

London, 26 April 2007  
Product name: Humira/Trudexa  
Procedure number: EMEA/H/C/481-482/II/33

**SCIENTIFIC DISCUSSION**

*Medicinal Product no longer authorised*

## 1. Introduction

Adalimumab is a recombinant human immunoglobulin (IgG<sub>1</sub>) monoclonal antibody containing human peptide sequences that binds to human Tumor Necrosis Factor (TNF) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab is currently approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

The MAH applied for an extension of the therapeutic indication for adalimumab to include treatment of moderately to severely active Crohn's disease (CD) in adult patients who have had an inadequate response to conventional therapy and to include treatment in patients with moderately to severely active CD who have lost response to or are intolerant to infliximab.

Crohn's disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (40%)<sup>1</sup>, followed by a disease in the small bowel only (30%), and in the colon only (25%). It occurs in a relatively young population and there is no marked sex difference. The incidence of CD in European countries is estimated to be 6-7/100.000. Patients with CD have a normal life expectancy, however, most individuals experience an impact of the disease on their daily life.

The application for the present type II variation was supported by 2 induction studies (M02-403 and M04-691) and one maintenance study (M02-404). Additional data from long-term extension studies (M02-433 and M04-690) was provided as supportive data.

The MAH proposed to amend the text of the SPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 to reflect the results of the above mentioned studies, and to update the PL accordingly.

## 2. Clinical pharmacology

### Pharmacokinetics/Pharmacodynamics<sup>2</sup>

The pharmacokinetics (PK) of adalimumab were evaluated in 211 and 276 anti-TNF-naïve subjects in study M02-403 and study M02-433, respectively. The PK of adalimumab were also evaluated in 159 subjects who had lost response or were intolerant to infliximab in study M04-691. The immunogenicity of adalimumab and its potential impact on efficacy and safety were examined in these three studies.

In the clinical trials, the 160 mg induction dose was administered as four subcutaneous injections of 40 mg in a single day followed by a single dose of 80 mg at week 2. To support administration of the 160 mg dose as two 80 mg doses on two consecutive days, a population PK analysis and simulations were performed based on data from the study M02-403.

Adalimumab concentrations and anti-adalimumab antibodies (AAA) were determined using validated ELISA (enzyme-linked immunosorbent assay) methods. Approximately half of the total number of samples were analysed for AAA.

### Population PK model

A nonlinear mixed effects modelling (NONMEM) approach was applied to the PK data to build a population-PK model to estimate adalimumab apparent clearance (CL/F) and apparent volume of distribution (V/F).

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<sup>1</sup> All figures presented in this report are approximate

<sup>2</sup> For details of the studies referred in this section, please see section 3.3 Clinical efficacy

### Population PK/PD modelling

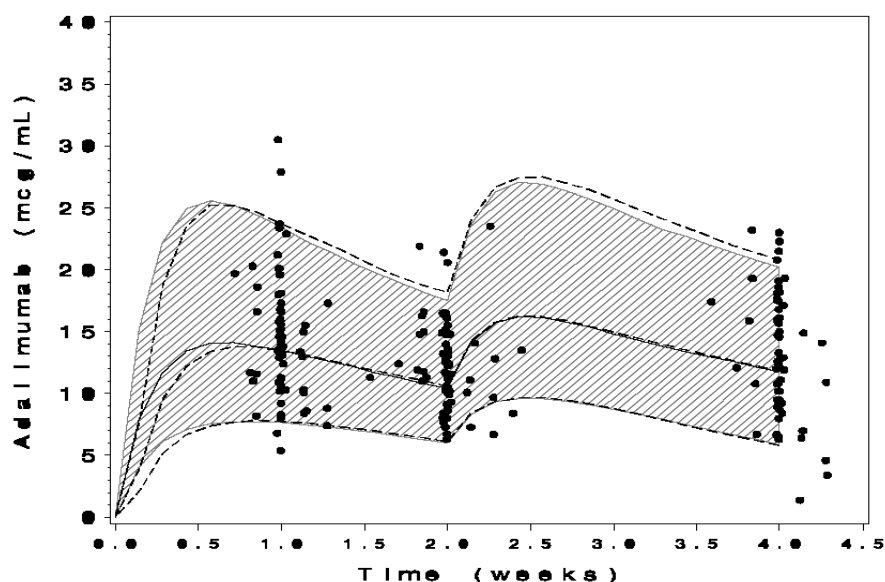
The model was built with the NONMEM software. All subjects from study M02-403 (n=211) who received at least one dose and who had at least one measurable concentration were included in the PK/PD analysis. The efficacy measure used was the CDAI (Crohn's Disease Activity Index)<sup>3</sup> score, which reflects the severity of the CD.

The effects of covariates including weight, age, sex, baseline CRP (C reactive protein) concentration, presence of AAA, concomitant MTX (methotrexate), 6-MP (6-mercaptopurine) or AZA (azathioprine), and baseline CDAI score were explored in the analysis. Only log-transformed CRP reached statistical significance, but this only explained 3% of the variability in IC<sub>50</sub> values.

The CHMP considered that the range of data was not large enough to support estimation of the I<sub>max</sub>. It was agreed that dose adjustment based on CRP is not warranted. From the graphical exploration of individual estimates (although not reliable due to the sparse data), the only remaining trend was a relation between IC<sub>50</sub> and presence of AAA. This relation was not found statistically significant, which could be due to the low number of subjects with AAA included (3%), but the relation could still be clinically relevant. Review of the few subjects in whom antibodies had been detected, gave signals of an association between presence of antibodies and reduced effect. The MAH was requested to revise the figures presented in the product information of percentages of patients with AAA, based on their respective individual exposure to adalimumab.

Two 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 2500 subjects were simulated for each regimen. Notwithstanding the identified uncertainties regarding the PK/PD modelling, the simulation results of the different dosing regimens tested (160 mg adalimumab given over 1 or 2 days at week 0, followed by 80 mg on at week 2) showed similar profiles.

Figure 1. Serum adalimumab concentrations for 160 mg adalimumab given over 1 or 2 days at week 0, followed by 80 mg adalimumab on 1 day at week 2

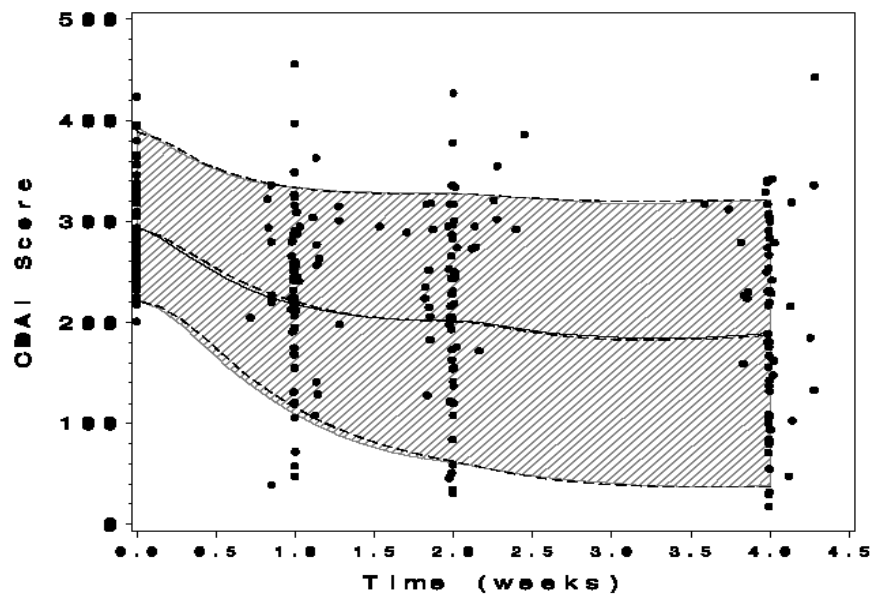


Notes: Simulated 160 mg given over 1 day (shaded area: 5-95<sup>th</sup> percentiles; solid line: median).  
Simulated 160 mg given over 2 days (dashed lines: 5<sup>th</sup> and 95<sup>th</sup> percentiles and median).  
Observed 160 mg given over 1 day (dots).  
The percentiles for the simulated profiles reflect inter-subject variabilities.

<sup>3</sup> The CDAI is a research tool used to quantify the symptoms of patients with Crohn's disease, during a one-week assessment period. It consists of eight factors, such as number of liquid or soft stools each day for seven days, abdominal pain, general well being, presence of complications (uveitis, joint pains, fistulas, abscesses, fever, among others), number of infirm days, presence of an abdominal mass, haematocrit below a certain value and the percentage deviation from standard weight. The score ranges from zero up to approximately 600. Lower scores correlate with less severe CD activity.

Regarding the simulated pharmacodynamic profiles, the CHMP agreed that the two profiles seem to perform very similar with regard to the range of decrease in CDAI scores within the population, however it only shows the first four weeks of treatment and on an individual basis this may not be true. Depending on the initial baseline value, the decrease may be small or not observed. Figure 2 below shows all subjects, both for patients who achieved remission and those who did not. Individual observations in this graph were also presented, showing that during the first four weeks of treatment, some patients achieved remission, while some patients did not achieve remission or their CDAI score was even increased.

Figure 2. CDAI scores for 160 mg adalimumab given over 1 or 2 days at week 0, followed by 80 mg adalimumab on 1 day at week 2



Notes: Simulated 160 mg given over 1 day (shaded area: 5-95<sup>th</sup> percentiles; solid line: median).  
 Simulated 160 mg given over 2 days (dashed lines: 5<sup>th</sup> and 95<sup>th</sup> percentiles and median).  
 Observed 160 mg given over 1 day (dots).  
 The percentiles for the simulated profiles reflect inter-subject variabilities.

### Discussion on pharmacokinetics

The CHMP identified certain uncertainties regarding the PK/PD modelling, but since the MAH did not intend to use the model further, no issue remained regarding this question. The MAH presented a discussion regarding the percentage of patients with AAA based on the patients individual exposure to adalimumab and updated the SPC accordingly. The alternate dosing regimen over two days for the first dose was considered acceptable from a pharmacokinetic point of view.

## 3. Clinical efficacy

### Introduction

To support this application the MAH presented the following study programme:

### Induction studies

Study M02-403 was a multicentre, randomised, double-blind, placebo-controlled phase 2/3 study to evaluate the efficacy, safety, and PK of adalimumab, in comparison with placebo, as induction treatment for anti-TNF-naïve subjects with moderate to severe CD. Subjects were to have had a diagnosis of CD for > 4 months.

Study M04-691 was a multicentre, randomised, double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy, safety, and PK of adalimumab 160/80 mg, in comparison to placebo,

as induction treatment for subjects with moderate to severe CD who either initially responded to infliximab and lost response or who were intolerant to infliximab. Subjects with a diagnosis of CD for any length of time were enrolled.

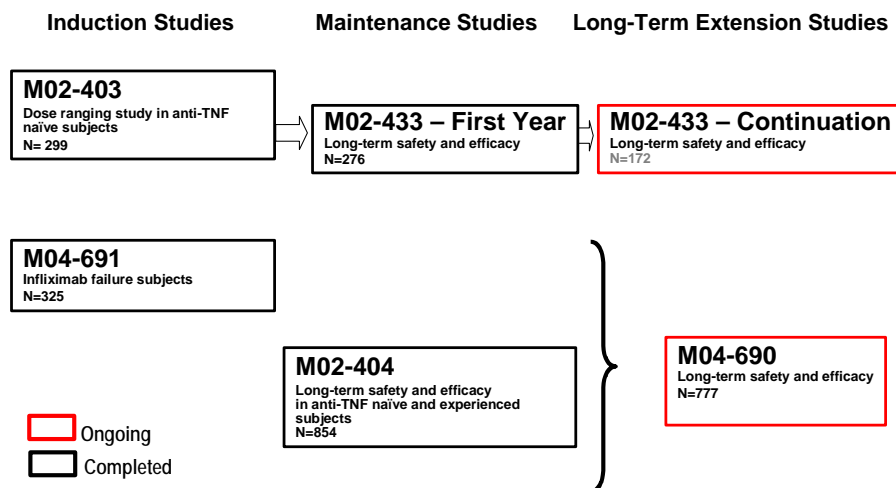
#### Maintenance study

Study M02-404 consisted of a 4-week open label (OL) induction phase followed by a 52-week double blind, randomised, parallel, placebo-controlled phase. It was designed to evaluate the efficacy and safety of adalimumab in subjects who had initially responded to an OL adalimumab induction regimen. Subjects who were naïve to anti-TNF agents and subjects who had been previously treated with an anti-TNF agent other than adalimumab were enrolled.

#### *Extension program*

Subjects who completed studies M02-403, M04-691 or M02-404 were eligible to be enrolled in a long-term extension program, study M02-433 or study M04-690 (see Figure 3 below). Study M02-433 is an ongoing maintenance study. Study M04-690 is a long-term safety and efficacy study. However, only safety data collected through 14 February 2006 were presented. Figure 3 shows a flow diagram of the studies:

Figure 3 Flow diagram of studies



#### Methods

##### Subject Population

Patients included had severe CD, with a disease activity defined by a CDAI score between 220 and 450 points. The definition of severe disease according to CDAI score is a score  $>450$ . No such patients were included in the studies. The MAH defined subjects with a score over 300 and concomitant medication as having severe disease, which was agreed with by the CHMP. This information was included in the SPC. The enrolled subjects represented a heterogeneous spectrum of treatment patterns which included subjects who had previously failed conventional therapy for moderate to severe disease (corticosteroids and/or immunosuppressants) and were no longer candidates for these treatments based on the judgment of their healthcare providers, subjects who were being treated with conventional therapy, and subjects who had been previously treated with anti-TNF agents, primarily infliximab.

Entry criteria were similar across studies and included the following: males and females  $\geq 18$  and  $\leq 75$  years of age; females who were not pregnant or breast feeding; diagnosis of CD confirmed by endoscopy or radiologic evaluation; and no history of ulcerative colitis, cancer, lymphoproliferative disease, active or untreated tuberculosis (TB), listeria, or human immunodeficiency virus.

##### Concomitant Crohn's-related medications

Concomitant Crohn's-related medications were to remain constant throughout each study and could include immunosuppressants (AZA, 6-MP, MTX), aminosaliculates, Crohn's-related antibiotics, or

corticosteroids. No new Crohn's-related medications were to be started during a subject's study participation and doses of concomitant medications were not to change during study participation, except for steroid tapering. Corticosteroid users were allowed to taper corticosteroids after week 8 in study M02-404 and in the OL cohort in study M02-433, or were required to taper corticosteroids after week 8 in the randomised cohort in study M02-433 if the subject had responded to study therapy. Subjects were not to receive cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks of screening and during the trials. Subjects were also not to receive therapeutic enemas, but were permitted to be treated with enemas as preparation for a colonoscopy.

#### Efficacy endpoint

The same primary endpoint, clinical remission defined as a CDAI score < 150, was evaluated in all of the studies. Some secondary efficacy endpoints were clinical response (CR) endpoints based on CDAI scores, such as CR-100 and CR-70, which are defined as decreases from baseline in CDAI scores of  $\geq 100$  points and  $\geq 70$  points, respectively. Other secondary endpoints included durability of response, ability of subjects to discontinue steroid use, heal draining cutaneous fistulas for the maintenance studies, the Inflammatory Bowel Disease Questionnaire (IBDQ)<sup>4</sup> (all studies) and SF-36 health survey<sup>5</sup> (study M02-404 only) to assess the effect on subject well-being.

#### Statistical Methods

The statistical methods in general were considered acceptable.

#### ***Main clinical studies***

##### **Study M02-403 (induction)**

###### *Study participants*

The study participants were adults above 18 and below 75 years of age, anti-TNF $\alpha$  naïve, with a diagnosis of CD (CDAI score  $\geq 220$  and  $\leq 450$ ) > 4 months confirmed by endoscopy or radiology. The primary endpoint was clinical remission (CDAI < 150) at week 4. Subjects who completed study M02-403 and met entry criteria for study M02-433 were given the opportunity to rollover into this study which evaluated the maintenance of clinical remission in subjects with CD.

The CHMP noted that the design of a dose finding and an induction study together made the compared groups small. It was considered acceptable, although the observed difference in terms of remission between the adalimumab 160/80 mg group and the placebo group was just slightly less than the predefined effect (23.3% vs. 25%, respectively). Additionally, patients included had CDAI scores of  $\geq 220$  and  $\leq 450$ , which correspond to patients with moderate disease only. The MAH was asked to calculate the number of subjects corresponding to a severe population, based on overall clinical condition of the patient. No patients with CDAI score > 450 were included in the study. The MAH's proposed a definition of severe disease as patients with CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants. The CHMP accepted this definition, which was then reflected in the product information.

The majority of subjects were women (54%), Caucasian (89%) and the median age was 37 years. The demographics characteristics were considered as generally similar between the groups with a few exceptions. For example, there were a greater proportion of younger subjects in the placebo group compared to the active treatment groups. Disease characteristics were similar between the groups except that a greater proportion of subjects in the highest dose group had CDAI score > 300.

It was noted that 50% of patients had neither steroids nor immunosuppressants at inclusion. Furthermore, approximately 20% of the patients had not received steroids or immunosuppressants prior to the study or at baseline. Consequently, they were naïve not only to TNF $\alpha$  inhibitors but also to

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<sup>4</sup> The Inflammatory Bowel Disease Questionnaire (IBDQ) is a patient status questionnaire, which includes several domains such as social function, systemic system, emotional function and bowel symptoms.

<sup>5</sup> SF-36 health survey is a brief and comprehensive generic, quality of life questionnaire, or rating scale, which is able to distinguish between patients with CD and the general population.

“conventional” treatment. Furthermore, only about 10% of patients had both steroids and immunosuppressants at baseline.

The MAH was asked to clarify the number of patients who represented the population with failure to conventional therapy. The MAH’s definition of refractory patients was not agreed with. It was further acknowledged that the minority of truly refractory subjects in the trial might be a problem in relation to the proposed indication, but this situation was still accepted. The CHMP therefore recommended that the indication should be restricted to patients with severe disease only, due to the safety profile of adalimumab (see discussion on clinical safety).

Steroids and a defined tapering of those were allowed. It was noted that the steroid dose permitted for the induction studies ( $\leq 20\text{mg}$ ) was lower than the permitted dose in the maintenance studies ( $\leq 30\text{mg}$ ). The CHMP asked for further details on steroid use and analyses of the effects of concomitant corticosteroids and/or immunosuppressive in the effect of adalimumab, which were provided by the MAH (see discussion of efficacy below).

#### *Treatment*

A total of 299 subjects were randomised to receive one of four treatment regimens (1:1:1:1) by subcutaneous (sc) injections. Subjects received either adalimumab 160 mg at baseline (week 0) followed by 80 mg at week 2, adalimumab 80 mg at week 0 followed by 40 mg at week 2, adalimumab 40 mg at week 0 followed by 20 mg at week 2, or placebo at week 0 and week 2.

The doses were chosen based on the approved RA dosing of 40 mg eow (every other week), which in RA results in serum concentrations of 4-8  $\mu\text{g/ml}$ . Based on the prediction generated from pharmacokinetic modelling, an initial doubling of the dose was utilised to provide enhanced and sustained adalimumab levels in the beginning of treatment. The dose of 160/80 mg was expected to yield a concentration slightly above 10  $\mu\text{g/ml}$ , which was the serum level that produced near maximal response in the RA programme.

Subjects who experienced disease flare or nonresponse during the CD studies were permitted to continue treatment by switching to open-label adalimumab therapy. Subjects who switched to open-label adalimumab therapy were imputed as failures for the efficacy endpoints.

#### *Results:*

##### Primary Efficacy Endpoint

Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at week 4 compared to placebo (36% vs. 12%;  $p = 0.001$ ), while the results in the 80/40 mg groups was borderline statistically significant ( $p < 0.061$ ). The odds ratios for the difference from placebo in the clinical remission rate were 4.0, 2.3, and 1.5 for the adalimumab 160/80 mg, 80/40 mg, and 40/20 mg groups, respectively. Time to clinical remission was evaluated across the induction regimens. The 25<sup>th</sup> percentile for time to clinical remission was 15 days for adalimumab 160/80 mg (statistically significantly different vs. placebo), 29 days for adalimumab 80/40 mg, and 33 days for placebo.

##### Secondary efficacy endpoints

Statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced CR-100 (49% and 24%, respectively) and CR-70 (58% and 34%, respectively) at week 4. For the adalimumab 80/40 mg and adalimumab 40/20 mg groups at week 4, the only statistically significant differences for adalimumab vs. placebo were for CR-70.

The mean change in IBDQ scores from baseline (week 0) to week 4 was 21 in the placebo group, and 18, 31 and 34 in the adalimumab 40/20 mg; 80/40 mg and 160/80 mg groups. Only the change in the 160/80 mg group reached statistical significance.

There was a greater percentage difference between placebo and CR-100 and CR-70 response in the lower dosing regimens compared to the results for remission. The percentage difference for the highest dosing regimen vs placebo was similar between remission rates and response rates. This might imply

that subjects that are responders to treatment have a good chance of reaching remission with higher doses.

### **Study M04 – 691 (induction)**

#### *Study participants*

The study participants were adults above 18 and below 75 years of age, with a diagnosis of CD confirmed by endoscopy or radiology (CDAI score  $\geq 220$  and  $\leq 450$ ). Subjects had to have responded to an initial infliximab dose, and to receive at least two subsequent doses of infliximab  $\geq 5$  mg/kg every 8 weeks. Subjects were to have discontinued infliximab at least 8 weeks prior to screening. The primary endpoint was clinical remission (CDAI  $< 150$ ) at week 4. The majority of patients were women (65%), Caucasian (94%) and the median age was 37 years. The demographics characteristics were generally similar with a few exceptions. For example, there were a greater proportion of females in the active treatment group compared to the placebo group. The disease characteristics were similar between the groups. The subjects represented a more severely ill population compared to the population in study M02-403. For instance, it was noted that more patients in this study compared with study M02-403 were treated with either steroids or immunosuppressants at inclusion. However, approximately 30% of the patients had not received steroids or immunosuppressants prior to the study or at baseline, which indicates that they had received infliximab as first line treatment earlier, which constitutes an off-label use in Europe.

#### *Treatment*

A total of 325 subjects were randomly assigned in a 1:1 ratio to receive adalimumab 160/80 mg or placebo, at week 0 and 2. Subjects who completed week 4 of the study could be enrolled into study M04-690.

#### *Results:*

##### Primary efficacy endpoint

The proportion of subjects who achieved clinical remission at week 4 was greater in the adalimumab 160/80 mg group compared to the placebo group (21% vs. 7%, respectively,  $p < 0.001$ ).

There were no obvious differences in response to treatment between patients that had loss of response compared to those who had become intolerant to infliximab, although there may be a trend towards a better response in patients with intolerance to infliximab. The effect did not seem to be driven by the anti-infliximab antibody status.

##### Secondary Efficacy Endpoints

The CHMP noted that the  $\Delta$  (delta) percentage of difference between active treatment and placebo was approximately 14 and 18% respectively for CR-100 and CR-70 response (38% vs. 25% and 52% vs. 34%, for adalimumab and placebo respectively). About 40-50 % of patients in this patient group who are generally difficult to treat, improved. Small but statistically significant differences were noted in the IBDQ score and CRP levels.

The CHMP considered that it would have been interesting to include primary non-responders to infliximab in this study. There were some withdrawals in the study and especially in the active treatment arm. As in study M02-403, this was considered as probably at least partly dependent on the short study duration. After clarification from the MAH, it became evident that the definition of loss of response was far too vague to justify an inclusion of a statement in the indication. To justify such statement, an infliximab arm would have been required. Although the justification for intolerance is more relevant, it is probable that subjects were included after minor reactions since only one symptom was required. Furthermore, the delayed reactions seemed unspecific and could have other explanations. The MAH proposed to include the information that primary non-responders were excluded from the studies in the revised product information. This was accepted by the CHMP.



## **Study M02-404 (maintenance)**

### *Study participants*

The study participants were adults above 18 and below 75 years of age, who may have used an anti-TNF $\alpha$  agent (excluding primary non-responders to previous anti-TNF $\alpha$  treatment) with a diagnosis of CD > 4 months (CDAI score  $\geq$  220 and  $\leq$  450).

The mITT<sup>6</sup> (modified intent to treat) analysis set (N = 499) included randomised subjects who achieved a CR-70 at week 4. The first co-primary endpoint was the proportion of subjects in clinical remission at week 26, and the second co-primary endpoint was the proportion of subjects in clinical remission at week 56.

The majority of subjects were women (62%), Caucasian (93%) and the median age was 36 years. The demographics, disease characteristics and the disease related study medication in this study was similar to the induction studies.

### *Treatment*

#### Open label (OL) phase

All 854 enrolled subjects received OL adalimumab induction therapy of 80 mg administered at week 0 and 40 mg administered at week 2.

#### Placebo controlled phase

After the OL phase, at week 4, subjects were stratified by responder status (subject who achieved CR-70) and previous anti-TNF use and were randomised in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg ew (every week), adalimumab 40 mg eow, or placebo. Subjects could have been switched to OL adalimumab 40 mg eow at or after week 12 if they experienced a protocol-defined flare or loss of response (i.e. an increase in CDAI score of at least 70 points and a CDAI score above 220). The dose could have been increased to adalimumab 40 mg ew for repeated flare or nonresponse. Subjects who met CR-70 after week 8 could have been tapered from corticosteroids.

There were a greater number of discontinuations in this maintenance study. The discontinuation due to lack of efficacy and adverse events was higher in the placebo group, at least compared to the adalimumab 40 mg ew group.

Further to the request for supplementary information, the MAH explained that the induction regimen was selected before results from the M02-403 induction dose-ranging study were available. Based on predicted serum concentrations and previous experience from RA, it was assumed that this induction regimen would provide adequate efficacy to initiate treatment of CD.

### *Results*

Of the 854 subjects who entered the OL induction phase, 25% achieved clinical remission, 45% CR-100, and 60% achieved CR-70 at week 4.

#### Primary endpoint

The proportions of mITT subjects who achieved clinical remission at weeks 26 and 56 were statistically significantly greater in the adalimumab 40 mg eow and 40 mg ew compared to placebo (46%, 39%, 17% and 41%, 36%, 12%, respectively). The clinical remission rate for each of the adalimumab groups was statistically significantly greater than placebo at each study visit from week 8 through week 56. The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant, but there was a trend towards a better efficacy in the subjects that received treatment ew.

Among the 260 subjects randomised to adalimumab 40 mg eow maintenance dosing, 71 (27%) dose escalated to 40 mg ew dosing. Among those, 54 (76%) achieved CR-70 response after dose escalation. The MAH argued that dose escalation from 40 mg eow to 40 mg ew may be beneficial for subjects who do not respond to the initial maintenance dose or who lose response. However, the CHMP considered that it has not been possible to identify criteria which could predict such benefit.

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<sup>6</sup> Modified intent-to-treat includes all randomised subjects who received at least one dose of randomised study drug and achieved clinical response at week 4.

Based on the results presented above, the MAH applied for the dosing regimen 40 mg eow, which was accepted by the CHMP.

#### Secondary Endpoint

The proportions of subjects with CR-100 and CR-70 at weeks 26 and 56 were statistically significantly greater for each adalimumab dose *vs.* placebo in the mITT analysis set. These significant treatment differences were noted early (week 8) and remained throughout the double blind phase (week 56).

The proportion of subjects who discontinued steroid use for at least 90 days and were in clinical remission was statistically significant between each of the adalimumab groups (about 20-30%) and the placebo group (3-5%) at weeks 26 and 56. In addition, the proportion of subjects in first steroid-free clinical remission was statistically significant between each of the adalimumab groups (about 30-35%) and the placebo group (3-6%) at week 26, week 56, and both week 26 and week 56. No statistically significant difference was observed between the adalimumab groups. Statistically significant effects were shown on most IBDQ scores.

#### Time to loss of response

The MAH was asked to address information on time to loss of remission when therapy is stopped. In study M02-404, there are controlled data on subjects who were initially treated with open-label induction regimen 80/40 mg and then randomised to blinded placebo maintenance therapy. Overall, 71% of the subjects in remission at week 4 following adalimumab 80/40 mg induction therapy, who were randomised to placebo, lost remission after 12 weeks off therapy (receiving placebo) and 43% of these subjects lost remission after only 4 weeks off therapy (receiving placebo). These data were considered sufficient to address loss of remission. Nevertheless, it is evident that only approximately 35-40% of subjects in the trial were in remission at week 56.

#### Concomitant medication

The CHMP noted that adalimumab showed a steroid-sparing effect in the maintenance trial M02-404, where 23-39% of patients treated with adalimumab were able to be steroid free and still in remission at weeks 26 and 56. However, nearly 80 % of subjects received concomitant medications (corticosteroid and/ or immunosuppressants) during the maintenance study. The MAH presented week 56 data on clinical response and remission for subjects not receiving immunomodulators. The results indicated that more patients on adalimumab than on placebo could be successfully treated without concomitant use of immunosuppressant and corticosteroid treatment.

#### Randomised Non-Responder (RNR) analysis set

A total of 279 subjects did not achieve CR-70 after OL adalimumab 80/40 mg induction therapy and were randomised (RNR analysis set) in a 1:1:1 ratio to one of three blinded treatment groups as described before. The proportions of RNR subjects who achieved clinical remission at weeks 26 and 56 were greater in the adalimumab 40 mg eow (22% and 16%, respectively) and 40 mg ew (9% and 13%, respectively) groups compared to the placebo group (8% and 8%, respectively), however not statistically significant. The only statistically significant difference was between adalimumab 40 mg eow and placebo at week 26.

The CHMP noted that the fact that there is a statistically significant difference between placebo and adalimumab 40 mg eow in this non-responder analysis might indicate that two doses and evaluation after 4 weeks may be a too short time for some subjects to respond on.

#### Fistula analysis

The fistula analysis set consisted of 117 randomised subjects who had draining cutaneous fistulas at both screening and baseline evaluations, to ensure that only subjects with persistent fistulas were included. Based on the anticipated small sample size, the adalimumab 40 mg eow and adalimumab 40 mg ew groups were combined for all fistula analyses *vs.* the placebo group.

The proportions of subjects with one or more draining cutaneous fistulas at both screening and baseline were 18%, 11%, and 16% in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg

ew treatment groups, respectively. Most subjects (97%) had perianal fistulas and most subjects (61%) had only one fistula.

A greater proportion of subjects in the combined adalimumab group compared to the placebo group had no draining cutaneous fistulas at the last two evaluations during double blind treatment, the seventh ranked secondary endpoint (33% and 13%, respectively [ $p = 0.016$ ]). Based on the hierarchical ranking of the major secondary endpoints, this evaluation was not statistically significant.

The difference between the combined adalimumab group and the placebo group in the proportion of subjects with no draining cutaneous fistulas at the last two evaluations on or before week 26 and week 56 were statistically significant (30% and 13% respectively;  $p = 0.043$ ; and (33% and 13%, respectively;  $p = 0.016$ ).

Although the effects described above were noted, the CHMP considered the data insufficiently robust for inclusion in the SPC.

#### *Supportive clinical study*

##### **Study M02 – 433 (maintenance)**

##### *Study participants and treatment*

A total of 276 subjects from study M02-403 were enrolled. Subjects who achieved clinical remission at study M02-433 baseline (week 0), and remained in clinical remission at week 4 were randomised in a 1:1:1 ratio to adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo. Subjects not achieving clinical remission at one or both of these timepoints were assigned to receive OL adalimumab 40 mg eow. Subjects in the randomised group who experienced a protocol-defined flare or were considered non-responders could be switched to OL adalimumab 40 mg eow. Subjects receiving adalimumab 40 mg eow from either the randomised or OL groups who met these criteria for flare or non-response could be switched to adalimumab 40 mg ew.

At week 4, 55 subjects were randomised to placebo, adalimumab 40 mg eow, or adalimumab 40 mg ew and 204 subjects were assigned to OL adalimumab 40 mg eow. A total of 17 enrolled OL subjects discontinued prior to week 4.

The primary efficacy analysis included all randomised subjects who received at least one dose of study drug. The primary efficacy variable was the maintenance of clinical remission at week 56.

#### *Results*

##### **Primary endpoint:**

The proportion of subjects achieving clinical remission for OL, adalimumab ew, adalimumab eow and placebo was 36%, 94% ( $p < 0.05$  vs. placebo), 58% and 39% at week 24 and 36%, 67%, 47% and 33% at week 56, respectively. No statistically significant differences were observed in the OL analysis between the treatment groups. The subjects were to proceed to the adalimumab 40 mg ew regimen only if the adalimumab 40 mg eow regimen was not effective.

##### **Secondary endpoints**

Time in clinical remission was longer in each of the randomised adalimumab groups than in the placebo group. Median time in clinical remission was 120 and 337 days for placebo and adalimumab 40 mg eow, respectively, and could not be determined for the adalimumab 40 mg ew because more than 50% of subjects who attained clinical remission remained in clinical remission at study completion. The difference between placebo and adalimumab 40 mg ew was statistically significant. These results were similar to the time in clinical remission results seen in study M02-404.

##### *Clinical studies in special populations*

No clinical data were submitted on efficacy in special populations. Only 28 patients  $> 65$  and 5 patient  $> 75$  were included. No children were included.

##### *Analysis performed across trials (pooled analyses and meta-analysis)*

There were no significant differences between placebo groups and active treatment concerning for example severity of the disease with the exception that there was a difference in the remission rate

between placebo and active treatment for subjects treated with corticosteroids at baseline. The answer to treatment was higher in patients with corticosteroids at baseline.

### **Discussion on clinical efficacy**

The MAH presented a study programme to support the application for extension of the therapeutic indication to include treatment of patients with moderate to severe CD.

The study program included study M02-403 as a combined dose finding and induction study. At week 4, efficacy was only established for the 160/80 mg induction dosing regimen while the results in the 80/40 mg groups was borderline statistically significant ( $p < 0.061$ ). However, the CHMP considered it not unlikely that patients treated with 80/40 mg eventually should have responded to therapy. The MAH was asked to further present and discuss efficacy and safety data at the 8 and 12 weeks time points in patients who had continued in study M02-433, for the respective induction dose groups. Additional analyses showed similar efficacy for the 160/80 mg and 80/40 mg induction doses at week 8, 38% and 36% of subjects were in clinical remission for the 160/80 mg and 80/40 mg regimens, respectively. In addition, the 12-week data indicated that the total frequency of adverse events (AEs), and especially serious and severe AEs, was higher in the 160/80 mg compared with the 80/40 mg dosing regimen; and that there were higher frequencies of for example, infectious AEs and injection related AEs in the 160/80 mg group (see 4. Clinical safety). Therefore, the CHMP concluded that the 80/40 mg induction regimen should be the first option. However, in situations when a rapid response is required the 160/80 mg dose regimen would be an option, provided that the prescriber is aware of the risks associated with this dose regimen. The MAH revised the product information accordingly.

Further analyses on the impact of concomitant steroid use indicated a statistically significant better efficacy at week 4 in the 160/80 mg induction dose regimen group, for those using corticosteroids at baseline (40% vs. 8%, for adalimumab vs. placebo respectively) than for those not using corticosteroids at baseline (19% vs. 9%, for adalimumab vs. placebo respectively). Thus, concomitant steroid use in the induction phase was considered a predictor for clinical efficacy. The product information was updated to recommend that adalimumab is to be used concomitantly with corticosteroids in the induction phase. However, adalimumab may be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate

The other induction study M04-691 evaluated the 160/80 mg adalimumab dosing regimen in patients who had earlier response to infliximab but lost the response or developed intolerance to infliximab. There was a statistical significant difference (14%) among adalimumab and placebo treated groups, which was smaller than the difference observed in study M02-403. Primary non-responders to infliximab were not included. Treatment with adalimumab might be an alternative in patients who lost response or are intolerant to infliximab. However, the definition of loss of response was far too vague to justify an inclusion of a statement in the indication. To justify such statement, an infliximab arm would have been required in the trial. Also the definition for intolerance to infliximab was insufficient to justify an indication. The MAH agreed to add this information to section 5.1 of the SPC.

In the pivotal maintenance study M02-404 (ITT n=499) the sustained response with patients in clinical remission at week 56 in the treatment group with 40 mg adalimumab eow was 36% compared to 12% for placebo. This was statistically significant and considered a clinically relevant difference; comparable with the results for the earlier approved anti-TNF $\alpha$  agent. However, the CHMP noted that only responders to treatment were included. In the supportive maintenance study M02-433 there were very few subjects in the randomised analyses which made the data difficult to interpret.

## **4. Clinical safety**

The safety of adalimumab was determined through evaluation of AEs, serious adverse events (SAEs), TNF-inhibitor related AEs of interest (which include infections, hypersensitivity reactions, malignancies, congestive heart failure, hepatic events and demyelinating disease events), injection site reactions, clinical laboratory evaluations, physical examinations and vital signs. Safety was assessed in three analysis sets (induction, double-blind maintenance, and all studies).

### *Patient exposure*

The adalimumab development program in CD included safety experience from 1459 subjects who received at least one dose of adalimumab; for cumulative exposure of 1506 patient years, through 14 February 2006. Table 1 below presents the analysis sets for the safety analysis.

**Table 1. Analysis sets for safety analysis**

<b>Analysis Set</b>	<b>studies included</b>	<b>Safety Population</b>	<b>Number of Subjects</b>
Induction	M02-403 M04-691 M02-404	Subjects from M02-403 and M04-691 who received at least one injection of randomized study drug and subjects from M02-404 who received at least one injection of adalimumab during OL induction period	1478 (240 placebo, 74 adalimumab 40/20 mg, 75 adalimumab 80/40 mg DB, 854 adalimumab 80/40 mg OL, and 235 adalimumab 160/80 mg)
Double blind Maintenance	M02-404 M02-433	Subjects who received at least one injection of randomized study drug (adalimumab or placebo)	833 (279 placebo, 279 adalimumab 40 mg eow, 275 adalimumab 40 mg ew)
All Studies	M02-403 M02-404 M02-433 M04-690 M04-691	Subjects who received at least one injection of adalimumab (OL or DB)	1459 (1238 subjects in induction studies [225 in M02-403, 854 in M02-404, 159 in M04-691] and 221 placebo subjects who received adalimumab in extension studies [65 in M02-433 and 156 in M04 690])

The extent of adalimumab exposure during controlled Studies M02-403, M02-404, and M04-691 and extension Studies M02-433 and M04-690 was submitted.

### *Adverse events*

In the induction analysis set, the proportion of subjects reporting at least one treatment-emergent AE was statistically significantly greater in the placebo group compared with the adalimumab 160/80 mg group (73% vs. 63%, respectively;  $p=0.018$ ). The MAH presented the frequency of AEs at week 4, and there were no major differences between the 80/40 mg and the 160/80 mg dosing regimens although the numbers of subjects were considered low. After further analyses of data up to week 12 in study M02-403 patients only who continued to study M02-433 the total frequency of AEs, and especially serious and severe AEs, was higher in the groups who had received 160/80 mg compared with the 80/40 mg dosing regimen; and that there were higher frequencies of for example, infectious AEs and injection related AEs in the 160/80 mg group.

In the induction analysis set, the most frequently reported treatment-emergent AEs ( $\geq 5\%$  of subjects in any treatment group) included injection site irritation, headache, nausea, arthralgia, abdominal pain, injection site reaction, nasopharyngitis, fatigue, CD, and injection site pain. There was a greater proportion of placebo subjects reporting CD compared with adalimumab 160/80 mg treated subjects (9% vs. 3%, respectively;  $p = 0.010$ ). A  $\geq 2$ -fold increase in the incidence of arthralgia was noted in the adalimumab 160/80 mg group compared to the placebo group (5% vs. 2%, respectively). There was no significant difference between the commonly reported possibly drug related AEs ( $\geq 1\%$  of subjects in any treatment group) in the adalimumab group compared to the placebo except for fatigue.

During the double blind treatment in studies M02-404 and M02-433, the overall incidence of treatment-emergent AEs was 85%, 88%, and 85% in the placebo, adalimumab 40 mg eow, and adalimumab 40 mg ew treatment groups, respectively.

The most frequently reported ( $\geq 5\%$  of subjects in any treatment group) treatment-emergent AEs during double blind treatment included CD, arthralgia, nasopharyngitis, headache, nausea, abdominal pain, fatigue, upper respiratory tract infection, pyrexia, influenza, urinary tract infection, injection site reaction, diarrhoea, and pharyngolaryngeal pain.

### *Serious adverse events and deaths*

Two deaths were reported across the five studies. In study M02-404, a 72-year-old white male, died due to pulmonary embolism. In study M02-404, a 56-year-old white female, died from acute leukaemia, 6 months after discontinuation of OL adalimumab 40 mg eow in study M04-690 (definite exposure to adalimumab was approximately one year, with additional potential exposure of 4 months). The first case of death seemed unrelated to the study drug but the second case may be related.

The SAEs reported in the induction analysis set were gastrointestinal disorders, infections and infestations, metabolism and nutrition disorders, among others. From the data presented there were no major dose-dependent differences in SAEs. However, the CHMP alerted that these data have to be interpreted with caution since the number of patients was small. The number of SAEs leading to discontinuation was very small.

No higher risk of SAEs in the different dosing regimens was evident in the double blind maintenance analysis set. The significantly lower number of SAEs in the active treatment group compared to placebo was possibly due to more CD-related effects. There was no difference if SAEs concerning gastrointestinal events were excluded. There were 5 patients with small bowel obstruction in the 40 mg eow group, but there was no apparent relation to adalimumab treatment. Nevertheless, a warning statement was added to the SPC, and the MAH committed to monitor the occurrence of intestinal stricture in ongoing safety studies and the planned registry.

There were more discontinuations due to AEs in the active treatment group, at least with the 80/40 mg dosing regimen.

### *Adverse events of special interest*

#### Infections

In the all studies analysis set, the percentage of subjects reporting at least one infectious AE was 58%. Nasopharyngitis was the most commonly reported infection, followed by upper respiratory tract infection and sinusitis. Infectious AEs at least possibly drug related were reported by 15% of subjects. Furthermore, in the all studies analysis set, the percentage of subjects reporting at least one infectious SAE was 5%. Infectious SAEs at least possibly drug related were reported by 2% of subjects.

In the double blind maintenance analysis set, the percentage of subjects reporting at least one infectious AE was slightly higher in the adalimumab treatment groups compared to the placebo group. However, when summarised as events per 100 PYs (patient years), the pattern of infectious AE rates among treatment groups was lower in each of the adalimumab groups than placebo. Nasopharyngitis was the most commonly reported infectious AE, followed by upper respiratory tract infection and influenza.

#### Opportunistic infections (all analyses set)

Twenty-eight subjects (26 adalimumab and 2 placebo) reported at least one treatment – emergent opportunistic infection. The opportunistic infections resolved in 18 subjects and were ongoing in 10 subjects. Of the 28 subjects reporting an opportunistic infection, 14 had events considered at least possibly drug related. Only one of these events led to premature discontinuation of study drug.

Three subjects (2 from study M02-404 and 1 from study M04-690) reported tuberculosis (TB) or pulmonary TB. Each of the events was considered possibly or probably drug related. Two of the cases occurred in previously tuberculin negative subjects and one in a subject despite a history of adequate prophylaxis for latent TB. This underscores the need for continued surveillance for tuberculosis, with stringent surveillance techniques prior to administration of adalimumab.

#### Malignancy (all analyses set)

Eighteen subjects (16 adalimumab and 2 placebo) reported a total of 19 treatment – emergent neoplasms. Three of the 18 subjects experienced events coded as neoplasms that were not confirmed as malignancies. One additional adalimumab subject experienced an event coded as skin neoplasm that was not confirmed as a malignancy. Five of the 14 subjects with malignancies had non-melanoma skin malignancies. The most common treatment-emergent malignancy was basal cell carcinoma (3

subjects). Nine subjects experienced the following malignancies: breast cancer (2 subjects), papillary thyroid (2 subjects), non-Hodgkin's lymphoma, prostate cancer, ovarian cancer, acute myeloid leukaemia, and bladder cancer. The case of non-Hodgkin's lymphoma occurred in a 61-year-old male, who had also been treated with concomitant AZA.

Of the 18 subjects, six had events considered at least possibly drug related. Eight of the treatment-emergent neoplasm events led to premature discontinuation of study drug and ten were considered SAEs.

From the data presented it was noted that the standardised incidence ratio (SIR) is elevated for several malignancies. However, the number of cases is small and the 95% CI (confidence intervals) were wide and all including 1.00. Therefore no definite conclusions could be drawn but a small risk elevation for developing malignancies cannot be excluded.

#### Immune reactions and drug hypersensitivity

A total of 41 of 1459 subjects reported at least one event of immune reaction. A total of nine subjects prematurely discontinued study drug due to the following immune reactions: serum sickness (3 subjects), drug hypersensitivity (2 subjects), hypersensitivity (2 subjects), systemic lupus erythematosus (2 subjects), and lupus-like syndrome (1 subject).

Thirteen subjects reported AEs of drug hypersensitivity, including two subjects during induction, six subjects during double blind maintenance, four subjects during OL, and one subject during both double blind maintenance and OL. None of these events was considered a SAE. There were no reported cases of type I hypersensitivity or anaphylaxis. Seven subjects reporting seven AEs of drug hypersensitivity were in connection with non-study drugs. Eight of these events were considered at least possibly drug related. Two of the 14 events led to premature discontinuation of study drug.

#### Demyelinating Disease

Two subjects in the all studies analysis set reported demyelinating disease. One of these was considered to be related to study drug and led to premature discontinuation of the study drug.

#### Injection Site Reaction

In the induction analysis set, the most commonly reported injection site reactions treatment-emergent AEs ( $\geq 1\%$  of subjects in any treatment group) were reported in 12% (placebo), 21% (80/40 mg double blind), 13% (80/40 mg OL) and 17% (160/80 mg) of subjects. In the double blind maintenance analysis set, they were reported in 4% (placebo), 13% (40 mg eow) and 13% (40 mg ew) of subjects.

#### Hepatic Events

Hepatic AEs were categorised as hepatobiliary events or investigations. One adalimumab 160/80 mg subject with Gilbert's Syndrome reported hyperbilirubinemia and two adalimumab 80/40 mg OL subjects reported hepatic steatosis. Hepatic steatosis is the most common hepatobiliary lesion found in patients with CD. Adverse events of alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and/or alkaline phosphatase were reported in five adalimumab 80/40 mg subjects and one adalimumab 160/80 mg subject. Increased ALT/AST has been established with adalimumab in other indications.

#### Immunogenicity

Anti adalimumab antibody (AAA) levels were not monitored in the pivotal maintenance study (M02-404). In the induction studies and the supportive maintenance study (M02-433), the overall AAA frequency was 2% (7 of 436 subjects). It seems as AAAs started to appear only after a while in study M02-433, as in 6 out of the 7 patients, AAAs were detected from week 30, resulting in an AAA incidence of 2.6% (7/269 subjects). Consequently, the AAA positive rate was very low in the induction studies (1 of 366 subjects). Among the seven subjects who were AAA positive, 43% were in clinical remission (CDAI  $< 150$ ) at week 24 and 29% remained in clinical remission at week 56 in the maintenance study. In the limited number of subjects with antibodies, there appears to be a tendency of reduced effect, but so far, experience from CD and other indications does not point to safety problems. The CHMP acknowledged that the frequency of AAA seemed low, and lower than reported

for subjects with RA (5%), or in other indications. Currently the data do not allow an explanation of this difference.

Circulating levels of the drug often interfere with the analyses therefore underestimating the rate of antibodies.

#### Laboratory findings

In the induction analysis set, differences were observed between the adalimumab 160/80 mg and placebo treatment groups for the mean change from baseline to the final visit for the following clinical chemistry parameters: albumin, total protein, total cholesterol, lactic dehydrogenase (LDH), alkaline phosphatase, and total bilirubin. Increases in albumin and total protein generally reflected patterns of improvement in CD activity. The remaining treatment group differences were not considered clinically significant.

In the double blind maintenance analysis set, differences were observed between at least one of the adalimumab treatment groups and the placebo group for the mean change from baseline to the final value for the following clinical chemistry parameters: sodium, albumin, calcium, total protein, total cholesterol, alkaline phosphatase, and total bilirubin. Changes in albumin, total protein, and alkaline phosphatase generally reflected patterns of improvement in CD activity. Specifically, albumin and total protein increased relative to placebo and alkaline phosphatase decreased. The remaining treatment group differences were not considered clinically significant. No statistically significant treatment differences were observed between the adalimumab groups.

#### Safety in special populations

##### Intrinsic Factors

Intrinsic factors were investigated through an evaluation of AE incidence rates within specific sub-populations. Only those AEs with a statistically significant difference in relative risk and reported by  $\geq 5\%$  of subjects in any subgroup were discussed and displayed. The relative risk of arthralgia was higher for females than males. For adalimumab 40 mg ew vs. placebo, the relative risk of nausea and upper respiratory tract infection was higher for males than females. For adalimumab 40 mg ew vs. placebo, the relative risk of abdominal tenderness and dyspepsia was higher for males than females.

##### Extrinsic Factors

In the induction analysis set, the relative risk of injection site reaction was higher for subjects without previous anti-TNF use than subjects with previous anti-TNF use. The relative risk of injection site reaction was higher for users of immunosuppressants than non-users of immunosuppressants. For adalimumab 40 mg ew vs. placebo, the relative risk of influenza was higher for users of immunosuppressants than non-users of immunosuppressants. On the other hand, an opposite pattern of risk was observed for upper respiratory tract infection.

There seems to be no specific major sex related difference in AEs. Adalimumab has not been studied in the paediatric Crohn's population. The number of patients above the age of 65 in the Crohn's studies was limited.

#### Discussion on clinical safety

The safety profile observed in the CD studies seemed to correspond to the earlier known safety profile of anti-TNF $\alpha$  drugs with increased risk for infections, including opportunistic infections. Furthermore, uncertainties related to long-term effects remain. Therefore, the CHMP did not agree with the inclusion of moderate disease in the indication.

The total frequency of AEs, and especially serious and severe AEs, was higher with the 160/80 mg induction regimen compared with the 80/40 mg regimen up to week 12 in study M02-433 patients who continued in study M02-433 ; and there were higher frequencies of for example, infectious AEs and injection related AEs in the 160/80 mg group. The CHMP therefore recommended that the 80/40 mg regimen should be the primary option for induction treatment (see also 3. Clinical efficacy).



The CHMP considered that it is important to know if the treatment is effective even with episodic or on-demand treatment i.e. stopping treatment for different time periods and then starting treatment again. The MAH indicated that this kind of regimen is included in study M02-404 where a period of at most 8 weeks off treatment was included. However this period of time was considered too short to really evaluate on-demand treatment. The MAH committed to evaluate episodic treatment in the planned CD registry. Furthermore, the MAH proposed a revision of the product information on readministration if adalimumab has been stopped and signs and symptoms of disease recur. However, it should be noted that there is little experience from readministration after more than 8 weeks since the previous dose.

On request by the CHMP, the MAH presented a separate analysis of those patients (about 10%) who had both corticosteroids and immunosuppressants at baseline. In this limited number of patients, it did not seem that adalimumab treatment in combination with corticosteroids and immunosuppressive agents further increases the risk for opportunistic infections. However, the available safety data was too limited to allow conclusions on this issue. In a literature review, the safety signal about the higher risk of opportunistic infection in patients taking concurrent corticosteroids or other immunosuppressants and TNF-alpha was confirmed. The CHMP considered it important that the MAH undertakes an adequate educational programme on TB prevention. The MAH agreed with the CHMP proposal.

## 5. Risk management plan

No new safety concerns were observed in the CD population as compared to the RA, PsA, and AS clinical databases and post-marketing experience. Existing risk minimisation measures already in place include:

- Detailed instructions on the proper use of the product in the SPC and PL, along with appropriate warnings and precautions to be taken by the physician and patient.
- Regular follow-up of spontaneous adverse event reports as part of standard pharmacovigilance practices
- Patient registries, monitoring of malignancies, educational programs regarding TB prevention
- Patient alert card which reminds patients of the potential for infections/TB and heart failure.
- Analyses of TNF-inhibitor events of interest in PSURs, which include central demyelinating disease, congenital disorders, congestive heart failure, fatal outcomes, lupus and lupus-like illness, malignancies, opportunistic infections, T-cell lymphoma (hepatosplenic), tuberculosis, and vasculitis.

The MAH committed to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

A summary of the risk management plan for adalimumab highlighting the safety concerns with adalimumab is presented below:

### Summary of the risk management plan for adalimumab:

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks: - Tuberculosis (TB) and other opportunistic infections - Congestive heart failure - Serious infections - CNS demyelination - Fatal outcomes	Routine pharmacovigilance activities  Crohn's Disease patient registry: patients from the ongoing CD clinical studies as well as those newly prescribed adalimumab will be offered enrolment into this registry. Abbott plans to	Product information text, SPC sections 4.3, 4.4, 4.8, package leaflet.  TB educational programme extended to physicians treating patients with CD and development of tool to measure effectiveness of educational programme.

<ul style="list-style-type: none"> <li>- Lupus and lupus like-illness</li> <li>- Vasculitis</li> </ul>	<p>follow-up patients on adalimumab for five years. A final report will be submitted 12 months after the completion of the registry.</p> <p>Ongoing long term studies and registry in Rheumatoid Arthritis.</p>	<p>Patient alert card.</p>
<p>Potential risks</p> <ul style="list-style-type: none"> <li>- Malignancies, including lymphoma</li> <li>- Intestinal strictures</li> <li>- congenital disorder</li> </ul>	<p>Routine pharmacovigilance activities</p> <p>Crohn's Disease patient registry: patients from the ongoing CD clinical studies as well as those newly prescribed adalimumab will be offered enrolment into this registry. Abbott plans to follow-up patients on adalimumab for five years. A final report will be submitted 12 months after the completion of the registry.</p> <p>Ongoing long term studies and registry in Rheumatoid Arthritis.</p>	<p>Product information text, SPC sections 4.4, 4.6, 4.8, package leaflet</p>
<p>Missing information</p> <ul style="list-style-type: none"> <li>- Long-term safety in CD patients</li> <li>- Episodic treatment</li> <li>- Hepatosplenic T-cell lymphoma</li> </ul>	<p>Routine pharmacovigilance activities</p> <p>Crohn's Disease patient registry: patients from the ongoing CD clinical studies as well as those newly prescribed adalimumab will be offered enrolment into this registry. Abbott plans to follow-up patients on adalimumab for five years. A final report will be submitted 12 months after the completion of the registry. This registry will collect data on treatment interruptions and readministration of adalimumab.</p> <p>Ongoing long term studies and registry in Rheumatoid Arthritis.</p>	

In the safety specifications provided by the MAH, reference was made to the CD indication. In future submissions, the safety specifications should address all approved indications. The MAH committed to submit an updated risk management plan as per the CHMP Guideline on Risk Management Systems for medicinal products for human use, covering all indications. This information was reflected in the annex II of the CHMP opinion.

## 6. Overall discussion and benefit/risk assessment

Crohn's disease is a chronic inflammatory bowel disease which most often begins during adolescence and young adulthood and in severe cases the patients may suffer from e.g. malabsorption and abdominal pain which results in a severe impact on the daily activities with a decreased ability to work or study. Therefore it is important to evaluate new treatments for this disease. At present there is one approved anti-TNF $\alpha$  agent for treatment of Crohn's disease. One of the main issues with anti-TNF therapy is to satisfactorily describe the population intended for treatment because of uncertainties about the long-term safety but also long-term efficacy. Risk for malignancies is still under surveillance.

Three pivotal studies, two induction studies (M02-403 and M04-691) and one maintenance study (M02-404) and one supportive maintenance study (M02-433) have been submitted to justify the indication in Crohn's disease.

Study M02-403 was a combined dose finding and induction study. The MAH initially claimed that efficacy was only established for the 160/80 mg induction dosing regimen (n=76), a higher dose than the doses used in other indications. However, the MAH investigated the difference in remission rate and safety profile between patients that received 160/80 mg or 80/40 mg as an induction regimen after 8 and 12 weeks, in patients on maintenance treatment (40mg eow). The efficacy and safety data suggested that the different treatment regimens are similar according to remission rate at week 12. Furthermore, there were trends towards a lower frequency of adverse events in the 80/40 mg compared to the 160/80 mg regimen. The induction regimen proposed for this indication was thus 80/40 mg. However, in situations when a rapid response is required the 160/80 mg dose regimen would be an option, provided that the prescriber is aware of the higher risk for adverse events with this dose regimen. The data indicated also a statistically significant better efficacy at week 4 when adalimumab 160/80 mg was used together with corticosteroids compared with adalimumab without steroids. Thus, concomitant steroid use was a predictor for clinical efficacy.

With respect to episodic treatment, the MAH agreed to study the interruption and readministration of adalimumab in the registry setting. The option for readministration if signs and symptoms of the disease recur is considered important, given e.g. the uncertainties with long-term anti-TNF treatment. The product information was updated accordingly.

In the pivotal maintenance study M02-404 (mITT n=499) the sustained response with patients in clinical remission at week 56 in the treatment group with 40 mg adalimumab eow was 36% compared to 12% for placebo. This was statistically significant and a clinically relevant difference; comparable with the results for the earlier approved anti-TNF $\alpha$  agent. However, the CHMP noted that only responders to treatment were included. In the supportive maintenance study M02-433 there were very few subjects in the randomised analyses set which made the data difficult to interpret.

The CHMP noted that adalimumab showed a steroid-sparing effect in the maintenance trial M02-404, where 23-39% of patients treated with adalimumab were able to be steroid free and still in remission at weeks 26 and 56. However, nearly 80 % of subjects received concomitant medications (corticosteroid and/ or immunosuppressants) during the maintenance study. The week 56 data on clinical response and remission for subjects not receiving immunomodulators indicated that more patients on adalimumab than on placebo could be successfully treated without concomitant use of immunosuppressant and corticosteroid treatment.

The safety profile seemed to be correspondent to the earlier known safety profile of anti-TNF $\alpha$  drugs with increased risk especially for opportunistic infections. There were trends towards more AEs in the higher induction dosing regimen of 160/80 compared to 80/40mg. However, the groups directly comparing safety data between induction doses 160/80 and 80/40 were small.

The RMP was considered acceptable. The MAH agreed for the next revision of this plan, to update the safety specification section with all approved indications. The RMP has also been updated with a presentation of ongoing safety studies in CD, but still lacks such tabulation for all indications. The MAH committed to long-term follow up of patients from the CD trial, to be reported within PSURs, as

well as setting up a registry in the EU. The MAH also committed to expand the TB educational programme to CD, and to study its effectiveness.

Based on the data presented, the CHMP did not agree to include moderate disease in the indication, and agreed that treatment should be severe, active disease.

The review of the MAH's different proposals for the SPC, section 4.8, and particularly Table 1 in this section led to doubts regarding the MAH's procedures to adequately handle the safety data base, including undertake adequate medical assessment. With respect to overall pharmacovigilance, the MAH provided a brief summary of its global system and of signal detection, which, on the level described, seem to be in line with requirements. Nevertheless, the CHMP considered there are still some questions related to the MAH's approach for handling these different activities. The need for a GCP/Pharmacovigilance inspection was agreed with by the CHMP, not precluding the approval of the current application.

#### **IV. CONCLUSION**

On 26 April 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the summary of product characteristics, annex II and the package leaflet, subject to the additional commitments undertaken.

Medicinal Product no longer authorised