European Medicines Agency

London, 24 July 2008
EMEA/CHMP/479654/2008

ASSESSMENT REPORT
FOR

Humira

International Nonproprietary Name:
Adalimumab

Procedure No. EMEA/H/C/II/39

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

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 the therapeutic indication to include treatment of active polyarticular juvenile idiopathic arthritis (JIA), in children and adolescents aged 4 to 17 years who had had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). The MAH presented the results of the JIA clinical trial to demonstrate adalimumab's safety and efficacy in this population.

Juvenile idiopathic arthritis is an autoimmune disease with a complex genetic predisposition that has been observed in children under the age of 16 years. It is the most common rheumatic disease of childhood and a cause of disability in children with an incidence of 15 per 100,000, 2.5 times more common in females (North America and European populations).

In the progression of inflammatory synovitis (an inflammation of the synovial membrane, a layer of tissue that lines a joint) and articular matrix degradation the two cytokines (molecules produced by the immune system, e.g. during an inflammatory reaction), TNF-α and interleukin (IL)-1 are involved. When TNF-α is inhibited, the levels of other pro-inflammatory cytokines are also reduced, such as IL-1 and IL-6. TNF-α is elevated in serum, synovial fluid, and synovial tissue of children with JIA.

The MAH proposed to amend the text of the summary of product characteristics (SPC) sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.8, 5.1 and 5.2, and to update the package leaflet (PL) accordingly.

Clinical aspects

To support the variation application the MAH presented one pivotal study; DE038; where adalimumab was studied in paediatric subjects with polyarticular JIA, who were either MTX-naïve, inadequate responders or intolerant to MTX.

Pharmacokinetics/Pharmacodynamics[1]

The pharmacokinetics and immunogenicity of adalimumab were evaluated in paediatric (4 – 17 years) subjects with polyarticular JIA in study DE038. In the 16-week open-label lead-in (OL LI) phase and the 32-week double-blind (DB) phase the dosing regimen was 24 mg per m^2 (max 40 mg) sc (subcutaneously) eow, with or without concomitant methotrexate (MTX). The open-label extension comprised the same dosing based on body surface area (OLE BSA) and a period with fixed dosing (OLE FD) treatment (20 mg for subjects with body weights < 30 kg and 40 mg for subjects with body weights >30 kg).

The average (SD) serum concentrations observed in the OL LI and DB phases (average from all time points measured during weeks 20 to 48) in adalimumab treated patients were 10.9 (5.2) μg/ml and 5.5 (5.6) μg/ml in patients with and without MTX, respectively. The inter-individual variability was very large, in particular in patients without concomitant MTX treatment. Comparative data (adult versus juvenile) on drug exposure was provided and it appeared that the serum concentrations in subjects with JIA were within the range of those previously observed in adult subjects, both during monotherapy and concomitant MTX treatment. There was a tendency for a higher inter-individual

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

variability and higher immunogenicity rate in juvenile subjects compared with. During concomitant MTX treatment the serum levels were on average higher and the variability was lower.

One-hundred and six patients completed the OLE BSA phase and entered the OLE FD phase, in which serum concentrations of adalimumab were measured only in patients who had their dose changed (N=56). When the dose was increased based on the fixed dose regimen serum concentrations increased (as expected) with individual values ranging from 0 to 30.7 μg/ml. For the patients where the dose was decreased it was not possible to draw any conclusions based on the very sparse data.

A population pharmacokinetic model was developed on the basis of data from juvenile (DE038) and adult (DE011 and DE009) patients with RA, with the purpose to assess pharmacokinetic differences between adults and children. However, the CHMP concluded that at present a conclusion of no difference in the pharmacokinetics between adults and juvenile subjects cannot be drawn, due to deficiencies in the analysis. Further, on the basis of juvenile data only (DE038), a population pharmacokinetic analysis and clinical trial simulations were conducted to support the appropriateness of the proposed fixed dose regimen, since the controlled part of the study was conducted with BSA dosing. Several deficiencies were identified in the modelling and simulation activities and the pharmacokinetic documentation did not contribute in the assessment of safety and efficacy of the fixed dosing strategy. The quantitative assessment of the simulations, e.g. 5th, median and 95th percentiles of various age groups, was not considered appropriate as the population model did not appear to fit to the data and the predictiveness of the model was not assessed properly.

Immunogenicity
Only samples with low adalimumab concentrations (<2 microg/ml) were analysed for anti-adalimumab antibodies (AAA).

Twenty-seven subjects (16%) had at least one AAA positive observation during the OL LI and DB phases, whereof 5 (6%) and 22 (26%) with and without MTX, respectively. The incidence of antibodies was higher in juvenile subjects on monotherapy, compared with adults on monotherapy, while there was no obvious difference in the antibody incidence between juvenile and adult subjects on concomitant MTX.

In all phases, the overall proportion of patients treated with adalimumab achieving a PedACR30[2] response was lower in AAA positive patients compared with AAA negative patients. In the OL LI, the overall proportion of patients treated with adalimumab achieving a PedACR30 response at week 16 was lower in AAA positive patients (12 of 19, 63%) compared with AAA negative patients (132 of 152, 87%). Also in the DB phase, the overall proportion of patients treated with adalimumab achieving a PedACR30 response at week 48 was lower in AAA positive patients (6 of 14, 43%) compared with AAA negative patients (35 of 54, 65%). In the OLE FD phase at week 16, the overall proportion of patients treated with adalimumab achieving a PedACR30 response in AAA positive patients (12 of 17, 71%) compared with AAA negative patients (79/89, 89%). Overall, presence of AAA did not affect safety.

The high number of anti-adalimumab antibodies in children without MTX is of concern and the incidence appears considerably higher than observed in adults. Furthermore, the data show that presence of AAA was associated with reduced effect.

[2] PedACR30 (American College of Rheumatology Paediatric 30) is a standardised outcome measure to assess relative efficacy in clinical trials, i.e., a measure of disease activity in JIA. It is defined as a 30% improvement in a minimum of three variables in the core set with worsening of one variable by no more than 30%. The ACR Paediatric 20, ACR Paediatric 50, ACR Paediatric 70, and ACR Paediatric 90 measures are also used as outcome measures in paediatric trials, and are defined as 20%, 50%, 70%, 90% improvement respectively in a minimum of three variables in the core set with worsening of one variable by no more than 30%.

Clinical efficacy

Study DE038

Study DE038 was a multicentre, phase III, randomised withdrawal, double-blind, stratified, parallel-group study in children and adolescents (4 to 17 years old) with polyarticular JIA. Stratification into two groups, MTX-treated or non-MTX-treated, was made prior to study enrollment. Subjects in the MTX stratum were treated concomitantly with MTX during the study and the current dose of MTX was to have been stable for at least 3 months prior to screening. Subjects who were in the non-MTX stratum were either naïve to MTX or had been withdrawn from MTX at least two weeks prior to study drug administration and were not treated concomitantly with MTX during the study.

The study had four phases. During the first three of these, adalimumab was given at a dose of 24 mg/m^2 of BSA (up to a maximum total body dose of 40 mg) sc eow. The phases are listed below and table 1 presents the number of subjects in each phase of the study:

1. a 16-week open-label lead-in (***OL LI***) phase, (24 mg/m^2 BSA eow sc. N: 171)
2. a 32-week double blind (***DB***) phase, (24 mg/m^2 BSA eow sc – or – placebo. N: 133)
3. an open-label extension BSA dose (***OLE BSA***) phase. (24 mg/m^2 BSA eow sc. N: 128).
4. an open label extension fixed dose (***OLE FD***) phase in which subjects had their dose changed from a regimen based on BSA to a fixed dose regimen. (20 mg or 40 mg FD eow sc. N: 106).

The randomised withdrawal from study drug occurred at week 16 of the OL LI phase. Patients with a PedACR30 response were randomised within their stratum in a 1:1 ratio to placebo or adalimumab during the 32-week DB phase of the study. Subjects, who experienced disease flare during the DB phase, and those who completed, were eligible to immediately enroll into the open label extension BSA (OLE BSA) phase.

Subjects in the OLE BSA phase at the time of approval of the OLE FD protocol amendment were eligible to receive a fixed dose of either 20 mg or 40 mg eow adalimumab based on their body weight. Duration of participation in the OLE BSA phase varied for each subject.

The OLE FD phase was implemented to gather safety and efficacy data on a fixed dosing regimen based on body weight. In this phase, subjects with a body weight below 30 kg received 20 mg adalimumab eow and subjects with a body weight equal or above 30 kg received 40 mg adalimumab eow. Subjects may continue the OLE FD phase for a maximum of five years or up to sixty days post marketing approval of the JIA indication in their respective country.

Table 1 Number of subjects in each respective phase of the study

Disposition of patients in Study DE038			
Open label lead in phase (171 enrolled)			
Non-MTX : 86		MTX : 85	
77 completed		83 completed	
58 continued		75 continued	
Double-blind withdrawal phase (133 = 58 + 75 enrolled)			
Non-MTX/Ada	Non-MTX/Pl	MTX/Ada	MTX/Pl
30	28	38	37
29 completed	28 completed	35 completed	36 completed
Open label BSA (128 = 57 + 71 enrolled)			
29	28	35	36
24 completed	23 completed	31 completed	28 completed
Open label Fixed Dose			
106 enrolled			

The CHMP considered the design of the pivotal study as acceptable, although complicated. For ethical reasons, a withdrawal design is acceptable and has also been previously recognised in JIA trials. Inclusion of both MTX- and a non-MTX strata, allows for a comparison of monotherapy and combination therapy with MTX; which is of clinical value. The CHMP noted that the efficacy evaluation was undertaken when subjects were treated with the BSA dose regimen, although the MAH applied for a fixed dose, based on body weight. The fixed dose was only studied during a 16 weeks open phase.

Subject Population

The main inclusion criteria were subjects between 4 and 17 years with a diagnosis of polyarticular course JIA as defined by the ACR criteria. Subjects were to have had continuing active disease defined as ≥ 5 swollen joints and ≥ 3 joints with limitation of passive motion joint count (LOM). Disease onset may have been systemic, polyarticular, or pauciarticular. If the disease was systemic onset, subjects were to be free of any systemic JIA manifestations for at least three months before the time of qualification. Subjects were to have been either naïve to MTX, inadequate responders to MTX, or intolerant to MTX. Subjects who were refractory to MTX after 3 months of treatment were to have active disease after 3 months prior to enrollment. The duration of disease was to have been at least long enough for a subject to be given an adequate test of NSAIDs. Subjects were not to have received other DMARDs for at least four weeks prior to receiving the 1st dose of study drug and were to have demonstrated active disease prior to a minimum four weeks (28 days) washout of all DMARDs. Subjects were not to have received an intra-articular glucocorticoid injection within four weeks (28 days) prior to enrollment into the study. Overall, the CHMP considered the inclusion and exclusion criteria as acceptable.

Efficacy Variables

The primary efficacy endpoint was the proportion of adalimumab-treated subjects in the non-MTX stratum who experienced disease flare in the DB phase. The criteria for disease flare were both a ≥30% worsening in at least 3 out of 6 JIA core set criteria and also a minimum of two active joints and ≥30% improvement in not more than one of the six JIA core set criteria. The DB baseline was used as the reference point for the disease flare calculation.

The following JIA core set of variables were used to determine disease flare:

- Physician's Global Assessment of subject's disease severity by VAS (Visual analog scales)
- Parent's Global Assessment of subject's overall well-being by VAS
- Number of active joints (joints with swelling not due to deformity or joints with LOM and with pain, tenderness or both)
- Number of joints with LOM
- DICHAQ (disability Index of the Childhood Health Assessment Questionnaire)
- CRP (C-reactive protein) - Change in CRP from baseline was evaluated for clinical improvement or worsening only if at least one of the CRP values, baseline value, or the visit value was outside the normal reference range.

Among secondary efficacy variables, there were a number related to disease flare, as well as assessment of PedACR30/50/70/90 responses. The PedACR30 response in OL LI phase and DB phase was defined as ≥30% improvement in at least 3 of the JIA core set of criteria and ≥30% worsening in not more than one of the JIA core set. The PedACR50/70/90 in the DB phase were defined similarly to the PedACR30 using improvement percentages of 50, 70, and 90, respectively, while the worsening percentage criteria was kept unchanged at 30%.

Baseline disease characteristics

In the OL LI and the OLE BSA phases, there were no statistically significant differences in baseline disease characteristics between treatment groups or within the respective strata. Different ages were reasonably well represented in the two groups. For all parameters describing disease activity, there was a tendency towards more active disease in the non-MTX treated group. This was not found surprising as a non-treated population is more likely to have more active disease than a population with active disease despite MTX.

Statistical Methods
The statistical methods used were considered appropriate.

Dose selection
The controlled part of study was undertaken with a dose of 24 mg/m^2 BSA. The MAH justified the proposed fixed dose regimens since individualised dosing based on BSA could be disadvantageous because: 1) patients/parents may attempt to re-use a dosage unit intended for single use and thereby increase the potential for infection; 2) additional efforts are needed to calculate the individualised dose and administer the correct volume from the single use dosage unit.

Results

Main efficacy endpoints
Open label lead in phase (OLE LI)
The response rate, defined as PedACR30, during this phase was high in both groups, 80/85 (94%) with MTX and 64/86 (74%) without MTX. There were more responders among the patients with "active disease despite MTX" compared with patients without MTX, which indicate an increased efficacy with combination therapy. Six patients in the non-MTX stratum discontinued treatment due to lack of efficacy, but none in the MTX group. Of those who completed the OLE LI, 8 (9%) from the MTX group and 19 (22%) from the non-MTX group did not continue into the DB phase. This indicates that monotherapy was insufficient to achieve adequate response in certain individuals.

There were 27 subjects, who were PedACR responders at the end of the OL LI phase but who were not enrolled into the DB phase. The submitted LOCF analysis was questioned when considering the long-term treatment, the chronic disease intended and the paediatric contest.

Due to the low threshold for flare and the use of imputation (drop out for any reason, missing values and LOCF), the results of the primary efficacy analysis were questioned. It was considered that in the DB phase, a proportion of patients who were in the placebo arm may improve, also after a flare. The imputation assumes there will be no further improvement and could weaken the control arm. Because more patients drop out of the placebo condition than the adalimumab arm, imputation (particularly LOCF) results in a bias in favour of the alternative hypothesis. After further to discussions it was concluded that short term efficacy was demonstrated for adalimumab, but due to the trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. It was considered of importance to collect efficacy data in the 'real-world' practice. The MAH agreed to set up a registry in JIA patients (see Attachment 10, letter of undertaking). The secondary objective of this registry will be to evaluate the long-term effectiveness of Humira in JIA patients who are treated as recommended in the approved product information. Patients treated with MTX will be considered a reference group. Additionally, section 4.2 of the SPC contains the statement '*Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.*' which should reduce the risk that patients not responding receive continued treatment.

Double blind phase – primary efficacy analysis
The primary endpoint was the proportion of patients with disease flare in the non-MTX population in the DB phase. A statistically significantly lower proportion of adalimumab-treated subjects demonstrated disease flare compared to placebo-treated subjects in the non-MTX stratum (43% for adalimumab vs. 71% for placebo; p = 0.031) as well as in the MTX stratum (37% for adalimumab vs 65% for placebo; p= 0.015). The CHMP noted that in both strata, the numbers of patients with flares in these enriched populations given continuous active treatment during the treatment period of 32 weeks, was rather high, 43% in the adalimumab group and 37% in the MTX + adalimumab group. Long-term efficacy may thus be questioned. The rather high number of flares may also suggest that there was a considerable placebo response with the defined response criteria during the LI phase. Logistic regression analyses showed no influence of prior use of NSAIDs or corticosteroids on disease flare.

Among the secondary endpoints, time to disease flare was statistically different in favour of the adalimumab treated groups in both strata. It was more than 32 weeks in both adalimumab groups, and 14 – 20 weeks for subjects who received placebo (both strata). Further, it was noted that there were at least 21/65 patients in the placebo-treated groups without disease flare during the 32-week treatment period, in addition to the patients on placebo who flared after a treatment free period of several weeks. In the group of patients who had a treatment free period, the safety profile following reintroduction of adalimumab was presented in detail. Among patients with no flare during the DB phase, a tendency towards more injection site reactions was found, but also a lower number of infections. These data are however, very limited due to a low number of patients. More knowledge on the risks and/or loss of efficacy in patients who interrupt treatment and restart again was considered important and should be collected in e.g. the registry. Clarifications that data from week 36 to week 48 in the adalimumab arm were not based on LOCF were provided.

In the analysis of PedACR30 responders at week 48, the result for the non-MTX group was not statistically significant. The endpoint PedACR30 responders in the MTX strata reached statistical significance in favour of adalimumab, the observed difference between placebo and active in the two strata was the same; 25%. PedACR30 values tended to decrease over time, relatively parallel in all four groups, with a slightly higher decline in the placebo groups. For the measures PedACR50/70 (indicating a higher degree of improvement), the CHMP noted that there appeared to be a tendency towards a better effect with the MTX+adalimumab combination.

Long-term efficacy

All subjects who completed 32 weeks of DB phase or experienced a flare were eligible to receive OL adalimumab during the OLE BSA phase. Due to the study design, subjects had different durations of exposure during the OLE BSA phase. There were only five subjects with exposure of 136 weeks. The CHMP noted this limited amount of data following longer term treatment, and that the numbers of treated patients decreased over time in the open BSA phase, partly due to recruitment of patients into the FD regimen.

Initially only 16 weeks data from the FD phase was included. It was concluded that, since individuals were treated in an open setting with the fixed dose, evaluation of efficacy of the fixed dose was not possible. Further to answers to outstanding issues data for the fixed dose period up to week 64 was submitted. However, given the few subjects included, and the open design, these data were considered of limited value.

Discussion on clinical efficacy

One pivotal trial was performed to study efficacy and safety in children aged 4-17 years, with polyarticular JIA. The table 2 below shows an overview of the study. An open initial phase study design, including two strata (non-MTX and MTX), followed by a double-blind withdrawal phase was chosen mainly from the ethical point of view. However, this design may not be optimal to prove efficacy. The study population was adequate as well as the chosen clinical endpoints.

Table 2: Study overview

Time	design	Dosage Adalimumab	+ MTX results	- MTX results	evaluation
16-week	OL LI	24 mg/m^2 BSA eow sc	N= 85 94.1%	N=86 74.4%	PedACR30 criterion
32-week	DB	24 mg/m^2 BSA eow sc vs placebo	N=75 37% vs 67%	N=58 43% vs 71%	% of pts with disease flare (in the non-MTX stratum): PedACR30 criterion
	OLE BSA	24 mg/m^2 BSA eow sc	N=71	N=57	Pts w/ disease flare immediately enrolled into the OLE BSA
16-week	OLE FD	20 mg or 40 mg eow based on subject weight	N=59	N=47	

In the open initial phase of the study, the response rate, according to the predefined 30% improvement criteria, was 94% with MTX + adalimumab and 74% in the group given adalimumab without MTX. There were more responders among the patients with "active disease despite MTX" (i.e. the group given combination therapy) compared with patients without MTX, and more patients without MTX discontinued the open phase, which indicates an increased efficacy with combination therapy.

The primary endpoint, proportion of subjects with disease flare in the non-MTX stratum during the DB phase, was statistically significantly in favour of adalimumab. The same result was shown in the MTX stratum. However, due to the low threshold for flare and the use of imputation the results of the primary efficacy analysis were questionable. It was accepted that adalimumab prevents disease flares compared to placebo but due to the trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. The current measures should reduce the risk of patients not responding: the product information advises caution if a patient does not respond within 12 weeks of treatment; furthermore, a registry aiming to collect more data in this regard will be set up.

The MAH applied for two fixed doses, with a weight cut off of 30 kg, despite that the controlled phase of the study was undertaken with BSA dosing. It was concluded that the available data with the fixed doses was insufficient, both in terms of efficacy and safety (see section 3.24 on clinical safety), due to the open label treatment in a limited number of subjects. Following assessment of the responses to the first set of questions raised, it remains evident that only BSA dosing has been adequately documented. The MAH provided a justification for use of a fixed dose of 40 mg from the age of 13 years, which was endorsed. For younger children, the CHMP did not agree that there is sufficient evidence to support a fixed dose regimen. Consequently, there was a need for a syringe that can reassure accurate dosing for younger children. The MAH did not find it possible to currently provide such syringe, and therefore withdrew a claim (section 4.1 and 4.2) for children below 13 years of age. The CHMP considered it disappointing that younger children would not be addressed in the indication and posology, due to such reason, but the approach was accepted. The CHMP agreed on describing the clinical study in section 5.1 of the SPC, including the age of the patients studied and dose regimens used.

There were tendencies of better efficacy in the combination group compared with the group given adalimumab monotherapy. In the initial OL LI phase a higher percentage of responders were found in the MTX-group, 94 %, versus 74% in non-MTX group. In addition, the number of discontinuations was higher in the non-MTX during the initial phase, and there was a higher number of responders achieving the more stricter Ped ARC50/70 criteria in the combination group. Anti-adalimumab antibodies developed in a higher number in the non-MTX group, 26% versus 6%, which also raised concerns regarding long term efficacy. Further, the pharmacokinetic data indicate a higher adalimumab plasma level in the combination group. Overall, these data support combination therapy with MTX, and therefore combination therapy is the primary recommendation for this indication.

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

In the OL LI phase and the DB phase, there were 55 subjects exposed to adalimumab, corresponding the 44 patients years (PYs). During the subsequent open label phases, exposure corresponded to 118 PYs. The table 3 below shows an overview of the safety analysis set for the FD phase.

Table 3: Safety analysis set by amount of dose increase – open label extension fixed dose phase

non-MTX				MTX				Total
Same/decreased dose	Increased dose			Same/decreased dose	Increased dose			
	5 mg	10 mg	>10 mg		5 mg	10 mg	>10 mg	
N=25	N=7	N=7	N=8	N=28	N=18	N=9	N=4	N=106
n(%)								
25 (100)	7(100)	7(100)	8(100)		28 (100)	9(100)	4(100)	106(100)

Adverse events

An overview of the treatment emergent AEs in the four phases of the study is presented in tables 4-7 below.

Table 4: Overview of treatment emergent adverse events (ITT population, open label lead in phase)

	MTX N=85	non-MTX N=86	Total N=171
Adverse event	n(%)		
Any adverse event	74 (87.1)	71 (82.6)	145 (84.8)
Serious adverse event	3 (3.5)	5 (5.8)	8 (4.7)
Severe adverse event	5 (5.9)	4 (4.7)	9 (5.3)
Leading to discontinuation of study drug	2 (2.4)	7 (8.1)	9 (5.3)
At least possibly related to drug	53 (62.4)	55 (64.0)	108 (63.2)
Infections	37 (43.5)	39 (45.3)	76 (44.4)
Serious infections	0	2 (2.3)	2 (1.2)
Malignancies	0	0	0
Injection site reactions	35 (41.2)	37 (43.0)	72 (42.1)
Immunologic	7 (8.2)	5 (5.8)	12 (7.0)
Opportunistic infections including TB	0	0	0
Death	0	0	0

Table 5: Overview of treatment emergent adverse events (ITT population, double blind phase)

	MTX		non-MTX		Overall	
	placebo N=37	adalimumab N=38	placebo N=28	adalimumab N=30	placebo N=65	adalimumab N=68
Adverse event	n (%)					
Any adverse event	27 (73.0)	32 (84.2)	21 (75.0)	28 (93.3)	48 (73.8)	60 (88.2)
Serious adverse event	2 (5.4)	3 (7.9)	0	1 (3.3)	2 (3.1)	4 (5.9)
Severe adverse event	0	2 (5.3)	0	1 (3.3)	0	3 (4.4)
Leading to discontinuation of study drug	0	0	0	0	0	0
At least possibly related to drug	15 (40.5)	22 (57.9)	9 (32.1)	16 (53.3)	24 (36.9)	38 (55.9)
Infections	19 (51.4)	22 (57.9)	11 (39.3)	19 (63.3)	30 (46.2)	41 (60.3)
Serious infections	0	1 (2.6)	0	1 (3.3)	0	2 (2.9)
Malignancies	0	0	0	0	0	0
Injection site reactions	9 (24.3)	14 (36.8)	4 (14.3)	11 (36.7)	13 (20.0)	25 (36.8)
Immunologic	0	2 (5.3)	0	3 (10.0)	0	5 (7.4)
Opportunistic infections including TB	0	0	0	0	0	0
Death	0	0	0	0	0	0

Table 6: Overview of treatment emergent adverse events (ITT population, OLE BSA phase)

	MTX		non-MTX		Overall	
	Adalimumab (placebo during DB phase)	adalimumab	Adalimumab (placebo during DB phase)	adalimumab	Adalimumab (placebo during DB phase)	adalimumab
	N=36	N=35	N=28	N=29	N=64	N=64
Adverse event	n (%)					
Any adverse event	34 (94.4)	33 (94.3)	27 (96.4)	25 (86.2)	61 (95.3)	58 (90.6)
At least possibly related to drug	20 (55.6)	18 (51.4)	18 (64.3)	18 (62.1)	38 (59.4)	36 (56.3)
Severe adverse event	6 (16.7)	3 (8.6)	0	2 (6.9)	6 (9.4)	5 (7.8)
Serious adverse event	7 (19.4)	6 (17.1)	3 (10.7)	5 (17.2)	10 (15.6)	11 (17.2)
Leading to discontinuation of study drug	0	1 (2.9)	1 (3.6)	0	1 (1.6)	1 (1.6)
At least possibly related to drug SAE	0	5 (14.3)	0	2 (6.9)	0	7 (10.9)
Infections	27 (75.0)	29 (82.9)	21 (75.0)	20 (69.0)	48 (75.0)	49 (76.6)
Serious infections	1 (2.8)	3 (8.6)	0	2 (6.9)	1 (1.6)	5 (7.8)
Malignancies	0	0	0	0	0	0
Injection site reactions	11 (30.6)	9 (25.7)	10 (35.7)	8 (27.6)	21 (32.8)	17 (26.6)
Opportunistic infections	0	0	0	0	0	0
Congestive heart failure related	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0
Hepatic related adverse event	2 (5.6)	4 (11.4)	1 (3.6)	0	3 (4.7)	4 (6.3)

Table 7: Overview of the treatment emergent AEs in the open label fixed dose phase.

	MTX		non-MTX		Overall	
	Same/decreased	increased	Same/decreased	increased	Same/decreased	increased
	N=28	N=31	N=25	N=22	N=53	N=53
Adverse event	n (%)					
Any adverse event	16 (57.1)	19 (61.3)	9 (36.0)	17 (77.3)	25 (47.2)	36 (67.9)
At least possibly related to drug	3 (10.7)	5 (16.1)	2 (8.0)	8 (36.4)	5 (9.4)	13 (24.5)
Severe adverse event	1 (3.6)	1 (3.2)	0	2 (9.1)	1 (1.9)	3 (5.7)
Serious adverse event	1 (3.6)	0	1 (4.0)	1 (4.5)	2 (3.8)	1 (1.9)
Leading to discontinuation of study drug	1 (3.6)	0	0	0	1 (1.9)	0
At least possibly related to drug SAE	0	0	0	0	0	0
Infections	6 (21.4)	11 (3.5)	3 (12.0)	9 (40.9)	9 (17.0)	20 (37.7)
Serious infections	0	0	0	1 (4.5)	0	1 (1.9)
Malignancies	0	0	0	0	0	0
Injection site reactions	1 (3.6)	2 (6.5)	0	3 (13.6)	1 (1.9)	5 (9.4)
Opportunistic infections	0	0	0	0	0	0
Congestive heart failure related	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0
Hepatic related adverse event	0	1 (3.2)	0	0	0	1 (1.9)
Allergic reactioin related	0	0	0	1 (4.5)	0	1 (1.9)
Lupus like syndrome	0	0	0	0	0	0
Serious blood dyscrasias	0	0	0	0	0	0
Non-serious blood dyscrasias	1 (3.6)	0	0	0	1 (1.9)	0
Fatal adverse event	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Serious adverse events and deaths

There were no deaths, malignancies, congestive heart failure (CHF), central nervous system (CNS) demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions reported in the study DE038.

Overall, 35 subjects reported 55 SAEs of which most were mild to moderate in severity. There were 9 SAEs that were reported as severe of which 3 were considered by the investigator to be at least possibly related to study drug. Pneumonia was reported during the OL LI phase and bronchopneumonia was reported during the OLE BSA phase; both events were reported for subjects in the non- MTX stratum. The third event, herpes zoster was reported for a subject in the MTX stratum during the OLE BSA phase. These events were resolved and the subjects continued in the study. Eight events were related to infections and three cases of appendicitis were reported.

Adverse events leading to discontinuation of study drug

Twelve subjects reported AEs that lead to the discontinuation of study drug. Nine AEs were reported in the OL LI phase. Disease flare occurred in 7/12 (whereof 5 in non-MTX, OL LI), one had leucopenia, two infections (pneumoniae) and one dizziness. One individual in the MTX stratum was discontinued from the study due to elevated transaminases approximately 2 months after first drug administration.

Laboratory findings

No new safety signals were found from changes in laboratory parameters during the phases of the study.

Discussion on clinical safety

The CHMP concluded that there were no new safety signals in the treated children/adolescents compared with the already well known safety profile in adults. Infections were the most common events, as for adults. No cases of death, malignancies, CHF, CNS demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions were reported. However, it was noted that the database is very small, and long-term safety cannot be assessed. In this regard, the main concerns are the development of malignancies. Regarding the fixed dose regimens applied for there is very limited safety data to assess possible implications of the dose changes, particularly in the younger children. In the FD phase of the study, a substantial number of patients, mainly in the lower age groups (and early Tanner stages) received an increased dose of ≥10 mg with the FD regimen. This is of concern, since no data are available to properly assess whether an increased dose is of any benefit to the young child, or to assess neither short-term nor long-term safety, in the younger children. Further, it appears that the number of subjects with any AE was higher (67.9%) in the group who received an increased adalimumab dose vs. those who stayed on the same or decreased the dose (47.2%). The difference was particularly evident for infectious AEs irrespective to the MTX stratum.

The MAH provided some further comparisons on the safety profile in patients with or without disease flare during the double-blind phase. There was a tendency towards more injection site reactions in subjects without flare, but also a lower number of infections. These data are very limited. More knowledge on risks and/or loss of efficacy from patients who interrupt treatment and restart again is of importance, and should be followed in the registry.

Risk management plan

The MAH submitted a risk management plan (RMP), which covered all approved indications as well as the indication which was under evaluation (JIA).

The risk minimisation activities for the safe and effective use of the medicinal product as defined in the annex II are applicable to this new indication. The new version (4.0) of the risk management plan was reflected in the annex II.

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

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Serious infections including opportunistic infections and TB	Routine pharmacovigilance with use of specialized 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 Minimization 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.
Hepatosplenic T-cell lymphoma	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries. Meta-analysis across three TNF inhibitors.	Warning regarding hepatosplenic T-cell lymphoma in Section 4.4 and information on rates from clinical trials and post-marketing is included in Section 4.8 of the SPC. Educational Program
NMSC	Routine pharmacovigilance activities and special reporting in PSURs. Monitoring through long -term clinical studies and registries. Meta-analysis across three TNF inhibitors	Warning regarding NMSC in Section 4.4 and 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 specialized 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.
CNS and peripheral demyelinating disorders	Routine pharmacovigilance with specialized questionnaires for events such as ALS, and MS 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.
Hematologic 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. Monitoring through long-term clinical studies and registries.	Vasculitis is listed as an undesirable event identified in post-marketing surveillance in Section 4.8 of the SPC.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Diverticulitis	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Diverticulitis is listed as a rare undesirable event identified in clinical studies in Section 4.8 of the SPC.
Intestinal perforation	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Intestinal perforation is listed as an undesirable event identified in post-marketing surveillance in Section 4.8 of the SPC.
Elevated ALT levels in PsA	Routine Pharmacovigilance activities with specialized questionnaires for additional information on confounding factors and outcome.	The risk of elevated ALT levels in PsA patients is addressed in Section 4.8 of the SPC.
Medication error and maladministration	Routine pharmacovigilance activities Root cause analysis of medication errors and maladministration. Report on Questionnaire analysis in Aug 2009.	Abbott will review all data on this issue. Recommendations for minimizing the risk of medication errors and maladministration associated with adalimumab will be made based on the findings of root cause(s) of the problem from postmarketing reports and complaint report analysis.
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.
CHF	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Contraindication in Section 4.3 for moderate to sever 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.
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.
Stevens-Johnson Syndrome	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	SJS will be listed as an undesirable event identified in post-marketing surveillance in Section 4.8 of the SPC.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Missing Information		
Subjects with immune-compromised conditions (i.e. Subjects with HIV, post-chemotherapy, organ transplant); subjects with a history of clinically significant drug or alcohol abuse	Routine pharmacovigilance activities. Monitoring through registries.	Warnings regarding patients with immuno-compromised conditions are included in several places in Section 4.4 of the SPC
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, leukaemia, 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.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Children < 4 years of age for JIA indications	Incidence of JIA in children below 4 years is low. However, data for children from age 2 onwards will be collected in a compassionate use study (Study M10-444) followed by data from the JIA registry (P10-262).	Section 4.2 of the SPC addresses the lack of information in paediatric patients. As data in this paediatric populations (less than 4 years) are collected and submitted this information will be included in the SPC once available. A planned clinical trial for these paediatric patients will provide safety and efficacy information for this group. Routine pharmacovigilance combined with the results of clinical trials will characterize the overall safety of paediatric patients and adalimumab use. Safety findings will be communicated in future PSURs and updates will be made to the CCDS and SPC as necessary.
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 and abatacept 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 (Studies DE013, DE019, DE020)	Information on clinical data available for 5 years duration is currently included in Section 5.1 of the SPC.
Long-term PsA data	Routine pharmacovigilance activities.	Information on clinical data available for 3 years is included in Section 5.1 of the SPC.
Long-term AS data beyond 3 years	Routine pharmacovigilance activities. 5-year long-term studies (M03-606 and M03-607)	Information on clinical data is included in Section 5.1 of the SPC. Clinical data for up to 3 years exposure is available.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Long-term CD data	Routine pharmacovigilance activities. Long-term open-label studies (Studies M02-433 and M04-690) 5-year registry	Information on clinical data available is included in Section 5.1 of the SPC.
Episodic treatment in CD data	Routine pharmacovigilance activities. Evaluation of treatment interruptions defined as dosing holidays of at least 70 days with the CD registry (Study P06-134)	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.
Long-term Ps data	Routine pharmacovigilance activities. 10-year registry Continuation of Study M03-658 for up to 6 years.	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. Evaluation of treatment interruptions with the Ps registry (Study P10-023)	Episodic treatment is not proposed in the SPC. A planned registry for Ps will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.
Long-term JIA data	Routine pharmacovigilance activities. 10-year registry Continuation of Study DE038 for up to 60 days after regulatory approval in the respective country.	Information on clinical data available is proposed to be included in Section 5.1 of the SPC.
Episodic treatment in JIA data	Routine pharmacovigilance activities. Evaluation of treatment interruptions with the JIA registry (Study P10-262)	Episodic treatment is not proposed in the SPC. A planned registry for JIA will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.

Benefit risk assessment

One pivotal study was performed with adalimumab in children/adolescents aged 4-17 years with polyarticular JIA. Subjects were stratified according to MTX use or no MTX (either naïve or intolerant). Initially, there was an open label lead-in phase where all patients received adalimumab, 24 mg/m^2 BSA. Week 16, responders were randomised into a double-blind withdrawal phase of 32 weeks, where the primary endpoint (the proportion of subjects in the non-MTX stratum with a disease flare) was assessed. In this phase, 58 subjects were enrolled into the non-MTX stratum and 75 into the MTX-stratum. The design was chosen from ethical reasons, but disadvantages in proving efficacy were noted. The study population and clinical endpoints were adequate.

After the blinded phase, patients could continue on open label BSA dosing. Thereafter, patients were switched to open label fixed dosing of 20 mg (subjects up to 30 kg body weight) or 40 mg ($\geq$ 30 kg) eow. The MAH initially proposed fixed dosing across the indication but this was not agreed with by the CHMP. The data presented allowed fixed dose of 40 mg from the age of 13 years. For younger

children, dosing based on BSA was recommended. However, the MAH has not yet developed a presentation which allows for the accurate dosing according to BSA, and therefore the indication was restricted to adolescents 13-17 years of age.

Pharmacokinetics
Overall, following the BSA-based dosing in juvenile subjects (24 mg/m^2 with a maximum dose of 40 mg eow) steady-state serum concentrations obtained in subjects with JIA appeared to be within the range of those previously observed in adult subjects (40 mg eow in RA, AS and PsA patients), both during monotherapy and concomitant methotrexate treatment. There was a tendency for a higher inter-individual variability in juvenile subjects compared with adults. In addition, during monotherapy the immunogenicity rate was higher in juvenile subjects than in adults, which may explain the larger variability. During concomitant methotrexate treatment the serum levels were on average higher and the variability was lower. Furthermore, the number of subjects developing AAA was lower when MTX was given concomitantly compared with monotherapy (5.9 vs. 25.6%).

On the basis of data from study DE038 PK modelling was undertaken to support the fixed dose regimens applied for. However, due to deficiencies in the model building and also in assessing how well the model simulates data, the pharmacokinetic documentation did not at present contribute in the assessment of safety and efficacy of the fixed dosing strategy. The conclusions made on the basis of the simulations can only be qualitative and those made could have been foreseen by predicting the dose change in various weight groups on the basis of correlation between BSA and weight as follows: a) increased exposure for children weighing 15-20 kg, 30-40 kg and 40-50 kg with the largest difference for children weighing 30-40 kg, b) decreased exposure for children weighing 20-30 kg. The quantitative assessment was not considered appropriate as the population model did not fit to the data and the predictive properties of the model were not assessed properly.

Benefit
In the open initial phase, the response rate, according to the predefined 30% improvement criteria, was 94% with MTX + adalimumab and 74% in the adalimimab monotherapy group. There were more responders among the patients with "active disease despite MTX" (i.e. the group given combination therapy) compared with patients without MTX, and more patients without MTX discontinued the open phase, which indicate an increased efficacy with combination therapy. Therefore it was considered that combination therapy is the primary recommendation, but in case of MTX intolerance, monotherapy might be an option.

During the blinded withdrawal phase, the primary endpoint, proportion of subjects with disease flare in the non-MTX stratum, as well as the same endpoint in the MTX stratum, was statistically significantly in favour of adalimumab, but due to the low threshold for flare and the use of imputation the results of the primary efficacy analysis were questionable. It was accepted that adalimumab prevents disease flares compared to placebo in the non-MTX stratum. However, due to the trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. It was considered of importance to collect efficacy data in the registry setting, which the MAH agreed to undertake (see Attachment 10, letter of undertaking).

The MAH applied for two fixed doses, with a weight cut off of 30 kg, despite the fact that the controlled phase of the study was undertaken with BSA dosing. It was concluded that the available data with the fixed doses was insufficient, both in terms of efficacy and safety, due to the open label treatment in a limited number of subjects. A justification for use of a fixed dose of 40 mg from the age of 13 years was agreed with. However, due to lack of a syringe that can reassure accurate dosing for younger children, where BSA dosing needs to be applied, the use in children less than 13 years cannot be recommended for approval. The indication was revised accordingly.

There are tendencies of better efficacy in the combination group compared with the group given adalimumab monotherapy. In the initial open lead-in phase a higher percentage of responders were found in the MTX-group, 94 %, versus 74% in non-MTX group. In addition, the number of discontinuations was higher in the non-MTX during the initial phase, and there was a higher number of responders achieving the more stricter Ped ARC50/70 criteria in the combination group. Anti-

adalimumab antibodies developed in a higher number in the non-MTX group, 26% versus 6%, which also raises concerns regarding long term efficacy. Finally, the pharmacokinetic data indicate a higher adalimumab plasma level in the combination group. Overall, these data support combination therapy with MTX. This is resolved by adequate descriptions in the SPC, including that combination therapy is the primary recommendation in the indication.

Risk
No alarming safety signals were found in the performed study. No cases of death, malignancies, CHF, CNS demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions were reported. However, the data base is very small, and long-term safety cannot be assessed; main concerns being development of malignancies. In terms of the fixed dose regimens applied for, there is very limited safety data to assess possible implications of the dose changes, particularly in the younger children. The additional data from open label fixed dose use up to 64 weeks are still insufficient, particularly for the smallest and youngest population. Thus, in terms of safety, there is insufficient support for the fixed dose regimens applied for.

Overall, the RMP is acceptable. The MAH agreed to develop a registry where both safety and effectiveness data will be collected, which is endorsed. The MAH will follow subjects for 5 years for all events specified in the Registry protocol and an additional 5-years on an annual basis to collect events of Congestive Heart Failure and Malignancies.

Benefit / Risk Balance
Efficacy has been sufficiently demonstrated with the body surface area dosing of 24 mg/m^2. There are tendencies of better efficacy with a combination of adalimumab and MTX. The indication was revised and combination therapy with MTX is the primary option. A fixed dose of 40 mg from the age of 13 years was agreed. Due to lack of an appropriate dosing device, no claim for children less than 13 years of age is made.

The safety profile demonstrated in the study shows no unexpected findings, but long-term safety remains a concerns. To conclude, the benefit / risk balance for the treatment of subjects aged 13-17 years, with active polyarticular juvenile idiopathic arthritis, who have inadequate response to one or more DMARDs, was considered positive.

The changes to the product information were agreed with, including the update of the annexes in line with the latest QRD template.
The conditions as detailed before remained unchanged. However, the annex II was updated to clearly mention the new indication (JIA) and to include the new version of the RMP approved with this indication.

CONCLUSION

On 24 July 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the summary of product characteristics and package leaflet.