscopy or flexible sigmoidoscopy (for patients that had had a colonoscopy during the previous 6 months) during the screening period and a flexible sigmoidoscopy at weeks 8 and 52 (or at the early termination visit).

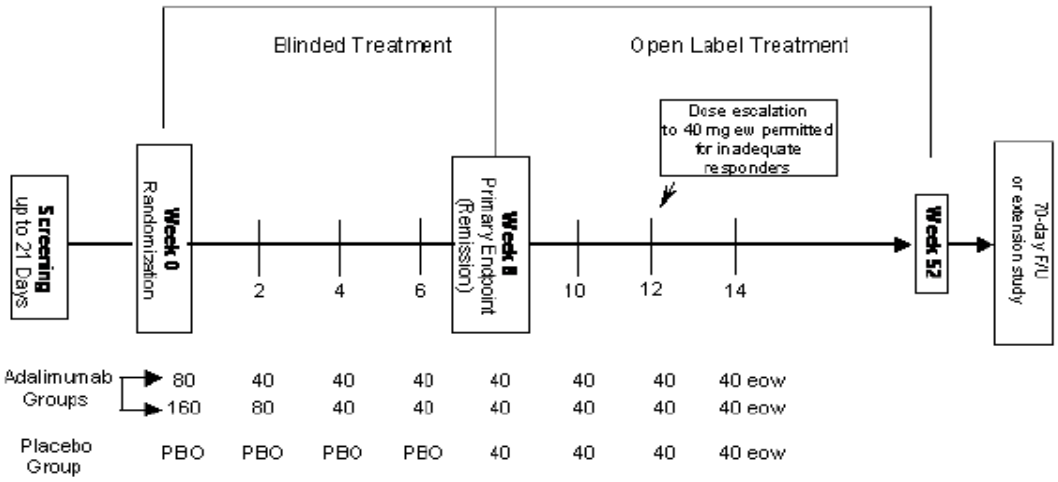

Figure 2 Schematic design of study M06-826

Study participants

Adult patients with moderate to severe UC were enrolled at 80 sites worldwide.

Main inclusion criteria:

- male or female ≥18 years of age with diagnosis of UC for >90 days prior to baseline
- diagnosis of active UC confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy during the screening period, with exclusion of infection
- active UC with a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite concurrent treatment with at least 1 of the following (oral corticosteroids or immunosuppressants or both as defined below):
    - stable oral corticosteroid dose (prednisone dose of ≥20 mg/day or equivalent) for at least 14 days prior to baseline or stable oral corticosteroid dose (prednisone of <20 mg/day) for at least 40 days prior to baseline

      and/or
    - at least a consecutive 90 day course of azathioprine or 6-MP prior to baseline, with a dose of azathioprine ≥1.5 mg/kg/day or 6-MP ≥1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g. due to leucopenia, elevated liver enzymes, nausea) during that time. Subject was to be on a stable dose for at least 28 days prior to baseline.

If subjects were on both oral corticosteroid and immunosuppressants, only 1 of the drugs had to meet the above criteria. Concurrent therapy was not required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the previous 5 years and, in the judgment of the investigator, have failed to respond to or could not tolerate their treatment.

Main exclusion criteria:

- history of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery
- received infliximab or any other anti-TNF agent or any biological therapy in the past
- received previous treatment with adalimumab or previous participation in adalimumab study
- received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to baseline
- received IV corticosteroids within 14 days prior to screening or during the screening period
- received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the screening endoscopy and during the remainder of the screening period
- current diagnosis of fulminant colitis and/or toxic megacolon
- subjects with disease limited to the rectum (ulcerative proctitis)
- current diagnosis of indeterminate colitis
- current diagnosis and/or history of CD
- discontinued use of azathioprine or 6-MP within 28 days of baseline
- discontinued use of corticosteroid within 14 days of Baseline
- subjects using aminosalicylates for less than 90 days prior to Baseline, not on a stable dose for at least 28 days prior to baseline, or discontinued use within 28 days of baseline

Treatments

The adalimumab 160/80/40 mg and 80/40 mg dosing induction regimens were selected based on a combination of expert clinical advice, clinical data from the adalimumab development program in CD, PK data accumulated in the adalimumab RA and CD development programs along with PK modelling. They were in accordance with the dosage recommendations in the SmPC for induction therapy in CD.

Prior to protocol Amendment 3, patients received induction therapy of 160/80 mg or placebo. At week 8, placebo treated patients received 160 mg adalimumab and at week 10 placebo treated patients received 80 mg adalimumab while the actively treated patients continued to receive 40 mg eow. At week 12 all patients received open label 40 mg adalimumab eow. From week 14, dose escalation was allowed for patients with inadequate response to treatment (40 mg ew).

Amendment 3 introduced an additional treatment arm on which patients received induction therapy of 80/40 mg. After the week 8 assessment, all patients received open label 40 mg adalimumab every other week until week 52. From week 12, dose escalation was allowed for patients with inadequate response to treatment (40 mg ew).

Patients taking aminosalicylates, azathioprine, or 6-MP who qualified for enrolment into the study were to continue their medication dose. Patients were not permitted to change the dosage of UC-specific concomitant medications throughout the study with the following 2 exceptions: decrease in corticosteroid dose between Weeks 8 and 52, and a dose decrease of other UC-related concomitant treatments in the event of UC treatment-related toxicities.

Objectives

The aim of this study was to assess the efficacy and safety of two adalimumab dosing regimen (160/80/40 and 80/40) versus placebo for the induction of clinical remission in patients with moderately to severely active UC. Supportive information concerning the maintenance of remission was collected during the OL phase of the study.

Outcomes/endpoints

Primary endpoint: Proportion of patients in clinical remission per Mayo score at week 8

Main secondary endpoints:

- proportion of patients with clinical response per Mayo score at week 8
- proportion of patients with mucosal healing at week 8
- proportion of patients with rectal bleeding subscore (RBS) indicative of mild disease (≤1) at week 8
- proportion of patients with Physician's Global Assessment (PGA) subscore indicative of mild disease (≤1) at week 8
- proportion of patients with stool frequency subscore indicative of mild disease (≤1) at week 8
- proportion of Inflammatory bowel disease questionnaire (IBDQ) responders at week 8

The following definitions were used to describe the primary and secondary endpoints:

Term	Definition
Clinical Remission	Mayo score ≤ 2 with no individual subscore > 1
Clinical Response per Mayo Score	A decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
Clinical Response per Partial Mayo Score	A decrease in Partial Mayo Score ≥ 2 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
IBDQ Responder	A subject with at least a 16 point increase from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score
Mucosal Healing	Endoscopy subscore of 0 or 1

Sample size

The sample size was calculated using nQuery Advisory 4.0. Assuming 15% of patients in the placebo group achieved clinical remission at Week 8, a sample size of 125 in each treatment group in the ITT population would be adequate to detect a 15% difference using a chi-square test with 80% power at a 0.05 two-sided significance level. A total of 375 subjects were to be randomized following Amendment 3 of the study.

Randomisation

All subjects were assigned a unique identification number as they were screened for the study. The number assigned at screening was used during the screening period only. A new unique identification number was assigned to each subject upon randomization and used throughout the study. All subjects were centrally randomized at baseline (Week 0) and assigned to a treatment group according to the randomization scheme generated by the MAH before the start of the study.

Blinding

Throughout the duration of the study, the investigator, site study personnel and patients remained blinded to patient's treatment allocation. The MAH remained blinded until the database of the 8-week DB study phase was locked and the interim analysis was conducted.

Statistical methods

The analyses were carried out in the following hierarchical order to handle the multiplicity issues induced by the 2 comparisons to placebo.

1. Compare the remission rates of adalimumab 160/80/40 mg group and placebo at Week 8.

2. Compare the remission rates of adalimumab 80/40 mg group and placebo at Week 8.

For both comparisons the superiority over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05. A *p* value ≤0.05 from comparison 1 was necessary to initiate comparison 2 at a significance level of 0.05. Since a hierarchical procedure was used, each comparison was to be tested at a significance level of 0.05 and overall alpha level of 0.05 could be preserved.

The secondary efficacy analysis was to be performed in the ITT-A3 population. Statistically significant results (*p* value ≤0.05) had to be achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank. The difference in proportion of subjects achieving response between adalimumab group and placebo group was to be assessed using the chi-square test, or Fisher's exact test as appropriate.

Other ranked dichotomous variables that included proportion of subjects with mucosal healing, proportion of subjects having mild disease indicated by components of the Mayo score (RBS, PGA and stool frequency subscore), and proportion of IBDQ responders, were to be analyzed using the same method used to analyze clinical response. Non-ranked dichotomous efficacy variables were analyzed using the same methods listed above. Change from baseline in the IBDQ scores; SF-36 scores; Mayo score and partial Mayo score were to be summarized using descriptive statistics. The treatment difference in mean change was to be analyzed using the ANOVA model including factors of treatment and baseline scores, or non-parametric test, as appropriate. Both the data as-observed and the LOCF method could be used as appropriate. The median time to achieve response per partial Mayo score from baseline was to be calculated using the Kaplan-Meier method.

Descriptive statistics were to be presented for the variables analyzed from the open-label period of the study. The response rate based on Mayo score and the colectomy rate during the study was to be tabulated and could be tested using the chi-square test or Fisher's exact test, as appropriate.

Results

Numbers analysed

The data sets seen in Table 3 were analysed.

Table 3 Number of subjects by analysis set

	Number of Subjects			
Analysis Set	Placebo	Adalimumab 80/40	Adalimumab 160/80/40	Total
ITT-A3	130	130	130	390
ITT-E	222	130	223	575
Per Protocol	120	122	124	366
Safety	223	130	223	576

The Intent-To-Treat A3 (ITT-A3) analysis set included all subjects with confirmed UC at Baseline who were randomized under Protocol Amendments 3 or 4 and received at least 1 injection of study drug (adalimumab 160/80/40 mg, adalimumab 80/40 mg, or placebo). The ITT-A3 analysis set was used for the primary analyses of the induction endpoints of the DB period through Week 8 of the study. According to the MAH, it allowed for a comparison of a homogeneous population. A second analysis set, the Intent-to-Treat Extended (ITT-E) analysis set, was used for the analyses of maintenance during the open-label period through Week 52 of the study. This analysis set included all subjects with confirmed UC at Baseline who were randomized under any version of the protocol and received at least 1 injection of study drug (adalimumab 160/80/40 mg, adalimumab 80/40 mg, or placebo). The differences between ITT-A3 and ITT-E populations are shown in Table 4.

Table 4 Key differences in study design before and after Amendment 3

Prior to Amendment 3	After Amendment 3
Two treatment arms: Placebo Adalimumab 160/80/40	Three treatment arms: Placebo Adalimumab 80/40 Adalimumab 160/80/40
Double-blind period lasting for 12 weeks.	Double-blind period lasting for 8 weeks.
Stable (± 5 mg) corticosteroid dose (prednisone of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline or maintenance corticosteroid dose (prednisone of ≥ 10 mg/day and < 20 mg/day or equivalent) for at least 40 days prior to Baseline.	Subjects had to be stable on prednisone ≥ 20 mg/day or equivalent for at least 14 days prior to Baseline; for doses of prednisone < 20 mg/day or equivalent, subjects had to be stable for at least 40 days prior to Baseline.
Prior and concurrent infliximab or anti-TNF excluded.	All prior and concurrent biologics excluded (including infliximab and anti-TNFs).
Immunosuppressants other than azathioprine or 6-MP (e.g., cyclosporine, methotrexate, or tacrolimus) prohibited within 60 days prior to Baseline and during the study.	Cyclosporine, tacrolimus, mycophenolate mofetil, and investigational agents prohibited 30 days or 5 half-lives prior to Baseline and during the study. Intravenous corticosteroid use prohibited within 14 days prior to Screening, during the Screening Period, and during the study.

Participant flow

Table 5 Disposition of patients (Study M06-826, ITT-E, all randomized patients)

Subject Status	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223	Total N = 575
Completed study	153 (68.9)	86 (66.2)	143 (64.1)	382 (66.4)
Discontinued study at any time	69 (31.1)	44 (33.8)	80 (35.9)	193 (33.6)
Reasons for discontinuation[a]				
Adverse event	39 (17.6)	19 (14.6)	33 (14.8)	91 (15.8)
Withdrew consent	7 (3.2)	9 (6.9)	16 (7.2)	32 (5.6)
Lost to follow-up	0	3 (2.3)	3 (1.3)	6 (1.0)
Lack of efficacy	44 (19.8)	22 (16.9)	38 (17.0)	104 (18.1)
Protocol violation	3 (1.4)	1 (0.8)	6 (2.7)	10 (1.7)
Other[b]	1 (0.5)	4 (3.1)	6 (2.7)	11 (1.9)
Completed Week 8	204 (91.9)	118 (90.8)	199 (89.2)	521 (90.6)
Discontinued study prior to Week 8	18 (8.1)	12 (9.2)	24 (10.8)	54 (9.4)
Reasons for discontinuation[a]				
Adverse event	12 (5.4)	7 (5.4)	12 (5.4)	31 (5.4)
Withdrew consent	2 (0.9)	4 (3.1)	6 (2.7)	12 (2.1)
Lost to follow-up	0	2 (1.5)	0	2 (0.3)
Lack of efficacy	7 (3.2)	5 (3.8)	7 (3.1)	19 (3.3)
Protocol violation	2 (0.9)	0	4 (1.8)	6 (1.0)
Other[c]	0	0	2 (0.9)	2 (0.3)

a. Subjects could have discontinued for more than one reason. b. Reasons for discontinuation recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator decision, subject noncompliance, positive TB skin test, subject wanted to start family, or total colectomy surgery within the 70-day follow-up period. c. Reasons for discontinuation recorded as "other" included: diagnosis of CD and investigator decision.

A total of 575 subjects enrolled in the study and were included in the efficacy analysis (ITT-E set), of whom 54 (9.4%) discontinued prior to week 8. The most frequently reported reasons for discontinuation during the DB period through Week 8 in the ITT-E set were AEs, lack of efficacy, and withdrawn consent. More subjects in the adalimumab 80/40 treatment group withdrew consent than in the adalimumab 160/80/40 or placebo treatment groups. There was no death during the DB period through Week 8 of the study. The most frequently reported reasons for discontinuation during the whole study in the ITT-E set were lack of efficacy, AEs, and withdrawn consent; all other reasons for discontinuation were each reported by <2% of subjects in the ITT-E set overall. The global

discontinuation rate from the study rate was approximately 34% (31.1% placebo and 33.8% and 35.9% in the active treatment group).

Conduct of the study

During the study there were 4 protocol amendments. Amendment 1, 2 and 4 had no major impact on the assessment of the study results. Amendment 3 contained a major revision to the protocol: inclusion of the 80/40 mg adalimumab induction dosing, revision of the objective to include two induction-dosing regimens, change of the blinded period from 12 weeks to 8 weeks. The statistical methods were also changed.

Baseline data

Table 6 Baseline demographic characteristics (Study M06-826, ITT-E)

Demographic Characteristic	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Sex (n [%])			
Female	83 (37.4)	52 (40.0)	85 (38.1)
Male	139 (62.6)	78 (60.0)	138 (61.9)
Race (n [%])			
White	202 (91.0)	119 (91.5)	206 (92.4)
Black	9 (4.1)	6 (4.6)	4 (1.8)
Asian	7 (3.2)	5 (3.8)	10 (4.5)
Other	4 (1.8)	0	3 (1.3)
Hispanic or Latino ethnicity (n [%])	7 (3.2)	6 (4.6)	13 (5.8)
Age range (n [%])			
< 40 years	120 (54.1)	63 (48.5)	124 (55.6)
40 to ≤ 64 years	93 (41.9)	59 (45.4)	92 (41.3)
≥ 65 years	9 (4.1)	8 (6.2)	7 (3.1)
Age (mean ± SD, years)	39.7 ± 12.72	41.6 ± 13.99	38.5 ± 13.06
Weight (mean ± SD, kg)	78.4 ± 18.06	76.8 ± 15.01	73.9 ± 13.77
Height (mean ± SD, cm)	172.7 ± 10.05	172.7 ± 9.27	171.7 ± 9.81
Nicotine use (n [%])			
User	10 (4.5)	8 (6.2)	23 (10.3)
Ex-user	65 (29.3)	46 (35.4)	63 (28.3)
Non-user	147 (66.2)	76 (58.5)	137 (61.4)
Alcohol use (n [%])			
Drinker	102 (45.9)	62 (47.7)	108 (48.4)
Ex-drinker	14 (6.3)	5 (3.8)	12 (5.4)
Non-drinker	106 (47.7)	63 (48.5)	103 (46.2)

SD = standard deviation. Note: Subjects randomized to placebo switched to OL adalimumab at Week 8 or Week 12 after visit evaluations were performed.

Table 7 Baseline disease history (Study M06-826, ITT-E)

Demographic Characteristic	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Duration of UC (mean ± SD, years)	7.89 ± 7.524	8.57 ± 7.511	8.41 ± 7.284
Site of UC (n [%])			
Pancolitis	132 (59.5)	70 (53.8)	114 (51.1)
Descending colon	67 (30.2)	48 (36.9)	87 (39.0)
Other	23 (10.4)	12 (9.2)	22 (9.9)
UC confirmed by biopsy (n [%])			
Yes	219 (100)	129 (99.2)	223 (100)
No	0	1 (0.8)	0
Evidence of dysplasia/malignancy (n [%])			
Yes	1 (0.5)	0	0
No	218 (99.5)	129 (100)	223 (100)
Missing	3	1	0
Evidence of infection (n [%])[a]			
Yes	0/92	–	0/93
No	89/92 (100)	–	93/93 (100)
Missing	3	–	0

SD = standard deviation. a. Evidence of infection from biopsy was collected only for subjects enrolled prior to Amendment 3. Note: Percentages calculated based on non-missing values.

Table 8 Baseline disease activity (Study M06-826, ITT-E)

	Mean ± SD		
Efficacy Measure	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Mayo score	8.8 ± 1.58	9.0 ± 1.62	8.9 ± 1.65
Partial Mayo score	6.3 ± 1.41	6.5 ± 1.43	6.4 ± 1.51
Endoscopy subscore (mucosal healing)	2.5 ± 0.51	2.5 ± 0.50	2.5 ± 0.51
Rectal bleeding subscore	1.6 ± 0.86	1.7 ± 0.78	1.7 ± 0.86
Physician's Global Assessment subscore	2.2 ± 0.50	2.3 ± 0.62	2.2 ± 0.60
Stool frequency subscore	2.5 ± 0.75	2.5 ± 0.72	2.5 ± 0.75
IBDQ score[a]	125.2 ± 32.18	125.6 ± 35.25	126.0 ± 35.01
SF-36 physical component score[b]	40.70 ± 8.143	40.85 ± 7.850	40.89 ± 8.699
SF-36 mental component score[b]	37.61 ± 11.217	37.22 ± 11.791	36.00 ± 12.428

SD = standard deviation. a. Assessed in 218 placebo subjects, 125 adalimumab 80/40 subjects,and 212 adalimumab 160/80/40 subjects. b. Assessed in 217 placebo subjects, 126 adalimumab 80/40 subjects, and 221 adalimumab 160/80/40 subjects.

Table 9 Baseline disease severity by Mayo subscore (Study M06-826, ITT-E)

	Number (%) of Subjects		
Efficacy Measure	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Endoscopy subscore			
Normal or inactive disease	0	0	0
Mild disease	1 (0.5)	0	1 (0.4)
Moderate disease	113 (50.9)	60 (46.2)	115 (51.6)
Severe disease	108 (48.6)	70 (53.8)	107 (48.0)
Rectal bleeding subscore			
Normal	21 (9.5)	9 (6.9)	23 (10.3)
Mild disease	78 (35.1)	34 (26.2)	58 (26.0)
Moderate disease	89 (40.1)	70 (53.8)	106 (47.5)
Severe disease	34 (15.3)	17 (13.1)	36 (16.1)
Physician's Global Assessment subscore[a]			
Normal	0	0	1 (0.4)
Mild disease	8 (3.6)	11 (8.5)	17 (7.6)
Moderate disease	156 (70.3)	69 (53.1)	133 (59.6)
Severe disease	58 (26.1)	50 (38.5)	72 (32.3)
Stool frequency subscore			
Normal	3 (1.4)	0	2 (0.9)
Mild disease	25 (11.3)	17 (13.1)	29 (13.0)
Moderate disease	63 (28.4)	37 (28.5)	54 (24.2)
Severe disease	131 (59.0)	76 (58.5)	138 (61.9)

a. Statistically significant (P = 0.009) differences observed between treatment groups based on CMH test with protocol amendment (prior or post Amendment 3) as stratification factor.

Table 10 UC related medication at baseline (Study M06-826, ITT-E)

	Number (%) of Subjects		
Generic Name[a]	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Any UC-related medications at Baseline	209 (94.1)	124 (95.4)	211 (94.6)
Any corticosteroid	138 (62.2)	74 (56.9)	133 (59.6)
Beclometasone	2 (0.9)	0	2 (0.9)
Budesonide	8 (3.6)	2 (1.5)	2 (0.9)
Methylprednisolone	25 (11.3)	8 (6.2)	19 (8.5)
Prednisolone	8 (3.6)	9 (6.9)	19 (8.5)
Prednisone	96 (43.2)	55 (42.3)	91 (40.8)
Any aminosalicylate	165 (74.3)	99 (76.2)	180 (80.7)
Aminosalicylic acid	1 (0.5)	0	1 (0.4)
Balsalazide	18 (8.1)	8 (6.2)	24 (10.8)
Mesalazine	137 (61.7)	86 (66.2)	147 (65.9)
Olsalazine	0	1 (0.8)	3 (1.3)
Sulfasalazine	9 (4.1)	5 (3.8)	6 (2.7)
Any azathioprine/6-MP	85 (38.3)	51 (39.2)	84 (37.7)
Azathioprine	73 (32.9)	44 (33.8)	75 (33.6)
Mercaptopurine	12 (5.4)	7 (5.4)	9 (4.0)

6-MP = 6-mercaptopurine. a. WHODRUG dictionary Q1 2009.

Overall subjects were predominantly white and male with moderate to severe UC (Mayo score ≥6 and an endoscopy subscore ≥2). Subjects in the ITT-A3 and ITT-E Sets had a mean duration of UC of 8.06 and 8.25 years, respectively, with disease comprising primarily pancolitis (52.1% and 55.0%, respectively). All but 1 subject in the ITT-A3 Set had confirmed UC using biopsy results, and 1 subject in the ITT-E Set had evidence of dysplasia and was discontinued after the Baseline visit due to this finding. In the ITT-A3 Set, the DB treatment groups had comparable UC histories, although placebo subjects had a slightly lesser mean duration of disease, with a notable difference between the frequency of subjects reporting pancolitis versus UC of the descending colon. By comparison, subjects in the adalimumab treatment groups had smaller differences between pancolitis and descending colon.

A statistically significant difference (P = 0.009) was observed across treatment groups in baseline PGA subscore in the ITT-E Set. A greater proportion of subjects randomized to adalimumab had mild disease or severe disease compared with subjects randomized to placebo (7.9% versus 3.6% and 34.6% versus 26.1%, respectively), whereas a greater proportion of subjects randomized to placebo had moderate disease compared with subjects randomized to adalimumab (70.3% versus 57.2%, respectively).

Subjects mostly received previous corticosteroids or azathioprine prior to study entry. No significant differences in demographics, medical history, mean baseline disease activity scores, electrocardiogram (ECG), tuberculosis (TB) skin test for positivity at baseline, chest x-ray (CXR), and prior/concomitant medications observed between the placebo, adalimumab 80/40, and adalimumab 160/80/40 treatment groups was observed.

Outcomes and estimation

Primary endpoint

Table 11 Numbers of patients in remission per Mayo score at week 8 (ITT-A3, ITT-E and PP populations)

	Placebo		Adalimumab 80/40			Adalimumab 160/80/40		
Analysis	N	n (%)	N	n (%)	*P* value[a]	N	n (%)	*P* value[a]
Primary Efficacy Analysis								
ITT-A3 Set – NRI	130	12 (9.2)	130	13 (10.0)	0.833	130	24 (18.5)	0.031
Sensitivity Analyses								
ITT-A3 Set – LOCF[b]	123	12 (9.8)	120	13 (10.8)	0.782	124	24 (19.4)	0.033
Per Protocol Set – NRI	120	10 (8.3)	122	12 (9.8)	0.684	124	23 (18.5)	0.020
ITT-E Set – NRI	222	16 (7.2)	130	13 (10.0)	0.358	223	35 (15.7)	0.005

LOCF = last observation carried forward; NRI = non-responder imputation. a. *P* values for adalimumab versus placebo in ITT-A3 set (NRI and LOCF analyses) and placebo set from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5). For subjects in the ITT-E set, the *P* value to compare adalimumab 160/80/40 versus placebo is from CMH test with subjects in/not in the ITT-A3 set as the stratification factor; and the *P* value to compare adalimumab 80/40 versus placebo is from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5). b. Per the LOCF analysis, the last non-missing post-Baseline values were carried forward.

A statistically significantly higher percentage of subjects in the adalimumab 160/80/40 treatment group compared with placebo achieved the primary endpoint of clinical remission per Mayo score at Week 8 (18.5% versus 9.2%; P=0.031). No statistically significant difference was observed for this endpoint between the adalimumab 80/40 treatment group and the placebo group (10.0% versus 9.2%; P = 0.833).

Similar results were seen in the PP analysis set and in the intent-to-treat A3 (ITT-A3) set when last observation carried forward (LOCF) imputation was used instead of the non-responder imputation (NRI) method. In 4 subgroups, the difference in clinical remission at Week 8 between either of the adalimumab treatment groups and placebo was >10%, with the lower bound of the 95% CI for the difference greater than zero: subjects in the adalimumab 160/80/40 treatment group with CRP <10mg/L, nicotine users, use of azathioprine or 6-MP at Baseline, or no aminosalicylate use at Baseline; and subjects in the adalimumab 80/40 treatment group with no aminosalicylate use at Baseline. In all other subgroups including corticosteroid use at Baseline, the majority of the differences in clinical remission at Week 8 between adalimumab and placebo were ≤10%, and the 95% CIs for the difference included zero.

Secondary endpoints

Twelve ranked secondary variables were to be tested in a hierarchical order to account for multiple testing. The first ranked secondary endpoint "clinical response per Mayo score at Week 8" in the adalimumab 160/80/40 treatment group versus placebo did not meet the criteria for statistical significance (44.6% for placebo compared with 54.6% for adalimumab 160/80/40 mg; P = 0.107). Data from the ITT-A3 population are summarised below.

Table 12 Summary of results of ranked secondary endpoints (ITT-A3, set NRI)

Proportion of Subjects With:[a]	Number (%) of Subjects: Placebo N = 130	Number (%) of Subjects: Adalimumab 160/80/40 N = 130	*P* value[b]
1. Clinical response at Week 8	58 (44.6)	71 (54.6)	0.107
2. Mucosal healing at Week 8	54 (41.5)	61 (46.9)	0.382
3. RBS ≤ 1 at Week 8	86 (66.2)	101 (77.7)	0.038
4. PGA ≤ 1 at Week 8	61 (46.9)	78 (60.0)	0.035
5. SFS ≤ 1 at Week 8	49 (37.7)	63 (48.5)	0.080
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
6. Clinical response at Week 8	58 (44.6)	67 (51.5)	0.264
7. Mucosal healing at Week 8	54 (41.5)	49 (37.7)	0.526
8. RBS ≤ 1 at Week 8	86 (66.2)	91 (70.0)	0.506
9. PGA ≤ 1 at Week 8	61 (46.9)	70 (53.8)	0.264
10. SFS ≤ 1 at Week 8	49 (37.7)	47 (36.2)	0.797
	Placebo N = 130	**Adalimumab 160/80/40 N = 130**	
11. IBDQ response at Week 8	75 (57.7)	79 (60.8)	0.614
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
12. IBDQ response at Week 8	75 (57.7)	70 (53.8)	0.532

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore. a. Listed in rank order, as indicated by the number preceding each endpoint variable. b. *P* value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

The adalimumab 160/80/40 treatment group had a statistically significantly greater proportion of subjects meeting the endpoints of RBS ≤1 at Week 8 (*P*=0.038) and PGA subscore ≤1 at Week 8 (*P*=0.035), while all other ranked secondary endpoints (mucosal healing, SFS ≤1, and IBDQ response at Week 8) had numerically greater, but not statistically significant proportions of subjects in the adalimumab 160/80/40 treatment group compared to placebo.

The adalimumab 80/40 treatment group had numerically greater, but not statistically significant, proportions of subjects meeting the ranked secondary endpoints compared with placebo, with the exception of mucosal healing, stool frequency subscore, and IBDQ response, which were observed at frequencies less than or equal to the frequencies observed in the placebo group.

Analysis of secondary endpoints data for the IIT-E population showed consistent results with the ITT-A3 population analysis.

Table 13 Summary of results of endpoints used in the ranked secondary analyses for study M06-826 (ITT-E Set; NRI)

	Number (%) of Subjects		
Proportion of Subjects with:[a]	Placebo N = 222	Adalimumab 160/80/40 N = 223	*P* value[b]
Clinical response at Week 8	95 (42.8)	116 (52.0)	0.051
Mucosal healing at Week 8	79 (35.6)	99 (44.4)	0.056
RBS ≤ 1 at Week 8	147 (66.2)	162 (72.6)	0.140
PGA ≤ 1 at Week 8	98 (44.1)	119 (53.4)	0.050
SFS ≤ 1 at Week 8	81 (36.5)	95 (42.6)	0.185
	Placebo N = 222	Adalimumab 80/40 N = 130	
Clinical response at Week 8	95 (42.8)	67 (51.5)	0.112
Mucosal healing at Week 8	79 (35.6)	49 (37.7)	0.692
RBS ≤ 1 at Week 8	147 (66.2)	91 (70.0)	0.464
PGA ≤ 1 at Week 8	98 (44.1)	70 (53.8)	0.079
SFS ≤ 1 at Week 8	81 (36.5)	47 (36.2)	0.950
	Placebo N = 222	Adalimumab 160/80/40 N = 223	
IBDQ response at Week 8	128 (57.7)	130 (58.3)	0.890
	Placebo N = 222	Adalimumab 80/40 N = 130	
IBDQ response at Week 8	128 (57.7)	70 (53.8)	0.487

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore a. Listed in the hierarchical order used in the ranked secondary efficacy analyses in the ITT-A3 Set. b. P value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

Maintenance treatment during open-label period

Table 14 Number of patients in remission per Mayo score at weeks 8 (before switch to open label) and 52 (ITT-E set (NRI, mNRI) and dose escalation set.

	Number (%) of Subjects by Randomization Group				
	Placebo[a]				
Analysis Set Visit	Adalimumab 40	Adalimumab 160/80/40	All Placebo	Adalimumab 80/40	Adalimumab 160/80/40
ITT-E (NRI)[b]	**N = 130**	**N = 92**	**N = 222**	**N = 130**	**N = 223**
Week 8	12 (9.2)	4 (4.3)	16 (7.2)	13 (10.0)	35 (15.7)
Week 52	34 (26.2)	24 (26.1)	58 (26.1)	26 (20.0)	55 (24.7)
Weeks 8 and 52	7 (5.4)	3 (3.3)	10 (4.5)	7 (5.4)	21 (9.4)
ITT-E (mNRI)[c]	**N = 130**	**N = 92**	**N = 222**	**N = 130**	**N = 223**
Week 52	41 (31.5)	25 (27.2)	66 (29.7)	30 (23.1)	62 (27.8)
Dose escalators (NRI)[d]	**N = 49**	**N = 20**	**N = 69**	**N = 39**	**N = 51**
Week 52	7 (14.3)	1 (5.0)	8 (11.6)	4 (10.3)	7 (13.7)

a. Subjects randomized to placebo switched to OL adalimumab at Week 8 or Week 12 after visit evaluations were performed. b. According to the NRI analysis method, all missing response (or remission) values and values after dose escalation were imputed as non-response (or non-remission). c. According to the mNRI method, only missing values were imputed as non-response (or non-remission). d. According to the NRI analysis method, for dose escalators, only subjects who increased dosing to adalimumab 40 mg weekly were included and missing values were imputed as non-response (or non-remission).

In both adalimumab treatment groups, the proportion of subjects with clinical remission per Mayo score increased from Week 8 to Week 52. In the placebo treatment group, the proportion of subjects with clinical remission per Mayo score increased after subjects switched from placebo to adalimumab at Week 8. This improvement was similar between subjects who switched from placebo to adalimumab 40

mg eow directly and those who switched to the adalimumab 160/80/40 induction regimen. A numerically higher percentage of subjects who switched to adalimumab 40 mg eow directly were in remission at both Week 8 and Week 52 compared with those who switched to adalimumab 160/80/40; however, a higher proportion of placebo patients who directly went to 40 mg eow had already been in remission at Week 8 compared to placebo patients who went on to adalimumab 160/80/40 therapy.

Fewer subjects in the adalimumab 160/80/40 treatment group required dose escalation (from 40 mg eow to 40 mg weekly) as compared to the adalimumab 80/40 or placebo groups (22.9% versus 30.0% and 31.1%, respectively). Within the placebo group, a lower proportion of subjects who received adalimumab 160/80/40 at the start of the OL period dose escalated as compared to those who switched directly to adalimumab 40 mg eow (21.7% versus 37.7%, respectively). When analyzed using the NRI method, the clinical remission rate per Mayo score at Week 52 among all subjects combined was 24.2% (139/575 subjects). When analyzed using the modified NRI method under which dose escalators were not considered non-responders, the clinical remission rate per Mayo score at Week 52 was 27.5% (158/575 subjects).

Study M06-827

A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of adalimumab verus placebo for the induction and maintenance of clinical remission in subjects with moderately to severely active UC

Methods

Patients received double-blind treatment (active/placebo) for up to 52 weeks. Patients underwent colonoscopy or flexible sigmoidoscopy during the screening period and a flexible sigmoidoscopy at Weeks 8, 32, and 52/Early Termination Visits to assess disease activity. From week 10 and onwards, patients that met the criteria for inadequate response could receive open-label treatment with adalimumab 40 mg eow. Patients with an inadequate response at 2 consecutive visits 14 days apart could receive dose escalation to 40 mg ew. Figure 3 displays the schematic design of the study.

Inadequate response was defined as:

- partial Mayo score ≥ their baseline score on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 4 to 7 at baseline).
- partial Mayo score ≥7 on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 8 or 9 at baseline).

Upon completion of the study, patients were invited to enrol into Study M10-223 and continue to receive adalimumab treatment.

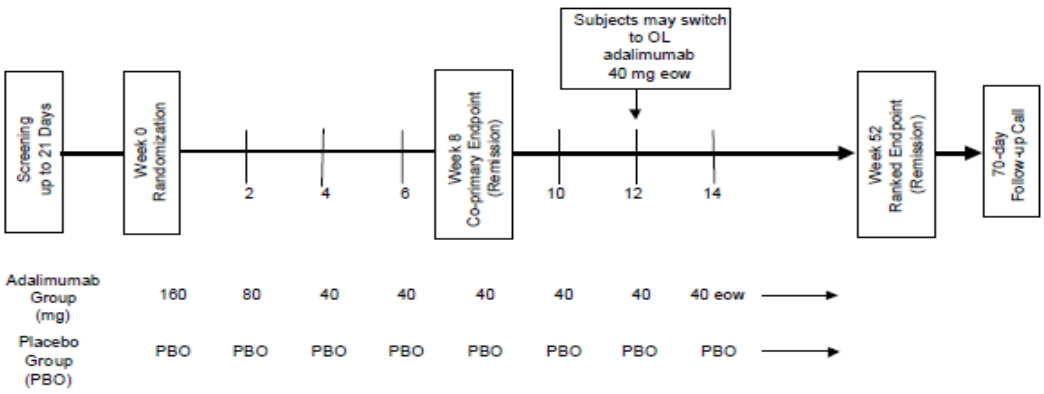

Figure 3 Schematic design of study M06-827

Subjects were not permitted to change their corticosteroid dose during the first 8 weeks of the study. At or after Week 8, subjects who were receiving corticosteroids at baseline were permitted to taper their corticosteroid dose at the discretion of the investigator. Steroid-free remission was evaluated at Week 32 and Week 52 but could not be assessed at Week 8 since subjects taking concomitant corticosteroids at baseline could not change the dose until after Week 8.

Study participants

Adult patients with moderate to severe UC were enrolled at 103 centres worldwide.

Inclusion criteria

The same inclusion criteria as in Study M06-826 were used apart from the following:

Previous use of anti-TNF agents other than adalimumab was permitted if the patient had discontinued its use due to a loss of response or intolerance to the agent, defined as follows:

Loss of response was defined as meeting either of the following criteria after the last dose (a subject with prior infliximab exposure must have responded to a dose of ≥5 mg/kg and demonstrated loss of response ≥14 days after receiving at least 2 subsequent and sequential doses of ≥5 mg/kg at an interval not exceeding 56 days):

- experienced an overall lack of improvement
- experienced a worsening of the following, but not inclusive, UC-related signs/symptoms: stool frequency, abdominal pain, rectal bleeding, fever, and/or weight loss.

Intolerance to anti-TNF agent was considered when therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction was considered significant if at least 1 of the clinical characteristics listed below was captured in the medical history and documented:

- *Acute reaction*: An adverse reaction, whether immunologically or non-immunologically based, which occurs during or within 24 hours of administration of an anti-TNF agent that is manifested by ≥1 of the sign/symptoms and is judged to be related to the medication: fever >100°F, chills or rigors, itching, rash, flushing, urticaria or angioedema, breathing difficulties (dyspnea, chest pain or tightness, shortness of breath, wheezing, stridor), and/or clinical hypotension (pallor, diaphoresis, faintness, syncope), or orthostatic decrease in blood pressure.
- *Delayed reaction*: An adverse reaction occurring more than 24 hours and <14 days after anti-TNF agent administration manifested by ≥1 of the following signs/symptoms and judged to be related to the medication: myalgias, arthralgias, fever >100°F, malaise, and/or rash.

Exclusion criteria

The same exclusion criteria as in Study M06-826 were used apart from the following:

- previous treatment with adalimumab or previous participation in an adalimumab study
- used infliximab or any other anti-TNF agent during the previous 56 days
- previously used infliximab or any other anti-TNF agent without clinical response at any time ('primary non-responder') unless patient experienced a treatment-limiting reaction

Treatments

Patients randomized to active treatment received 160 mg adalimumab at week 0, 80 mg at week 2 and 40 mg thereafter eow with start from week 4. Patients with an inadequate response at 2 consecutive visits, 14 days apart, were permitted to dose escalation (40 mg ew). Patients randomized to the placebo arm received matching treatment during the same period.

Objectives

The primary objective of the study was to assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in patients with moderately to severely active UC.

The secondary objective was to assess the PK of adalimumab following subcutaneous administration.

Outcomes/endpoints

Primary endpoint

The following ranked efficacy endpoints were used:

- proportion of patients in remission at week 8
- proportion of patients in remission at week 52

Main secondary endpoints

- proportion of patients with sustained remission at both weeks 8 and 52
- proportion of patients in clinical response by Mayo score (at weeks 8 and 52, sustained at both weeks 8 and 52)
- proportion of patients with mucosal healing (at weeks 8 and 52, sustained at both weeks 8 and 52)
- proportion of patients who discontinued corticosteroid use before and were in remission at week 52
- proportion of patients with PGA subscore indicative of mild disease (≤ 1) at Week 8
- proportion of patients who were IBDQ responders at weeks 8 and 52

Sample size

The sample size was calculated using nQuery Advisory 4.0. Assuming that 5% of the patients in the placebo group achieved clinical remission at Week 52 or Week 8, a sample size of 250 in each treatment group was adequate to detect a difference of at least 7 percentage points from the adalimumab group using Chi-square test with 80% power at a 0.05 two-sided significance level. A total of 500 subjects were to be randomized in this study.

Randomisation

All subjects were assigned a unique identification number as they were screened for the study. The number assigned at screening was used during the screening period only. A new unique identification number was assigned to each subject upon randomization and used throughout the study. All subjects were centrally randomized at baseline (Week 0) and assigned to a treatment group after stratifying by prior exposure to infliximab and/or other anti-TNF agents according to the randomization scheme generated by the MAH before the start of the study.

Blinding

The MAH, the investigator, site study personnel, and patient were to remain blinded to each patient's treatment throughout the course of the study.

Statistical methods

The primary efficacy analysis was performed on the ITT analysis set and consisted of two ranked efficacy endpoints: (1) proportion of subjects achieving clinical remission at Week 8 and (2) proportion of subjects achieving clinical remission at Week 52. Hypothesis testing for the ranked endpoints was carried out in a hierarchical order using a two-sided Cochran Mantel Haenszel (CMH) test adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 8 was tested first. If the null hypothesis of no difference between adalimumab and placebo was rejected at α=0.05, then the remission rate at Week 52 was to be tested at a significance level of 0.05.

However, in order to claim maintenance of remission, it was necessary to reject not only both hypotheses on the two ranked co-primary endpoints but also to reject the hypothesis on the first ranked secondary endpoint: proportion of subjects in remission at both Week 8 and 52. This first ranked secondary endpoint was incorporated in the confirmatory testing procedure conducted in hierarchical order from the first to the second ranked co-primary efficacy endpoint, and then to the ranked secondary endpoints, and stopped whenever a hypothesis could not be rejected at a significance level of 0.05. If a ranked endpoint did not meet the criteria for statistical significance, the analyses of the rest of the ranked secondary endpoints would be considered exploratory. This ensured that the multiple significance level was controlled at 0.05.

The following non-responder imputation method was used in the analysis. Using the analysis of clinical remission at Week 52 as an example, subjects who discontinued the study for any reason prior to Week 52, and subjects with a missing Mayo Score at Week 52 were counted as "no" to remission. Subjects who switched to open-label drug were counted as "no" to remission from the time of switching onward.

The last observation carried forward (LOCF) method was used for sensitivity analyses. For subjects who switched to OL drug, the non-missing value at the visit when the subject switched to the OL drug was to be carried forward in the LOCF analysis.

The secondary efficacy analysis was performed on the ITT analysis set. The testing of ranked secondary endpoints was initiated only in case of statistically significant differences between the treatment groups for both ranked co-primary endpoints.

Results

Numbers analysed

There were four sets of study data that were analysed, see Table 15.

Table 15 Number of patients by analysis sets

	Number (%) of Subjects		
Analysis Set	Placebo N = 260	Adalimumab N = 258	Total N = 518
Safety	260	257[a]	517
Intent-to-Treat	246	248	494
Modified Intent-to-Treat	246	247	493
Per Protocol	212	212	424

a. One subject was randomized to adalimumab but never treated. Note: A total of 24 subjects were excluded from the ITT and mITT analysis set due to non-compliance with GCP and protocol requirements at the investigative sites.

The modified analysis set consisted of patients from the ITT set that had received at least one dose of the study drug or placebo. Exploratory analyses were performed on this population.

Participant flow

Table 16 Disposition of patients in Study M06-827

Subject Status – All randomized	Number (%) of Subjects		
	Placebo	Adalimumab	Total
Randomized	260	258	518
Treated	260	257	517
Subject Status – Final (ITT Analysis Set)	**Number (%) of Subjects**		
	Placebo N = 246	**Adalimumab N = 248**	**Total N = 494**
Discontinued study	115 (46.7)	94 (37.9)	209 (42.3)
Reasons for discontinuation[a]			
Adverse event	25 (10.2)	12 (4.8)	37 (7.5)
Withdrew consent	4 (1.6)	8 (3.2)	12 (2.4)
Lost to follow-up	0	1 (0.4)	1 (0.2)
Lack of efficacy	70 (28.5)	63 (25.4)	133 (26.9)
Protocol violation	5 (2.0)	1 (0.4)	6 (1.2)
Other[b]	11 (4.5)	9 (3.6)	20 (4.0)
Subject Status – Week 8 (ITT Analysis Set)			
Discontinued study prior to Week 8	36 (14.6)	23 (9.3)	59 (11.9)
Reasons for discontinuation[a]			
Adverse event	10 (4.1)	5 (2.0)	15 (3.0)
Withdrew consent	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0	0	0
Lack of efficacy	15 (6.1)	13 (5.2)	28 (5.7)
Protocol violation	3 (1.2)	1 (0.4)	4 (0.8)
Other[b]	6 (2.4)	3 (1.2)	9 (1.8)

a. Primary reason. b. Reasons for discontinuation recorded as "other" included: diagnosis of CD, loss of response, primary nonresponder, UC symptoms not improving, investigator decision, subject non-compliance, positive TB skin test, subject wanted to start family, or total colectomy surgery within the 70-day follow-up period.

A total of 518 subjects were randomized into the study. A total of 11.9% of subjects in the ITT analysis set discontinued prior to Week 8, most frequently due to lack of efficacy, which occurred at a higher incidence rate in the placebo group compared to the adalimumab group. By the end of the study (Week 52), a total of 42.3% of subjects discontinued prematurely. The most frequently reported reasons for premature discontinuation were lack of efficacy, AE, and other, all of which were experienced in a numerically greater proportion of subjects randomized to the placebo group. All other reasons for discontinuation were each reported by <3.5% of subjects.

Conduct of the study

The original protocol underwent 3 amendments. In Amendment 1 a clarification that current therapy with either a corticosteroid or an immunosuppressant would satisfy this inclusion criteria and expansion of prohibited therapies to include natalizumab and abatacept. In Amendment 2 the primary and secondary efficacy variables were revised in accordance with EMA guidelines. Strict ordering of ranked co-primary and secondary efficacy endpoints were implemented. Amendment No 3 introduced the final statistical plan and was added before the blind was broken.

Baseline data

Table 17 Baseline demographic characteristics (Study M06-827, ITT)

Characteristic	Placebo N = 246	Adalimumab N = 248	Total N = 494
Sex, n (%)			
Female	94 (38.2)	106 (42.7)	200 (40.5)
Male	152 (61.8)	142 (57.3)	294 (59.5)
Race, n (%)			
White	234 (95.1)	236 (95.2)	470 (95.1)
Black	4 (1.6)	7 (2.8)	11 (2.2)
Asian	4 (1.6)	1 (0.4)	5 (1.0)
Other[a]	4 (1.6)	4 (1.6)	8 (1.6)
Hispanic or Latino ethnicity, n (%)	7 (2.8)	6 (2.4)	13 (2.6)
Age range, n (%)			
< 40 years	118 (48.0)	136 (54.8)	254 (51.4)
40 to 64 years	116 (47.2)	105 (42.3)	221 (44.7)
≥ 65 years	12 (4.9)	7 (2.8)	19 (3.8)
Age, mean ± SD (years)	41.3 ± 13.22	39.6 ± 12.47	40.4 ± 12.86
Weight, mean ± SD (kg)	77.1 ± 17.31	75.3 ± 17.71	76.2 ± 17.52
Height			
N	242	243	485
Mean ± SD (cm)	172.8 ± 9.82	172.4 ± 9.40	172.6 ± 9.60
Nicotine use, n (%)			
User	19 (7.8)	20 (8.1)	39 (7.9)
Ex-user	88 (35.9)	94 (37.9)	182 (36.9)
Non-user	138 (56.3)	134 (54.0)	272 (55.2)
Alcohol use, n (%)			
Drinker	125 (51.0)	132 (53.2)	257 (52.1)
Ex-drinker	11 (4.5)	8 (3.2)	19 (3.9)
Non-drinker	109 (44.5)	108 (43.5)	217 (44.0)

a. Includes American Indian/Alaska native, native Hawaiian or other pacific islander, "other," and multi-race.

Table 18 Baseline disease history (Study M06-827, ITT)

Characteristic	Placebo N = 246	Adalimumab N = 248	Total N = 494
Duration of UC, mean ± SD (years)	8.5 ± 7.37	8.1 ± 7.09	8.3 ± 7.23
Site of UC, n (%)			
Pancolitis	120 (48.8)	120 (48.4)	240 (48.6)
Descending colon	96 (39.0)	96 (38.7)	192 (38.9)
Other	30 (12.2)	32 (12.9)	62 (12.6)
UC confirmed by biopsy, n (%)[b]			
Yes	242 (99.6)	244 (100)	486 (99.8)
No	1 (0.4)	0	1 (0.2)
Missing	3	4	7
Evidence of dysplasia/malignancy, n (%)			
Yes[a]	1 (0.4)	2 (0.8)	3 (0.6)
No	241 (99.6)	243 (99.2)	484 (99.4)
Missing	4	3	7

a. Details on these protocol deviations are provided in Section 10.2. b. Subject 79903 did not have confirmed UC at Baseline because of a missing biopsy. Subject 73506 was erroneously enrolled with a history of CD; for this reason, the subject was discontinued.

Subjects in the ITT analysis set had a mean duration of UC of 8.3 years, with the primary disease site of pancolitis (48.6%). There were no statistically significant differences in baseline disease histories between treatment groups, and histories similar to the ITT analysis set were found for the PP and safety analysis sets.

Table 19 Baseline disease activity (Study M06-827, ITT)

Parameter	Placebo N = 246	Adalimumab N = 248	Total N = 494
Mayo score			
N	245	246	491
Mean ± SD	8.9 ± 1.75	8.9 ± 1.50	8.9 ± 1.63
Partial Mayo score			
N	245	247	492
Mean ± SD	6.5 ± 1.55	6.5 ± 1.39	6.5 ± 1.47
Endoscopy subscore (mucosal healing)			
N	246	247	493
Mean ± SD	2.5 ± 0.50	2.5 ± 0.50	2.5 ± 0.50
Rectal bleeding subscore			
N	245	247	492
Mean ± SD	1.7 ± 0.94	1.7 ± 0.85	1.7 ± 0.89
Physician's Global Assessment subscore			
N	245	247	492
Mean ± SD	2.2 ± 0.57	2.2 ± 0.55	2.2 ± 0.56
Stool frequency subscore			
N	245	247	492
Mean ± SD	2.6 ± 0.66	2.5 ± 0.71	2.5 ± 0.69
IBDQ score			
N	230	230	460
Mean ± SD	123.2 ± 33.26	127.7 ± 28.68	125.5 ± 31.10
SF-36 physical functioning component score			
N	239	245	484
Mean ± SD	44.6 ± 9.79	45.7 ± 9.53	45.1 ± 9.67
SF-36 mental component summary			
N	237	245	482
Mean ± SD	36.5 ± 11.57	39.0 ± 10.67	37.8 ± 11.18
WPAI – overall work impairment			
N	155	168	323
Mean ± SD	52.9 ± 31.34	50.1 ± 31.98	51.4 ± 31.66

Adalimumab treated patients had statistically significantly higher SF-36 mental component summary score and role-emotional functional and mental health component scores than placebo treated patients. There were no other statistically significant differences observed between treatment groups (ITT analysis set).

Table 20 Baseline disease severity by Mayo subscore (Study M06-827, ITT)

	Number (%)[a] of Subjects		
Parameter	Placebo N = 246	Adalimumab N = 248	Total N = 494
Endoscopy subscore			
0 = Normal or inactive disease	0	0	0
1 = Mild disease	0	0	0
2 = Moderate disease	133 (54.1)	132 (53.4)	265 (53.8)
3 = Severe disease	113 (45.9)	115 (46.6)	228 (46.2)
Rectal bleeding subscore			
0 = Normal or inactive disease	31 (12.7)	21 (8.5)	52 (10.6)
1 = Mild disease	66 (26.9)	68 (27.5)	134 (27.2)
2 = Moderate disease	99 (40.4)	114 (46.2)	213 (43.3)
3 = Severe disease	49 (20.0)	44 (17.8)	93 (18.9)
Physician's Global Assessment subscore			
0 = Normal or inactive disease	1 (0.4)	2 (0.8)	3 (0.6)
1 = Mild disease	16 (6.5)	10 (4.0)	26 (5.3)
2 = Moderate disease	155 (63.3)	168 (68.0)	323 (65.7)
3 = Severe disease	73 (29.8)	67 (27.1)	140 (28.5)
Stool frequency subscore			
0 = Normal or inactive disease	3 (1.2)	4 (1.6)	7 (1.4)
1 = Mild disease	15 (6.1)	20 (8.1)	35 (7.1)
2 = Moderate disease	65 (26.5)	66 (26.7)	131 (26.6)
3 = Severe disease	162 (66.1)	157 (63.6)	319 (64.8)

a. Percent based on number of subjects with non-missing values.

The majority of subjects in both treatment groups had moderate to severe disease at Baseline as assessed by endoscopy, rectal bleeding, PGA, and SFS. Subscores were very similar between groups and no statistically significant differences were found.

Table 21 UC related medications at baseline (by >5 % of patients) (Study M06-827, ITT)

	Number (%) of Subjects		
Generic Name[a]	Placebo N = 246	Adalimumab N = 248	Total N = 494
Any UC-related medications used at Baseline	218 (88.6)	224 (90.3)	442 (89.5)
Any corticosteroid	140 (56.9)	150 (60.5)	290 (58.7)
Prednisone	80 (32.5)	87 (35.1)	167 (33.8)
Methylprednisolone	33 (13.4)	26 (10.5)	59 (11.9)
Prednisolone	20 (8.1)	26 (10.5)	46 (9.3)
Budesonide	7 (2.8)	10 (4.0)	17 (3.4)
Deflazacort	0	1 (0.4)	1 (0.2)
Hydrocortisone	1 (0.4)	0	1 (0.2)
Any azathioprine/6-MP	80 (32.5)	93 (37.5)	173 (35.0)
Azathioprine	64 (26.0)	76 (30.6)	140 (28.3)
Mercaptopurine	16 (6.5)	17 (6.9)	33 (6.7)
Any Aminosalicylate	155 (63.0)	146 (58.9)	301 (60.9)
Mesalazine	120 (48.8)	112 (45.2)	232 (47.0)
Sulfasalazine	22 (8.9)	14 (5.6)	36 (7.3)
Balsalazide	13 (5.3)	16 (6.5)	29 (5.9)
Aminosalicylic acid	0	3 (1.2)	3 (0.6)
Olsalazine	0	1 (0.4)	1 (0.2)

a. WHODRUG dictionary Q1 2009. Note: Subjects may have had more than one generic therapy within each category.

Overall there were no significant differences in demographics, medical history, Baseline diseases characteristics, ECG, TB skin test for positivity at Baseline, CXR, and prior/concomitant medications observed between the placebo and adalimumab 160/80/40 treatment groups. Subjects were predominantly white and male with moderate to severe UC (Mayo score ≥6 and an endoscopy subscore ≥2) who mostly received previous corticosteroids or azathioprine prior to study entry.

Outcomes and estimation

Primary endpoint

Table 22 Number of patients in remission per Mayo score at weeks 8 and 52 (ITT, mITT and PP populations; NRI and LCOF)

	Placebo		Adalimumab		
	N	n (%)	N	n (%)	*P* value[a]
Week 8 Remission per Mayo score					
Primary Efficacy Analysis					
ITT Analysis Set – NRI[b]	246	23 (9.3)	248	41 (16.5)	0.019
Sensitivity Analyses					
mITT Analysis Set – NRI	246	23 (9.3)	247	41 (16.6)	0.018
PP Analysis Set – NRI	212	21 (9.9)	212	36 (17.0)	0.027
ITT Analysis Set – LOCF[c]	246	23 (10.6)	248	41 (18.2)	0.024
Week 52 Remission per Mayo score					
Primary Efficacy Analysis					
ITT Analysis Set – NRI[b]	246	21 (8.5)	248	43 (17.3)	0.004
Sensitivity Analyses					
mITT Analysis Set – NRI	246	21 (8.5)	247	43 (17.4)	0.004
PP Analysis Set – NRI	212	19 (9.0)	212	35 (16.5)	0.015
ITT Analysis Set – LOCF[c]	246	23 (10.5)	248	46 (19.9)	0.006

NRI = non-responder imputation. a. *P* value to compare treatment groups was based on CMH test (stratification levels: prior anti-TNF versus anti-TNF-naïve). b. According to the NRI method, all missing remission values were considered to be non-remission. Subjects who switched to OL adalimumab were considered to be non-remitters at and after the time of the switch. c. According to the LOCF method, missing values after study Day 1 were imputed using the latest non-missing values after Day 1 and prior to the missing value. For subjects who switched to OL adalimumab, the latest non-missing value before or at the visit when the subject switched to OL adalimumab was carried forward.

A statistically significantly greater proportion of subjects in the adalimumab group were in clinical remission per Mayo score at Week 8 and Week 52 compared to subjects in the placebo group in all analysis sets (16.5% vs 9.3% and 17.3% vs 8.5% respectively). In the adalimumab arm, 41 patients out of 248 patients and 43 patients out of 248 patients were in clinical remission per Mayo score at Week 8 and Week 52 i.e. approximately 16.9% patients achieved a remission.

Secondary endpoints

Of the 15 ranked secondary variables, the first 8 met criteria for statistical significance as compared with placebo.

Table 23 Summary of results of ranked secondary endpoints (ITT population, NRI- non-responder imputation)

Ranked Secondary Endpoints:[a]	Number (%) of Subjects: Placebo N = 246	Number (%) of Subjects: Adalimumab N = 248	*P* value
1. Sustained remission per Mayo score at Week 8 and Week 52	10 (4.1)	21 (8.5)	0.047
2. Response per Mayo score at Week 8	85 (34.6)	125 (50.4)	< 0.001
3. Response per Mayo score at Week 52	45 (18.3)	75 (30.2)	0.002
4. Sustained Response per Mayo score at Week 8 and Week 52	30 (12.2)	59 (23.8)	< 0.001
5. Mucosal healing at Week 8	78 (31.7)	102 (41.1)	0.032
6. Mucosal healing at Week 52	38 (15.4)	62 (25.0)	0.009
7. Sustained mucosal healing at Week 8 and Week 52	26 (10.6)	46 (18.5)	0.013
8. Discontinued corticosteroid use before Week 52 and achieved remission at Week 52	8 (5.7)	20 (13.3)	0.035
9. PGA ≤ 1 at Week 8	92 (37.4)	114 (46.0)	0.058
10. SFS ≤ 1 at Week 8	70 (28.5)	94 (37.9)	0.028
11. RBS ≤ 1 at Week 8	143 (58.1)	174 (70.2)	0.006
12. Discontinued corticosteroid use for ≥ 90 days before Week 52 and achieved remission at Week 52	8 (5.7)	20 (13.3)	0.035
13. Discontinued corticosteroid use and achieved sustained remission at both Weeks 32 and 52	2 (1.4)	15 (10.0)	0.002
14. IBDQ responders at Week 52	40 (16.3)	65 (26.2)	0.007
15. IBDQ responders at Week 8	112 (45.5)	144 (58.1)	0.006

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = Rectal bleeding subscore; SFS = stool frequency subscore. a. Listed in ranked order, as indicated by the number preceding each endpoint variable.

The eight secondary variables which met the criteria for statistical significance were: sustained clinical remission per Mayo score at both Week 8 and Week 52, clinical response per Mayo score at Week 8 and at Week 52, sustained clinical response per Mayo score at Week 8 and at Week 52, mucosal healing (defined as endoscopy subscore ≤1) at Week 8 and at Week 52, sustained mucosal healing at both Week 8 and Week 52, and corticosteroid-free clinical remission per Mayo score at Week 52. Concerning the first ranked secondary endpoint, of the 41 patients who achieved remission at week 8, 21 patients in the adalimumab group (8.5% of the whole population treated with adalimumab) maintained a sustained remission up to week 52.

Ranked endpoint No. 9 (PGA≤1 at Week 8 in the adalimumab 160/80/40 treatment group versus placebo) missed statistical significance (P=0.058), although it exhibited a numerical benefit of the adalimumab 160/80/40 treatment group versus placebo (37.4% placebo compared with 46.0% adalimumab). The adalimumab 160/80/40 treatment group had a statistically significantly greater proportion of subjects meeting the rest of the ranked endpoints (P value ranged from 0.002 to 0.035) compared with placebo.

Table 24 Efficacy endpoints by prior anti-TNF strata (ITT, NRI)

Endpoints	No Prior Anti-TNF			Prior Anti-TNF		
	Placebo N = 145	Ada N = 150	*P* value[a]	Placebo N = 101	Ada N = 98	*P* value[a]
Ranked co-primary endpoints						
Clinical remission per Mayo score at Week 8	16 (11.0)	32 (21.3)	0.017	7 (6.9)	9 (9.2)	0.559
Clinical remission per Mayo score at Week 52	18 (12.4)	33 (22.0)	0.029	3 (3.0)	10 (10.2)	0.039
Ranked secondary endpoints						
1. Sustained clinical remission per Mayo score at Week 8 and Week 52	9 (6.2)	16 (10.7)	0.169	1 (1.0)	5 (5.1)	0.115
2. Clinical response per Mayo score at Week 8	56 (38.6)	89 (59.3)	< 0.001	29 (28.7)	36 (36.7)	0.228
3. Clinical response per Mayo score at Week 52	35 (24.1)	55 (36.7)	0.019	10 (9.9)	20 (20.4)	0.038
4. Sustained clinical response per Mayo score at Week 8 and Week 52	24 (16.6)	44 (29.3)	0.009	6 (5.9)	15 (15.3)	0.032
5. Mucosal healing at Week 8	51 (35.2)	74 (49.3)	0.014	27 (26.7)	28 (28.6)	0.772
6. Mucosal healing at Week 52	28 (19.3)	47 (31.3)	0.018	10 (9.9)	15 (15.3)	0.250
7. Sustained mucosal healing at Week 8 and Week 52	20 (13.8)	36 (24.0)	0.025	6 (5.9)	10 (10.2)	0.269
8. Discontinued corticosteroid use before Week 52 and achieved clinical remission at Week 52	N = 81 5 (6.2)	N = 110 15 (13.6)	0.096	N = 59 3 (5.1)	N = 40 5 (12.5)	0.263
9. PGA ≤ 1 at Week 8	63 (43.4)	88 (58.7)	0.009	29 (28.7)	26 (26.5)	0.731
10. SFS ≤ 1 at Week 8	43 (29.7)	69 (46.0)	0.004	27 (26.7)	25 (25.5)	0.844
11. RBS ≤ 1 at Week 8	86 (59.3)	116 (77.3)	< 0.001	57 (56.4)	58 (59.2)	0.695
12. Discontinued corticosteroid use for ≥ 90 days before Week 52 and achieved clinical remission at Week 52	N = 81 5 (6.2)	N = 110 15 (13.6)	0.096	N = 59 3 (5.1)	N = 40 5 (12.5)	0.263
13. Discontinued corticosteroid use and achieved sustained clinical remission at both Weeks 32 and 52	N = 81 1 (1.2)	N = 110 11 (10.0)	0.014	N = 59 1 (1.7)	N = 40 4 (10.0)	0.155
14. IBDQ responders at Week 52	31 (21.4)	48 (32.0)	0.039	9 (8.9)	17 (17.3)	0.078
15. IBDQ responders at Week 8	75 (51.7)	102 (68.0)	0.004	37 (36.6)	42 (42.9)	0.370

Ada = adalimumab. a. *P* values to compare adalimumab treatment group with placebo were based on chi-square test (or Fisher's exact test if ≥ 20% of the cells had an expected cell count < 5)

Among subjects who were naive to anti-TNF agents at study entry, the proportion of those achieving the ranked co-primary and most ranked secondary endpoints was statistically significantly greater in the adalimumab group compared to the placebo group. Among subjects who had previously used anti-TNF agents, a statistically significantly greater proportion of adalimumab-treated subjects compared to placebo-treated subjects achieved clinical remission per Mayo score at Week 52, clinical response per Mayo score at Week 52, and sustained clinical response per Mayo score at both Week 8 and Week 52).

Table 25 Number of dose escalators who achieved clinical remission / clinical response per Mayo score (ITT, as observed)

Study Visit	Placebo/OL Adalimumab n (%)[b]	Adalimumab/OL Adalimumab n (%)[b]
Remission		
Week 32 (N[a])	64	49
Yes	2 (4.7)	2 (5.3)
No	41 (95.3)	36 (94.7)
Missing	21	11
Week 52 (N[a])	84	68
Yes	15 (34.1)	5 (12.2)
No	29 (65.9)	36 (87.8)
Missing	40	27
Response		
Week 32 (N[a])	64	49
Yes	13 (30.2)	14 (35.9)
No	30 (69.8)	25 (64.1)
Missing	21	10
Week 52 (N[a])	84	68
Yes	27 (61.4)	19 (46.3)
No	17 (38.6)	22 (53.7)
Missing	40	27

a. N = total number of subjects per treatment group at each visit who dose escalated from adalimumab 40 mg eow to ew, including subjects with missing Mayo scores.
b. Percent remitters/responders determined only from subjects with non-missing Mayo scores.

After Week 12 of the study, 135/246 (54.9%) subjects in the placebo and 116/248 (46.8%) subjects in the adalimumab treatment group had inadequate clinical response and switched to the OL adalimumab administration. Of these 251 subjects who switched, 84 (34.1%) and 68 (27.4%) in the placebo and adalimumab group, respectively, dose escalated from 40 mg eow to 40 mg ew. Of the subjects who dose escalated to OL adalimumab ew, a greater proportion of subjects previously randomized to the placebo group than to the adalimumab group achieved clinical remission (34.1% versus 12.2%, respectively) and clinical response per Mayo score (61.4% versus 46.3%, respectively) at Week 52. A total of 158 patients dose escalated from adalimumab eow to ew.

Table 26 Number and percentage of subjects in clinical remission at Week 8 and Week 52 by presence or absence of pancolitis at baseline (ITT Analysis Set; NRI)

	Number (%) of Subjects			
	Placebo		Adalimumab 160/80/40	
Study Visit	Pancolitis at Baseline N = 120	No Pancolitis at Baseline N = 126	Pancolitis at Baseline N = 120	No Pancolitis at Baseline N = 128
Week 8	9 (7.5)	14 (11.1)	23 (19.2)	18 (14.1)
Week 52	6 (5.0)	15 (11.9)	17 (14.2)	26 (20.3)

In addition, an analysis of the percentage of patients who acquired remission as per Mayo score and maintained it up to week 52 was performed by stratifying data according to the anatomical extent of the disease: pancolitis, descending colon and other.

Among subjects with pancolitis, despite the small subgroup, >10% more subjects treated with adalimumab achieved clinical remission per Mayo score at Week 8 compared with placebo. Nearly 10% more subjects treated with adalimumab achieved clinical remission at Week 52 compared with placebo.

Table 27 Number and percentage of subjects taking corticosteroids at baseline who discontinued corticosteroid use and achieved clinical remission per Mayo score at Week 32 and Week 52 (ITT Analysis Set; NRI)

	Number (%) of Subjects		
Endpoint	Placebo N = 140	Adalimumab 160/80/40 N = 150	*P* value[a]
Clinical remission at Week 32			
Discontinued CS at any time prior to Week 32	10 (7.1)	21 (14.0)	0.107
Discontinued CS for ≥ 90 days prior to Week 32	9 (6.4)	17 (11.3)	0.229
Clinical remission at Week 52			
Discontinued CS at any time prior to Week 52	8 (5.7)	20 (13.3)	0.035
Discontinued CS for ≥ 90 days prior to Week 52	8 (5.7)	20 (13.3)	0.035

CS = corticosteroids ; a. *P* value to compare treatment groups was based on CMH test (stratification levels: prior anti-TNF versus anti-TNF-naïve).

Steroid-free remission was evaluated in Study M06-827 at Week 32 and Week 52. At Week 32, a numerically higher proportion of subjects in the adalimumab group discontinued corticosteroids and achieved clinical remission, regardless of whether they were steroid-free for more than or less than 90 days. At Week 52, a statistically significantly higher proportion of subjects in the adalimumab group discontinued corticosteroid use and achieved clinical remission. A statistically significantly greater

proportion of subjects in the adalimumab group discontinued corticosteroid use at Week 52 compared with placebo (34.0% versus 22.9%, *P*=0.039).

Supportive study

Study M10-223 (open label extension study)

A multicenter, open-label study to evaluate the long term safety and tolerability of repeated administration of adalimumab as maintenance therapy in subjects with UC who completed studies M06-826 and M06-827.

Methods

Patients were administered 40 mg eow or ew by SC injection. Data presented have been collected through 31 December 2009 a cut-off date.

The day 1/baseline visit for patients entering M10-223 is Week 52 of Studies M06-826 or M06-827. Patients can participate for up to 240 weeks in the study.

Patients who entered this study from a blinded cohort were assigned to open-label adalimumab, 40 mg eow. Patients, who were inadequate responders upon entering the study and who do not show response during the study, or who show a response and then have a disease flare, may have their adalimumab dose increased to 40 mg ew, but no earlier than the Week 12 visit. Patients that continue to show inadequate response, or continue to have a flare while on 40 mg every week, may be discontinued from the study.

Beginning at Week 12 of participation in Study M10-223, UC-related concomitant medications, including immunosuppressants, may be decreased in dose or discontinued in those patients who show clinical response. Patients in whom corticosteroid tapering was started in the previous studies may continue their corticosteroid taper immediately upon enrolment into the extension study. If the patients experience loss of response the corticosteroid dose may be increased.

Study Participants

Subjects were eligible for enrolment if they successfully completed either Study M06-826 or M06-827. Patients who had not responded to dosing ew in the preceding study were not eligible for inclusion.

Treatment

All subjects are receiving adalimumab 40 mg eow or adalimumab 40 mg ew, administered as a single SC injection. For inadequate responder, the dose may be escalated to 40 mg ew starting at Week 12 (or at Week 2 for subjects who enter this study from an OL cohort and are inadequate responders).

Objective

The aim of this ongoing study is to demonstrate the long-term safety, tolerability and effectiveness of repeated administration of adalimumab in subjects with UC who completed one of 2 double-blind, placebo-controlled studies (Study M06-826 or M06-827).

Outcome/endpoints

Table 28 Study activities from baseline through week 96

Activity	Baseline (Day 1)	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
Inclusion/Exclusion Criteria	X											
Informed Consent	X											
Medical History	X[b]											
Pregnancy Test[a]	X							X				X
Concomitant Medication Changes	X[b]	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X[b]	X	X	X	X	X	X	X	X	X	X	X
General Lab	X[b]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[b]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[d]	X[b]	X	X	X	X	X	X	X	X	X	X	X
Partial Mayo Score	X[b]	X	X	X	X	X	X	X	X	X	X	X
Mayo Score	X[b]							X				X
IBDQ	X[b]	X	X	X	X	X	X	X	X	X	X	X
SF-36	X[b]						X	X	X	X	X	X
Health Care Resource Utilization Questionnaire	X[b]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Activity Impairment Questionnaire	X[b]	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid Start Taper					X[e]							
Endoscopy[f]	X[b]							X				X
Adverse Events	X[b]	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[g]	X	X	X	X	X	X	X	X	X	X	X	X

a. Serum pregnancy test to be performed on all women; serum testing every 48 weeks throughout the duration of the study. b. At the Day 1/Baseline visit, the following procedures are completed as part of Week 52 of the Study M06-826 and Study M06-827 protocol: concomitant medication changes, physical exam, vital signs, general lab, CRP, urinalysis, Mayo Score, IBDQ, SF-36, Health Care Resource Utilization, WPAI (for Study M06-827 subjects only), endoscopy and adverse events. WPAI is collected at Day 1/Baseline visit for Study M06-826 subjects only. Medical History is updated from the medical history recorded during the subject's previous study. c. Vital signs are taken at each visit to include weight, blood pressure, heart rate, temperature, and respiration rate. d. Microscopic urinalysis performed if dipstick urinalysis is abnormal, where protein, blood, ketones, or glucose is defined as greater than a trace. e. Subjects entering this study may begin a taper starting at the Week 12 visit if qualifications for a taper are met. f. Subjects to have flexible sigmoidoscopy every 48 weeks (12 months). g. Subjects must inject within ± 3 days of their scheduled weekly or every other week injections.

Table 29 Study activities week 108 through week 192

Activity	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192
Inclusion/Exclusion Criteria								
Informed Consent								
Pregnancy Test[a]				X				X
Concomitant Medication Changes	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X
General Lab	X	X	X	X	X	X	X	X
CRP	X	X	X	X	X	X	X	X
Urinalysis[c]	X	X	X	X	X	X	X	X
Partial Mayo Score	X	X	X	X	X	X	X	X
Mayo Score				X				X
IBDQ	X	X	X	X	X	X	X	X
SF-36	X	X	X	X	X	X	X	X
Health Care Resource Utilization Questionnaire	X	X	X	X	X	X	X	X
Work Productivity and Activity Impairment Questionnaire	X	X	X	X	X	X	X	X
Corticosteroid Start Tape[d]								
Endoscopy[e]				X				X
Adverse Events	X	X	X	X	X	X	X	X
Study Drug Administration[f]	X	X	X	X	X	X	X	X

a. Performed on all women. b. Vital signs are taken at each visit to include weight, blood pressure, heart rate, temperature, and respiration rate. c. Microscopic urinalysis performed if dipstick UA is abnormal, where protein, blood, ketones, or glucose is defined as greater than a trace. d. Subjects entering this study may begin a taper starting at the Week 12 visit if qualifications for a taper are met. e. Subjects to have flexible sigmoidoscopy every 48 weeks (12 months). f. Subjects must inject within ± 3 days of their scheduled weekly or every other week injections.

Results

Numbers analysed

The following data sets were analysed:

- ITT-1 (n=494) patients that received at least one dose of the study drug.

- ITT-2 (n=448) ITT-1 patients who had a gap of ≤17 days between the previous and present study.

- SA analysis set (n=498) all patients that received at least one dose.

Participant flow

Table 30 Patient accountability by previous treatment and study

Previous Study Previous Treatment	Analysis Sets Safety N = 498	 ITT-1 N = 494	 ITT-2 N = 448
	n (%)		
M06-826	290 (58.2)	290 (58.7)	274 (61.2)
DB treatment period			
Placebo	122 (24.5)	122 (24.7)	114 (25.4)
Adalimumab 80/40 mg	57 (11.4)	57 (11.5)	57 (12.7)
Adalimumab 160/80/40 mg	111 (22.3)	111 (22.5)	103 (23.0)
OL treatment period			
dose escalated to ew	60 (12.0)	60 (12.1)	58 (12.9)
dose not escalated to ew	230 (46.2)	230 (46.6)	216 (48.2)
M06-827	208 (41.8)	204 (41.3)	174 (38.8)
DB treatment period			
Placebo – only DB[a]	40 (8.0)	39 (7.9)	29 (6.5)
Placebo – DB + OL eow[b]	26 (5.2)	26 (5.3)	23 (5.1)
Placebo – DB + OL ew[b]	27 (5.4)	27 (5.5)	25 (5.6)
Adalimumab 16/80/40 mg – only DB[a]	61 (12.2)	60 (12.1)	51 (11.4)
Adalimumab 16/80/40 mg – DB + OL eow[b]	25 (5.0)	25 (5.1)	20 (4.5)
Adalimumab 16/80/40 mg – DB + OL ew[b]	29 (5.8)	27 (5.5)	26 (5.8)
OL treatment period			
dose escalated to ew	56 (11.2)	54 (10.9)	51 (11.4)
dose not escalated to ew	152 (30.5)	150 (30.4)	123 (27.5)

DB = double-blind; eow = every other week; ew = every week; OL = open-label. a. Study M06-827: Subjects entered Study M10-223 from DB treatment period. b. Study M06-827: Subjects entered Study M10-223 from OL treatment period. Note: All subjects from Study M06-826 entered Study M10-223 from OL treatment period.

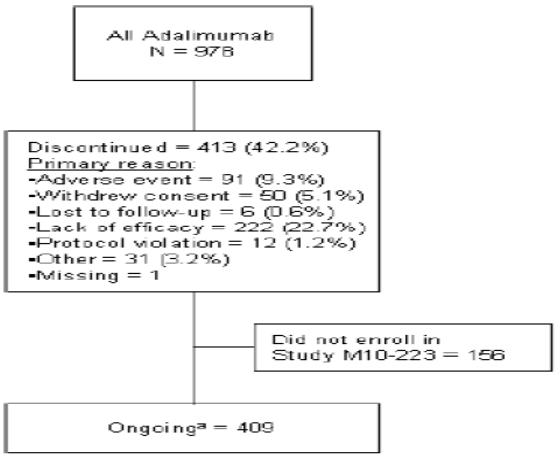

Figure 4 Disposition of patients (all adalimumab analysis set)

Baseline data

There were no major differences in baseline demographic characteristics of patients included in this study as compared to the 2 previous, except for a reduction in numbers of patients <40 years. The

baseline disease activity was lower than the moderate to severe disease activity (mayo score of 6 to 12) that was required for inclusion into studies M06-826 and M06-827.

Outcomes and estimation

Results of the partial Mayo score is shown in the table below.

Table 31 Partial Mayo scores over time, LOCF (ITT-1)

	Adalimumab 40 mg eow/ew N = 498		
Time Point	n	Mean ± SD	Median
Week 0 (Baseline)	493	2.5 ± 1.99	2.0
Week 2	466	2.3 ± 2.06	2.0
Week 4	460	2.4 ± 2.06	2.0
Week 8	441	2.3 ± 2.04	2.0
Week 12	416	2.3 ± 2.09	2.0
Week 24	348	2.3 ± 2.0	2.0
Week 36	281	2.3 ± 2.15	2.0
Week 48	183	2.3 ± 2.26	2.0
Week 60	130	2.5 ± 2.50	2.0

eow = every other week; ew = every week; ITT = intent-to-treat; LOCF = last observation carried forward
Notes: At Weeks 2 through 60, only subjects with both Baseline and Visit Values are shown. The observation period stopped on 31 December 2009. No data were carried forward beyond this point. Data after Week 60 are not shown, because less than 10% of subjects had reached a visit later than Week 60 as of the cut-off date.

Mean partial Mayo score at baseline (mean score of 2.5) was improved compared with baseline of the lead-in Studies M06-826 and M06-827 (mean scores of 6.4 and 6.5, respectively). This improved mean partial Mayo score was generally maintained from baseline to Week 60 with only slight fluctuations over time, while median partial Mayo scores remained stable through Week 60. Mean and median Mayo scores were low at Baseline of Study M06-223 compared to the moderate to severe disease activity (Mayo score of 6 to 12) required for entry into Study M06-826 and Study M06-827, and these scores were maintained from Baseline to Week 48.

A total of 42/498 subjects (8.4%) required dose escalation from 40 mg eow to 40 mg ew. Partial Mayo scores decreased by >40% among subjects in the ITT-1 analysis set who switched from eow dosing to ew dosing. Five patients underwent colectomies (ITT-1). Endoscopy subscores were maintained through week 48 (mean score 1.0).

Analysis performed across trials (pooled analyses)

Subjects undergoing colectomies

An analysis has been conducted to evaluate subject outcomes with respect to colectomy. All colectomies were performed during the follow-up period after the last dose of the study drug. None of the patients in studies M06-826 and M06-827 that underwent colectomies were enrolled in study M10-223. Although the difference did not reach statistical significance due to the low event rates, the incidence rate of colectomies was numerically lower, at a risk reduction of 22%, in the adalimumab treatment group compared with placebo.

Table 32 Analysis of incidence rates of colectomies in Study M06-826 and M06-827

	Events/PYs (E/100 PY)[a]			
Outcome	Placebo N = 468	Adalimumab N = 471	Relative Risk Ratio[b] (95% CI)	*P* value[c]
Colectomy	10/223 (4.5)	14/399 (3.5)	1.3 (0.6, 2.9)	0.554

PYs = person-years at risk; a. The first occurrence (i.e., incidence) of colectomy is included in the analysis; b. Relative risk of placebo versus adalimumab; c. *P* value based on Z score.

Efficacy analyses for escalation to weekly dosing of adalimumab

Dose escalation from adalimumab 40 mg eow to adalimumab 40 ew was permitted in these studies if a subject experienced disease flare. A total of 354/978 (38.2%) subjects in the all adalimumab analysis Set required dose escalation to adalimumab 40 mg weekly over the course of Studies M06-826, M06-827, or M10-223.

The proportion of subjects achieving clinical remission or clinical response per Mayo score or clinical remission or response per partial Mayo score after dose escalation increased continuously through 52 weeks of exposure to adalimumab 40 mg and was maintained thereafter. Based on the LOCF analysis, 15.7% of subjects were in clinical remission per Mayo score and 34.2% of subjects had achieved clinical response per Mayo score after 52 weeks of weekly adalimumab treatment, rates that were maintained over time through 100 weeks of weekly dosing (16.0% and 33.1%, respectively). Similar findings were observed for the rates of clinical remission and clinical response per partial Mayo score following dose escalation. Among subjects who required dose escalation to adalimumab 40 mg weekly, a mean decrease in Mayo score from Baseline was observed 12 weeks after dose escalation (–0.7 ± 3.38), which improved through 52 weeks of ew dosing (–1.8 ± 3.58) and was maintained over time through 100 weeks of weekly therapy (–1.8 ± 3.60) .

These results according to the MAH support increasing the adalimumab dosing from 40 mg eow to 40 mg ew in those subjects who do not achieve or lose sufficient response on the adalimumab 40 mg eow regimen.

Discussion on clinical efficacy

The clinical development program for adalimumab in subjects with moderately to severely active UC (defined as a Mayo of 6 to 12 points with endoscopy subscore of 2 to 3 points) included a pivotal induction study (M06-826), a pivotal maintenance study (M06-827), and a supportive long-term OL extension study (M10-223). Both pivotal studies were randomized, double-blind, placebo-controlled studies. Study M10-223 was ongoing at the time of submission of this application. A data cut-off of 31 December 2009 was used for this submission. Data from these studies form the basis for all efficacy data to support the claimed indication. This program is in line with the guideline on the development of new medicinal products for the treatment of ulcerative colitis which recommends studying induction of remission and prevention of relapse in separate randomised, double-blind, placebo-controlled and/or active comparator phase III trials (CHMP/EWP/18463/2006).

Study M06-826

Study M06-826 compared the efficacy and safety of adalimumab 160/80/40 (160 mg at Week 0, 80 mg at Week 2, and 40 mg eow thereafter) and adalimumab 80/40 (80 mg at Week 0 and 40 mg eow thereafter) to placebo and consisted of an 8-week double-blind placebo-controlled period followed by an OL period through 52 weeks. The placebo controlled study design is appropriate and according to the guideline. The inclusion and exclusion criteria as well as the primary (remission at week 8) and secondary endpoints are also considered adequate and in line with the guideline.

A statistically significantly higher percentage of subjects in the adalimumab 160/80/40 mg treatment group compared with placebo achieved clinical remission per Mayo score at Week 8 (18.5% versus 9.2%; P=0.031). Although there was a statistically significant difference between the effect of adalimumab (160/80/40 dose) and placebo treatment on the primary efficacy endpoint (proportion of patients in clinical remission at week 8), the overall difference was <10 % irrespective of analysis set (9.2% placebo vs 18.5% adalimumab 160/80/40 mg, p=0.031). The results of study M06-826 for

induction of clinical remission therefore showed a limited treatment effect of adalimumab. The effect of the lower induction dose 80/40 mg was similar to that of placebo (9.2% placebo vs 10.0% adalimumab 80/40 mg). The difference was not statistically significant.

Results of the secondary efficacy endpoints also showed modest treatment effect. For instance, clinical response at week 8 did not meet the criteria for statistical significance (44.6% for placebo compared with 54.6% for adalimumab 160/80/40 mg) in the ITT-A3 population. In the adalimumab 160/80/40 treatment group a statistically significant greater proportion of subjects met the endpoints at Week 8 only for RBS ≤ 1 (P = 0.038) and PGA subscore ≤ 1 (P = 0.035) but all other secondary endpoints did not meet statistical significance. Since the first ranked secondary endpoint failed to reach statistical significance the p-values of all the following ranked secondary endpoints should be considered only as descriptive. Secondary endpoints data for the ITT-E population showed similar results i.e. limited but consistent effect of the treatment on secondary endpoints. Overall a consistency across the results was observed through the secondary endpoints although statistical significance was not achieved for all of them.

Concerning the open-label maintenance period, of patients randomized to the 160/80/40 mg, 80/40 mg and placebo group there were 23, 30 and 31% respectively, that required dose escalation. At week 52, approximately one fourth (n=139, 24%, ITT-E, NRI) of the actively-treated patients were in remission as per Mayo score. Additional endpoints, including quality-of-life questionnaires, provided supportive evidence for the superiority of the adalimumab 160/80/40 treatment group compared with placebo at Week 8 (mean change from Baseline in IBDQ score 35.9 versus 26.6; mean change from baseline in SF-36 physical component score 6.53 versus 3.78; mean change from baseline in SF-36 mental component score 7.62 versus 5.79). Although the clinical relevance of these observations should be taken with caution due to the open-label design of this part of the study they provide supportive evidence of efficacy of the adalimumab 160/80/40 treatment group.

Study M06-827

Study M06-827 compared the efficacy and safety of adalimumab 160/80/40 (160 mg at Week 0, 80 mg at Week 2, and 40 mg eow thereafter) to placebo and consisted of a 52-week double-blind placebo-controlled period.

The two ranked co-primary endpoints of the study M06-827 were remission per Mayo score at week 8 and 52. The CHMP noted that the primary efficacy parameter should have been the proportion of patients maintaining remission throughout the period as per the guideline in force. The MAH clarified that the guideline was not in effect at the time of study initiation. As specified in the statistical plan, the success of study M06-827 was dependent on the achievement of both ranked co-primary endpoints as well as the first ranked secondary endpoint. The first ranked secondary endpoint of sustained clinical remission at both Week 8 and 52 should therefore be viewed in conjunction with the 2 co-primary endpoints which demonstrates both that remission is present at Week 52 and that it is maintained from Week 8 through Week 52. This was accepted by the CHMP.

The efficacy result of study M06-827 showed a statistically significantly greater proportion of patients in the adalimumab group in clinical remission per Mayo score at Week 8 and Week 52 compared to the placebo group (16.5% vs 9.3% and 17.3% vs 8.5% respectively). At week 8, 41 patients out of 248 were in remission. At week 52, 43 patients (17.3%) were in remission as compared to 139 patients (24%) after open-label treatment in study M06-826. Overall approximately 17% of adalimumab treated patients achieved remission at week 8 and at week 52. Of the 41 patients who achieved remission at week 8, 21 patients in the adalimumab group (8.5 %) maintained a sustained remission (first ranked secondary endpoint) up to week 52 compared with 4.1% for the placebo group, the

difference with placebo accounting for less than 5%. Therefore approximately half of the patients that achieved remission at week 8 maintain this remission at week 52. A gain of less than 10% (7.2% and 8.8%) over placebo was achieved in the remission per Mayo score at Week 8 and 52 respectively in patients treated with adalimumab. Importantly, when patients achieving sustained remission per Mayo score both at Week 8 and Week 52 are considered, the gain of adalimumab over placebo was 4.4 % (p=0.047). Overall, the percentage of patients that achieved and maintained clinical remission is modest.

The primary efficacy endpoints were supported by the results of the first 8 ranked secondary endpoints. Statistically significant differences between active and placebo treatment were demonstrated although the difference in actual numbers of patients between the groups was limited. The percentage of patients in clinical response week 8 was 34.6% for placebo and 50.4% for adalimumab 160/80/40 mg (16% observed difference), and week 52 was 18.3% for placebo and 30.2% for adalimumab 160/80/40 mg (11.9% observed difference). Since the 9th ranked secondary endpoint failed to reach statistical significance, the other following secondary p-values should be considered only as descriptive. Nevertheless they provided consistent supportive evidence of efficacy of the adalimumab 160/80/40 treatment group.

Results in study M06-827 were stratified by presence or absence of previous treatment with other anti-TNF agents. For anti-TNF naïve patients, the remission results were statistically significant at week 8 and 52, with observed difference of 10.3% and 9.6% respectively. For anti-TNF experienced subjects, the difference is limited and statistically non-significant i.e. 2.3% and 7.2 % more subjects reached remission at weeks 8 and 52 respectively. For sustained remission, results were non-significant in these subgroups (observed difference 4.5% for naïve and 4% for experienced). Based on these data it is uncertain whether prior treatment with anti-TNF agent could decrease the efficacy of subsequent adalimumab treatment.

According to the guideline CHMP/EWP/18463/2006, the study population should be defined "in terms of severity and anatomical extent of the disease." The anatomical extent of the disease was defined in this application by three categories: pancolitis, descending colon, and “other”. The MAH clarified that of 120 patients with a UC localization of "other" in both studies, only 5 subjects did not have sufficient information to confirm presence of the requested UC localization while 115 subjects (95.8%) definitely met inclusion criteria and could have been classified among "descending colon" or "pancolitis.

An analysis of the percentage of patients who acquired remission as per Mayo score and maintained it up to week 52 was performed by stratifying data according to the anatomical extent of the disease: pancolitis, descending colon and other. The data presented support that adalimumab effect in patients with pancolitis is comparable to the global population studied in M06-827 (observed differences for remission weeks 8 and 52, 10-12%). The MAH also showed that there is no correlation between disease severity and anatomical extent of the disease. Data showed that clinical remission at week 52 was achieved by 14.2% of patients with pancolitis and by 20.3% of patients with no pancolitis. The same pattern, of a higher remission rate in patients with no pancolitis, was seen in the placebo subgroups (5 % and 11.9%, for those with pancolitis and no pancolitis, respectively). The observed difference between active and placebo in these two subgroups was closely similar (9.2 % and 8.4 %, respectively). These results may suggest that, in the remission setting, patients with a partial anatomical extent of the disease may benefit more from the treatment than those with pancolitis.

Because maintenance of clinical remission without corticosteroids is desired with UC, subjects who were responders at or after Week 8 were to be permitted to taper corticosteroids. Steroid-free remission was evaluated at Week 32 and Week 52. At week 32 a positive trend in the corticosteroids discontinuation for adalimumab versus placebo-treated patients was observed, regardless of whether they were steroid-free for more than or less than 90 days. However, statistical significance was not

achieved. In patients achieving clinical remission at Week 52, the difference between adalimumab and placebo patients discontinuing corticosteroids was statistically significant (p=0.035).

In response to questions from the CHMP regarding the patient population included in the pivotal studies, the MAH presented data showing that reasons for discontinuing prior UC therapy was inadequate response or intolerance/medical complication rather than suboptimal treatment. Concerns on the accuracy of the diagnosis, as suggested by uncertainties on the number of biopsy per patient, lower number of dysplastic lesions than that expected in the UC target population, absence of focus on the different spread of the disease in the inclusion criteria were also addressed by the MAH. The MAH has presented data regarding baseline / prior to treatment, together with further explanation regarding dysplasia screen, which respond to the issues raised. Based on these clarifications, the patient population included was considered appropriate by the CHMP.

There were no major apparent differences of the study populations other than the inclusion criteria concerning anti-TNF treatment in the 2 pivotal studies. Two hundred patients included in study M06-827 had a history of previous anti-TNF treatment. In general anti-TNF treatment is a second-line alternative and it would therefore be expected that patients in study M06-827 would have more severe disease. However, a larger portion of patients in study M06-826 had pancolitis and severe disease measured by endoscopy subscore at baseline. There appeared to be a lower response rate in the anti-TNF subgroup as discussed above.

The MAH has presented data on colectomies in studies M06-826 and M06-827;38 colectomies in total appear to have been undertaken across all data sets . For the data presented, it is acknowledged that the rate of colectomies was low during the studies with a lower rate in actively treated patients compared with placebo treated. However, due to the low numbers, no definite conclusion can be drawn.

The MAH discussed the high rate of discontinuation due to lack of efficacy or UC worsening that was initially reported >33% in the adalimumab and >30% in the placebo treatment groups. An updated analysis regarding the discontinuation rate was presented to include those patients that had escaped to open label treatment. In both Studies M06-826 and M06-827, at week 8 the overall discontinuation rate was <10 % in all treatment group (except for placebo in M06-827 which was almost 15%) and at week 52 was 47% in the placebo treatment group and 38% at week 52 in the adalimumab treatment group. In M06-826 the discontinuation rate due to lack of efficacy was at week 8: 3.2% (placebo), 3.8% (adalimumab 80/40), 1.5% (adalimumab 160/80/40) in the ITT-E set. In M06-827 the discontinuation rate due to lack of efficacy was at week 8: 7.6% (placebo), 5.6% (adalimumab). In Study M06-827, the exposure-adjusted rate of discontinuation due to lack of efficacy or UC worsening while on DB treatment was higher in the placebo than in the adalimumab treatment group (1.48 versus 1.09 E/100 PY).

The MAH presented an integrated analysis of the double blinded data at Week 8 from both studies for the induction of remission. For the maintenance of remission the integrated analysis combined the 52-week double blinded data from Study M06-827 with the 52-week double blinded (up to Week 8) + OL (after Week 8) data from Study M06-826. As stated in the relevant guideline, the induction of remission and prevention of relapse should be assessed in two separate phase III trials. The integration of data from the two trials can only be regarded as descriptive. Overall, the MAH analyzed the association between adalimumab higher induction dose (160mg, 80mg followed by 40 mg eow) and lower induction dose (80 mg followed by 40 mg eow) with the percentage of patients who needed to switch to adalimumab 40 mg every week. Patients receiving the higher induction dose seem to be less prone to increase the adalimumab dose according to a weekly schedule.

Although statistical significance was demonstrated on the primary endpoints for both pivotal trials, the CHMP expressed concerns regarding the modest effect size over placebo observed in the both studies.

To address this concern, the MAH submitted updated analyses mainly focused on efficacy data on the subgroup of early responders.

Based on this analysis the MAH addressed for how long it may be meaningful to continue treatment in a patient not responding. Analyses conducted for Study M06-827 indicated that among patients who had not achieved clinical remission at Week 8, 22/207 (10.6%) of subjects who were randomized to receive adalimumab achieved clinical remission at Week 52, as compared to 11/223 (4.9%) of subjects who were randomized to receive placebo. The MAH therefore proposed to add the recommendation in section 4.2 of the SmPC that continued therapy is not recommended in patients not responding within 2-8 weeks of treatment as available data suggest that clinical response is usually achieved within this time period.

In this set of new analyses, the MAH selected "early" responders and long-term outcome in this subgroup has been compared with that in the placebo group. The selection of a subgroup based on early response, means that there are no longer comparisons of randomised groups. Therefore, these analyses can only be regarded as supportive. Nevertheless, this analysis in early responder suggests that patients demonstrating early responses benefit the most from adalimumab treatment. In order to ensure that patients not responding will not be put on maintenance treatment, discontinuation of treatment in non-responders within 2-8 weeks is agreed by the CHMP.

Study M10-223

Results from study M10-223 (open-label extension study) indicate that patients included benefited from adalimumab treatment. Disease activity measured with Mayo scores was reduced at baseline and remained relatively stable up to week 60 in a subset of patients, indicating that the therapy was effective in a selected population of responders. However, there was also a large proportion of patients who did not benefit from the treatment and discontinued the study due to lack of efficacy (23%). Overall, due to the open-label design of the study the clinical relevance of the observed effect is difficult to ascertain.

Conclusion on clinical efficacy

The UC clinical program showed that induction of clinical remission at week 8 (per Mayo score) was statistically significantly different between the adalimumab (160/80/40 mg) and placebo. The CHMP noted that the overall difference compared to placebo was <10 % irrespective of analysis set. The effect of the lower induction dose 80/40 mg was similar to that of placebo. A consistency across the beneficial effect was observed through the secondary endpoints although statistical significance was not achieved for all of them.

Concerning maintenance of remission, statistically significant differences as compared to placebo were demonstrated for the ranked primary endpoints as well as for the first ranked secondary endpoint (sustained remission weeks 8 and 52). As for the induction treatment the CHMP noted that the actual number of patients in remission was limited. A gain of less than 10% (8.8%) over placebo was achieved in the remission at Week 52. When patients achieving sustained remission both at Week 8 and Week 52 are considered, the gain of adalimumab over placebo was 4.4 % (p=0.047). Thus, the percentage of patients that achieved and maintained clinical remission is modest. The observed beneficial effect was supported by a statistically significant difference over placebo treatment for the first 8 ranked secondary endpoints. Consistency across the result of all other endpoints was seen although could not be considered statistically significant since the 9th secondary endpoint missed statistical significance. Steroid-free remission was evaluated at Week 32 and Week 52. At week 32 a positive trend for adalimumab versus placebo-treated patients was observed, but statistical

significance was not achieved. At Week 52, the difference between adalimumab and placebo patients discontinuing corticosteroids was statistically significant.

Concerning Study M10-223, clinical remission per partial Mayo scores was increasing over time. However, these observations are difficult to ascertain due to the open nature of this follow up study.

The MAH submitted several additional analyses to address the questions raised by the CHMP on the modest effect size of the observed clinical benefit. The MAH's response was mainly focused on efficacy data on the subgroup of early responders (responders per PM and TM score at W2 and W 4, up to W 8). These data were considered of interest even though it was acknowledged that such analysis was not a predefined analysis in the original statistical plan and lacks a randomized comparison.

Overall the CHMP acknowledges that there is a benefit of adalimumab in the claimed indication as shown by the statistically significant results observed over placebo for both induction and maintenance of remission. Based on the data presented this beneficial effect was considered modest compared to placebo, however, taking all the data presented together there was a recognised consistency toward a beneficial effect across the results of all endpoints in the UC clinical program. The additional analyses on the early responders can only be regarded as descriptive but overall provide further insight in the therapeutic effect of adalimumab in patients with UC. Data showed that patients demonstrating early responses benefit the most from adalimumab treatment. Therefore it is considered appropriate that early responder patients who have shown inadequate response/intolerance to conventional UC therapies including corticosteroids or immunomodulators should be given the option of adalimumab maintenance treatment. In patients not responding within 2-8 weeks it is considered appropriate by the CHMP that adalimumab therapy should not be continued in order to ensure maintenance treatment only in patients with highest expected benefit.

1.2.3. Clinical safety

The safety of adalimumab in UC was determined using data from 3 clinical studies: 2 completed controlled Phase 3 studies (Study M06-826 and Study M06-827) and 1 ongoing open-label extension study (Study M10-223) with a cut-off date of 31 December 2009. These 3 studies were conducted in adult subjects with moderately to severely active UC, defined as a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite treatment with oral corticosteroids, immunosuppressants or both (or having failed to respond to or been unable to tolerate these treatments), and confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy. Two hundred patients included in study M06-827 had a history of previous anti-TNF treatment. Safety of adalimumab throughout the studies was monitored and assessed by adverse events (AEs), physical examination, laboratory data, and vital signs.

Patient exposure

Four sets of data have been analysed:

- Induction set (n=1093), all patients receiving at least one dose of placebo or adalimumab between week 0 and 8.
- Maintenance set (n=457), patients that received at least one dose of placebo or adalimumab between week 8 and 52 in study M06-827.
- All adalimumab set (n=995), all patients that received at least one dose of adalimumab.
- Placebo set (n=483) patients receiving at least one dose of placebo.

A total of 1,093 subjects received study drug (adalimumab or placebo) in the UC clinical program. This includes all 576 randomized subjects in Study M06-826 and 517 of the 518 randomized subjects in Study M06-827.

Table 33 Extent of study drug exposure (induction, maintenance and all adalimumab sets)

	Induction Set		Maintenance Set		All Adalimumab Set
	Placebo N = 483	Adalimumab N = 610	Placebo N = 223	Adalimumab N = 234	Adalimumab N = 995
Duration of treatment (days)					
Mean ± SD	52.5 ± 9.52	53.3 ± 7.90	134.2 ± 118.39	167.6 ± 120.77	382.1 ± 248.02
Median (range)	55.0 (14 – 68)	55.0 (14 – 68)	69.0 (14 – 323)	142.0 (14 – 315)	364.0 (8 – 1122)
Total number of injections					
Mean ± SD	7.7 ± 0.84	7.8 ± 0.68	9.6 ± 8.41	12.0 ± 8.62	35.6 ± 23.91
Median (range)	8.0 (4 – 8)	8.0 (3 – 8)	5.0 (1 – 22)	10.0 (1 – 22)	31.0 (1 – 147)
Average monthly number of injections					
Mean ± SD	4.58 ± 0.887	4.50 ± 0.701	2.16 ± 0.145	2.16 ± 0.115	3.06 ± 1.113
Median (range)	4.36 (3.3 – 8.6)	4.36 (3.2 – 8.6)	2.15 (1.2 – 2.9)	2.15 (1.3 – 2.7)	2.57 (1.6 – 8.6)
Patient-years	69.4	89.0	81.9	107.4	1041.0

a. The All Adalimumab Set includes subjects randomized to adalimumab in Study M06-826 or Study M06-827 (N = 610), as well as those subjects randomized to placebo in Study M06-826 or M06-827 who switched to open-label adalimumab treatment in Studies M06-826, M06-827, or M10-223 (N = 385).

Overall subject exposure to adalimumab in Studies M06-826, M06-827, and M10-223 (all adalimumab set) as of the 31 December 2009 data cut-off date for Study M10-223 is presented below.

Table 34 Overall adalimumab exposure over time (all adalimumab set)

Duration of Exposure to Adalimumab[a]	Number (%) of Subjects
All subjects	995 (100)
> 6 months	745 (74.9)
> 12 months	538 (54.1)
> 18 months	263 (26.4)
> 24 months	113 (11.4)
> 30 months	24 (2.4)
> 36 months	4 (0.4)

a. As of 31 December 2009. Note: Includes Studies M06-826, M06-827, and M10-223.

Adverse events

Table 35 Overview of treatment-emergent adverse events (induction set)

	Number (%) of Subjects			
Subjects with:	Placebo N = 483	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 480	Total Adalimumab N = 610
Any AE	282 (58.4)	70 (53.8)	265 (55.2)	335 (54.9)
Any AE at least possibly drug related[a]	112 (23.2)	28 (21.5)	110 (22.9)	138 (22.6)
Any severe AE	41 (8.5)	9 (6.9)	35 (7.3)	44 (7.2)
Any serious AE	40 (8.3)	5 (3.8)	25 (5.2)	30 (4.9)
Any serious AE at least possibly drug related[a]	7 (1.4)	1 (0.8)	5 (1.0)	6 (1.0)
Any AE leading to study drug discontinuation	32 (6.6)	8 (6.2)	23 (4.8)	31 (5.1)
Any AE at least possibly drug related leading to discontinuation	7 (1.4)	3 (2.3)	5 (1.0)	8 (1.3)
Any AEs leading to death	0	0	0	0
Any allergic reaction	1 (0.2)	0	4 (0.8)	4 (0.7)
Any injection site reaction	15 (3.1)	7 (5.4)	30 (6.3)[b]	37 (6.1)
Any opportunistic infection (excluding TB)	2 (0.4)	0	5 (1.0)	5 (0.8)
Any congestive heart failure	0	0	0	0
Any demyelinating disease	0	0	0	0
Any lupus-like syndrome	0	0	0	0
Any malignancy	2 (0.4)	0	1 (0.2)	1 (0.2)
Any lymphoma	0	0	0	0
Any NMSC	1 (0.2)	0	1 (0.2)	1 (0.2)
Any malignancy excluding lymphoma and NMSC	1 (0.2)	0	0	0
Any malignancy including lymphoma, excluding NMSC	1 (0.2)	0	0	0
Any infectious AE	89 (18.4)	26 (20.0)	82 (17.1)	108 (17.7)
Any serious infection	7 (1.4)	2 (1.5)	3 (0.6)	5 (0.8)
Any hematological event	1 (0.2)	2 (1.5)	6 (1.3)	8 (1.3)
Any hepatic event	3 (0.6)	1 (0.8)	10 (2.1)	11 (1.8)
Any vasculitis event	0	0	0	0
Any diverticulitis event	0	0	0	0
Any intestinal perforation event	1 (0.2)	0	0	0
Any interstitial lung disease	0	0	0	0
Any Stevens-Johnson syndrome	0	0	0	0
Any pancreatitis event	0	0	0	0
Any UC worsening/flare	59 (12.2)	10 (7.7)	35 (7.3)[c]	45 (7.4)

AE = adverse event; eow = every other week; NMSC = non-melanoma skin cancer; TB = tuberculosis; UC = ulcerative colitis a. As assessed by investigator. b. *P* = 0.022 for comparison between placebo and adalimumab 160/80/40 using Fisher's exact test. c. *P* = 0.012 for comparison between placebo and adalimumab 160/80/40 using Fisher's exact test.

The percentages of subjects who experienced TEAEs ranged from 54% to 58% across treatment groups in the induction set. Injection site reactions were reported by a statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group compared with the placebo group (6.3% versus 3.1%; *P*=0.022), and UC worsening/flare reported by a statistically significantly smaller proportion of subjects in the adalimumab 160/80/40 group compared with the placebo group (7.3% versus 12.2%; *P*=0.012). No other differences in AE categories were found to be statistically significant among treatment groups in the induction set. In both, the placebo and adalimumab 160/80/40 treatment groups, a greater proportion of prior anti-TNF users had TEAEs compared with subjects who were naïve to anti-TNF agents (not reported in the table above).

Table 36 Overview of treatment-emergent adverse events (maintenance set)

	Placebo N = 223 PY = 81.91		Adalimumab 160/80/40 N = 234 PY = 107.36	
Subjects with:	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**
Any AE	152 (68.2)	569 (694.66)	172 (73.5)	706 (657.60)
Any AE at least possibly drug related[a]	48 (21.5)	98 (119.64)	72 (30.8)[b]	168 (156.48)
Any severe AE	16 (7.2)	24 (29.30)	24 (10.3)	29 (27.01)
Any serious AE	11 (4.9)	14 (17.09)	15 (6.4)	25 (23.29)
Any serious AE at least possibly drug related[a]	2 (0.9)	3 (3.66)	1 (0.4)	1 (0.93)
Any AE leading to study drug discontinuation	14 (6.3)	20 (24.42)	12 (5.1)	13 (12.11)
Any AE at least possibly drug related leading to discontinuation	7 (3.1)	13 (15.87)	2 (0.9)	2 (1.86)
Any AEs leading to death	0	0	0	0
Any allergic reaction	1 (0.4)	1 (1.22)	2 (0.9)	2 (1.86)
Any injection site reaction	3 (1.3)	5 (6.10)	16 (6.8)[c]	34 (31.67)
Any opportunistic infection (excluding TB)	1 (0.4)	1 (1.22)	2 (0.9)	2 (1.86)
Any congestive heart failure	0	0	1 (0.4)	1 (0.93)
Any demyelinating disease	0	0	0	0
Any lupus-like syndrome	0	0	1 (0.4)	1 (0.93)
Any malignancy	0	0	1 (0.4)	1 (0.93)
Any lymphoma	0	0	0	0
Any NMSC	0	0	0	0
Any malignancy excluding lymphoma and NMSC	0	0	1 (0.4)	1 (0.93)
Any malignancy including lymphoma, excluding NMSC	0	0	1 (0.4)	1 (0.93)
Any infectious AE	68 (30.5)	111 (135.51)	89 (38.0)	154 (143.44)
Any serious infection	1 (0.4)	2 (2.44)	1 (0.4)	1 (0.93)
Any hematological event	0	0	1 (0.4)	1 (0.93)
Any hepatic event	5 (2.2)	8 (9.77)	5 (2.1)	8 (7.45)
Any vasculitis event	0	0	0	0
Any diverticulitis event	0	0	0	0
Any intestinal perforation event	0	0	0	0
Any interstitial lung disease	0	0	0	0
Any Stevens-Johnson syndrome	0	0	0	0
Any pancreatitis event	1 (0.4)	1 (1.22)	0	0
Any UC worsening/flare	37 (16.6)	41 (50.05)	39 (16.7)	41 (38.19)

AE = adverse event; E/100 PY = events per 100 patient-years; NMSC = non-melanoma skin cancer; PY = patient-year; TB = tuberculosis. a. As assessed by investigator. b. *P* = 0.026 for comparison with placebo using Fisher's exact test. c. *P* = 0.004 for comparison with placebo using Fisher's exact test.

With the longer duration of treatment in the maintenance set, greater proportions of subjects in both the placebo and adalimumab groups experienced TEAEs (68.2% and 73.5%, respectively). Compared to the placebo group, a statistically significantly greater proportion of subjects in the adalimumab 160/80/40 treatment group experienced related AEs (30.8% versus 21.5%; *P*=0.026) and injection site reactions (6.8% versus 1.3%; *P*=0.004). No other differences in any AE categories were found to be statistically significant between treatment groups in the maintenance set. Among prior anti-TNF users in the maintenance set, the proportions reporting TEAEs were similar between the placebo and adalimumab treatment groups (67.9% and 68.2%). Among subjects who were naïve to anti-TNF agents, TEAEs were reported by a smaller proportion of placebo-treated subjects compared to adalimumab-treated subjects (68.3% versus 76.5%).

Table 37 Overview of treatment-emergent adverse events (all adalimumab set)

	Adalimumab 40 mg ew N = 360 PY = 370.57		Adalimumab 40 mg eow N = 635 PY = 670.45		All Adalimumab N = 995 PY = 1041.02	
Subjects with:	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**
Any AE	310 (86.1)	2262 (610.41)	496 (78.1)	2983 (444.92)	806 (81.0)	5245 (503.83)
Any AE at least possibly drug related[a]	165 (45.8)	568 (153.28)	254 (40.0)	725 (108.14)	419 (42.1)	1293 (124.20)
Any severe AE	83 (23.1)	148 (39.94)	140 (22.0)	214 (31.92)	223 (22.4)	362 (34.77)
Any serious AE	66 (18.3)	94 (25.37)	115 (18.1)	151 (22.52)	181 (18.2)	245 (23.53)
Any serious AE at least possibly drug related[a]	14 (3.9)	14 (3.78)	26 (4.1)	27 (4.03)	40 (4.0)	41 (3.94)
Any AE leading to study drug discontinuation	56 (15.6)	65 (17.54)	94 (14.8)	108 (16.11)	150 (15.1)	173 (16.62)
Any AE at least possibly drug related leading to discontinuation	13 (3.6)	13 (3.51)	31 (4.9)	36 (5.37)	44 (4.4)	49 (4.71)
Any AEs leading to death	1 (0.3)	1 (0.27)	0	0	1 (0.1)	1 (0.10)
Any allergic reaction	5 (1.4)	5 (1.35)	8 (1.3)	9 (1.34)	13 (1.3)	14 (1.34)
Any injection site reaction	36 (10.0)	71 (19.16)	66 (10.4)	156 (23.27)	102 (10.3)	227 (21.81)
Any opportunistic infection (excluding TB)	10 (2.8)	11 (2.97)	11 (1.7)	14 (2.09)	21 (2.1)	25 (2.40)
Any congestive heart failure	1 (0.3)	1 (0.27)	1 (0.2)	1 (0.15)	2 (0.2)	2 (0.19)
Any demyelinating disease	0	0	1 (0.2)	1 (0.15)	1 (0.1)	1 (0.10)
Any lupus-like syndrome	1 (0.3)	1 (0.27)	1 (0.2)	1 (0.15)	2 (0.2)	2 (0.19)
Any malignancy	1 (0.3)	1 (0.27)	9 (1.4)	10 (1.49)	10 (1.0)	11 (1.06)
Any lymphoma	1 (0.3)	1 (0.27)	2 (0.3)	2 (0.30)	3 (0.3)	3 (0.29)
Any NMSC	0	0	2 (0.3)	2 (0.30)	2 (0.2)	2 (0.19)
Any malignancy excluding lymphoma and NMSC	0	0	5 (0.8)	6 (0.89)	5 (0.5)	6 (0.58)
Any malignancy including lymphoma, excluding NMSC	1 (0.3)	1 (0.27)	7 (1.1)	8 (1.19)	8 (0.8)	9 (0.86)
Any infectious AE	180 (50.0)	464 (125.21)	270 (42.5)	558 (83.23)	450 (45.2)	1022 (98.17)
Any serious infection	13 (3.6)	14 (3.78)	27 (4.3)	29 (4.33)	40 (4.0)	43 (4.13)
Any hematological event	6 (1.7)	7 (1.89)	14 (2.2)	15 (2.24)	20 (2.0)	22 (2.11)
Any hepatic event	11 (3.1)	16 (4.32)	32 (5.0)	49 (7.31)	43 (4.3)	65 (6.24)
Any vasculitis event	0	0	0	0	0	0
Any diverticulitis event	2 (0.6)	3 (0.81)	1 (0.2)	1 (0.15)	3 (0.3)	4 (0.38)
Any intestinal perforation event	1 (0.3)	1 (0.27)	3 (0.5)	3 (0.45)	4 (0.4)	4 (0.38)
Any interstitial lung disease	0	0	0	0	0	0
Any Stevens-Johnson syndrome	0	0	0	0	0	0
Any pancreatitis event	0	0	1 (0.2)	1 (0.15)	1 (0.1)	1 (0.10)
Any UC worsening/flare	120 (33.3)	162 (43.72)	143 (22.5)	191 (28.49)	263 (26.4)	353 (33.91)
Death	1 (0.3)	1 (0.27)	0	0	1 (0.1)	1 (0.10)

AE = adverse event; ew = subjects who switched to every week dosing; eow = subjects who received treatment every other week only; E/100 PY = events per 100 patient-years; NMSC = non-melanoma skin cancer; PY = patient-years; TB = tuberculosis; UC = ulcerative colitis a. As assessed by investigator.

In the all adalimumab set, 81.0% of subjects reported TEAEs, with a higher percentage among subjects who dose escalated to the ew regimen compared with those who remained on the eow regimen (86.1% and 78.1%, respectively). Among subjects with prior anti-TNF agent experience, the proportions reporting TEAEs were similar between the 40 mg ew and 40 mg eow groups (89.9% and 86.0%, respectively). Among subjects who were naïve to anti-TNF agents, TEAEs were reported by a larger proportion of subjects who dose escalated to the ew regimen compared to those who remained on the eow regimen (85.1% versus 76.9%, respectively).

Overall, the majority of TEAEs were of mild or moderate severity. In the induction set, a slightly higher percentage of placebo-treated subjects (8.5%) reported severe TEAEs, mostly UC, as compared with adalimumab-treated subjects (7.2%). In the maintenance set, severe TEAEs were also reported by a greater proportion of adalimumab-treated subjects compared with placebo-treated subjects (10.3% versus 7.2%, respectively), although the incidence was higher in placebo-treated subjects (27.01 E/100 PYs versus 29.30 E/100 PYs, respectively). In the all adalimumab set, severe TEAEs were reported by 23.1% of subjects who dose escalated to 40 mg ew and 22.0% of subjects who remained on 40 mg eow.

The most frequently reported TEAE in all analysis sets was colitis ulcerative (range across treatment groups, 7.3% to 12.2% in the induction set; 16.6% to 16.7% in the maintenance set; and 26.4% in the all adalimumab set). The preferred term colitis ulcerative comprises the category of UC

worsening/flare, where it is discussed as an adverse event of special interest. Other commonly reported TEAEs (≥ 5% in any treatment group) in the induction set were nasopharyngitis (5.2% with any adalimumab versus 4.8% with placebo) and headache (4.8% and 8.7%, respectively), with additional common events in the maintenance set of abdominal pain (7.7% with any adalimumab and 5.4% with placebo), arthralgia (7.3% and 4.0%, respectively), and nausea (3.8% and 5.4%, respectively).

Other reported TEAEs (≥2% of subjects per treatment group) in the induction set were injection site pain (2.3%) in the adalimumab 160/80/40 treatment group, rash (3.1%) in the adalimumab 80/40 group, and headache (4.1%) and injection site pain (2.3%) in the placebo group. In the maintenance set it was: injection site erythema (3.0%), colitis ulcerative (2.6%), injection site reaction (2.6%), arthralgia (2.1%), and rash (2.1%) in the adalimumab 160/80/40 treatment group.

Injection site reactions were reported in a statistically significantly greater proportion of adalimumab 160/80/40-treated subjects compared with placebo during the induction period (6.3% versus 3.1%) as well as the maintenance period (6.8% versus 1.3%); however, none of these events was serious.

The incidence of AEs considered to be related to study drug was comparable between adalimumab and placebo groups during the induction period but was statistically significantly higher in the adalimumab 160/80/40 treatment group compared with placebo during the maintenance period.

Serious adverse events / deaths / other significant events

Serious adverse events

Serious AEs were reported by 3.8% to 8.3% of subjects across treatment groups in the induction and maintenance sets and by 18.2% of subjects in the all adalimumab set. A similar percentage of subjects who dose escalated to adalimumab 40 mg weekly experienced SAEs compared with subjects who remained on adalimumab 40 mg eow (18.3% versus 18.1%). The most frequently reported SAE in all analysis sets was ulcerative colitis (8.2%), followed by anemia (0.6%), appendicitis (0.6%), deep vein thrombosis [DVT] (0.5%), and pneumonia (0.4%). SAEs of abdominal abscess, abdominal pain, abortion induced, B-cell lymphoma, colitis, and inguinal hernia were reported by 3 subjects each (0.3%). All other SAEs were reported by 1 or 2 subjects only. Of the 5 subjects with SAEs of DVT, all had recent concomitant corticosteroids use, 1 had a history of DVT, and another had recent trauma and surgery of a thigh wound.

Table 38 Serious adverse events reported by 2 or more patients (all adalimumab set)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects Adalimumab 40 mg ew N = 360	Adalimumab 40 mg eow N = 635	All Adalimumab N = 995
Any SAE	66 (18.3)	115 (18.1)	181 (18.2)
Blood and lymphatic system disorders			
Anaemia	4 (1.1)	2 (0.3)	6 (0.6)
Cardiac disorders			
Coronary artery disease	1 (0.3)	1 (0.2)	2 (0.2)
Gastrointestinal disorders			
Abdominal pain	1 (0.3)	2 (0.3)	3 (0.3)
Colitis	2 (0.6)	1 (0.2)	3 (0.3)
Colitis ulcerative	34 (9.4)	48 (7.6)	82 (8.2)
Crohn's disease[a]	2 (0.6)	0	2 (0.2)
Inguinal hernia	2 (0.6)	1 (0.2)	3 (0.3)
Large intestine perforation	0	2 (0.3)	2 (0.2)
Peritonitis	0	2 (0.3)	2 (0.2)
Rectal haemorrhage	0	2 (0.3)	2 (0.2)
Small intestinal obstruction	1 (0.3)	1 (0.2)	2 (0.2)
Hepatobiliary disorders			
Cholelithiasis	1 (0.3)	1 (0.2)	2 (0.2)
Infections and infestations			
Abdominal abscess	0	3 (0.5)	3 (0.3)
Anal abscess	0	2 (0.3)	2 (0.2)
Appendicitis	2 (0.6)	4 (0.6)	6 (0.6)
Cytomegalovirus colitis	1 (0.3)	1 (0.2)	2 (0.2)
Herpes zoster	0	2 (0.3)	2 (0.2)
Lobar pneumonia	1 (0.3)	1 (0.2)	2 (0.2)
Perirectal abscess	1 (0.3)	1 (0.2)	2 (0.2)
Pneumonia	1 (0.3)	3 (0.5)	4 (0.4)
Respiratory tract infection	1 (0.3)	1 (0.2)	2 (0.2)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (0.6)	0	2 (0.2)
Osteoarthritis	0	2 (0.3)	2 (0.2)
Neoplasms benign, malignant and unspecified			
B-cell lymphoma	1 (0.3)	2 (0.3)	3 (0.3)
Renal and urinary disorders			
Nephrolithiasis	0	2 (0.3)	2 (0.2)
Renal failure acute	2 (0.6)	0	2 (0.2)
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	1 (0.3)	1 (0.2)	2 (0.2)
Surgical and medical procedures			
Abortion induced	0	3 (0.5)	3 (0.3)
Vascular disorders			
Deep vein thrombosis	3 (0.8)	2 (0.3)	5 (0.5)

a. Two subjects were diagnosed with Crohn's disease while on study. Both subjects had met the entrance criteria for ulcerative colitis.

Deaths

A 34-year-old male died during the study (9 days after the last dose of adalimumab). A few days before death, the patient had flu syndrome, cephalgia, myalgia and fever. The event was reported as death by cardio-respiratory arrest. The investigator assessed the event as possibly related to study drug. After autopsy the probable cause of death was shock associated with bilateral adrenal hemorrhage secondary to an infectious process (since the day before his death the subject had presented a picture of fever and muscle pain), whose etiology could not be determined.

Events of special interest

Infections

Infections were reported with a similar frequency in the induction set across the treatment group (18% for 80/40 dose, 20% for 160/80/40 and 17% for placebo), whereas the percentage was slightly higher in the 160/80/40 adalimumab (38%) vs placebo (30.5%) in the maintenance set. They were reported

in 45.2% of all patients (all adalimumab set). The majority of infections were nasopharyngitis and upper respiratory tract infections.

Among subjects who dose escalated to 40 mg ew, 55.7% of prior anti-TNF users and 48.4% of anti-TNF naïve subjects had infections whereas among subjects who remained at 40 mg eow, lower frequency were observed (46.5% prior anti-TNF users and 41.9% of those who were naïve to anti-TNF agents had infections).

Serious infections occurred in 40 patients [4%] (all adalimumab set). Twenty (50.0%) of these patients were on concomitant immunosuppressant at baseline and 23 (57.5%) were receiving corticosteroids. The most common infections were appendicitis (n=6), pneumonia (n=4, in addition there were 2 patients with lobar pneumonia and one patient had bacterial and one *Legionella* pneumonia), abdominal abscess (n=3), and anal abscess, cytomegalovirus colitis, herpes zoster, perirectal abscess and respiratory tract infection in 2 patients each. All other serious infections occurred in 1 subject only.

Twenty-one patients (2.1%) had an opportunistic infections (all adalimumab set). Of 21, 6 (28.6%) were receiving concomitant immunosuppressant at Baseline and 14 (66.7%) were receiving corticosteroids. Two subjects had SAEs of cytomegalovirus colitis; 1 was using concomitant prednisolone and AZA, and the other subject was receiving concomitant prednisolone and had also dose escalated to 40 mg ew adalimumab. All other opportunistic infections were candida infections: gastrointestinal candidiasis in 1 subject, esophageal candidiasis in 2 subjects, oral candidiasis in 12 subjects, and unspecified candidiasis in 6 subjects. There have been no reports of TB.

Malignancies

Malignancies occurred in 10 patients (1.0%) all adalimumab set. Two of the cases (squamous cell carcinoma and basal cell carcinoma) were not assessed as being related to the study drug and did not lead to discontinuation. The remaining 8 cases were reported as SAEs and the patients discontinued the study. The malignancies were B-cell lymphoma (n=3) and breast cancer, breast cancer *in situ*, gastric cancer, spindle cell carcinoma and malignant melanoma in one patient each.

The lymphomas were assessed as being related to the study drug nevertheless all 3 patients had confounding factors with history of previous AZA treatment and were smokers. Two of the patients had UC diagnosed at least 8 years earlier and the third patient was >70 years. All three patients received active treatment and concomitant immunomodulating therapy at baseline. According to investigators' assessments, the case of spindle cell sarcoma was considered not related to study drug, and the case of gastric cancer was considered probably not related to study drug. Colon cancer cases were not reported in the study.

Injection site reactions

Ten percent of the patients had injection site reactions (all adalimumab set). None of the reactions were serious although in 4 cases the event led to discontinuation of the study. One subject had a severe event of injection site pruritus, and 2 had severe events of injection site reaction; all other events were mild or moderate in severity.

Worsening of ulcerative colitis

In the induction set, UC worsening/flare was experienced by 12.2%, 7.7%, and 7.3% of subjects in the placebo, adalimumab 80/40, and adalimumab 160/80/40 groups, respectively; the difference between the placebo and adalimumab 160/80/40 group was statistically significant (P=0.012). In the

maintenance set, UC worsening/flare was experienced by 16.6% of subjects in the placebo group and 16.7% of subjects in the adalimumab 160/80/40 group. However, when using the events per 100 patient-years (E/100PYs) measure, the incidence rate was higher in placebo patients (50.1E/100PYs) compared to ADA patients (38.2E/100PYs). Higher proportions of subjects who were prior anti-TNF users had UC worsening/flare (21.4% in the placebo group and 18.8% in the adalimumab 160/80/40 group) compared with subjects who were anti-TNF naïve (13.7% in the placebo group and 15.4% in the adalimumab 160/80/40 group). Overall, 26.4% of subjects in the all adalimumab set had UC worsening/flare, with a higher percentage among subjects who dose escalated to 40 mg ew compared with those who received 40 mg eow (33.3% vs 22.5%). Higher proportions of subjects in the all adalimumab set who were prior anti-TNF users had UC worsening/flare compared with subjects who were anti-TNF naïve (35.8% versus 24.6%).

Congestive heart failure

In total there were 2 cases with congestive heart failures. Both of the cases were non-serious and considered to be unrelated. One patient that had a history of COPD and mitral valve prolapsed experienced right ventricular overload on day 73 of active treatment. The patient continued to receive active treatment. The second patient had a history of hypertension and asthma and had an event of pulmonary congestion on day 198 of treatment. The patient was lost to follow-up.

Demyelinating diseases

There was one case of leukoencephalopathy, reported as serious but mild in severity and possibly related to the study drug. The patient had a history of numbness of his soles of the feet and chronic inflammatory CNS disease, felt numbness in the legs 12 days after the last dose of adalimumab. The patient required hospitalization and improved on corticosteroid therapy. The causality assessment cannot be definitely established as the reported leukoencephalopathy but rather suggestive of multiple sclerosis; a separate autoimmune process but also possibly linked to adalimumab use.

Hepatic events

Hepatic events were reported in 43 (4.3%) patients. In 3 cases, the events were reported as serious but not related to the study drug: cholelithiasis in 2 subjects; 2 separate SAEs of cholelithiasis and cholecystitis in 1 subject and portal vein thrombosis in 1 subject. No hepatic events resulted in study drug discontinuation. Concomitant immonumodulators were used by 23 of the 43 subjects (53.5%) with hepatic events. Events in 28 subjects (65.1%) resolved while on treatment.

Allergic reactions

Allergic reactions were reported in 13 (1.3%) patients (all adalimumab set), these included 4 patients with hypersensitivity. One was an itching response to a non-study drug, 2 were skin reactions to adalimumab, and 1 was a mild allergic reaction to adalimumab. None of the reactions were serious but in 2 cases the patients discontinued the study. Four events were assessed as probably related to study drug; all others were considered probably not or not related. Three of the 13 subjects had previously used anti-TNF agents.

There are antibody data available for 6 of 7 patients in Study M06-827 who had allergic TEAEs. None of the 6 subjects were AAA positive at baseline. One subject from the adalimumab 160/80/40 group, who had an event of urticaria, became AAA positive.

Lupus-like syndrome

There were 2 reports of lupus-like syndrome. Subjects discontinued the study, one case remained unresolved and one resolved after treatment. Both were assessed as probably related to the study drug.

Haematological events

Overall there were 20 patients (2%) with haematological events. Sixteen had leucopenia, 3 neutropenia and 1 had thrombocytopenia. In 4 cases were the events reported as severe and in one case also as serious. Events in 6 subjects were assessed as possibly related to study drug; all others were assessed as probably not or not related to study drug. Of the 20 adalimumab-treated subjects who experienced hematological events, 19 were receiving concomitant immunomodulators.

Diverticulitis and intestinal perforation

Three patients (0.3%) in the all adalimumab set had diverticulitis. One subject had a known history of diverticulitis, and all events were deemed not related or probably not related to the study drug. Two of the 3 subjects were receiving concomitant corticosteroids at baseline, and 2 subjects were obese.

Four actively treated patients experienced intestinal perforation. All were reported as a SAE. Of the 4 subjects, 1 was receiving concomitant corticosteroids at baseline, and 3 were receiving concomitant mesalazine. One placebo treated patient experienced a SAE of rectal perforation.

Pancreatitis

One adalimumab-treated subject (all Adalimumab Set), with a history of alcohol-induced pancreatitis, experienced a non-serious event of pancreatitis which resolved. The pancreatitis was assessed as not related to study drug. One placebo-treated subject in the Maintenance Set had a SAE of pancreatitis acute.

Laboratory findings

Evaluation of the clinical laboratory data did not reveal any safety concerns. Overall, there were no clinically meaningful changes from a safety standpoint in measures for hematological, clinical chemistry or urinalysis parameters.

Immunological events

In study M06-827 the numbers of AAA positive patients was assessed. In all there were 19 of 487 (3.9%) that were positive for AAA. TEAEs were stratified by AAA status for the double-blind and the open-label period of study M06-827. There were 6 subjects who received placebo treatment in the double-blind period and developed AAA after switching to open-label adalimumab treatment; they were not AAA+ during the double-blind period.

For the double-blind period, the percentage of TEAE was lower in AAA– than AAA+ subjects (82.6% vs 100.0%). Injection site reactions were higher in the AAA+ than the AAA– group (23.1% vs 11.6%). The rate of severe AE, serious AE and AE leading to discontinuation was lower in the AAA+ group. However, the number of AAA+ subjects (n=1) in each category was too small to make any meaningful assessment. Infections rate was comparable between AAA+ and AAA– subjects (38.5% vs 45.9%). Allergic reaction, opportunistic infection, CHF, lupus-like syndrome, malignancies, serious infection,

hematologic related AE and hepatic event was less than 10% in both AAA– and AAA+ groups. No incidence of demyelinating disease, lymphomas, AEs leading to deaths and deaths were reported during the double-blind period.

For the open-label period, the overall percentage of AEs was comparable between AAA– and AAA+ subjects (73.3% vs 78.6%). Injection site reactions were higher in the AAA+ than the AAA– group (14.3% vs 6.6%); however, the overall percentage was higher in the placebo (9.3%) than the adalimumab group (4.3%). A comparison of the rate of severe AE, serious AE, AE leading to discontinuation, serious infection and hematologic related AE between the AAA+ and AAA– group was inconclusive as the number of AAA+ subjects (n≤2) in each category was too small. The rate of infectious AE was similar between AAA+ and AAA– subjects (42.9% vs 38.7%). Allergic reaction, opportunistic infection, malignancies and hepatic related AE was less than 10% in both AAA– and AAA+ groups. No incidence of demyelinating disease, CHF, lupus-like syndrome, lymphomas, AEs leading to deaths and deaths were reported during the open-label period.

Safety in special populations

Pregnancy and Lactation

Female subjects were required to have a negative pregnancy test at Screening for all studies and were requested to use a reliable method of contraception during the studies and up to 150 days after the last dose. If a pregnancy occurred, the subject discontinued from the study. There were 9 pregnancies reported in the UC clinical program. Five were terminated by elective abortion, 3 resulted in live birth of a healthy infant with no complications or birth defects (including 1 placebo-treated subject), and in 1 case the outcome is unknown.

The adalimumab SmpC does not recommend the use of adalimumab during pregnancy and lactation, and no change in the prescribing information is recommended at this time.

Discontinuation due to adverse events

Discontinuations due to TEAEs were infrequent in the induction and maintenance sets in all treatment groups In the Induction Set, TEAEs leading to premature discontinuation of study drug were reported for 6.6%, 6.2%, and 4.8% of subjects in the placebo, adalimumab 80/40, and adalimumab 160/80/40 groups, respectively. In the Maintenance Set, 6.3% of subjects in the placebo group (24.42 E/100 PYs) and 5.1% of subjects in the adalimumab 160/80/40 group (12.11 E/100 PYs) experienced AEs leading to premature discontinuation of study drug. Discontinuation was experienced by more placebo-treated subjects than adalimumab-treated subjects in both the induction and maintenance sets. Worsening UC led to discontinuation in the greatest percentages of subjects.

In the all adalimumab set, 15.1% of subjects experienced AEs leading to discontinuation of study drug. The percentage of subjects who had AEs leading to discontinuation of study drug was generally similar for subjects who dose escalated to 40 mg weekly (15.6%) compared with those who remained on Adalimumab 40 mg eow (14.8%). The most frequently reported AE leading to discontinuation was colitis ulcerative (8.3%), followed by colitis (1%). Rash, B-cell lymphoma, and Crohn's disease led to discontinuation in 3 subjects each (0.3%). All other AEs leading to discontinuation were reported by no more than 2 subjects each.

Observations Related to Safety

Analyses were performed to assess whether there was any impact of prior use of anti-TNF agents or concomitant corticosteroids and immunomodulators use at baseline on the AE profile of adalimumab.

Prior use of anti-TNF Agents

In the induction set, the percentages of subjects who had at least 1 TEAE were higher among prior anti-TNF users compared with non-users in both the placebo (76.0% vs 53.6%) and adalimumab 160/80/40 (68.4% vs 51.8%) treatment groups. In the maintenance set, TEAEs were reported by similar proportions of prior anti-TNF users and non-users in the placebo group (67.9% and 68.3%), although the incidence of events was almost twice as high among those with prior anti-TNF experience. In the adalimumab 160/80/40 group, 68.2% of those with prior anti-TNF experience had 1 or more TEAEs compared with 76.5% of those who were naïve, again with a higher incidence of events among those with prior anti-TNF experience.

Among subjects receiving adalimumab 160/80/40 in the induction set, higher percentages of prior anti-TNF users compared with those who were anti-TNF naïve experienced injection site reactions (10.2% vs 5.2%), infections (26.5% vs 14.7%), serious infections (3.1% vs 0%), and opportunistic infections (3.1% vs 0.5%). A similar pattern with regard to infections was apparent in the all adalimumab set, with infections reported by 50.9% of prior anti-TNF users and 44.1% of naïve subjects. In the maintenance set, infections were reported by 36.5% of those with prior anti-TNF experience compared with 38.9% of anti-TNF naïve subjects in the adalimumab 160/80/40 group. UC worsening/flare was reported by higher percentages of subjects who were prior anti-TNF users compared with non-users in both placebo and adalimumab 160/80/40 treatment groups in all analysis sets.

Concomitant use of immunosuppressants and corticosteroids

Greater percentages of subjects who were receiving concomitant immunomodulators at baseline (all adalimumab set) reported the following events compared with subjects who were not receiving immunomodulators: injection site reactions (13.5% versus 8.2%), haematological events (4.9% versus 0.2%), and hepatic events (6.0% versus 3.3%).

A smaller percentage of subjects who were receiving concomitant corticosteroids at baseline (all adalimumab set) compared to those who were not receiving concomitant corticosteroids reported TEAEs (77.5% versus 85.7%) and infections (42.7% versus 48.6%).

Discussion on clinical safety

Data from the studies M06-826, M06-827 and M10-223 support the safety of adalimumab in adult subjects with moderately to severely active UC, defined as a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite treatment with oral corticosteroids, immunosuppressants or both (or having failed to respond to or been unable to tolerate these treatments), and confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy. The safety of adalimumab throughout the studies was monitored and assessed by AEs, physical examination, laboratory data, and vital signs.

The most frequently reported TEAE (≥5%) in both the induction and maintenance analyses sets was colitis ulcerative (that includes disease worsening or flare). The incidence of UC worsening/flare was statistically significantly lower in the adalimumab 160/80/40 group compared with placebo during the induction period (7.3% with adalimumab versus 12.2% with placebo) but was similar in these 2 groups during the maintenance period (16.7% versus 16.6% respectively). However, the events/patient-year rate was higher in placebo-treated patients. Other commonly reported TEAEs (≥5%) were nasopharyngitis and headache in the induction set. In the maintenance set, the most frequently reported TEAEs (≥5%) were: nasopharyngitis, abdominal pain, arthralgia, and headache. Infections

were reported in 45.2 % of all patients (all adalimumab set). The majority of infections were nasopharyngitis and upper respiratory tract infections. Among adalimumab-treated subjects in all sets, a greater proportion of those with prior anti-TNF use, compared to those who were anti-TNF naïve, experienced infections. Serious infections occurred in 4% (all adalimumab set). In most of the case patients were on concomitant immunosuppressant at baseline or receiving corticosteroids. No cases of TB infection were reported. Ten (10) % of the patients had injection site reactions in a statistically significantly greater proportion of adalimumab 160/80/40-treated subjects compared with placebo. The overall frequency of TEAEs was consistent with the known established profile of adalimumab. Overall these adverse drug reactions reported are consistent with the known safety profile of adalimumab and in line with the current adalimumab SmPC.

One death occurred. The patient was young without relevant concomitant morbidities and with a 20-year history of UC. The report concluded that the subject died of shock associated with bilateral adrenal haemorrhage secondary to an infectious process. The infection's aetiology could not be determined.

The most frequently reported SAE in all analysis sets was colitis ulcerative (8.2%), followed by anemia, appendicitis, DVT and pneumonia. Stratifying patients by prior use of anti-TNF-alfa vs naïve patients a significant difference is noted in UC occurrence: 21.2% in prior anti-TNF-alfa users versus 9.8% in patients anti-TNF-alfa naïve. Overall, approximately 26% of the patients experienced worsening/flare of UC in the all adalimumab set. One third of it being patients escalated to 40 mg ew. A higher proportion of patients who were prior anti-TNF users had UC worsening/flare compared with subjects who were anti-TNF naïve (35.8% versus 24.6%). The incidence rate for UC worsening/flare as AE in the integrated maintenance set was higher in the placebo group than in the adalimumab group (50 versus 38 E/100pty). The MAH has presented further data that indicate that the incidence of UC worsening/flares is influenced by prior use of anti-TNF (75 events/ 100 pty versus 56 E/100 pty for adalimumab) compared with anti-TNF-naïve subjects (39 placebo versus 31 E/100 pty for adalimumab). The CHMP acknowledged that the incidence rate of UC worsening is influenced by previous treatment with anti-TNF therapy. The discontinuation rate of both placebo and adalimumab treatment groups during the double-blind period of Study M06-827 was clarified by the MAH. Total discontinuation from double-blind treatment was shown to be higher in the placebo group than in the adalimumab treatment group, when all adalimumab-treated subjects or the subgroups of adalimumab Week 8 TM and PM responders are considered (1.48 placebo vs 1.09. all adalimumab vs 0.50 adalimumab week 8 TM responders)

One (1) % of malignancies was observed (all adalimumab sets). Eight cases were reported as SAEs, related to the study drug and the patients discontinued the study. The malignancies were B-cell lymphoma, breast cancer, gastric cancer, spindle cell carcinoma and malignant melanoma.

B -cell lymphoma was diagnosed in 3 subjects. All 3 patients had confounding factors with a history of previous AZA treatment and were all smokers. One was over 70 years. An increased risk of lymphoma has been described among UC patients treated with azathioprine/6-MP. However, there is uncertainty regarding how disease severity, duration, and other individual risk factors, as well as the degree of immunosuppression, contribute to the risk of developing lymphoma in UC subjects. The data presented do not allow drawing conclusions on a potential impact of concomitant use of immunomodulators and adalimumab and lymphomas. The risk of lymphoma is a safety concern that is already addressed in the product information and the RMP. No new signal is identified based on the data provided in this application and it is considered that this risk is addressed satisfactorily for the time being. The MAH will continue to monitor lymphoma as part of ongoing routine pharmacovigilance activities and long-term clinical studies and registries as addressed in the RMP.

No case of colon cancer was reported in the studies. It is nevertheless known that patients with UC are at an increased risk for certain malignancies, such as colon cancer, which increases with the duration of disease, use of immunomodulators, and the extent of colon affected by the disease. It is recognized that with the current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. This potential risk was further discussed by the MAH and addressed in section 4.4 of the SmPC with a precautionary statement informing that patients who are at increased risk for dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. The MAH will continue to closely monitor the occurrence of malignancies and in particular colon cancer in the ongoing study M10-223. In addition, the MAH included colon cancer as an important potential risk in UC patients in the RMP. The risk is followed by the MAH through routine pharmacovigilance activities and monitoring through long-term clinical studies and registries. The MAH will also monitor this risk through the Ulcerative Colitis Registry Program (further described below). Overall, based on the number of malignancies reported in the UC clinical program, there is no signal for an increased malignancy rate linked with adalimumab use. The risk is addressed in the PI and the RMP and will be followed on the long term through the UC registry program. The CHMP considered these measures as sufficient at the present time.

A case of leukoencephalopathy with adalimumab was reported as serious but mild in severity and possibly related. The patient was reported to have a prior history of numbness in the soles of the feet and chronic inflammatory CNS disease. The clinical presentation of the reported case included myelitis, lesion of the optical nerve on both sides associated with motor disorder and supra-tentorial infra-tentorial MRI lesions. Several studies suggested a potential role for anti-TNF agents in the pathogenesis of inflammatory demyelinating CNS disease. These disorders include, among others, multiple sclerosis, optic neuritis, and various forms of peripheral demyelinating neuropathy. Demyelinating disorders have been described in both postmarketing surveillance and isolated case reports for the main anti-TNF agents. As of July 2009, over 140 cases had been reported of demyelinating CNS processes, including multiple sclerosis and optic neuritis, after starting biological therapies (Bosch X et al, Nature Rev Neurol 2011). Demyelinating disorder including multiple sclerosis is already reported in section 4.8 of the current SmPC as a rare adverse event together with a precautionary statement in section 4.4. Additionally it is reported in the RMP as an important identified risk monitored through routine pharmacovigilance activities and through long-term clinical studies and registries. Overall based on the data provided in this application no new safety signal is identified and no change to the way this risk is currently addressed is deemed necessary. The MAH will continue to monitor demyelinating disorder as part of ongoing routine pharmacovigilance activities with infliximab as addressed in the RMP.

Two cases of congestive heart failures were reported. Cases of worsening CHF have previously been reported in patients receiving adalimumab. Adalimumab is already contraindicated in moderate to severe heart failure and must be discontinued in patients who develop new or worsening of CHF. This identified risk is followed through routine pharmacovigilance activities and through long-term clinical studies and registries. As an additional risk minimization activity an educational program to prescribers is also running. These measures are considered sufficient to address this known risk. The presented data do not trigger amendment to these measures.

Hepatic toxicity has been reported in the clinical UC program. Approximately 50% of patients reporting hepatic events were taking concomitant immunomodulators. The reported increases of ALT and AST in patients taking concomitant immunomodulators are expected. The reported serious events of cholecystitis and cholelithiasis are already listed in the current SmPC as uncommon events. No amendment to the SmPC is deemed necessary.

Hypersensibility and autoimmune symptoms/signs were reported in a small percentage of subjects. Allergic reaction TEAEs were reported in 7 patients. AAA were detected at baseline on 6 of these 7 patients and all tested samples were negative for AAA. Analysis of the TEAEs stratified by AAA status showed that overall, AAA did not affect the tolerability to adalimumab and there were no indications of any clinically important differences in safety between subjects who developed AAA versus those who did not.

In two subjects lupus-like syndrome was reported. Lupus like syndrome has been described previously in association with anti-TNF agents. The SmPC already include a precautionary statement informing that if a patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA, adalimumab treatment should be discontinued. This important identified risk is also listed in the RMP and monitored through routine pharmacovigilance activities and long-term clinical studies and registries.

In order to further characterize the long-term safety profile in a clinical real setting the MAH presented a planned Ulcerative Colitis Registry Program Study P11-282. This program is a multicenter, non-interventional registry of patients with UC treated in a routine clinical setting with adalimumab. The primary objective of this Registry is to evaluate the long-term safety of Humira in UC adult patients (18 years of age or older). The secondary objective is to evaluate long-term effectiveness of Humira in patients with moderately to severely active UC. Approximately 8250 patients in the US and Europe will be enrolled. The proposed registry is aimed at collecting safety information for a period of 6 years. In addition, physicians will be asked to continue to collect safety data from patients who discontinue from the registry. The sample size includes 5,500 patients with UC for at least 6 months and on immunomodulators who will receive Humira, and 2,750 patients with UC who will be used as the comparator group (immunomodulators received for at least 6 months). The addition of the comparator group was on the request of the CHMP to allow for better assessment of both safety and effectiveness. Also clarifications were made concerning the sample size calculation, the representativeness of the participating physicians as well as how loss to follow-up of AEs will be minimised in order to reduce the risk of underestimating the incidence of safety concerns.

Ulcerative colitis is a disease with natural remissions that can last several years. The MAH discussed the risk of rebound effect with worsening of symptoms in patients stopping therapy as well as the risk for infusion reactions and reduced efficacy due to e.g. antibody formation related to re-treatment after a longer period without treatment. The effects of withdrawal and re-treatment with adalimumab were studied in psoriasis in the absence of data in UC. Results indicated that discontinuation was associated with a statistically significant and clinically meaningful loss of response. Looking at time to loss of response showed that the proportion of subjects losing adequate response increased over time. No rebound effects were observed. When patients were re-treated with adalimumab, clinical response was generally attained in the long-term but success of re-treatment and timing of re-gaining response is partially affected by the amount of disease recurrence while off adalimumab therapy. Additionally, “episodic dosing” data will be followed in the proposed UC Registry P11-282. Patients who interrupt adalimumab at least once for at least 12 weeks and receive at least 1 dose of adalimumab after the treatment interruption, and who do not receive any other biologics during the treatment interruption will be described. Analyses are expected to provide information on whether there is a rebound effect or reduced efficacy in those patients.

During the procedure the MAH submitted analysis on “AE-free remission days”. In addition to the remission rate at fixed time points, the "days in remission" were evaluated by the MAH for both placebo and adalimumab-treated subjects. Particularly, a new indicator of benefit/risk defined as AE-free remission days (AE-free remission days for a subject were defined as the difference of total days

in remission and total days with an underlying AE) was considered as a parameter of therapy benefit over the full course of therapy which is able to describe the duration of the remission period adjusted for safety events. The CHMP acknowledged that the benefit/risk analysis by mean AE-free remission days indicator favours adalimumab treatment. The mean AE-free remission days almost double compared to the one observed in the placebo group. Among the ITT population in Study M06-827, more than 30 days of remission without AEs were achieved in the adalimumab arm beyond those in the placebo group, demonstrating a more than 60% increase in the AE-free days in remission. A new benefit/risk analysis was proposed by the MAH by defining the following ratio between: the number of AEs per subject that led to discontinuation during the study period and the number of subjects who achieved a therapeutic benefit (response or remission) at both Week 8 and Week 52. AEs that led to discontinuation represent a composite of the most relevant AEs, including lack of efficacy events and all impactful serious adverse events. The ratio of these two numbers was considered by the MAH as a measure of adalimumab benefit/risk. This analysis showed that placebo subjects had approximately 4-times more AEs per remitter compared with adalimumab-treated subjects, showing the maintenance benefits of treatment with adalimumab compared with placebo. For example, 4.4 AEs leading to discontinuation per 1 sustained remitter on placebo were observed compared with only 1.1 AEs leading to discontinuation per 1 sustained remitter treated with adalimumab, supporting a positive benefit/risk profile of adalimumab compared with placebo.

From a methodological perspective, the CHMP noted that these new proposed indicators introduce the time length of remission adjusted for AE occurrence, substituting the previously reported dichotomous time length-independent outcome (remission rate). The CHMP noted that these new parameters, although of significance in the evaluation of clinical response in patients affected by a chronic inflammatory disease, were not previously specified in the submitted statistical plan and for this reason should be considered of limited value as surrogate indicators of the benefit/risk of adalimumab treatment in the sought indication.

The MAH also presented an analysis showing the reduction in the rate of hospitalisation with adalimumab therapy. All hospitalizations were reviewed and adjudicated as to whether they were related to UC or not in a blinded manner. These events were analyzed based on exposure to adalimumab or placebo. All analyses reveal that adalimumab therapy prevents hospitalization regardless of whether they were UC-related or not. Overall, statistically significant risk reductions in hospitalization rates versus placebo were noted, whether UC-related or not, in all adalimumab-treated subjects (relative risk of adalimumab over placebo was 0.5 to 0.7) and ADA Week 8 TM and PM responders (relative risk of adalimumab over placebo was 0.2 to 0.4). Statistically significant reductions in all-cause hospitalization were observed with adalimumab treatment, which is unique for anti-TNF treatment in UC patients.

The ADR table in section 4.8 was updated to include data from the clinical data. The following preferred terms (PT) diabetic neuropathy, neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral sensorimotor neuropathy have been combined under the new grouped term "Neuropathy" describing the similar medical concept of these PTs. Based on a doubling of the rate in the adalimumab group (0.4%) compared to the control group (0.23%) the term was added as to the ADR table as an uncommon event. A warning for serious polyneuropathies like Guillain-Barré Syndrome already exists in the SmPC. The current RMP contains already the important identified risk of central and peripheral demyelinating disorders including serious polyneuropathies like the Guillain-Barré syndrome together with adequate risk minimization activities. This addresses satisfactorily the reported term of neuropathy. The update also included: the term "dehydration" changed from uncommon to common and systemic lupus erythematosus changed from rare to uncommon. Two changes were also made to correct two oversights from variation EMEA/H/C/00481/II/61: “blood potassium increased” is deleted as was wrongly added previously (it was overlooked initially that no

related events were reported in clinical studies) and "vascular arterial occlusion", "thrombophlebitis" and "aortic aneurysm" are reported as uncommon instead of rare.

Conclusion on clinical safety

There is no new safety signal identified in the UC clinical development program submitted. Adalimumab has a well characterised safety profile in several authorised indications, including adult CD. Data submitted in this application confirm the known safety profile observed with the approved indications. Overall, the safety profile of adalimumab in the treatment of ulcerative colitis seems to be similar to that for other approved indications.

Events more related to the underlying disease i.e. worsening of UC (adverse events and serious adverse events), were reported in both placebo and actively-treated patients, and represented the most common reported adverse events leading to adalimumab discontinuation. The CHMP acknowledged that the incidence rate of UC worsening is influenced by previous treatment with anti-TNF therapy.

Of special concern in the UC population, is the potential risk of malignancy associated with the disease. No signal for lymphoma was observed in the presented data. Lymphoma is a known important identified risk. It is already addressed in the product information and the RMP. Based on the data provided in this application it is considered that this risk is currently addressed satisfactorily. No case of colon cancer was reported in the studies submitted. Nevertheless, it is well documented that there is an increased risk of developing cancer, such as colon cancer, in ulcerative colitis patients when compared to the general population. This risk is enhanced by different factors such as the concomitant immunomodulators therapy, extent and time to onset of the disease. The MAH addressed this risk in the RMP and the product information with addition of a precautionary statement requiring those UC patients who are at increased risk for dysplasia or colon carcinoma to be screened for dysplasia at regular intervals before therapy and throughout their disease course. The MAH will continue to closely monitor the occurrence of malignancies and in particular colon cancer in the ongoing study. In addition this risk be also followed through the Ulcerative Colitis Registry Program Study P11-282

The results showing that the proportions of patients with disease-related and all-cause hospitalisation were reduced in actively treated patients are acknowledged by the CHMP. These data were considered as supportive.

Risk Management plan

The MAH submitted a risk management plan (version 9.2.1) which included a risk minimisation activity.

Table 39 Extract from the summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Potential Risks		
Colon cancer in UC patients	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding colon cancer in UC patients will be updated in the adverse reaction section of the product information if further evidence for the association with TNF antagonist treatment becomes available.
[…]		

Important Missing information		
Episodic treatment in UC data	Routine pharmacovigilance activities. Evaluation of treatment interruptions defined as dosing holidays of at least 12 weeks with the UC registry (Study P11-282)	A planned registry for UC will complement the safety experience especially on episodic treatment gained from spontaneous postmarketing AE reporting for all patients on adalimumab.

2. OVERALL conclusion and Benefit-risk assessment

Benefits

Beneficial effects

In the induction study M06-826 a statistically significantly higher percentage of subjects in the adalimumab 160/80/40 mg treatment group compared to placebo achieved clinical remission per Mayo score at Week 8 (18.5% versus 9.2%).

In the maintenance pivotal study M06-827 a statistically significantly greater proportion of subjects in the adalimumab group were in clinical remission per Mayo score at Week 8 and Week 52 compared to subjects in the placebo group (16.5% vs. 9.3% and 17.3% vs. 8.5% respectively). A statistically significant higher number of patients treated with adalimumab 160/80/40 mg achieved remission at week 8 and maintained a sustained remission up to week 52 compared to placebo.

The results of the analysis on the rate of hospitalisation with adalimumab therapy showed that the proportions of patients with disease-related and all-cause hospitalisation were reduced in adalimumab treated patients. These results are considered supportive of the beneficial effect of adalimumab.

Results from the ongoing open-label study M10-223 showed that, at baseline, the disease activity was reduced and remained stable on treatment with adalimumab 40 mg every other week or every week, in some patients up to 60 weeks.

Uncertainty in the knowledge about the beneficial effects

In study M06-826, although there was a statistically significant difference between the effect of adalimumab (160/80/40 mg dose) and placebo treatment on the proportion of patients in clinical remission at week 8, the overall difference was <10 % (18.5% adalimumab 160/80/40 mg vs 9.2% placebo, p=0.031). In study M06-827, a gain of less than 10% over placebo was achieved in the remission per Mayo score at Week 8 (7.2% difference) and 52 (8.8%) respectively in patients treated with adalimumab. Overall approximately 17% of adalimumab treated patients achieved remission at week 8 and at week 52. In the maintenance setting, the gain in the clinical benefit of adalimumab over placebo decreases i.e. 8.5% of patients maintained remission per Mayo score in the adalimumab group, with a difference of only 4.4% (p=0.047) over placebo.

The MAH has presented further data to support that patients demonstrating early responses benefit the most from the treatment. Recommending the discontinuation of the treatment in patients who do not respond within a time period of 2 to 8 weeks ensures that these patients are not put on maintenance treatment.

Results in study M06-827 suggest that prior treatment with anti-TNF agents could decrease the efficacy of subsequent adalimumab therapy. Therefore, uncertainty was expressed on the possibility that patients switched to a different anti-TNF agent, as not showing early response with prior

adalimumab treatment, would show a decreased response in terms of magnitude of effect. There is currently no known mechanistic reason to suspect that such tolerance would develop.

There were 38 patients who underwent a colectomy; all were performed during the follow-up period after the last dose of the study drug. Data were presented for colectomies undertaken within studies M06-826 and M06-827, where it is possible to compare placebo and adalimumab groups. It is evident that the rate of colectomies was low during the studies with a lower rate in adalimumab treated patients compared with placebo treated. However, due to the low numbers, no firm conclusions can be drawn whether adalimumab affects the need for colectomy. This also cannot be expected to be addressed within these types of clinical studies, and therefore colectomy requires to be further followed in the planned UC registry as described in the RMP.

Ulcerative colitis is a disease with natural remissions that can last several years. Uncertainties related to the risk of rebound effect when stopping therapy and to the risk of infusion reaction/reduced efficacy (e.g. due to antibody formation) when administration re-start after a long period off treatment were discussed. The MAH presented the experience from a study in patients with psoriasis which addresses these points satisfactorily. In addition, data will become available from the UC registry as these parameters will be monitored, as described in the RMP.

Risks

Unfavourable effects

There were no new safety signals observed during the study period. The observed safety events were consistent with the well-characterised adalimumab safety's profile. However, events more related to the underlying disease i.e. worsening of UC (adverse events and serious adverse events), were frequently reported in both placebo and actively-treated patients (more so in placebo patients). They also represented the most common reported adverse events leading to adalimumab discontinuation.

Uncertainty in the knowledge about the unfavourable effects

Treatment with adalimumab is connected with several serious risks i.e. increased risk of infections and the potential risk of lymphoproliferative disorders or malignancies, including hepatosplenic T-cell lymphoma. More rare potential safety concerns include risk for demyelination. All these risks are already addressed in the adalimumab product information as well as in the RMP. Based on the data analysed in this application this is considered sufficient at the present time.

No signal of dysplasia and colo-rectal cancer was observed in the population studied. No signal for increased rate of dysplasia and colon rectal cancer was observed in clinical studies. The potential risk of malignancy, which is also associated with the disease, has been addressed in the product information and the RMP. Based on the data analysed in this application this is considered sufficient at the present time. The MAH will continue to monitor gastrointestinal dysplasia or malignancy as part of ongoing routine pharmacovigilance activities as described in the RMP. In addition the MAH will provide regular safety update through the Ulcerative Colitis Registry Program Study P11-282 as described in the RMP.

Balance

Importance of favourable and unfavourable effects

Treatment with adalimumab induced a clinical remission at week 8 and maintained remission at week 52. These findings were statistically significant. The magnitude of the remission rate for 160/80/40 mg adalimumab was <10% compared to placebo. A difference of 4.4% in favour of adalimumab compared to placebo is observed in the patients achieving sustained remission per Mayo score both at Week 8 and 52. Among patients actively treated who were in remission at Week 8, 51% were in remission at

Week 52. Secondary endpoints, in the induction and the maintenance phase, show a modest treatment effect of adalimumab, nevertheless, a consistency across the results toward a beneficial effect was observed through the secondary endpoints. Data showed that patients demonstrating early responses benefit the most from adalimumab treatment. Discontinuation of treatment in non-responder patients within 2-8 weeks ensure that patients not responding will not be put on maintenance treatment.

The safety profile of adalimumab is well established, and treatment with adalimumab is connected with several potentially serious risks. Moreover, UC worsening/UC flare remain the most commonly reported AEs leading to adalimumab discontinuation, as well as the SAE reported by the highest percentage of subjects in all 3 treatment groups. The safety of adalimumab in comparison with the safety of alternatives for the treatment of UC is of clinical relevance. The disadvantages with steroid treatment are the systemic adverse events i.e. osteoporosis and increased risk of infections. The safety profile for AZA/6-MP is also serious with increased risks of bone marrow suppression, malignancy/lymphoproliferation, hepatic events and pancreatitis.

Although the incidence rate of colectomies was numerically lower, with a risk reduction of 22%, in the adalimumab treatment group compared with placebo, it is not known, at present, whether adalimumab can delay or prevent colectomy in patients with UC. Since this is of clinical importance and could not be assessed within the clinical studies undertaken due to the few cases occurring, the MAH will follow this within the UC registry as described in the RMP.

Benefit-risk balance

Although the demonstrated effect of adalimumab was modest in that the number of patients benefiting from the treatment was limited, the CHMP considered it appropriate that patients who have shown inadequate response/intolerance to conventional UC therapies including corticosteroids or immunomodulators should be given the option of adalimumab treatment.

The MAH has presented further data to support that patients demonstrating early responses benefit the most from the treatment. Recommending the discontinuation of the treatment in patients who do not respond within a time period of 2 to 8 weeks ensures that these patients are not put on maintenance treatment.

Furthermore, the possibility of self-administration of a subcutaneous injection is another benefit of adalimumab which also should be taken into account. For patients responding, the safety profile is considered acceptable, with the proposed product information, and proposed RMP measures.

The analysis on the rate of hospitalisation with adalimumab therapy showed that the proportions of patients with hospitalisation were reduced in adalimumab treated patients. These results are considered supportive of the beneficial effect of adalimumab.

Overall, based on the available efficacy data and the extensive knowledge about the safety profile of adalimumab, the benefit/risk balance of adalimumab in the sought indication is considered positive 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.

3. Conclusion

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore does recommend, by a majority, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type
C.I.6 Change(s) to therapeutic indication(s)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of 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. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated accordingly as well as Annex II and IIIB.

APPENDIX

DIVERGENT POSITIONS

Divergent Positions

The undersigned members of the CHMP did not agree with the CHMP's positive opinion on the variation of the terms of the marketing authorisation.
The reasons for divergent opinion were as follows:

In the pivotal studies, more than 80% of UC patients in the adalimumab arm had no significant clinical improvement.
In the induction of remission setting, the integrated analyses of the efficacy of adalimumab showed a very limited gain of adalimumab treatment over placebo, about or less than 10%, the clinical relevance of which is highly questionable.
Sustained remission is the goal of UC treatment, however, in the maintenance setting, the gain in the clinical benefit of adalimumab over placebo further decreases. Only 8.5% of patients maintained remission per Mayo score in the adalimumab group, with a difference of only 4.4% (p=0.047) over placebo. Similar or even less pronounced beneficial effects of adalimumab were observed for the secondary endpoints

The absence of an active comparator further hinders the interpretation of the magnitude of the efficacy seen with adalimumab.

The proposal to restrict the indication of adalimumab in UC patient early responders and to not recommend the continuation of therapy in patients not responding within 2-8 weeks raises a concern on patients selection and clinical management.
Differences in the selection of the placebo and adalimumab arms hamper the interpretation of the results obtained in the early responders.
The medical choice of starting adalimumab would not be based on indicators/markers of response as no predictive parameters of response are available to identify the early responder population. No characterization of the earlier responder population has been provided by the MAH. Early response (Weeks 2 to 8) is thus the sole parameter to drive clinical decision to continue long term adalimumab therapy. However:

1. Data show that even in the population of earlier responder a significant percentage, roughly 50%, of patients will not achieve sustained remission. This further questions the benefit of adalimumab treatment even in the restricted indication.

2. Data indicate that previous exposure to anti-TNF alpha therapies decreases the efficacy of adalimumab therapy, thus there is the possibility that patients exposed to adalimumab who do not show an early response and are thus discontinued from adalimumab treatment, if switched to a different anti-TNF alpha, will show a decreased response in terms of magnitude of effect. Thus a detrimental effect of adalimumab in these patients cannot be ruled out.

The totally humanized nature of adalimumab could confer an advantage for patients in terms of reduced infusion-related side effects, however, the absence of a direct comparison with the other anti-TNF alpha drug that is present on the market, prevents the evaluation of the impact of this potential benefit of adalimumab in the clinical setting.

In light of all the above mentioned considerations, the clinical benefit/risk ratio of adalimumab is considered negative.

London, 15 March 2012

…….	…….
Pierre Demolis	Concepcion Prieto Yerro
…….	…….
Daniela Melchiorri	Barbara van Zwieten-Boot
…….	…….
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