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Product name: Humira
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SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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) and Crohn's disease (CD).

The marketing authorisation holder (MAH) applied for an extension of indication for adalimumab in the treatment of plaque psoriasis (Ps) in adult patients. The MAH presented the results of the psoriasis development program to demonstrate adalimumab's safety and efficacy in the treatment of moderate to severe chronic Ps.

Psoriasis is a chronic immunologic disease, characterised by marked inflammation and thickening of the epidermis resulting in thick, scaly plaques involving the skin. It affects 1 to 3% of the general population, with the highest disease prevalence in North America and Europe. Affecting men and women equally, psoriasis is a life-long disease often diagnosed early in life. Genetic factors may predispose a person to psoriasis, and it may be induced or exacerbated by exogenous triggers such as physical trauma, medications, infections, and emotional stress.

Psoriasis may be classified as plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalised pustular and localised pustular psoriasis, and inverse or intertriginous psoriasis. Plaque psoriasis is the most common form seen in 75 to 80% of psoriasis patients. Approximately 6% up to 40% of patients may have associated PsA.

The MAH proposed to amend the text of the summary of product characteristics (SPC) sections 4.1, 4.2, 4.8, 5.1 and 5.2, and to update the package leaflet (PL) accordingly.

Clinical aspects

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

- three pivotal studies with the respective extension studies: M02−528 + M02−529, M03−656, M04−716
- an additional study to evaluate time to relapse with the respective extension studies M02−538 + M03−596.
- an open-label extension study, Study M03−658, for subjects who show a clinical benefit and tolerate the treatment in Studies M02−529, M03−656, M04−716, M02−538, M03−596.

Pharmacokinetics/Pharmacodynamics[1]

The pharmacokinetics of adalimumab as monotherapy were evaluated in subjects with moderate to severe chronic plaque psoriasis during a 12-week study (Study M02-528, N = 95) and a 52- week study (Study M03-656, N = 840).

Two dosing regimens were studied in Study M02-528: Regimen A (an initial dose of adalimumab 80 mg administered subcutaneously (SC) at week 0, followed by 40 mg every other week (eow) starting at week 1) and Regimen B (two initial doses of adalimumab 80 mg administered SC at weeks 0 and 1 followed by 40 mg weekly starting at week 2). Serum adalimumab concentrations reached steady state in subjects given Regimen A by at least week 8, and the mean steady-state adalimumab trough concentration was 6.0 µg/ml. The mean concentrations achieved after the initial 80 mg dose (6.0 µg/ml and 8.8 µg/ml at weeks 1 and 2, respectively) were slightly (within 28%) and

[1] For details of the studies referred in this section, please see section Clinical efficacy

temporarily higher than the steady-state concentrations during 40 mg eow dosing (6.0 µg/ml and 6.9 µg/ml at weeks 11 and 12, respectively).

In Study M03-656, the mean steady-state trough concentration was 5.2 µg/ml during treatment with adalimumab at an initial dose of 80 mg at week 0, followed by 40 mg eow starting at week 1. The mean steady-state trough concentration in subjects with psoriasis (5.3 µg/ml, combining results from M02 - 528 and M03 - 656) was within the range of those observed in subjects with RA (5 µg/ml), AS (6 to 7 µg/ml), and PsA (6 to 10 µg/mL) during treatment with SC adalimumab 40 mg eow as monotherapy.

Effect of weight on efficacy
Because weight was a statistically significant covariate for adalimumab pharmacokinetics, the potential effect of weight on PASI (psoriasis area and severity index) at week 16 was analysed using the data from two studies, M03 − 656 Period A and M04 − 716.

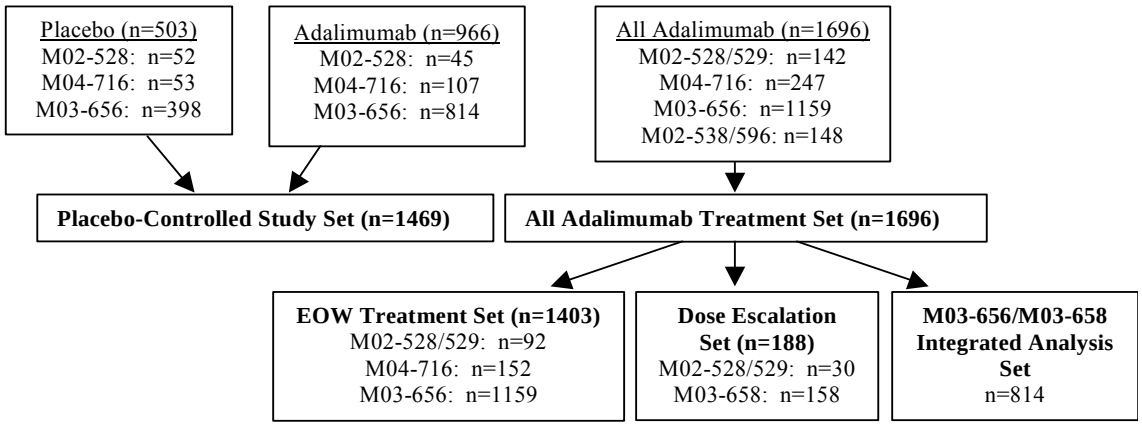
The results showed that at week 16 the PASI 75 response rate (subjects achieving ≥ 75% improvement in PASI score) was slightly lower in subjects with higher body weights in the adalimumab group. However, the percentage of PASI 75 responders in the fourth weight quartile was only 15% less than that in the first weight quartile (62% vs. 77%), even though the weight increased about three fold from the first to the fourth weight quartile. Weight, as a univariate predictor, accounted for less than 2% of the overall variability in adalimumab efficacy. Thus, a fixed dosing regimen was applied for. The CHMP agreed that the influence of weight was rather limited and the variability in overall efficacy was low, and therefore accepted the use of a fixed dose.

Immunogenicity
Immunogenicity of adalimumab was assessed in Study M02−528 over a 12 weeks treatment period and in Study M03−656 over a 52 weeks treatment period. Overall, the immunogenicity of adalimumab in subjects with psoriasis was 8.4%; 77 of 920 subjects for the combined 40 mg eow and weekly regimens (after one or two initial 80 mg doses) which is in the range of those observed in subjects with RA (12%; 54/434), AS (8.6%; 16/185), and PsA (13.5%; 24/178) during adalimumab monotherapy. For CD, the overall immunogenicity rate (7 subjects among 269 receiving longer term treatment; all monotherapy) appeared to be lower than those for other indications.

In Study M02-528, none of the four AAA+ (anti-adalimumab antibodies positive) subjects achieved a PASI 75 response. In Study M03-656, AAA+ subjects had a statistically significantly lower PASI75 response rate than AAA-subjects at week 16 (11% vs. 76%; $p < 0.001$); thus that presence of AAA reduces adalimumab's efficacy. There was no indication that the development of AAA increased safety problems in adalimumab - treated subjects. The CHMP noted that anti-adalimumab antibodies were found in similar frequencies as in other indications and that they were associated with a lower number of responders, as expected. As seen in previous indications, presence of antibodies did not appear to be associated with safety problems. The MAH will continue to follow on how the development of AAA may affect long term efficacy and safety. Section 5.1 was revised to address adequately the current data on immunogenicity.

Clinical efficacy

The populations analysed in the psoriasis program is showed in Figure 1 below.



Methods

Subject Population

Subjects enrolled in the psoriasis program were patients with moderate to severe psoriasis. In the placebo-controlled study set, the mean duration of psoriasis since diagnosis was greater than 18 years, and > 50% of subjects reported a family history of psoriasis. The majority of subjects were white, male, and younger than 65 years of age. The majority (66%) of subjects presented with baseline mean PASI scores of 12-20, a PGA (physicians global assessment) of moderate (52%) or severe/very severe (42%/6%). There was 57% of subjects with a BSA (body surface area) involvement ≥ 20%. The majority of subjects previously received topical therapy, phototherapy, and/or non-biologic systemic therapies.

The study populations in Studies M02-528, M03-656, and M04-716 were similar and generally comparable, with the exceptions that subjects in Study M02-528 had on average more moderate disease at baseline (lower PASI scores) as a consequence of the different inclusion criteria of the study and in M04-716 subjects were to be naïve to systemic therapy. No clinically important differences were observed between the treatment groups in the placebo-controlled studies with respect to demographics or baseline characteristics for psoriasis. No remarkable differences in the other analysis sets compared with the Placebo-Controlled Study Set regarding demographic and baseline characteristics were noted.

Efficacy Variables

The PASI75 response rate (i.e., the proportion of subjects with a 75% reduction in PASI) was the primary efficacy variable in all pivotal studies. In Study M03-656, an additional primary endpoint was a comparison of the proportion of subjects losing an adequate response (i.e., achieving an event). An "event" was defined as a PASI score after week 33 that resulted in a < PASI50 response relative to the baseline PASI score and at least a 6-point increase in PASI score relative to the week 33 PASI score.

The PGA response of "Clear or Minimal" was the principal secondary endpoint in all pivotal studies. PGA was determined using the 6-point static scale. Additional secondary efficacy endpoints of clinical response included PASI50, PASI90, and PASI100 response rates, as well as endpoints based on PASI and PGA responses: time to PASI50/75/90/100 response, change and percent change from baseline in PASI response, and the improvement from baseline in PGA.

Patient-reported outcomes (PROs) were the Dermatology Life Quality Index (DLQI) and the Short Form 36 Health Survey (SF-36). Additional PROs included the proportion of subjects achieving a Patient's Global Assessment of psoriasis severity (4-point scale); psoriasis and/or psoriatic arthritis (Ps/PsA) pain (visual analog scale [VAS]); the degree of pruritus related to psoriasis; the EuroQoL Health Questionnaire (EQ-5D); and the Work Productivity and Activity Impairment Questionnaire-

Specific Health Problem (WPAI-SHP). The CHMP agreed that the chosen endpoints were acceptable, and validated for assessment of efficacy.

Statistical Methods
The statistical methods in general were considered acceptable. The MAH undertook sensitivity analysis (last observation carried forward [LOCF]) of the PASI75 response rates at week 16 of the Placebo − Controlled Study Set. The CHMP questioned the use of LOCF statistical analyses for the evaluation of chronic diseases, such as chronic Ps. The MAH clarified that the LOCF statistical method was only used as a supportive sensitivity analysis. The CHMP considered this approach acceptable, as long as no information from such analyses was included in the SPC.

Dose selection
The adult psoriasis maintenance dose, which was similar to that approved for RA, was selected based on PK, efficacy, and safety data from Study M02-528 and Study M03-656 in subjects with psoriasis and on data from the RA development program. However, an initial single dose of 80 mg was given in the psoriasis studies. The CHMP noted that the adalimumab concentration at steady-state achieved with the 80 mg initial dose was only slightly higher than the steady-state concentrations achieved with the 40 mg eow dose regimen. Considering that the main aim of psoriasis treatment is maintenance of efficacy and not a very rapid onset of effect, and in view of the safety profile of adalimumab, the MAH was asked to discuss the need for a 80 mg initial dose and the clinical data supporting it in terms of efficacy and safety. The MAH explained that the 80 mg starting dose was selected to induce a rapid response, including on the patients' quality of life. This explanation was accepted, and the dose recommendations accepted.

Main clinical studies
Study M02-528

In this 12-week, randomised, double-blind, placebo-controlled, multicentre study, adult subjects with moderate to severe chronic Ps (defined by ≥ 5% BSA at screening and baseline) were included. Stratification was made by weight (< 70 kg, 70 kg − 100 kg, > 100 kg). All subjects enrolled in this study who completed at least 12 weeks of active treatment were eligible to roll over into the extension study (M02-529), for continued treatment.

Subjects in both active treatment groups received an initial dose of adalimumab 80 mg at week 0. Subjects assigned to the first arm then received 40 mg eow starting at week 1. Subjects assigned to the second arm received 80 mg at week 1 and thereafter received adalimumab 40 mg weekly, starting at week 2.

Approximately 150 subjects were planned for enrolment. The primary efficacy analyses included 148 subjects. The primary efficacy variable was the proportion of subjects who achieved a ≥ PASI 75 response at week 12. Other endpoints were PGA and quality of life (QoL) assessments.

The CHMP noted that subjects in this study had on average more moderate disease at baseline (lower PASI scores) due to different inclusion criteria of the study, compared with the other trials. The value of this study to evaluate efficacy was considered limited, and therefore not justified to include in the SPC.

Study M03-656 (REVEAL)
This study included adult subjects with moderate to severe chronic Ps (baseline ≥ 10% BSA involvement, a PASI score of ≥ 12, and a PGA of at least moderate disease). It consisted of three phases, namely:

Period A: Adalimumab vs. placebo was evaluated in a 16-week, double-blind, placebo-controlled treatment period in which subjects were randomised to receive either:

- 80 mg adalimumab week 0, followed by 40 mg adalimumab eow from week 1 to week 15, or

- Two placebo injections week 0, followed by one placebo injection eow from week 1 to week 15.

In Period A, the primary efficacy variable was at least a 75% reduction in PASI score (≥ PASI 75 response) at week 16 relative to the baseline (week 0) PASI score.

Period B: a 17-week, open-label treatment period in which all subjects who achieved at least a PASI 75 response at week 16, defined as a PASI score improvement of at least 75% relative to baseline, received 40 mg adalimumab eow from week 17 to week 31.

Period C: Subjects who maintained at least a PASI 75 response at week 33 entered the 19-week, double-blind, placebo-controlled treatment period as follows:

- Subjects who were randomised to adalimumab in Period A were re-randomised to receive 40 mg adalimumab eow or placebo injections from week 33 to an 'event' (i.e., loss of an adequate response; see definition above), early termination, or the week 52 visit, whichever came first.
- Subjects who were originally randomised to placebo in Period A were to continue to receive 40 mg adalimumab eow in a blinded fashion from week 33 to an 'event', early termination, or the end of the study, whichever came first.

In Period C, the primary efficacy variable was the proportion of subjects experiencing an 'event' after week 33 and on or before week 52.

Approximately 1200 subjects were planned for enrollment, and 1212 subjects (ITT (intention-to-treat) Analysis Set) were evaluated for efficacy in the placebo-controlled Period A. In Period B and Period C, 606 and 490 subjects, respectively, were evaluated for efficacy in the ITT Analysis Set.

The CHMP considered this trial as pivotal for demonstration of efficacy. The CHMP nevertheless noted that in study M03-656, only patients who showed clinical efficacy in the previous phase were admitted into the following phase, and that consequently, patients in periods B and C were highly selected.

Study M04-716 (CHAMPION)
Study M04-716 was a 16-week, multicentre, double-blind, double-dummy study, studying adalimumab 40 mg eow vs. placebo and vs. MTX (methotrexate) in adult subjects with chronic plaque psoriasis (≥ 10% BSA involvement and PASI score of ≥ 10 at baseline). The study aimed to show superiority of adalimumab vs. placebo for clinical efficacy and non-inferiority of adalimumab vs. MTX, if the superiority of adalimumab vs. placebo was established. An MTX and anti-TNF naïve population was selected for this study. The following treatment regimens were given:

Regimen A: Adalimumab: 80 mg adalimumab (two 40 mg injections) week 0, followed by 40 mg eow, week 1 to week 15. Placebo capsule(s) orally once weekly from week 0 to week 15.

Regimen B: MTX: Two subcutaneous placebo injections week 0, followed by one sc. placebo injection week 1 to week 15. MTX (7.5-25 mg) capsule(s) orally once weekly from week 0 to week 15

Regimen C: Placebo: Two sc. placebo injections week 0, followed by one sc. placebo injection week 1 to week 15. Placebo capsule(s) orally once weekly from week 0 to week 15.

The dose of MTX was 7.5 mg week 0 and 1, 10 mg week 2 and 3, and 15 mg from week 4 to 15. It was to be adjusted to AST (aspartate aminotransferase), ALT (alanine aminotransferase), white blood cell count, platelet count, and serum creatinine from week 2 to week 15. The MTX dose was to be increased to 20 mg at week 8 and 25 mg at week 12 if PASI 50 response was not achieved and if there was no safety concern. When PASI ≥50 was achieved, the dose of MTX was not increased and the dose was kept unchanged for the remaining part of the study.

The CHMP noted that in M04-716, a high initial starting dose followed by a stable dose of Humira was compared with MTX, with the need for step-wise titration and slow onset of effect. The outcome of the study confirmed that a continuous increase of the MTX dose was necessary, and in many patients for up to week 12. Further, it has not been shown that the optimal dose and maximum efficacy of MTX was reached at the study endpoint of 16 weeks. Nevertheless, the CHMP acknowledged that MTX was an appropriate comparator and that the MTX dose increase was performed according to clinical practice.

The duration of the comparison was questioned. In response to that, an estimation submitted by the MAH suggested that no efficacy plateau was reached at week 16 for MTX. The CHMP acknowledged that a placebo comparison might be unethical for more than 3 months, but a longer study period comparing adalimumab with MTX, without placebo, would have been possible. The CHMP questioned the value of the efficacy comparison of MTX and adalimumab in this 16 week study.

Continuation Studies

Study M02-529 (continuation trial of M02-528).

Subjects who previously received placebo in Study M02-528 received 80 mg adalimumab on week 0 and then 40 mg eow from week 1. Subjects who received adalimumab 40 mg eow or weekly in Study M02-528 could continued to receive their previously assigned M02-528 dose of adalimumab (40 mg eow or 40 mg weekly). Study medication administration remained blinded until all subjects completed week 12. Thereafter, a 36-week open-label treatment period followed.

On or after week 12, subjects with ≥ PASI 50 response relative to the Study M02-528 baseline PASI score continued their current therapy for up to an additional 36 weeks. At any time on or after week 12, subjects with < PASI 50 response were eligible to receive open-label, weekly adalimumab. If, after at least eight weeks of weekly therapy, the subject did not achieve ≥ PASI 50 response relative to the Study M02-528 baseline score, the subject was discontinued. The primary efficacy variable was the proportion of subjects who achieved clinical response as defined by a ≥ PASI 75 response relative to the baseline value of Study M02-528 at week 12.

Study M03-658

Study M03-658 was a multicentre, open-label continuation study in subjects who previously participated in studies M02-529, M02-538, M03- 596, or studies M03-656 and M04-716.

Subjects were evaluated for entry into Study M03-658 at the final visit of the most recent psoriasis study in which they participated. All subjects received open-label 40 mg adalimumab eow at Study entry (week 0). The maximum duration of enrollment for any subject was an open-label period of at least 2 years and a follow-up telephone call 70 days after the final dose, addressing safety.

Dose escalation: Efficacy was determined by the PASI response and the PGA measured every 12 weeks. If, at any time on or after week 24, a subject did not maintain or achieve a ≥ PASI 50 from his/her week 0 score in the original study, a dose escalation to 40 mg weekly was possible.

Subjects whose dose was escalated continued on 40 mg weekly dosing until a ≥ PASI 75 response was achieved, then resumed 40 mg eow dosing. If the subject's PASI response fell back to less than 50% from his/her week 0 score in the original psoriasis study after resuming 40 mg eow treatment, a second dose escalation to 40 mg weekly was permitted. If the subject dose escalated a second time, the subject had to remain on 40 mg weekly dosing for the remainder of the study regardless of the PASI response achieved.

Other Studies

Study M02-538

This was a 76-week, phase 2, multicentre, exploratory efficacy and safety study to evaluate the time to relapse after adalimumab 40 mg weekly withdrawal (placebo treatment) or dose decrease (adalimumab 40 mg eow treatment) in subjects with moderate to severe chronic Ps following the receipt of 12 weeks of adalimumab 40 mg weekly therapy (open-label).

All subjects received 2 loading doses of open-label adalimumab 80 mg followed by 40 mg weekly (weeks 2-11). At week 12, responders, defined as ≥ PASI 50, were to be randomised to one of two blinded treatment arms: adalimumab 40 mg eow or placebo eow.

Results

Main efficacy endpoints

All three pivotal studies (M03 − 656 Period A, M04 − 716, M02 − 528) met their primary endpoint by demonstrating statistically significantly higher PASI75 response rates for adalimumab treated patients compared with placebo − treated ones. Similarly, the principal secondary endpoint, PGA-response of "Clear or Minimal" for Studies M03 − 656 (Period A) and M04 − 716 and PGA response of "Clear or Almost Clear" for Study M02 − 528, also showed a statistically significant response in adalimumab groups when compared to placebo groups. The CHMP also noted that for the more stringent efficacy criteria (PASI100 or PASI90), representing full or almost full clearance of skin disease, adalimumab showed a significant response in a subset of subjects. The table below shows an overview of the key efficacy results from the placebo-controlled studies.

Comparison of the Key Efficacy Results from the Placebo- Controlled Studies in the Adalimumab

Psoriasis Development Program

Study Time point	Placebo n/N (%)	MTX n/N (%)	ADA 40 mg eow n/N (%)	Difference (%) (95% CI)	p-value
≥ PASI 75 Response Rate					
M02-528 Week 12	2/52 (3.8)	N/A	24/45 (53.3)	49.5 (33.8, 64.6)[a]	<0.001[d]
M03-656 **Period A** Week 16	26/398 (6.5)	N/A	578/814 (71.0)	64.4 (58.4, 70.4)[b]	<0.001[e]
M04-716 Week 16	10/53 (18.9)	39/110 (35.5)	86/108 (79.6)	**PBO:** 60.5 (44.5, 76.6)[c] **MTX:** 44.1 (30.8, 56.7)[c]	<0.001[f] <0.001[f]
Proportion (%) of Subjects Losing an Adequate Response After Week 33 and On or Before Week 52					
M03-656 **Period C**	**ADA/ADA/PBO** 68/240 (28.4)	N/A	**ADA/ADA/ADA** 12/250 (4.9)	-23.5 (-30.2, 16.9)[b]	<0.001[e]
PGA of "Clear" or "Almost Clear" Response Rate					
M02-528 Week 12	1/52 (1.9)	N/A	22/45 (48.9)	47.0 (31.9, 62.0)[a]	<0.001[d]
PGA of "Clear or Minimal" Response Rate					
M03-656 Week 16	17/398 (4.3)	N/A	506/814 (62.2)	--	<0.001[g]
M04-716 Week 16	6/53 (11.3)	33/110 (30.0)	79/108 (73.1)	**PBO:** 61.8 (49.9, 73.8)[c] **MTX:** 43.1 (31.2, 55.1)[c]	<0.001[g] <0.001[g]

ADA = adalimumab; ADA/ADA/PBO = subjects who were randomised to withdraw from adalimumab treatment; ADA/ADA/ADA = subjects who were randomised to continue on adalimumab treatment eow = every other week; MTX = methotrexate; PBO = placebo -- = Not determined; N/A = not applicable.

Note: Response rates calculated following imputation of missing values as non-responders.

a. Difference between the proportion (%) of adalimumab treated subjects having a PASI 75 or a PGA of "Clear" or "Almost Clear" response in Study M02-528 compared to that of placebo treated subjects. The 95% CI is adjusted for weight category in Study M02-528. **b.** Difference between the proportion (%) of adalimumab treated subjects having a PASI 75 or a PGA of "Clear or Minimal" response in Study M03-656 compared to that of placebo treated subjects. **c.** Difference between treatment groups (%) based on Cochran-Mantel-Haenszel (CMH) test Statistic. Based on the normal approximation of the binomial distribution for PGA "Clear or Minimal" in Study M04-716. **d.** The p-value is from the CMH test adjusted for Baseline body

weight. **e.** Based on CMH test stratified by centre. **f.** Two sided CMH test stratified by country. **g.** Fisher's Exact test for studies M03-656 and M04-716.

Study M03-656 was the largest study and considered as pivotal. Sufficient efficacy was shown compared with placebo in Phase A at 16 weeks (see table below).

Efficacy Results at 16 weeks: Study M03 − 656, Period A

Endpoint	Placebo (N=398) N (%)	Adalimumab 40 mg eow (N=814) N (%)%
PASI75	26 (6.5)	578 (70.9)[a]
PASI100	3 (0.8)	163 (20.0) [a]
PGA: Clear/Minimal	17 (4.3)	506 (62.2) [a]

a. $p < 0.001$, adalimumab vs. placebo
Note: Subjects with missing responses at week 16 were imputed as not achieving PASI75/100 response and as not achieving PGA of clear/minimal; PASI75 response rates were calculated as centre-adjusted rate;

In the following 17-week open phase of the study, where all PASI 75 responders at week 16, received 40 mg adalimumab eow, the response rate was similar.

In phase C of study M03-656, where patients were re-randomised to either placebo or adalimumab 40 mg eow, the majority of patients did not lose adequate response, 72% on placebo and 95% on adalimumab, during the 19 weeks period. During the assessment procedure, the MAH provided some additional data from this treatment interruption of 19 weeks. It is evident that more subjects did not regain response after period C among those who lost response during the 19 weeks period off treatment (36 /66 patients; 54.5%) compared to those who did not loose response during this period (135/161 patients; 83.94%).
The CHMP considered that information regarding on demand treatment is of importance and agreed with the MAH's proposal to gather further data from the post marketing setting, including the planned registry.

In study M02-528, subjects had on average more moderate disease at Baseline (lower PASI scores), due to different inclusion criteria in this study. The CHMP therefore considered the value of this study to evaluate efficacy as limited, and did not find it justified to include information on this study in the SPC.

Long-term efficacy
The MAH had presented support for long-term efficacy based on combined analyses of Studies M02-528, M02-529, M03-656, M03-658 and M04-716. However, the data presentation was considered misleading to assess persistence of efficacy. The number of patients at each visit decreased, both due to non-responders, other reasons for discontinuation and possibly also due to the fact that not all patients yet have reached the latter time-points. To be able to evaluate efficacy over time, the MAH was asked to present and further discuss available data. It is evident that due to the design of the psoriasis clinical trials, it is not possible to provide accurate information about responder rates at one year by the number of subjects initially started on treatment. The MAH submitted an estimation of efficacy at one year, which approximates PASI>75 responders to 56%. Although these data do not warrant inclusion in the SPC, they provide support for efficacy up to 1 year. Still, long-term benefit, beyond 1 year, including the impact on efficacy of antibody development is unknown.

Dose escalation
In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50 and were evaluated at 12 weeks after dose escalation, 59/243 (24.3%) of patients regained PASI 75 response.

Dermatology -specific and general health - related quality of life.
Subjects who received adalimumab 40 mg eow compared with placebo following 12 weeks or 16 weeks treatment showed statistically significant improvements in DLQI and in SF36 compared with placebo.

Clinical studies in special populations

No clinical data were submitted on efficacy in special populations. Among the 1469 patients included in the placebo-controlled study set, 98 subjects were > or equal to 65 years of age. No children were included.

Discussion on clinical efficacy

Overall, adalimumab has been evaluated in patients with moderate to severe psoriasis with sufficient disease activity to be candidates for systemic therapy. In one pivotal placebo-controlled study in psoriasis (M03 656), efficacy superior to placebo was shown in the short-term of 16 weeks. The primary endpoint, PASI75, was obtained in approximately 71% of the patients on adalimumab compared with 6.5% on placebo. A similar response rate for adalimumab (80%) was seen in study M04-716 while the placebo response in this trial was higher (19%). There are no controlled data for 1 year. However, results from M03-656 support that a proportion of subjects, although an exact estimation cannot be made, maintained adequate response during a 1 year treatment period. There are however still uncertainties regarding longer-term efficacy beyond 1 year, including impact of antibodies.

The first line indication proposed by the MAH was not agreed with due to the safety profile of adalimumab (see the section Overall discussion and benefit/risk assessment). However, subgroup analysis in the second line target population (moderate to severe chronic Ps in adult patients who failed to respond to or who have a contraindication to, or are intolerant top other systemic therapy including cyclosporine, MTX or PUVA) were submitted. It can be concluded that convincing short-term efficacy has been demonstrated and that the study programme and efficacy results up to one year are sufficient to support a second line indication in moderate to severe chronic Ps. The proposed dose regimen with an initial 80 mg dose followed by 40 mg eow was agreed.

The relevance of the data from the comparative study with MTX, was questioned, as the dose increase of MTX was stopped before the primary endpoint level, PASI 75, was reached and due to the limited study duration of 16 weeks. Optimal efficacy with MTX was likely not reached during that time period, which also was supported by efficacy estimations provided by the MAH.

Data from study M02-528 were not justified for inclusion in the SPC, since the population studied included subjects less severe disease, and the rather low number of patients treated with the recommended dose.

Limited data have been obtained on whether loss of adequate response occurs when maintenance therapy is stopped. In study M03-656 (period C), a substantial number of patients (72% on placebo and 95% on adalimumab), did not lose adequate response during the drug-free phase of 19 weeks. It is acknowledged that the efficacy of maintenance therapy in the long run likely will be superior to on demand treatment. Nevertheless, it remains to be proven that the risk/benefit of maintenance is non-inferior to on demand treatment. The MAH provided further data from study M03-656, which suggested a lower probability for subjects who lost response to regain effect, than those who did not loose response during the 19 weeks period off treatment. Nevertheless, the CHMP agreed with the MAH commitment to collect additional data regarding treatment interruptions and on demand treatment in the post marketing setting, including through the planned registry.

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, hematologic events, and hepatic events.

Patient exposure

The adalimumab development program in psoriasis includes safety experience on 1696 subjects who received at least one dose of adalimumab for cumulative exposure of 1684 patient years (PY), through 29 June 2006. The table below presents the analysis sets for the safety analysis in the placebo – controlled study set (Duration and Extent of Treatment (placebo – controlled study set))

Treatment	Patient–Years of Exposure	N	Mean Days ± SD	Median (Range)
PBO	147.7	503	107.3 ± 24.01	119.0 (14.0 – 133.0)
ADA	294.0	966	111.2 ± 13.78	112.0 (14.0 – 129.0)
Total	441.7	1469	109.8 ± 18.03	114.0 (14.0 – 133.0)

ADA = adalimumab; PBO = placebo

Adverse events

The table below shows an overview of treatment emergent AEs and treatment emergent AEs per 100 patient years of exposure in the placebo controlled study set.

AE Category Subjects with any:	PBO N = 503 n (%)	ADA N = 966 n (%)	PBO N = 503 PY = 147.7 E (E/100 PY)	ADA N = 966 PY = 294.0 E (E/100 PY)
AE	297 (59.0)	614 (63.6)	693 (469.1)	1455 (495.0)
AE at least possibly related	85 (16.9)	221 (22.9)**	157 (106.3)	406 (138.1)
Severe AE	15 (3.0)	27 (2.8)	17 (11.5)	32 (10.9)
SAE	8 (1.6)	18 (1.9)	8 (5.4)	20 (6.8)
AE leading to discontinuation of study drug	11 (2.2)	17 (1.8)	18 (12.2)	21 (7.1)
Fatal AE	0	0	0	0
Infections	120 (23.9)	293 (30.3)**	146 (98.8)	396 (134.7)
Serious infections	4 (0.8)	5 (0.5)	4 (2.7)	7 (2.4)
Malignancies	2 (0.4)	7 (0.7)	2 (1.4)	7 (2.4)
Lymphoma	0	0	0	0
Non–melanoma skin cancers	1 (0.2)	5 (0.5)	1 (0.7)	5 (1.7)
Other malignancies (excluding non–melanoma skin cancers and lymphomas)	1 (0.2)	2 (0.2)	1 (0.7)	2 (0.7)
Demyelinating Disorders	0	0	0	0
Congestive Heart Failure	0	1 (0.1)	0	1 (0.3)
Allergic Reactions	0	1 (0.1)	0	1 (0.3)
Injection Site Reactions	25 (5.0)	68 (7.0)	39 (26.4)	88 (29.9)
Opportunistic Infection (excluding TB)	0	0	0	0
TB	0	0	0	0
Lupus–like Syndrome	0	0	0	0
Hematologic Events	1 (0.2)	1 (0.1)	2 (1.4)	1 (0.3)
Hepatic Events	13 (2.6)	17 (1.8)	14 (9.5)	30 (10.2)

ADA = adalimumab; E = events; PY = patient–years of exposure; PBO = placebo.

***,**,* Statistically significant at the $p \leq 0.001$, ≤ 0.01, and ≤ 0.05 level, respectively.

Serious adverse events and deaths

Two subjects experienced a treatment–emergent AE leading to death: a cerebrovascular accident and a suicide. Both events were considered by the Investigator to be unrelated to study drug.

The overall incidence of SAEs was 5.2% of all adalimumab − treated subjects, with an event rate of 6.6/100 PY. In the Placebo − Controlled Study Set, the incidence of SAEs was comparable in the adalimumab (1.6%) and placebo (1.9%) groups. Individual SAEs were all uncommon, with the most frequently reported SAEs being coronary artery disease, which occurred in six subjects (0.4%; 0.4/100 PY), followed by cellulitis (5 subjects, 0.3%; 0.3/100 PY) and myocardial infarction (4 subjects, 0.2%; 0.2/100 PY). The serious cardiovascular events occurred in subjects who had pre-existing cardiovascular risk factors.

Discontinuation
The overall incidence (5.1%) and exposure-adjusted rate (6.8/100 PY) of AEs leading to discontinuation of study drug were also relatively low, with no single AE leading to discontinuation occurring in more than four subjects. In the Placebo − Controlled Study Set, the incidence of AEs leading to discontinuation was comparable in the adalimumab (1.8%) and placebo (2.2%) groups.
Other SAEs and AEs that led to premature discontinuation were consistent with those in other populations studied with adalimumab.

Rebound
Rebound, defined as the development of new generalised erythrodermic or pustular psoriasis or achievement of a PASI score ≥ 125% of Baseline within 3 months of discontinuation of adalimumab, was not observed among any of the subjects who underwent protocol − mandated discontinuation of adalimumab in Study M02 − 538 or in Study M03 − 656.

Adverse events of special interest
Infections
Infectious AEs most frequently reported among subjects in the All Adalimumab Treatment Set were nasopharyngitis, upper respiratory tract infection, sinusitis, bronchitis, and influenza. The table below shows the number (%) of subjects with treatment emergent infections occurring in ≥ 1% of subject in the placebo controlled study set.

Adverse Event[a] Preferred Term	**PBO N = 503 n (%)**	**ADA N = 966 n (%)**
Any infection	120 (23.9)	293 (30.3)
Nasopharyngitis	39 (7.8)	75 (7.8)
Upper Respiratory Tract Infection	15 (3.0)	62 (6.4)
Sinusitis	6 (1.2)	24 (2.5)
Bronchitis	5 (1.0)	15 (1.6)
Herpes simplex	3 (0.6)	11 (1.1)
Influenza	3 (0.6)	11 (1.1)
Tooth abscess	3 (0.6)	11 (1.1)
Urinary tract infection	3 (0.6)	11 (1.1)
Pharyngitis	3 (0.6)	10 (1.0)
Rhinitis	7 (1.4)	3 (0.3)

ADA = adalimumab; PBO = placebo.
a. More than one AE per subject possible.

The overall incidence of serious infectious AEs was 1.2%, 1.4/100 PY, with the most frequently reported serious infections being cellulitis in four subjects. The CHMP concluded that there was no new safety signal related to infections, beyond comments on TB given below.

Tuberculosis
Subjects with latent tuberculosis (TB) were eligible for Study M04-716 only if they consented to receive TB prophylaxis for nine months, as tolerated. Subjects with latent TB were included in the

study because of the scientific interest in collecting data in Ps subjects who were purified protein derivative (PPD) positive, received TB prophylaxis, and were treated with study drug in order to evaluate how this subgroup of subjects compared to the others with regard to potential hepatic toxicity. Three subjects were diagnosed with active TB, one subject having a normal chest X-ray and a negative PPD tuberculin skin test at screening. As a consequence, this subject appears as a newly developed case. Two other subjects had latent disease and developed TB in spite of prophylaxis (one of these two subjects was noncompliant with TB prophylaxis). Overall, within the psoriasis program there were 89 subjects diagnosed with latent TB who received anti-TB prophylaxis, representing a TB rate of 2.2 % (2/89) in subjects where prophylactic treatment for latent TB was undertaken. The risk for TB in association with adalimumab treatment remains an important factor for the overall benefit/risk balance. The wording in section 4.4 of the SPC was revised to reflect the currently available information.

Malignancy
The incidence of malignancies overall, was higher in the adalimumab group (7 cases =2.4/100PY) compared with placebo (2 cases= 1.4/100PY). No lymphomas were reported. Other malignancies reported included one case of malignant melanoma in a patient on adalimumab for 29 days and one breast cancer found after 11 days on adalimumab.
In the placebo-controlled study periods there were 6 reports on non-melanoma skin cancers, whereof 5 on adalimumab. Among those, 3 were basal cell carcinoma and one unspecified skin neoplasm. One squamous cell carcinoma occurred at day 15.

In the All-adalimumab treatment set, twelve (12) adalimumab–treated subjects reported a total of 15 individual non-melanoma skin cancers. Basal cell carcinoma were reported in 8 and squamous cell cancer in 5 individuals. Six of the 12 subjects had a history of keratoacanthoma or non-melanoma skin cancer. Eight individuals had been treated with phototherapy (PUVA or other UV-light therapy), 2 MTX and 2 Cyclosporine and 3 biologics. Duration of psoriasis was from 13-65 years.

The CHMP noted that the numbers of reported malignancies were higher in the adalimumab group compared with placebo, but that it is difficult to interpret due to the relatively short exposure time. Among the non-melanoma skin cancer cases, the majority had a very long lasting psoriasis with other risk factors including light therapy, but also previous skin malignancies in some cases. It is of note that some malignancies are reported within a short time from the start of adalimumab treatment. As previously discussed, this might be due to an activation of a pre-existing malignancy. The MAH stated that the educational program which will be extended to dermatologists will emphasise the importance of screening all patients, irrespective of which indication the patient is being treated, for the risk factors for non-melanoma skin cancers before initiating and during treatment with adalimumab. Additional wording was also proposed for section 4.4 and the PL. Overall, the CHMP considered these actions as appropriate. The risk for malignancies remains an important factor for the overall benefit/risk balance.

Lupus-like syndrome
One subject in the All Adalimumab Treatment Set developed lupus-like syndrome.

Allergic Reactions
Three adalimumab − treated subjects (0.2%, 0.2/100 PY) reported treatment − emergent allergic reactions (hypersensitivity [2], anaphylactoid reaction [1]), which were considered unrelated to study drug and none of which led to premature discontinuation from the study.

Demyelinating Disease
There were no cases.

Congestive heart failure (CHF)
One subject (1%, 0.1/100 PY) reported congestive heart failure, which developed early in the course of treatment with adalimumab (27 days after first dose) and did not lead to discontinuation from the study.

Injection Site Reaction
Overall, 159 adalimumab − treated subjects (9.4%, 18.2/100 PY) reported injection site reactions. Injection site reactions occurred at a higher incidence in adalimumab − treated (7.0%, 29.9/100 PY) vs. placebo subjects (5.0%, 26.4/100 PY). Most events were mild in severity. Two subjects (0.1%) treated with adalimumab discontinued due to an injection site reaction.

Haematologic Events
A total of three haematological events (0.2%, 0.2/100 PY) occurred in adalimumab − treated subjects (thrombocytopenia [2], leucopenia [1]).

Hepatic Events
Overall, 58 adalimumab − treated subjects (3.4%, 4.9/100 PY) reported hepatic events; the most commonly reported events were alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased. Hepatic events were serious in two subjects (one cholecystitis and one cholelithiasis) and led to discontinuation in seven subjects. Hepatitis was reported in two subjects. The overall incidence of treatment-emergent hepatic events was lower among adalimumab − treated subjects (1.8%) than placebo − treated subjects (2.6%).

Laboratory findings
In the MTX-controlled study M04-716, higher percentages of subjects in the adalimumab group compared with the placebo and MTX groups had shifts in total cholesterol and triglycerides from normal at Baseline to high at the final visit. These results have been seen previously with adalimumab and may be associated with the anti-inflammatory effect of adalimumab. Percentages of adalimumab-treated subjects with shifts in LFTs (alkaline phosphatase, AST, ALT, total bilirubin, and gamma GT) from normal at Baseline to high at the final visit were comparable or lower than those in the placebo and MTX treatment groups. A noticeably higher percentage of subjects in the MTX treatment group shifted to high ALT values compared with the adalimumab treatment group. In the overall placebo-controlled treatment set, ALT elevations from normal to high occurred in 6.3% with placebo and 7.8% with adalimumab.

Vital Signs
No clinically relevant changes in vital sign values among adalimumab − treated subjects in any of the analyses sets were observed.

Safety in special populations
There seems to be no specific major sex related difference in AEs. Adalimumab has not been studied in the paediatric psoriasis population. The number of patients above the age of 65 in the psoriasis studies was rather limited (approx. 6%).

Discussion on clinical safety
The adalimumab development program in psoriasis included safety exposure on 1696 subjects who received at least one dose of adalimumab, for a cumulative exposure of 1684 patient − years, through 29 June 2006. The safety profile of adalimumab in psoriasis was similar to that observed in populations previously studied, including AEs of special interest. An increase of non-serious infections was observed in the adalimumab groups compared with the placebo groups. Cases of TB also occurred at a rate similar to that seen in other patient populations treated with adalimumab. These cases emphasise the importance of screening and prophylaxis for TB in subjects treated with adalimumab, which should be further discussed. The numbers of non-melanoma skin cancers are of concern and should be further monitored. Patients with psoriasis are often at a higher risk for skin cancers due to previous therapy with e.g. phototherapy. To continuously follow malignancies is of importance. It is also necessary to further emphasise the importance of thorough screening and examination of the skin before start of, and continuously, during treatment in psoriasis.

Risk management plan

The MAH submitted a revised risk management plan (RMP), which covered all approved indications as well as indications which are under investigation or have been submitted to the CHMP.

A summary of the RMP for adalimumab highlighting the safety concerns with adalimumab is presented below:

Safety Concern	Proposed Pharmacovigilance	Activities (routine and additional)
Important Identified Risks		
Infections including opportunistic infections and TB	Routine pharmacovigilance with use of specialised questionnaires to identify the results of screening, medical history, administration of prophylaxis, outcomes, and special reporting in PSURs of cases by geographic region of origin. Monitoring through long-term clinical studies and registries.	Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections, warning regarding infections in section 4.4 and information on infections in section 4.8 of the SPC. Risk Minimisation actions in the form of an educational programme followed by measurement and communication of its effectiveness is planned
Lymphoma	Routine pharmacovigilance activities with particular interest in identification of hepatosplenic lymphoma cases. Monitoring through long-term clinical studies and registries. Meta-analysis across three TNF inhibitors.	Warning regarding lymphoma in section 4.4 and information on rates from clinical trials and post-marketing are included in section 4.8 of the SPC. Educational Program.
Non melanoma skin cancer (NMSC)	Routine pharmacovigilance activities and special reporting in PSURs. Monitoring through long-term clinical studies and registries. Meta-analysis across three TNF inhibitors	Rates for NMSC from clinical trials and post-marketing are included in section 4.8 of the SPC. Educational Program.
Immune reactions (including lupus-like reactions and allergic reactions)	Routine pharmacovigilance activities with specialised questionnaire for lupus-like reactions. Monitoring through long-term clinical studies and registries.	Warnings regarding serious allergic reactions and lupus-like reactions are included in section 4.4 of the SPC. Anaphylaxis is also listed as an undesirable event identified in post-marketing surveillance in section 4.8 of the SPC.
Central Nervous System (CNS) demyelinating disorders	Routine pharmacovigilance with specialised questionnaires for events such as ALS (amyotrophic lateral sclerosis), PML (progressive multifocal leukoencephalopathy), and multiple sclerosis and special reporting in PSURs. Monitoring through long-term clinical studies and registries.	Warning on CNS demyelinating disorders is included in section 4.4 of the SPC. Educational Program.
Haematological disorders	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding haematologic reactions is included in section 4.4 of the SPC.
Vasculitis	Routine pharmacovigilance activities.	Listed as post-marketing event in section 4.8 of the SPC

	Monitoring through long-term clinical studies and registries.	
Elevated ALT levels in PsA	Routine Pharmacovigilance activities with specialised questionnaires for additional information on confounding factors and outcome. Monitoring through long-term clinical study in PsA.	The risk of elevated ALT levels in PsA patients is addressed in section 4.8 of the SPC.
Important Potential Risks		
Other Malignancies (except lymphoma and NMSC)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries. Meta-analysis across three TNF inhibitors.	Warning regarding malignancies in section 4.4 and information on rates from clinical trials and post-marketing are included in section 4.8 of the SPC. Educational Program.
Congestive heart failure (CHF)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Contraindication in section 4.3 for moderate to severe heart failure (NYHA class III/IV) and warning regarding mild heart failure (NYHA class (I/II) included in section 4.4 of the SPC with instructions to stop adalimumab is symptoms become worse in these patients. Educational Program.
Reactivation of chronic hepatitis B	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding hepatitis B reactivation is included in section 4.4 of the SPC, and reactivation of hepatitis B is also listed as an undesirable event identified in post-marketing surveillance in section 4.8 of the SPC.
Interstitial lung disease	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Interstitial lung disease is listed as an undesirable event identified in post-marketing surveillance in section 4.8 of the SPC.
Hepatosplenic T-cell Lymphoma	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Hepatosplenic T-cell lymphoma is a specific form of lymphoma and therefore any risk minimisation activities implemented for lymphoma will cover also this specific form. No specific risk minimisation activities for Hepatosplenic T-cell lymphoma are necessary.
Intestinal stricture in CD	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding small bowel obstruction and intestinal stricture is included in section 4.4 of the SPC Routine pharmacovigilance activities are adequate to detect any increase in the severity or frequency of intestinal strictures from spontaneous reporting sources and ongoing clinical trials associated with adalimumab therapy.
Important Missing Information		
Subjects with immunocompromised conditions; subjects with a history of	Routine pharmacovigilance activities. Monitoring through registries.	Warnings regarding patients with immunocompromised conditions are included in several places in section 4.4 of the SPC.

clinically significant drug or alcohol abuse		
Subjects with poorly controlled medical conditions such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, CHF, recent cerebrovascular accidents	Routine pharmacovigilance activities. Monitoring through registries.	Warnings regarding patients with a history of recurring infections and mild heart failure are included in section 4.4 of the SPC. Contraindication for moderate to severe heart failure included in SPC.
Subjects with history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals, or antifungals, previous diagnosis of HIV	Routine pharmacovigilance activities. No additional activities since this population is contraindicated.	Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections, warning regarding infections in section 4.4.
Subjects with history of cancer, lymphoma, leukemia, or lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of CNS demyelinating disorders.	Routine pharmacovigilance activities. No additional activities since caution statement included in the product information.	Warnings regarding patients with a history of malignancy and pre-existing or recent-onset CNS demyelinating disorders are included in section 4.4 of the SPC.
Children < 18 years of age for PsA, AS, Ps, and CD indications	Routine Pharmacovigilance activities and assessment of AE profiles of patients by age and paediatric indications, when approved. Incidence of PsA and AS in children is low; therefore, no additional activities and studies are planned. Studies in children with Ps and CD are under development.	Section 4.2 of the SPC addresses the lack of information in paediatric patients. However with the completion of paediatric trials for JIA, CD, and Ps, this information will be communicated and the SPC changes made according to the findings
Pregnant or lactating women	Routine pharmacovigilance activities. Adalimumab is not foreseen to be used in pregnant and lactating women. A pregnancy exposure registry (Study M03-604) was set up by Abbott to monitor planned and unplanned pregnancies in women exposed to adalimumab.	Section 4.6 currently addresses the risks to women who may become pregnant or are lactating while being treated with adalimumab. It also addresses the risk to infants who are exposed in utero or via breast milk.
Subjects with renal or hepatic impairment	Routine pharmacovigilance activities. Monitoring through registries.	Section 4.2 of the SPC indicates that adalimumab has not been studied in this patient populations and that there are no specific recommendations

		about the dose or the use of adalimumab in these patients.
Patients taking concomitant biologic therapy.	Routine pharmacovigilance activities. No additional activities as it is anticipated that inclusion of these medications would seriously jeopardize the safety.	Warning regarding concomitant use with Anakinra is included in section 4.4 of the SPC. Combinations with other biologics are not specifically addressed in the SPC, but available data on combinations with other DMARDs are described in section 4.2 and 5.1.
Long-term RA data beyond 5 years	Routine pharmacovigilance activities. 10-year long-term studies	Information on clinical data available for 5 years duration is included in section 5.1 of the SPC.
Long-term PsA data	Routine pharmacovigilance activities. 3-year long-term study	Information on clinical data available is included in section 5.1 of the SPC.
Long-term AS data	Routine pharmacovigilance activities. 5-year long-term studies	Information on clinical data available is included in section 5.1 of the SPC.
Long-term CD data	Routine pharmacovigilance activities. 5-year registry	Information on clinical data available is proposed to be included in section 5.1 of the SPC
Episodic treatment in CD data	Routine pharmacovigilance activities. 5-year registry	Episodic treatment is not foreseen according to the approved SPC. An ongoing registry for CD will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab. This protocol is designed to collect information on patients for at least five years. Safety findings will be communicated in future PSURs and updates will be made to the CCDS and SPC as necessary.
Long-term Ps data	Routine pharmacovigilance activities. 5-year registry Continuation of Study M03-658 for 2 years; patients will then be offered to be rolled-over into the registry.	Information on clinical data available is proposed to be included in section 5.1 of the SPC.
Episodic treatment in Ps data	Routine pharmacovigilance activities. 5-year registry	Episodic treatment is not proposed in the SPC. An ongoing registry for Ps will complement the safety experience especially on episodic treatment gained from spontaneous postmarketing AE reporting for all patients on adalimumab. This protocol is designed to collect information on patients for at least five years. Safety findings will be communicated in future PSURs and updates will be made to the CCDS and SPC as necessary.

The annex II was updated to reflect the information on the educational plan which is to be extended to dermatologists.

Overall discussion and benefit/risk assessment

Psoriasis is a chronic immunologic disease, affecting men and women equally, and is a life-long disease often diagnosed early in life.

The MAH applied for an extension of indication in the treatment of chronic Ps. The decision about the treatment position of a new drug (e.g., first line v.s. second line treatment option) is the result of a combination of efficacy and safety data in a given disease context. This consideration particularly applies to a chronic disease like psoriasis where multiple treatment options are already available, disease suppression usually ceases after treatment withdrawal, and safety issues play an important role, given the benign nature of the disease itself, without obvious subsequent morbidities.

Although efficacy was demonstrated, the benefit/risk balance for first line therapy was not considered positive, due to the safety profile and safety concerns of adalimumab. The increased risk for serious infections, which may have fatal outcome, and for non-melanoma skin cancers and remaining doubts whether other malignancies are activated, seriously question adalimumab as a first line option in severe psoriasis. The second line indication proposed by the MAH was supported by subgroup analyses of the efficacy results in the second line target population (moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, MTX or PUVA.). The proposed dose regimen with an initial 80 mg dose followed by 40 mg eow was accepted.

Limited data have been obtained on whether loss of adequate response occurs when maintenance therapy is stopped. In study M03-656 (period C), a substantial number of patients (72% on placebo and 95% on adalimumab), did not lose adequate response during the drug-free phase of 19 weeks. It is acknowledged that the efficacy of maintenance therapy in the long run likely will be superior to on demand treatment. Nevertheless, it remains to be proven that the risk/benefit of maintenance is non-inferior to on demand treatment. The MAH has provided some further data from this M03-656, which suggest a lower probability for subjects who lost response to regain effect, than for those who did not lose response during the 19 weeks period off treatment. It is considered acceptable that additional data regarding treatment interruptions and on demand treatment is collected in the post marketing setting, including the planned registry.

The safety profile in the studies in patients with psoriasis was similar to the previously approved indications with an identified risk for serious infections, including opportunistic infections and TB. Non-melanoma skin cancers have been reported in a higher number of patients on adalimumab compared with placebo. The CHMP agreed that the MAH will, in the educational program, emphasise the need for screening of all patients for the risk for non-melanoma skin cancers before and during treatment with adalimumab. Malignancies should continue to be followed as well as other events of interest, following the evaluation of the PSURs. Furthermore, an additional warning was added to section 4.4 of the SPC, and information was also included in the PL.

The revised RMP submitted was agreed with, although some updates were recommended. The risk minimisation activities in place were agreed, as the MAH has proposed to expand the educational programs to involve dermatologists and to implement a registry.

Conclusion

On 15 November 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the SPC, annex II and PL.