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SCIENTIFIC DISCUSSION

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Introduction

Adalimumab is a recombinant human immunoglobulin (IgG_1) monoclonal antibody containing human peptide sequences that binds to human Tumor Necrosis Factor (TNF) alpha and neutralises the biological function of TNFα by blocking its interaction with the p55 and p75 cell surface TNFα receptors.

Adalimumab is currently approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD) and psoriasis (PsO).

The initial PsA indication was approved in 2005 through variation II.22 (Commission decision of 1 August 2005). To support the initial application the marketing authorisation holder (MAH) submitted two placebo-controlled Phase 3 clinical studies (M02-518 and M02-570) and an interim report of the open-label long-term extension study (M02-537).
In the present variation application, the MAH applied for an extension of the PsA indication for adalimumab to include reduction of the rate of progression of joint damage as measured by X-ray and improvement of physical function.
To support the joint damage claim the MAH submitted X-ray data, from the previously submitted study M02-518 and the long-term extension study M02-537. The claim of improved physical function was based on data from studies M02-518 and M02-570. With the submission of the final clinical study report (CSR) for Study M02-537, the MAH also fulfilled the outstanding follow up measure (FUM) No 25.

PsA is a chronic, inflammatory, usually rheumatoid factor (RF)-negative arthritis associated with psoriasis. According to European (EU) guidance for treating PsA, psoriasis is prevalent in 1% to 3% of the population. Estimates of those psoriasis patients who develop PsA vary widely (6%-42%). Affecting men and women equally, PsA typically appears between the ages of 30 and 50 years. PsA usually involves multiple peripheral joints, the axial skeleton, sacroiliac joints, fingernails, and entheses. The presentation of PsA has been categorized into 5 overlapping clinical patterns, which include oligoarthritis, polyarthritis, arthritis of distal interphalangeal (DIP) joints, spondylitis, and arthritis mutilans. More than one-half of the patients with PsA may have evidence of erosions on X-rays, and up to 40% of the patients may develop severe, erosive arthropathy.

PsA has some similar symptoms to RA, including joint pain and destruction and fatigue. PsA can be distinguished from RA by one or more factors (e.g. presence of psoriasis; seronegative for RF (> 80% of patients); patterns of joint involvement including asymmetry, distal interphalangeal disease, and spinal disease; dactylitis; enthesitis), but overall PsA and RA are closely related diseases. Most treatments used are similar.

The MAH proposed to amend the text of the summary of product characteristics (SPC) sections 4.1, and 5.1, and to update the package leaflet (PL) accordingly. Minor changes were proposed to sections 4.2 and 4.8.

Clinical aspects[1]

Clinical efficacy

Main studies
Adalimumab was studied in two controlled clinical studies (M02-518 and M02-570) in subjects with active PsA. Both were double-blind studies with a 1:1 randomisation of adalimumab 40 mg every other week (eow) versus placebo. Subjects who completed Study M02-570 (12 weeks duration) or

[1] A summary of the details of the studies referred in this section is presented in the Clinical efficacy section. This report addresses the data submitted for the proposed change to the indication and other product information wording changes. For more detailed information on the initial trials please refer to the scientific discussion published at http://www.emea.europa.eu/humandocs/PDFs/EPAR/humira/EMEA-H-481-II-22-AR.pdf.

M02-518 (24 weeks duration) and who met the inclusion criteria were eligible to participate in M02-537, a multicentre, open-label long-term extension study.

Study M02-518 was 24 weeks in duration. It was required that subjects had inadequate non steroid anti-inflammatory drug (NSAID) response and subjects were stratified by methotrexate (MTX) use and extent of Ps (≥ 3% body surface area [BSA] or < 3% BSA) at baseline. There were 313 subjects included.

Study M02-570 was 12 weeks in duration and included 100 subjects. It was required that subjects had inadequate response to DMARD therapy, and subjects were stratified by DMARD use at baseline.

Study M02-537 was conducted to study the long-term safety, efficacy, and pharmacokinetic (PK), including immunogenicity, of repeated administration of 40 mg adalimumab eow (or 40 mg adalimumab weekly for subjects who met criteria for dose escalation). Subjects were treated for up to 120 weeks or until adalimumab was commercially available for PsA in the subject's study participation country (whichever was later). Beginning at week 12, subjects who failed to respond (defined as failure to demonstrate ≤ 20% decrease from baseline in both swollen joint count (SJC) and tender joint count; TJC) were allowed to increase their dose of adalimumab to 40 mg weekly.

Methods

Subject Population

In studies M02-518 and M02-570, the main inclusion criteria were similar but with some differences, as described below:

- Diagnosis of PsA and with moderate to severe activity defined by ≥3 swollen joints and ≥3 tender or painful joints.
- Concurrent/history of inadequate response to DMARD (study 570).
- Inadequate response/intolerant to NSAIDs (study 518).
- Corticosteroid dose ≤10 mg/day and stable since 4 weeks, was allowed.
- Allowed to be on MTX since minimum 3 months and stable ≤30 mg/week since 4 weeks (study 570).
- Allowed to be on MTX/DMARD (except cyclosporine/tacrolimus) and as above (study 518).
- Presence of active/documented history of cutaneous chronique plaque psoriasis lesions.

Exclusion criteria included general contraindications for anti-TNF therapy and previous treatment with other anti-TNF/biologics.

For inclusion in M02-537, the subject should have completed Study M02-518 or M02-570.

Efficacy Variables

In Studies M02-570 and M02-518, the primary efficacy variable was ACR20[2] response at week 12. An additional primary efficacy variable in Study M02 − 518 was the inhibition of disease progression assessed by modified Total Sharp Score (mTSS) on X-rays of the hands and feet at week 24. mTSS ranged from 0 - 570 and included the JSN score (48 sites [0 - 4 for each site] for a range of 0 - 192) plus the erosion score (54 sites [0 - 7 for each site] for a range of 0 - 378). A lower score indicated a better result. An increase was defined as a change of > 0.5 of mTSS. The primary X-ray endpoint; the comparison of change in mTSS of adalimumab treated subjects at week 48 with the change in mTSS of placebo treated subjects at week 24; was defined upon consultation with the FDA. Since all placebo-treated subjects switched to open-label adalimumab at the week 24 Visit, no comparison to placebo could be made at week 48.

Several additional endpoints were evaluated, such as the HAQ−DI (disability index of the health assessment questionnaire), SF-36 PCS and MCS (the 36 question short-form health survey physical and mental component summaries), ACR50/70, PsARC (psoriatic arthritis response criteria), and

[2] The ACR response criteria were developed for RA. The ACR20 criteria is defined as a ≥20% reduction in the tender joint count, a ≥20% reduction in the swollen joint count and a ≥20% reduction in 3 of 5 additional measures: a) patient assessment of pain, b) patient global assessment of disease activity, c) physician global assessment of disease activity, d) disability index of the health assessment questionnaire (HAQ) and, e) acute phase reactant.

FACIT (functional assessment of chronic illness therapy) Fatigue Scale. In subjects with psoriasis involvement at enrolment the PGA (physician's global assessment for psoriasis), and DLQI (dermatology life quality index) were also assessed.

M02-537 full analysis set
The full analysis set was the primary analysis population for baseline and long-term efficacy parameters (with the exception of X-ray endpoints, see below) and consisted of all subjects who received at least one adalimumab injection in Study M02-518, M02-570, or M02-537. The M02-537 full analysis set consisted of 395 subjects: 382 subjects who received at least one adalimumab injection in Study M02-537 and 13 subjects who received adalimumab in Study M02-570 or M02-518 but did not enter M02-537.

X-ray analysis sets
Only data from subjects in Study M02-518 were used for analyses of X-rays. Baseline X-ray data were defined as an X-ray performed ≤56 days after the first study drug injection in M02-518. In study M02-537, X-rays were analysed at weeks 24, 72, and 120. Two analysis sets were used.

M02-537 week 48 X-ray analysis set: The week 48 X-ray analysis set included subjects who had baseline and week 24 X-ray data with ≥ 50% assessments made, and received at least one injection of adalimumab in Study M02-537. This data set included 133 subjects on adalimumab and 141 subjects on placebo in Study M02-518.

M02-537 week 144 X-ray analysis set: The M02 537 week 144 X-ray analysis set included all subjects in the week 48 X-ray analysis set, who had a value at week 48 and a X-ray at week 96 or week 144 with ≥ 50% assessments read for all time points. For subjects with a missing mTSS at week 144, the mTSS at week 96 was used. This dataset included 115 subjects on adalimumab and 128 subjects on placebo in Study M02-518.

Subgroup analyses for mTSS were performed for a number of subgroups, including symmetric polyarthritis.

Baseline disease characteristics
The demographic and baseline characteristics of PsA subjects were representative of patients with moderately to severely active PsA. Demographic and baseline characteristics for the M02-537 week 48 X-ray analysis set and M02-537 week 144 X-ray analysis set showed no meaningful differences from the characteristics of the M02-537 full analysis set (N = 395). A summary of the baseline mTSS for the M02-537 week 48 X-ray analysis set is presented in Table 1 below.

Table 1. Baseline Modified Total Sharp Score (M02-537 week 48 X-ray Analysis Set)

baseline Modified Total Sharp Score	**Placebo eow N = 141**	**Adalimumab 40 mg eow N = 133**
Mean ± SD	21.2 ± 37.92	22.2 ± 44.15
Median (range)	6.0 (0.0 – 216.8)	7.0 (0.0 – 358.8)

Statistical Methods
The statistical methods in general were considered acceptable.
The primary analysis of the mTSS was the comparison of the change from baseline to week 48 in the adalimumab group and the change from baseline to week 24 in the placebo group. This analysis was a superiority test. The primary analysis was performed on the M02−537 week 48 X-ray analysis set.

Results
X-ray analyses
Adalimumab-treated subjects had statistically significantly less progression in mTSS from baseline to week 48 compared to placebo-treated subjects from baseline to week 24 (0.0 vs. 0.8, $p<0.001$) as shown in the Table 2 below (results are shown in bold, underlined).

Table 2 Mean Changes in Modified Total Sharp Scores from Baseline to week 24, from baseline to week 48, and from week 24 to week 48 (M02-537 week 48 X-ray analysis set)

Modified Total Sharp Score Imputed[c]	**Placebo/Adalimumab**[a,b]	**Adalimumab**
Change from baseline to week 24, N	141	133
Baseline Mean	21.2	22.2
Mean Change from baseline ± SD	**0.8 ± 2.51**	-0.2 ± 1.22
Median Change from baseline (range)	0.0 (-2.5 – 15.7)	0.0 (-6.7 – 6.0)
Change from baseline to week 48, N	141	133
Baseline Mean	21.2	22.2
Mean Change from baseline ± SD	0.9 ± 4.23	**0.0 ± 1.89**
Median Change from baseline (range)	0.0 (-24.7 – 25.0)	0.0 (-5.0 – 16.1)
Change from week 24 to week 48, N	141	133
Baseline[d] Mean	22.0	22.0
Mean Change from Baseline ± SD	0.0 ± 2.90	0.2 ± 1.40
Median Change from Baseline (range)	0.0 (-23.6 – 15.7)	0.0 (-3.8 – 10.1)

a. Subjects received adalimumab 40 mg eow starting at week 24.
b. For subjects who were randomized to placebo at baseline and do not have a mTSS at week 48, the change from baseline to week 48 is imputed as the change from baseline to week 24 and the change from week 24 to week 48 is imputed as zero. There are no subjects from the adalimumab group with imputed values.
c. For change from week 24 to week 48, baseline = week 24.

In subjects treated with placebo, 29% had an increase in mTSS from baseline to week 24 compared to 10% of adalimumab-treated subjects. For subjects originally randomised to receive adalimumab in Study M02-518, 12% had an increase in mTSS from baseline to week 48.

The changes from baseline in both the erosion and joint space narrowing (JSN) scores demonstrated that adalimumab-treated subjects had statistically significantly less progression in Sharp Score components from baseline to week 48 compared to placebo-treated subjects from baseline to week 24 ($p=0.002$ for JSN, $p<0.001$ for erosion).

Long-term efficacy

Subjects with no progression from baseline to week 48 were evaluated at week 144 to determine the proportion of subjects that continued to show no progression as defined by a decrease or no change in mTSS. Of the 102 subjects that showed no progression through week 48, a total of 86 (84.3%) subjects continued to show no progression from week 48 to week 144. In Table 3 below, a summary of mean changes in mTSS up to week 144 is shown for subjects with and without progression from baseline to week 24. Table 4 shows the number of subjects who progressed, or did not progress during the complete study period.

Table 3 Summary of Mean Changes in Modified Total Sharp Scores for subjects with and without progression from baseline to week 24 (M02-537 week 144 X-ray analysis set)

	Subjects Without Progression		Subjects With Progression	
Modified Total Sharp Score[a]	**Placebo/ Adalimumab[b]**	**Adalimumab**	**Placebo/ Adalimumab[b]**	**Adalimumab**
Imputed[c]				
Change from baseline to W24, N	90	103	38	12
baseline Mean	14.9	16.1	38.5	74.9
Mean Change from baseline ± SD	-0.1 ± 0.51	-0.3 ± 0.93	3.0 ± 3.56	1.7 ± 1.62
Median Change from baseline (range)	0.0 (-2.5 – 0.5)	0.0 (-6.7 – 0.5)	1.5 (0.5 – 15.7)	1.1 (0.5– 6.0)
Change from baseline to week 48, N	90	103	38	12
baseline Mean	14.9	16.1	38.5	74.9
Mean Change from baseline ± SD	-0.3 ± 2.73	-0.3 ± 0.90	3.3 ± 5.85	2.9 ± 4.73
Median Change from baseline (range)	0.0 (-24.7 – 5.5)	0.0 (-5.0 – 2.5)	1.5 (-4.6 – 25)	1.8 (-1.1 – 16.1)
Change from week 24 to week 48, N	90	103	38	12
baseline[d] Mean	14.8	15.8	41.4	76.6
Mean Change from baseline ± SD	-0.1 ± 2.65	0.1 ± 0.97	0.4 ± 3.79	1.2 ± 3.38
Median Change from baseline (range)	0.0 (-23.6 – 5.5)	0.0 (-3.0 – 6.7)	0.0 (-7.6– 15.7)	0.5 (-2.2 – 10.1)
Change from baseline to W144, N	90	103	38	12
Baseline Mean	14.9	16.1	38.5	74.9
Mean Change from Baseline ± SD	0.1 ± 1.72	-0.1 ± 1.75	2.9 ± 11.23	6.2 ± 10.77
Median Change from Baseline (range)	0.0 (-10.0 – 5.5)	0.0 (-6.0 – 6.5)	1.0 (-26.2 – 55.9)	2.0 (-2.1 – 36.4)
Change from week 24 to week 144, N	90	103	38	12
Baseline[d] Mean	14.8	15.8	41.4	76.6
Mean Change from Baseline ± SD	0.2± 1.72	0.2± 1.88	-0.1± 10.23	4.4± 9.26
Median Change from Baseline (range)	0.0 (-10.0 – 6.5)	0.0 (-5.5 – 10.3)	-0.3 (-28.2 – 49.5)	1.0 (-3.0 – 30.4)
Change from week 48 to week 144, N	90	103	38	12
Baseline[d] Mean	14.7	15.9	41.8	77.8
Mean Change from Baseline ± SD	0.3± 2.96	0.1± 1.50	-0.4± 8.53	3.2± 6.33
Median Change from Baseline (range)	0.0 (-8.5 – 24.7)	0.0 (-6.0 – 7.0)	-0.5 (-26.1 – 33.8)	0.3 (-2.5 – 20.3)

b. Subjects received adalimumab 40 mg eow starting at week 24.

c. For subjects who do not have a week 144 mTSS, the week 96 mTSS was used.

d. For the change from week 24 to week 48, baseline is week 24; for the change from week 24 to week 144, baseline is week 24. For the change from week 48 to week 144, baseline is week 48.

Table 4 Number and Percentage of Subjects with a decrease, no change or an increase in Modified Total Sharp Score (M02-537 week 144 X − ray analysis set)

Modified Total Sharp Score Change Imputed[c]	**Placebo/Adalimumab**[b]	**Adalimumab**
Change from baseline to W24, N	128	115
Decrease	8 (6.3)	17 (14.8)
No Change	82 (64.1)	86 (74.8)
Increase	38 (29.7)	12 (10.4)
Change from baseline to W48, N	128	115
Decrease	15 (11.7)	23 (20.0)
No Change	79 (61.7)	79 (68.7)
Increase	34 (26.6)	13 (11.3)
Change from week 24 to W48, N	128	115
Decrease	22 (17.2)	14 (12.2)
No Change	83 (64.8)	85 (73.9)
Increase	23 (18.0)	16 (13.9)
Change from baseline to W144, N	128	115
Decrease	23 (18.0)	25 (21.7)
No Change	65 (50.8)	66 (57.4)
Increase	40 (31.3)	24 (20.9)
Change from W24 to W144, N	128	115
Decrease	25 (19.5)	18 (15.7)
No Change	74 (57.8)	71 (61.7)
Increase	29 (22.7)	26 (22.6)
Change from W48 to W144, N	128	115
Decrease	27 (21.1)	14 (12.2)
No Change	77 (60.2)	78 (67.8)
Increase	24 (18.8)	23 (20.0)

a. Decrease is < -0.5 change; no change is -0.5 to 0.5 change; increase is > 0.5 change.
b. Subjects received adalimumab 40 mg eow starting at week 24.
c. For subjects who do not have a week 144 mTSS, the week 96 mTSS was used.

Subgroups analyses

The MAH undertook a number of subgroup analyses for the mTSS endpoint, including age, race, sex, body weight, site, duration of PsA quartiles, various baseline parameters (e.g. MTX use, RF, CRP HAQ − DI, TJC, SJC, mTSS, ACR20 responses at various time points and in subjects with symmetric polyarthritis and for subjects who completed Study M02-537). In general, all subgroups showed similar clinical effects following treatment with adalimumab, including the subjects with symmetric polyarthritis.

Physical function

The MAH basis the claim of 'improved physical function' on analyses in study M02-518 of changes from baseline to week 12 and week 24 of various patient reported outcomes, such HAQ-DI and SF-36. These two were proposed to be included into the SPC, and are therefore described in further detail below. Maintenance of improvement of physical function was analysed in the open label extension study M02-537. It should be noted that the 24 weeks data had been assessed previously, with the consequent update of section 5.1 of the SPC with the following statement: "Humira treated patients demonstrated improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36), from base-line to week 24."

Results from Study M02-518

There was a statistically significant difference in mean change in HAQ-DI as well as for SF-36 PCS in adalimumab-treated subjects in Study M02-518 compared to placebo at both weeks 12 and 24. At week 24, changes in HAQ-DI scores from baseline were of -0.1 ± 0.42 for placebo and -0.4 ± 0.49 for

adalimumab, and for SF36 PCS 1.5 ± 9.72 for placebo and 9.3 ± 10.03 for adalimumab. For SF-36 MCS no statistically significant difference between treatment groups was seen at either time point.

For the mean change in HAQ-DI, a minimal clinically important difference (MCID) of 0.30 between adalimumab and placebo was seen at weeks 12 and 24. For PsA, a MCID for SF-36 was not established, but a general MCID of 3 to 5 points was determined, and was achieved for the SF-36-PCS component at weeks 12 and 24.

Open Label extension

From week 4 and onwards, up to week 144, the mean change from baseline in HAQ-DI was -0.4 ± 0.45/0.50, among the subjects who remained in the study (week 12 n=142; week 144 n=108). At week 12, 51% achieved a MCID of 0.30, and at week 144, 52% achieved this result.

For SF-36, the mean change from baseline in HAQ-DI ranged from 9.2 ± 9.97 (week 24) to 12.2 ± 9.91 (week 48), among the subjects who remained in the study (week 12 n=136; week 144 n=102).

ACR response: The MAH proposed to update section 5.1 of the SPC to reflect that ACR responses were maintained in the open-label extension study for up to 136 weeks. Table 5 shows a summary of the ACR 20/50 and 70 results during the open label extension study M02-537.

Table 5 ACR20/50/70 Response Rates − Observed (M02-537 full analysis set)

Week[a]	Number of ACR20 Responders	Total Number of Subjects	% ACR20 Responders
Week 12	198	363	54.5
Week 24	225	352	63.9
Week 36	223	342	65.2
Week 48	225	334	67.4
Week 72	226	321	70.4
Week 88	222	312	71.2
Week 104	211	289	73.0
Week 120	208	284	73.2
Week 136	99	133	74.4
Week[a]	**Number of ACR50 Responders**	**Total Number of Subjects**	**% ACR50 Responders**
Week 12	116	363	32.0
Week 24	151	352	42.9
Week 36	157	342	45.9
Week 48	165	334	49.4
Week 72	160	321	49.8
Week 88	160	312	51.3
Week 104	162	289	56.1
Week 120	158	284	55.6
Week 136	71	133	53.4
Week[a]	**Number of ACR70 Responders**	**Total Number of Subjects**	**% ACR70 Responders**
Week 12	59	363	16.3
Week 24	82	352	23.3
Week 36	103	342	30.1
Week 48	111	334	33.2
Week 72	110	321	34.3
Week 88	113	312	36.2
Week 104	106	289	36.7
Week 120	109	284	38.4
Week 136	48	133	36.1

a. Week relative to the first adalimumab injection.

A proportion of patients had an ACR 20 response at week 136; namely 99 of 133 subjects who remained in the study week 136, or 99 of the 363 patients who were in the study at the 12 week time point. These figures point to the drop out rate in the trial. Additionally, measures of physical function and quality of life remained improved in a proportion of subjects during the open label study period.

Discussion on clinical efficacy

The MAH applied to change the existing PsA indication to add that adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Data on physical function were assessed previously in variation II.22, and this was reflected in the SPC, section 5.1. The data showed that treatment with adalimumab resulted in improved physical function, measured by various patient reported outcomes, including HAQ-DI and the physical component of SF-36. Overall, these data support a revision of the indication as applied for, to align the indication for Humira with that of other anti-TNF agents.

The joint damage claim is based on newly submitted X-ray data from study M02-518 and the long-term extension study M02-537. The effect of adalimumab on progression of joint damage was assessed using the mTSS, which was considered as an acceptable parameter for assessment of X-ray data, but which is difficult to apply in a general clinical setting. The definition of an increase of the score (> 0.5 change) was agreed. The primary X-ray analysis was undertaken by comparing 24 weeks placebo results with 48 weeks results for adalimumab. This analysis was agreed with given the nature of the endpoint; i.e. progression of joint damage. It was shown that adalimumab-treated subjects had statistically significantly less progression in mTSS from baseline to week 48 compared to placebo-treated subjects from baseline to week 24 (0.0 vs. 0.8, $p<0.001$).

The magnitude of the natural progression during the study period was considered as one important factor when assessing whether the active treatment reduces the progression of joint damage. There were 24 weeks placebo data available from approximately 144 subjects. Although the placebo period was short for the assessment of progression of joint damage, 29% of patients showed an increase of the mTSS (i.e., change of mTSS > 0.5). The CHMP therefore concluded that the population in the trial was relevant for studying effects on structural damage. In the adalimumab group, 10 -12 % had an increased mTSS at weeks 24 and 48, respectively. These data support that adalimumab reduces the rate of progression of joint damage measured by X-ray, even if the evaluation period was short.

However, maintenance of reduced progression of joint damage was considered difficult to assess, due to the short placebo controlled period (24 weeks) and poor knowledge about the natural progression rate in PsA. The open label study results showed that rather few subjects on adalimumab progressed at all during the 144 weeks treatment period; 21 % had in increased mTSS from baseline to week 144. This is less than the number of placebo subjects who had an increased mTSS during the 24 weeks placebo period (29%). Although these data support a reduced progression rate following adalimumab treatment during at least a 2 years period, the magnitude of effect is difficult to assess, since it is unknown whether there is a linear joint damage progression rate; i.e. if the placebo patients would have continued with the same rate during a longer period. It was also unknown how many additional subjects in the placebo group who would have progressed during a 2 years period. Furthermore, the CHMP considered that it is unclear if this effect is relevant for all subtypes of PsA.

The CHMP considered that support can be gained from RA, where more knowledge about joint damage progression is available. Symmetric PsA shows greatest resemblance with RA. Experience from other anti-TNF agents supports an effect in subjects with symmetrical disease, while relevant effects in subjects with asymmetrical disease have been less convincing.
The MAH undertook subgroup analyses, in subjects with symmetric polyarthritis, which support an effect in this subgroup. The CHMP considered that, given the support from RA, other anti-TNF-agents and the subgroup analyses submitted by the MAH, an indication of treatment of subjects with polyarticular symmetrical subtypes of the disease could be agreed.

Clinical safety

The safety of adalimumab was determined through evaluation of AEs (adverse events), clinical laboratory evaluations, physical examinations, and vital signs. In addition, TNF − inhibitor related AEs of interest were evaluated: infections, serious infections, malignancies, opportunistic infections, tuberculosis (TB), demyelinating disorders, lupus − like syndrome, congestive heart failure (CHF), allergic reactions, injection site reactions, haematologic events, and hepatic events.

Patient exposure
All subjects who received at least one adalimumab injection in Study M02-570, M02-518, or M02-537 were included in the M02-537 safety analysis set. For analyses of laboratory parameters and vital sign parameters, subjects who were missing an evaluation were excluded from the analysis of that particular parameter/visit. There were 395 subjects who had received adalimumab. The mean treatment duration was 808 ± 286 days (± SD); the median (range) was 875 (15-1290) days. There were 342 (87%) who had > 60 weeks treatment, 318 (81%) who had > 104 weeks treatment and 84 (21%) who had > 152 weeks treatment.

There was also one M02-537 dose escalation analysis set, which included all subjects who were classified as undergoing dose escalation. The subjects increased their dose of adalimumab to 40 mg weekly. This dataset included 71 subjects. In the dose escalation subset, the median (range) of days on weekly treatments was 713 days (15 to 841 days), the mean (SD) exposure was 559 (251) days.

Adverse events
Adverse events leading to discontinuation of study drug
Thirty-eight subjects (9.6%) discontinued due to an AE during adalimumab treatment either in Study M02 518 (6) or Study M02 570 (1) or Study M02 537 (31). Of the 38 subjects who withdrew because of AEs, 4 did so following dose escalation. Of the 395 study subjects, 21 (5.3%) experienced 23 treatment emergent AEs resulting in the discontinuation of study drug judged by the Investigator to be possibly or probably drug related.

Severe AEs were reported in 80 subjects (20.3% of all 395 subjects reporting at least one AE). The most commonly reported severe AEs were all reported by ≤ 1% of subjects (myocardial infarction and psoriatic arthropathy each reported by 4 subjects, 1.0%). Table 6 shows an overview of adverse events in the safety analysis set.

Table 6 Adverse events in the safety analysis set

Treatment-emergent[a] adverse event[b] category	Adalimumab; N = 395; n (%)	Adalimumab N = 395 PYs = 874.4; E/100 PY
Any AE	368 (93.2)	2878 (329.2)
Any AE at least possibly drug-related	205 (51.9)	728 (83.3)
Any severe AE[c]	83 (21.0)	112 (12.8)
Any Serious AE (SAE)	74 (18.7)	95 (10.9)
Any AE leading to discontinuation of study drug	38 (9.6)	42 (4.8)
Infections	272 (68.9)	768 (87.8)
Serious infections	21 (5.3)	23 (2.6)
Malignancies[d]	9 (2.3)	10 (1.1)
Lymphoma	2 (0.5)	2 (0.2)
Other Malignancies	3 (0.8)	3 (0.3)
Non-melanoma skin cancer	5 (1.3)	5 (0.6)
CNS Demyelinating Disease	0	0
Allergic reaction	3 (0.8)	3 (0.3)
Injection site reaction	54 (13.7)	237 (27.1)
Opportunistic infection excluding TB	4 (1.0)	4 (0.5)
TB	1 (0.3)	1 (0.1)
Lupus and lupus-like syndrome	0	0
Congestive heart failure	0	0
Immunologic reactions	16 (4.1)	17 (1.9)
Any fatal AE	2 (0.5)	3 (0.3)
Deaths[e]	3 (0.8)	---

E: events; PY: patient-years

a. Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of adalimumab was administered to 70 days after the last dose of adalimumab.
b. Subjects may be counted in more than one AE category.
c. Includes the category of unknown.
d. Subject 570-0903 had non-melanoma skin cancer and other malignancy.
e. Includes non-treatment emergent deaths.

Serious adverse events (SAEs) and deaths

Deaths

A total of three deaths were reported during Study M02-537. One death occurred outside of the reporting period and was not considered treatment-emergent. Two of the deaths were the result of treatment-emergent AEs; lobar pneumonia and sepsis in one case, and sepsis and acute pulmonary edema for the other.

SAEs

SAEs were reported by 74 (18.7%) subjects. Among those, 18 (4.6%) subjects experienced SAEs that were at least possibly related to study drug (Table 7). Of the subjects who experienced SAEs, 12 experienced their SAE following dose escalation.

Table 7 Subjects with Treatment−emergent Serious Adverse Events at Least Possibly Related to the Study Drug (Safety Analysis Set)

Study	Sex	Age	Serious Adverse Event[b] Preferred Term	Causality (per Investigator)
M02-518	Male	36	Convulsion[c]	Not related
			Peritoneal tuberculosis	Probably related
M02-518	Female	42	Meningitis viral[c]	Possibly related
M02-570	Female	47	Diverticulitis[c]	Possibly related
M02-537	Female	50	Fall	Not related
			Abdominal wall abscess	Probably related
M02-537	Female	53	Urinary tract infection	Probably related
M02-537	Female	63	Lobar pneumonia[c,i]	Possibly related
			Sepsis syndrome[c,i]	Possibly related
			Cardio-respiratory arrest	Probably not related
			Myocardial infarction[c,i]	Probably not related
M02-537	Female	51	Cholecystitis[c,i]	Not related
			Diabetes mellitus[c,i]	Not related
			Infection[c,i]	Possibly related
			Arterial occlusion disease[c,i]	Not related
			Coronary artery disease[c,i]	Not related
M02-537	Male	48	Urinary tract infection[c,i]	Possibly related
			Chest pain	Not related
M02-537	Female	61	Myocardial infarction	Probably not related
			Pyelonephritis[c,i]	Possibly related
M02-537	Male	59	Obesity	Not related
			Panniculitis	Possibly related
M02-537	Female	70	B-cell small lymphocytic lymphoma[i]	Possibly related
M02-537	Male	73	Vascular encephalopathy	Possibly related
M02-537	Male	50	Sudden death	Possibly related
M02-537	Female	60	Pulmonary alveolar haemorrhage	Possibly related
M02-537	Male	61	Extradural abscess	Probably related
			Intervertebral discitis	Probably related
M02-537	Male	46	Bacterial pericarditis	Probably related
M02-537	Male	30	Renal failure[c,i]	Possibly related
			Rhabdomyolysis[c,i]	Possibly related
M02-537	Female	65	Urinary tract infection[c,i]	Possibly related

a. Relative to the first dose of adalimumab, which may have occurred in the pivotal study or in Study M02-537.
b. Treatment-emergent SAEs were defined as SAEs that were reported from the time that the first dose of adalimumab was administered to 70 days after the last dose of adalimumab.
c. Previously reported in the first interim M02-537 CSR (data cut-off 17 May 2004).

d. Subject prematurely discontinued from the pivotal study.
e. Subject prematurely discontinued from the open-label study (i.e., Study M02-537).
f. Subject #570-1451 discontinued Study M02-570 (due to diverticulitis), entered and subsequently discontinued open-label Study M02-537 (due to alopecia).
g. Ongoing as of the last study visit (Rx day of last follow-up).
h. Subject #518-1142 died secondary to cardio-respiratory arrest and myocardial infarction.
i. Previously reported in the second interim M02-537 CSR (data cut-of 25 Mar 2005).

Treatment-emergent infectious adverse events

The number and percent of subjects who reported treatment emergent infectious AEs (both non serious and serious) occurring in ≥ 2% of subjects was presented. A total of 272 subjects (68.9%) reported at least one infectious AE. The most commonly reported infectious AEs were upper respiratory tract infection (104/395, 26.3%), nasopharyngitis (68/395, 17.2%), sinusitis (39/395, 9.9%), influenza (29/395, 7.3%), bronchitis (27/395, 6.8%), herpes simplex (20/395, 5.1%), and urinary tract infection (20/395, 5.1%). All other infectious AEs were reported by < 5% of subjects.

Of the 395 subjects, 21 (5.3%) reported a serious infectious AE. Twelve (3.0%) were considered by the investigator to be possibly or probably related to study drug, including abdominal wall abscess, urinary tract infection, lobar pneumonia and sepsis syndrome, extradural abscess and intervertebral discitis, peritoneal tuberculosis, pacterial pericarditis, meningitis viral, pyelonephritis and diverticulitis

Opportunistic Infections (Excluding TB)

Four subjects (1.0%) reported treatment emergent opportunistic infections (excluding TB), in all cases oral or oesophageal candidiasis. One (0.3%) of the 395 subjects reported TB.

Malignancies

Overall, ten malignancies were reported in nine subjects (basal cell carcinoma (n=3), neuroendocrine carcinoma of the skin, B-cell small lymphocytic lymphoma, prostate cancer (n=2), follicle centre lymphoma, squamous cell carcinoma). One subject (518-2706) reported a malignancy (B-cell small lymphocytic lymphoma) that was considered possibly related to study drug by the investigator.

The CHMP noted that squamous cell carcinoma has been included into the SPC, section 4.8 as a rare event. Furthermore, non-melanoma skin cancers (including both squamous cell carcinoma and basal cell carcinoma) are mentioned specifically in section 4.8, with higher frequencies observed in adalimumab groups than in the placebo groups during the controlled portions of clinical trials.

Injection Site Reactions

Of the 395 subjects, 54 (13.7%) subjects reported treatment-emergent injection site reactions (including injection site: bruising, erythema, haemorrhage, irritation, pain, pruritus, reaction, and rash) most of which were mild and assessed by the Investigator as probably related to study drug.

Other events:

No subjects with treatment-emergent central nervous system (CNS) demyelinating disease, lupus/lupus-like syndrome, congestive heart failure (CHF) or immunologic reactions were observed.

Laboratory findings

Small mean increases in hemoglobin; hematocrit and red blood cells (RBC) were observed at all evaluation time points. Mean white blood cells (WBC) values decreased during treatment with adalimumab ranging from 0.84 $x10^3$/µl at week 12 to 1.24 $x10^3$/µl at week 136. Mean changes in WBC differential counts showed small decreases in neutrophil counts and small increases in lymphocyte counts at all time points. Mean platelet counts decreased at all time points. Changes observed are consistent and similar to subjects treated with adalimumab as previously seen in other studies. There were no clinically meaningful mean changes of clinical chemistry parameters or urine-analyses over 136 weeks.

Intrinsic and extrinsic factors

Although a few statistically significant differences were detected, analyses of the most commonly-reported treatment-emergent AEs (i.e., those reported by ≥ 5% of subjects in the safety analysis set) by

intrinsic factors did not indicate any clinically relevant differences for males vs. females, subjects < 65 years vs. those ≥65 years, Caucasians vs. non-Caucasians, or subjects with < 10 years of PsA vs. those with ≥10 years of PsA.
Analyses of the most commonly-reported treatment-emergent AEs (i.e., those reported by ≥5% of subjects in the All Studies grouping) by extrinsic factors did not indicate any clinically relevant differences for subjects with DMARD use at baseline vs. those without and subjects with oral corticosteroid use at baseline vs. those without.

Safety in special populations
Use in Pregnancy and Lactation
Overall, four subjects became pregnant during this study. Two (0.5%) subjects were pregnant during the course of the study. One subject experienced an ectopic pregnancy and one subject chose to have an elective abortion. Both were reported as SAEs. Two subjects reported pregnancies following completion of open-label adalimumab treatment (day 511 [62 days post-treatment] and day 449 [70 days post-treatment], respectively). Both delivered healthy babies.

Discussion on clinical safety
The MAH submitted long-term extension data from the open label study M02-537, which included data up to and beyond 2 years of treatment of PsA patients with adalimumab. The already established safety profile of adalimumab is confirmed. Infections, including some serious and severe, occurred in association with adalimumab treatment, and there was one case of TB. Malignancies (n=10) were reported in 9 subjects, and further support the need for continued long-term follow up. There were 71 patients who dose escalated to 40 mg ew during the study period. Although the safety data presentation in subjects who dose-escalated was brief in the report, no further information was requested, since the available data are limited and the higher dose is not approved for use in PsA. To conclude, there were no new safety signals identified.

Risk management plan

The CHMP considered that there was no need for an update of the RMP for this variation.

Overall discussion and benefit/risk assessment

Humira was approved for the use in PsA in August 2005 (variation 22), with the following indication: "Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti rheumatic drug therapy has been inadequate." In the present variation application the MAH proposed to change the current indication to add that adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Benefit
Data on physical function have been assessed previously, and were included in the SPC, section 5.1. Data showed that treatment with adalimumab resulted in improved physical function, measured by various patient reported outcomes. The joint damage claim was based on newly submitted X-ray data from study M02-518 and the long-term extension study M02-537. The effect of adalimumab on progression of joint damage was assessed using the mTSS. It was shown that adalimumab-treated subjects had statistically significantly less progression in mTSS from baseline to week 48 compared to placebo-treated subjects from baseline to week 24 (0.0 vs. 0.8, $p<0.001$).
However, maintenance of reduced progression of joint damage was considered difficult to assess, due to the short placebo controlled period and poor knowledge about the natural progression rate in PsA. As symmetric PsA somewhat resembles RA, and based on experience from other anti-TNF agents and the subgroup analyses provided by the MAH, the CHMP considered that an effect in subjects with symmetrical disease could be agreed, while relevant effects in subjects with asymmetrical disease were less convincing.

Risk
Based on the submitted data, the safety profile of adalimumab was confirmed. Overall, there were no new safety signals identified in this material.

To conclude, there is support for that adalimumab treatment reduced the rate of joint damage progression in PsA. Thus, the proposed revised indication is accepted, with the patient population specified to those having polyarticular symmetrical subtypes of the disease.
The benefit / risk balance remains positive.

CONCLUSION

On 13 December 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the SPC and PL.