

London, 27 April 2006
Product name: **HUMIRA/TRUDEXA**
Procedure number: **EMEA/H/C/481-482/II/26**

SCIENTIFIC DISCUSSION

3.1. Introduction

Adalimumab is a recombinant human immunoglobulin (IgG₁) monoclonal antibody 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) and psoriatic arthritis (PsA).

Ankylosing spondylitis (AS) is a chronic inflammatory disorder of unknown cause that involves primarily the sacroiliac joints and the axial skeleton. Clinical manifestations usually begin in the second or third decade, and include lower back pain with predominant nocturnal pain and morning stiffness. Chest pain, pain and swelling of peripheral joints and extra-articular tenderness may occur as well as several extraskeletal manifestations such as acute anterior uveitis (severe inflammatory eye disease), cardiac conduction defects, aortic valve disease or renal disease, mainly in the form of secondary renal amyloidosis.

The male to female prevalence is estimated to be 2-3:1. AS is a largely genetically determined disease correlated with the histocompatibility antigen HLA-B27 (human leukocyte antigen B27) and occurs worldwide roughly in proportion to the prevalence of this antigen. The association with B27 is independent of disease severity.

AS is an immunologically mediated disease state in which TNF is present as a cytokine mediating inflammation in the axial skeleton. Increased concentration of TNF in joints has also been shown.

The MAH submitted 2 clinical studies (M03-607 and M03-606) conducted in patients with AS to support an indication for adalimumab, administered at a dose of 40 mg subcutaneously (sc) every other week (eow), for "reducing the signs and symptoms of active ankylosing spondylitis".

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

3.2. Clinical aspects

To support the indication the MAH submitted 2 pivotal clinical studies designed primarily for the evaluation of efficacy and safety of adalimumab in patients with active AS. They were phase 3, placebo-controlled, double-blind, randomised, multicentre studies designed to demonstrate the safety and efficacy of adalimumab in the treatment of active AS in subjects who had an inadequate response or were intolerance to one or more non-steroidal anti-inflammatory drug(s) (NSAIDs) and who may have had additionally failed disease-modifying anti-rheumatic drug (DMARD) therapy.

3.2.1 Clinical pharmacology

Pharmacokinetics (PK) and pharmacodynamics (PD) and immunogenicity

The clinical pharmacology (PK/PD) and immunogenicity of adalimumab have been characterised in healthy subjects as well as in RA subjects.

PK analyses of trough concentrations were performed in study M03-607. The medium adalimumab apparent clearance (CL/F) value was 13.3 ml/h, which was lower than that observed in patients with RA (18 ml/h). This finding was consistent with the observation that the mean trough concentrations of adalimumab (6-7 µg/ml) observed in patients with active AS after treatment with sc adalimumab 40 mg eow as monotherapy were slightly higher than those observed in subjects with RA (5 µg/ml) in monotherapy. However, the true magnitude of the difference in CL/F between the two populations cannot be adequately quantified due to differences in timing of sample collection.

The median apparent volume of distribution (V/F) of adalimumab in subjects with AS (11.4 l) was comparable to the observed in subjects with RA (11.2 l).

Although the exposure to adalimumab in AS subjects on monotherapy appeared to be slightly higher, the safety profile from the study M03-607 in the AS population was considered favourable and similar to the data from the RA population.

The immunogenicity of adalimumab was evaluated in study M03-607. Subjects were classified as anti-adalimumab antibody positive (AAA+) if they tested AAA+ at weeks 12 or 24 of treatment. Overall, the AAA+ rate for adalimumab-treated subjects was 8% within the first 24 weeks (adalimumab 9% [16/185], adalimumab plus MTX 5% [1/19]).

The CHMP requested supplementary information related to the potential relationship between the presence of antibodies and efficacy and safety outcomes, as well as concomitant use of MTX/DMARD. Further to the assessment of supplementary information, the CHMP concluded that the data are too limited to draw definitive conclusions regarding the impact of AAA on both efficacy and safety.

3.2.2 Clinical efficacy

Studies M03-607 and M03-606

Study participants

The study participants were adults above 18 years of age, with AS at baseline, as defined by the modified New York criteria¹. Subjects had a diagnosis of active AS, as defined by a fulfilment of at least 2 of the following 3 criteria: bath AS disease activity index (BASDAI) score ≥ 4 , visual analog scale (VAS) score for total back pain ≥ 40 mm (4 cm) and/or morning stiffness ≥ 1 hour. Subjects were allowed to continue on sulfasalazine (SSZ) (≤ 3 g/day) and/or MTX (≤ 25 mg/week) and/or hydroxychloroquine (≤ 400 mg/day) and/or prednisone (≤ 10 mg/day) (and/or prednisone equivalents) and/or NSAIDs as long as these doses remained stable for 4 weeks prior to baseline. Patients who had been treated with anti-TNF therapy were excluded.

The majority of subjects were men (76%), Caucasian (95%) and the median age was 42 years.

In both studies, inclusion and exclusion criteria were similar except that patients with total spinal ankylosis were included in Study M03-607 (not to exceed 10% of total enrolment), but excluded at screening from Study M03-606.

The inclusion criteria were considered acceptable.

Treatments

Patients were randomised in a 2:1 (M03-607) or 1:1 (M03-606) ratio to each of the 2 treatment groups. In total, patients received adalimumab 40 mg eow sc (n=246) or matching placebo (n=151) during the 24-week placebo controlled period. The 24 week period of each study was followed by an open-label period during which subjects received adalimumab for up to an additional 80 weeks. The studies were unblinded after all subjects completed the 24-week double-blind portion.

¹ Modified New York criteria

1. History: low back pain ≥ 3 months improved by exercise and not relieved by rest;
2. Examination: limitation of lumbar spine in sagittal and frontal planes; chest expansion relative to normal values corrected for age and sex;
3. Radiology: bilateral sacro-iliitis grade 2 (minimal abnormality)-4 (severe abnormality) or unilateral sacro-iliitis grade 3 (unequivocal abnormality)-4.

Subjects who failed to achieve ASAS² 20 response criteria at the weeks 12, 16 or 20 visit could:

1. Remain on blinded study medication through week 24; or
2. Initiate open-label adalimumab 40 mg eow (early escape open-label, EEOL); or
3. Discontinue study medication and participation in the trial

Subjects who completed 24 weeks of blinded therapy and who failed to achieve ASAS 20 response criteria on or after the week 36 visit (*i.e.*, after 12 weeks of open-label treatment of adalimumab 40 mg eow) could:

1. Increase the frequency of adalimumab to 40 mg weekly; or
2. Discontinue study medication and participation in the trial.

Further to the request for supplementary information, the MAH submitted the safety data for the 38 patients in open label treatment that received 40 mg of adalimumab weekly. No conclusions could be drawn as the number of patients was limited, although there did not appear to be any increase in adverse events.

Regarding concomitant treatment, the dose of corticosteroids, MTX, SSZ, or hydrochloroquine should not have been initiated or increased before week 36. However, the dose of corticosteroids could be decreased, or completely eliminated after week 24 at the investigator's discretion. The dose of MTX, SSZ, or hydrochloroquine should not have been decreased prior to week 36.

The design of the studies was considered acceptable, however, the EEOL option was considered to add difficulties in the interpretation of the efficacy data beyond week 12.

Outcomes/endpoints

The primary efficacy endpoints in both trials were reduction of signs and symptoms as measured with the ASAS 20 response at week 12 and inhibition of progression of structural damage in spine as measured with the change of the modified stoke AS spine score (mSASSS) from baseline to week 104. The data relating to the inhibition of progression of structural damage in spine will be assessed when available.

ASAS 20 response was defined as improvement of at least 20% and absolute improvement of at least 10 units on a 0-100mm scale from baseline in at least 3 of the following 4 components: Patient's Global Assessment of disease activity, pain assessment represented by total back pain, function represented by the Bath AS functional index (BASFI), and inflammation (morning stiffness). An ASAS responder must have shown an absence of deterioration in the potential remaining domain, where deterioration was defined as a worsening of $\geq 20\%$ and a net worsening of ≥ 10 units (on a scale of 0-100).

The major secondary endpoints included:

- ASAS 20 response at week 24
- ASAS 50 and ASAS 70³ response at weeks 12 and 24
- Change from baseline in BASDAI (Bath AS disease activity index) score at weeks 12 and 24
- Change from baseline in BASFI (Bath AS functional index) at weeks 12 and 24
- Change from baseline in CRP (C-reactive protein) at weeks 12 and 24
- Change from baseline in the Bath AS metrology index (BASMI) at weeks 12 and 24
- Change from baseline in SF-36 (36 item short form health survey) physical component summary at week 24
- Change from baseline in the AS quality of life questionnaire (ASQoL) at week 24

2 ASAS: Assessment in Ankylosing Spondylitis Working Group (see Outcomes/endpoints).

3 ASAS 50: improvement of at least 50% and absolute improvement of at least 20 units response from baseline in at least 3 of 4 domains as defined for ASAS 20, , without deterioration in the potential remaining domain.

ASAS 70: improvement of at least 70% and absolute improvement of at least 30 units response from baseline in at least 3 of 4 domains as defined for ASAS 20, , without deterioration in the potential remaining domain.

Deterioration for ASAS50 and ASAS70 is defined as a change for the worse of at least 20% and a net worsening of at least 10 units.

➤ Change from baseline in the functional assessment of chronic illness therapy (FACIT) fatigue at week 24 (Study M03-606 only)

Statistical design

In total, 397 subjects were enrolled in both studies.

ASAS 20 response rates of the adalimumab group were compared with the placebo group using Pearson's Chi-square test. Analysis was conducted as a non-responder imputation so any subject who discontinued or had missing values at week 12 was considered a non-responder at subsequent visits. The secondary efficacy analyses of the primary efficacy variable were supportive.

To assess the impact of the missing data, a sensitivity analysis was performed if the analysis of the ASAS 20 at week 12 demonstrated significant difference between adalimumab and placebo.

Results

Patients disposition

Both studies had nearly identical populations, dosing regimens and primary and secondary endpoints.

M03-607

The median disease duration at baseline was approximately 8 years. Approximately 56% of subjects were not on DMARD treatment. At baseline, 79% of the subjects had concomitant NSAID and 10% of the subjects had concomitant corticosteroid treatments. Seventy nine percent of subjects were HLA-B27 positive.

Through 12 weeks of double blind study drug administration, 98% of the adalimumab treated subjects and 96% of the placebo treated subjects completed the study.

At week 24, around 94% of the subjects were still enrolled in the study, and 27% of subjects originally randomised to placebo completed week 24 while remaining on double blind study drug. Sixty seven percent of subjects originally randomised to placebo entered the early escape group and received open-label adalimumab. A total of 155 subjects entered the EEOL. Among subjects originally randomised to adalimumab, 58% completed through week 24 on double blind study drug while 36% entered the early escape group.

Six percent of subjects originally randomised to placebo and 6% of subjects originally randomised to adalimumab were discontinued from the study prior to week 24. The main reasons for discontinuation were adverse events (approximately 2% of placebo treated subjects and 3% of adalimumab treated subjects)

M03-606

The median disease duration at baseline was 13 years. Approximately 66% of subjects were not on DMARD treatment. At baseline, 90% of the subjects had concomitant NSAID and 16% of subjects had concomitant corticosteroids treatments. Eighty four percent of subjects were HLA-B27 positive.

Through 12 weeks of double blind study drug administration, 100% of the adalimumab and the placebo treated subjects completed the study.

At week 24, around 98% of the subjects were still enrolled in the study.

Efficacy results

The summary of the ASAS 20 response at week 12 and 24 is presented in Table 1 below.

Table 2 ASAS 20 response at week 12 and 24 – imputed

ASAS 20 Response	M03-607		M03-606		Combined M03-607 and M03-606	
	Placebo (N=107) n(%)	Adalimumab (N=208) n(%)	Placebo (N=44) n(%)	Adalimumab (N=38) n(%)	Placebo (N=151) n(%)	Adalimumab (N=246) n(%)
Week 12						
Reponder	22 (20.6)	121 (58.2)	12 (27.3)	18 (47.4)	34 (22.5)	139 (56.5)
Non-responder	82 (76.6)	83 (39.9)	32 (72.7)	20 (52.6)	114 (75.5)	103 (41.9)
Missing	3 (2.8)	4 (1.9)	0	0	3 (2.0)	4 (1.6)
Difference between treatment groups % (95% CI); p-value^a	37.6 (27.4, 47.8); <0.001***		20.1 (-0.5, 40.7); 0.060		34.0 (24.9, 43.1); <0.001***	
Week 24						
Reponder	20 (18.7)	105 (50.5)	7 (15.9)	13 (34.2)	26 (17.2)	118 (48.0)
Non-responder	83 (77.6)	96 (46.2)	37 (84.1)	24 (63.2)	121 (80.1)	120 (48.8)
Missing	4 (3.7)	7 (3.4)	0	1 (2.6)	4 (2.6)	8 (3.3)
Difference between treatment groups % (95% CI); p-value^a	31.8 (21.8, 41.8); <0.001***		18.3 (-0.3, 36.9); 0.054		30.7 (22.1, 39.4); <0.001***	

*** Statistically significant at the p=0.001 level.

CI: Confidence Interval

a. p-value is from Pearson's Chi-square test. Subjects with missing data at week 12 are counted as non-responders.

M03-607

The results from the 24 week double blind portion of study M03-607 showed that statistically significant differences were observed between adalimumab and placebo treatments in the primary endpoint, ASAS 12 at week 12. Statistical significant differences were also observed for other secondary endpoints.

Of note, 155 subjects entered EEOL adalimumab at week 12. Of these, 74 subjects in the placebo treatment group received EEOL therapy, 55% of which were ASAS 20 responders at week 16. In comparison, at week 16, of the 78 subjects in the adalimumab treatment group who received EEOL therapy, 31% of subjects were ASAS 20 responders. This response rate increased over the remaining weeks.

M03-606

Similar trends (not all statistically significant) were seen in the smaller randomised, double-blind, placebo controlled Study M03-606 of 82 adult patients with active ankylosing spondylitis.

For the primary analysis, 47% of the subjects in the adalimumab treatment group achieved a week 12 ASAS 20 response compared to 27% of the subjects in the placebo treatment group. This difference did not reach statistical significance (p=0.06). The same pattern was observed for the analysis of the secondary endpoint ASAS 20 at week 24.

Discussion on clinical efficacy

Overall, considering the pooled data, statistically significant differences towards placebo were reached in most efficacy endpoints at week 12. Fifty seven percent of adalimumab treated subjects combined across both studies achieved an ASAS 20 response at week 12, compared to 23% of placebo treated patients ($p < 0.001$). At week 24, 48% of adalimumab treated subjects combined across both studies achieved ASAS 20 response compared to 17% of placebo treated subjects ($p < 0.001$).

In study M03-607 efficacy was shown with ASAS 20 and its components at weeks 12 and 24. However, the number of patients fulfilling criteria for non-response at week 12 and entering into the EOL group was high in both the placebo and active groups. Although the proportion of non-responders was similar to other approved indications for adalimumab, the design of this study made further interpretation of efficacy results difficult.

Further to the CHMP request for supplementary information, subgroup analyses of the BASDAI response were performed. The results showed that there was no evidence of a treatment difference between subgroups.

The observed responses were similar in subjects who were HLA-B27 positive as compared to those who were negative. The number of subjects treated concomitantly with MTX or other DMARD was relatively low. However, no significant difference in response was observed between the groups.

The CHMP expressed concerns relating to intermittent treatment. The mean duration of interval between given doses was 42 days. However, a longer interval was considered of interest. The MAH committed to further investigate this issue.

3.2.3 Clinical safety

Patient exposure

In both M03-607 and M03-606, 397 subjects were randomised to 1 of the 2 treatment groups. The safety was determined from the 24 week double blind periods of the two pivotal studies.

The mean exposure for the 393 subjects receiving any adalimumab in the combined analysis was 248.5 days (median exposure 259 days). All subjects who enrolled in the two studies received at least 2 weeks of exposure to adalimumab until the cut-off date. As of the cut-off date, 6% of subjects had been exposed to the drug for more than 52 weeks.

Exposure to adalimumab within the sought indication was considered sufficient by the CHMP.

Adverse events (AE)

All subjects who received at least one dose of the study drug were included in the safety analysis. The safety of adalimumab in AS was determined through an evaluation of AEs, serious AEs (SAEs), AEs of interest (malignancy, lymphoma, tuberculosis (TB)/granulomatous infections, demyelination, drug-induced lupus, and congestive heart failure [CHF]), clinical laboratory evaluations, physical examinations, and vital signs.

During the AS clinical development program, a treatment-emergent AE (TEAE) was defined as any AE with onset or worsening reported by a subject from the time that the first dose of study drug was administered until five adalimumab half-lives (70 days) had elapsed following discontinuation of study drug administration.

M03-607

Up to week 24, a higher percentage of adalimumab-treated subjects experienced a TEAE compared to placebo-treated subjects.

No deaths, malignancies, or serious infectious were reported by adalimumab treated subjects. There were two reported cases of drug hypersensitivity, one considered not related to the study drug in a placebo treated subject and one considered as probably related in an adalimumab treated subject. No events of TB/granulomatous infections, demyelination, drug-induced lupus or congestive heart failure were reported by adalimumab treated subjects.

The mean changes from baseline in serum chemistry values observed in adalimumab-treated subjects were small. The increases in cholesterol and triglycerides to a more normal value observed in study M03-607 were similar to the ones observed in previous studies for RA and PsA.

Eight (8) adalimumab-treated subjects had post-baseline ALT (alanine aminotransferase) values ≥ 3.0 x upper limit of normal (ULN). Six of these 8 subjects had abnormally high values at baseline; the remaining 2 subjects had a single post-baseline ALT elevation that resolved on continued treatment with adalimumab. Two of the 8 subjects had AEs reported in association with elevated ALT values.

The most common reported AEs (incidence $\geq 5\%$) were nasopharyngitis (13% for adalimumab and 8% for placebo treated groups) and headache (10% for adalimumab and 8% for placebo treated groups). As compared to the known safety profile of adalimumab, no new safety signals were found in this study.

M03-606

The overall incidence of treatment-emergent AEs, irrespective of relationship to study drug, was higher in the adalimumab than placebo treatment groups. The incidence of infectious AEs was also higher in adalimumab treated groups as compared to placebo group. Most of the infectious AEs reported in either treatment group were mild or moderate in severity.

The most common reported AEs were nasopharyngitis (18% for adalimumab and 11% for placebo treated groups), headache (13% for adalimumab and 7% for placebo treated groups), upper respiratory tract infection (13% for adalimumab and 2% for placebo treated groups), arthralgia (11% for adalimumab and 12% for placebo treated groups) and dizziness (5% for both groups).

Risk management plan (RMP), pharmacovigilance plan and risk minimisation plan

The risk management plan submitted was specific to the AS clinical program and patient population. The currently identified risks for adalimumab will continue to be monitored. Events of interest will continue to be analysed in the periodic safety updated reports (PSURs), and are noted in the long-term studies and registries which are currently ongoing. As no new risks were identified in the AS clinical program, the relevant sections of the SPC will be updated as more information becomes available from the post authorisation commitments or clinical experience. With regard to monitoring of potential safety signals associated with adalimumab, the MAH has agreed to various follow-up measures (FUMs) in previous applications. Any potential safety issues and associated action plans identified in the course of these FUMs will be applied as appropriate to the AS population.

The MAH will continue to collect long-term safety and efficacy data. Additionally, the routine pharmacovigilance practices, and safety monitoring beyond routine pharmacovigilance undertaken as part of FUMs will continue.

In conclusion, as no new safety concerns were observed in the AS population as compared to the large RA and PsA clinical databases and post-marketing experience, no new risk minimisation measures were proposed. Existing risk minimisation measures already in place are applicable to the AS.

Discussion on clinical safety

In the performed studies no new safety signals were found.

At week 12, there was a statistically significant difference ($p=0.012$) in the AEs reported in the adalimumab group (72%, 177 subjects) when compared to the placebo (60%, 90 subjects) group. At Week 24, there was a statistically significant difference in the AEs reported in the adalimumab group ($p=0.001$), AEs at least possibly related to the study drug ($p=0.002$), and infectious AEs ($p=0.006$) when compared to the placebo group. At Week 24, severe AEs, AEs leading to discontinuation, and serious infectious AEs showed no statistically significant differences between adalimumab and placebo for the Controlled Studies. Adverse events at least possibly drug-related were more common in adalimumab treated subjects (adalimumab: 35.0%; placebo: 20.5%); with attribution of injection site reactions (adalimumab: 10.2%, placebo: 4.6%) and infectious AEs (adalimumab: 21.2 %, placebo: 34.1%).

The most common TEAEs (occurring in $\geq 5\%$ of subjects) in either the combined adalimumab or placebo treatment groups of the controlled studies were nasopharyngitis (13%), headache (11%), Upper respiratory tract infection (7%) and fatigue (5), were reported more frequently at week 24 in adalimumab-treated subjects.

Laboratory monitoring identified that ALT elevations ($\geq 3 \times$ ULN) were observed in 9 (6 during the double-blind period and 3 during the open-label period) adalimumab treated subjects.

One malignancy (Non-Hodgkin's lymphoma) was reported in the open-label period.

There were no TB/granulomatous infections, demyelination, drug induced lupus, or CHF reported during the open label.

The risk management plan was specific to the AS clinical program and patient population. It was noted that there were no safety issues specific to the AS patient population observed in the clinical program. Therefore, no additional risk minimisation measures were proposed.

3.3. Overall discussion and benefit/risk assessment

The MAH submitted 2 pivotal studies to support the use of adalimumab in AS. Patients included in these studies had similar disease activity, similar baseline characteristics and similar concomitant treatments as in previous anti-TNFs approved for treatment of AS.

In study M03-607, the primary endpoint, ASAS 20, was statistically significantly superior to placebo. However, in the smaller study M03-606, statistically significant superiority in ASAS 20 was not reached but statistical significance was reached in most secondary endpoints. Despite the lack of statistical significance for the primary endpoint in this smaller study, efficacy is generally supported based on the totality of data.

Discussions were held whether ASAS20 as a goal when using a TNF- α blocker seems too low. Consideration was given to the ASAS recommendation, that response to therapy be assessed by a 50% reduction or fall of two or more units in BASDAI. The MAH was therefore requested to provide data on BASDAI 50 response in patients with active disease (BASDAI score at baseline ≥ 4). The results of this subgroup analysis were consistent with the results of the previously submitted subgroup analyses in that adalimumab subjects achieved a greater clinical response when compared with placebo within each subgroup, and that there is no evidence of a treatment difference between the subgroups.

At baseline, the majority of patients had no concomitant DMARD therapy. However, approximately 20% were on DMARD therapy, which was allowed during the study. Although the data are limited, further analyses indicate that efficacy and safety have been shown in both populations. This was also found in additional subgroup analyses of patients positive and negative for HLA-B27.

In responding subjects, efficacy was generally achieved within a short time period after initiation of treatment. However, some patients will likely not gain benefit (non-responders), and in those termination of treatment should be considered.

No TB, opportunistic infections, malignancies or deaths occurred in the blinded period of the studies. One benign lung neoplasm and one Hodgkin's lymphoma were found during open-label treatment. The safety of adalimumab in the claimed indication was considered similar to the already known safety profile in other approved indications.

The MAH has submitted a risk management plan that was considered acceptable. In addition, the changes proposed to the product information reflect the information currently available on the claimed indication and were agreed with.

The CHMP concluded that the risk/benefit balance for adalimumab treatment 40 mg e.o.w., in AS, with the following indication : *Humira/Trudexa' is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy* is positive.

IV. CONCLUSION

On 27 April 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, and Package Leaflet, based on the observations and the appropriate conclusions, and subject to the post authorisation commitments undertaken by the MAH.