17 January 2013
EMA/76107/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0102

Note

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 ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

AAA	Anti-adalimumab antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CHQ-PF50	Child Health Questionnaire - PF50
CNS	Central nervous system
CRP	C-reactive protein
CTC	Common toxicity criteria
CVA	Cerebrovascular accident
DICHAQ	Disability Index of Childhood Health Assessment Questionnaire
DMARD	Disease-modifying anti-rheumatic drug
ELISA	enzyme-linked immunosorbent assay
eow	Every other week
ET	Early termination
GCP	Good Clinical Practices
ILAR	International League of Associations for Rheumatology
ITT	Intent-to-treat
JIA	Juvenile idiopathic arthritis
LOM	Limitation of passive motion
MAH	Marketing Authorisation Holder
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
OL	Open-label
PDCO	Paediatric Committee
PedACR	Pediatric American College of Rheumatology (scale)
PGA	Physician's global assessment
PIP	Pediatric investigational plan
PK	Pharmacokinetic
POM	Pain on passive motion

QRD	Quality review of documents
SAE	Serious adverse event
SC	Subcutaneous(ly)
SJC	Swollen joint count
SmPC	Summary of Product characteristics
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
VAS	Visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Abbott Laboratories Ltd. submitted to the European Medicines Agency on 13 June 2012 an application for a variation including an extension of indication. On 23 October 2012 the Marketing Authorisation has been transferred to AbbVie Ltd.

This application concerns the following medicinal products:

Medicinal product:	International non-proprietary name:	Presentations:
Humira	adalimumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age. Consequently, the MAH proposed the update of sections 4.1, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/63/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/63/2011 was not yet completed as some measures were deferred.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Krisitina Dunder

Co-Rapporteur: Prof. Daniela Melchiorri

Submission date:	13 June 2012
Start of procedure:	24 June 2012
Rapporteur's preliminary assessment report circulated on:	17 August 2012
Co-Rapporteur's preliminary assessment report circulated on:	10 August 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	15 November 2012
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	02 January 2013
CHMP opinion:	17 January 2013

2. Scientific discussion

2.1. Introduction

JIA is an autoimmune disease with a complex genetic predisposition with onset occurring in children under the age of 16 years. It is the most common rheumatic disease of childhood and an important cause of disability in children with an incidence of 15 per 100,000. In North American and European populations, it is 2.5 times more common in females than in males.

The onset of JIA is characterized by three primary modes: pauciarticular (<5 joints) – the most frequent mode, observed in 50% of patients, polyarticular (≥5 joints) – observed in 30% of patients and systemic arthritis (≥1 joint with fever and rash) – observed in 10% to 20% of patients.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the usual first line treatment for JIA as they are considered to be the least toxic agents in children. NSAIDs provide symptomatic relief but are not considered to be disease-modifying. Methotrexate (MTX) is considered to have an acceptable level of toxicity relative to its efficacy; most children do respond to MTX therapy; however, disease remission is rare. With MTX, the onset of response can range from 3 to 6 months, although many patients show an earlier response. However, many children have a disease relapse after the withdrawal of MTX, even after achieving a robust clinical response.

Other types of traditional medications commonly used to treat rheumatoid arthritis (RA) in adults are less preferable for use in pediatric patients. Cytotoxic drugs may have unacceptable risk in children because of their immunosuppressive and mutagenic properties. Systemic and intra-articular corticosteroids promote susceptibility to infections, osteoporosis and growth disturbance and have not been shown to be disease modifying in children with JIA.

Humira contains adalimumab, a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of tumor necrosis factor (TNF)-α and inhibits the binding of TNF-α to its receptors.

Humira is currently approved in the EU for the following indication for JIA: *Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as monotherapy in case of*

intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Humira has not been studied in children aged less than 4 year.

Humira is also indicated for treatment of moderate to severe active rheumatoid arthritis (RA), active and progressive psoriatic arthritis (PsA), severe active ankylosing spondylitis (AS), Axial spondyloarthritis without radiographic evidence of AS, severe active Crohn's disease (CD), moderate to severe active ulcerative colitis (UC) and moderate to severe chronic plaque psoriasis (Ps).

Data used for the initial approval for JIA in children and adolescents aged 4-17 years were from the Study DE038. As part of a Pediatric Investigation Plan, the MAH conducted Study M10-444 to investigate adalimumab treatment in children with JIA who are 2 to <4 years of age or ≥4 years of age weighing <15 kg.

The purpose of this variation is to extend the indication for Humira for the treatment of paediatric subjects with active polyarticular JIA from 4 to 17 years to 2 to 17 years of age. The recommended dose of adalimumab for this younger patient population is 24 mg/m^2 body surface area (BSA), administered every other week (eow) (same as that currently approved for patients 4 to 12 years of age). In support of this variation, the MAH has submitted the results of clinical study M10-444.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

A single Phase 3b study, Study M10-444, was conducted to support the indication extension to treat paediatric subjects with active polyarticular JIA who are 2 to <4 years of age. Study M10-444 is ongoing. Data on safety, efficacy, and pharmacokinetics from this study were presented, and put in context with available clinical data particularly from the clinical study DE038 that supported the use of adalimumab in JIA patients aged 4-17 years. The application initially contained data from Study M10-444 up to Week 24 and subsequent data for any subjects who continued past Week 24 at the time of the interim database lock (09 September 2011, the last subject's Week 24 visit). During the procedure the MAH provided an interim safety analysis (data cut-off 24 May 2012) up to Week 60.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Clinical pharmacology aspects

The clinical pharmacology and immunogenicity of adalimumab have been well characterized in healthy adult subjects as well as in adult subjects with RA, PsA, AS, CD and Ps. These data have been provided in previous submissions. Additional analytical studies were included in this variation because the assay methods for serum adalimumab and anti-adalimumab antibody (AAA) were modified for Study M10-444.

2.3.2.1.1. Methods – analysis of data submitted

Analytical methods

Adalimumab in serum

Serum adalimumab was assayed by means of enzyme-linked immunosorbent assay (ELISA) discussed in the previous submission for the JIA indication. A specific and sensitive assay was developed to measure adalimumab concentrations in serum for the human pharmacokinetic (PK) studies. A total of 52 human serum samples from Study M10-444 were received and 47 samples were analysed.

Anti-adalimumab antibodies in serum

Serum AAA was assayed by means of ELISA discussed in the previous submission for the RA indication. The AAA assay was re-validated. Study M10-444 was assayed for serum AAA using the new re-validation method. The re-validation parameters were summarized.

Study procedures

Study M10-444 included in total 32 children 2 to <4 years old or age 4 and above weighing less than 15 kg with JIA. Plasma concentration data and immunogenicity data were available from 15 subjects. Eleven of these 15 subjects were also treated with MTX. The administered dose of adalimumab was 24 mg/m^2 BSA up to a total dose of 20 mg adalimumab administered every other week (eow) as a single dose via subcutaneous injection. Trough serum samples for analysis of adalimumab and AAA were drawn at Baseline, at Week 12 and 24 or at Early Termination (ET).

The PK of adalimumab in Study M10-444 was also compared with data from the previous study (Study DE038) in children 4 to 17 years of age with JIA, receiving adalimumab at a dose or 24 mg/m^2. In Study DE038, the subjects were stratified as MTX-treated or non-MTX-treated prior to study enrollment. PK data were obtained from the open-label lead-in (OL LI) phase of the study, which included 16 weeks of treatment

2.3.2.2. Results

Demographics of the subjects included in the new study, M10-444, are shown in Table 1. Eleven of the 15 subjects received concomitant MTX.

Table 1 Baseline demographic summary for subjects in study M10-444

		Mean ± SD (min – max)	
		All Subjects (N = 32)[a]	Subjects with PK Analysis (N = 15)
Age (yr)		3.0 ± 0.7 (2.0 – 4.6)	3.0 ± 0.8 (2.0 – 4.2)
Weight (kg)		13.4 ± 2.0 (10.4 – 18.9)	13.1 ± 1.4 (11.0 – 16.0)
Height (cm)		93.0 ± 6.1 (83.0 – 104.0)	92.0 ± 5.3 (84.0 – 98.0)
Body Surface Area (m^2)		0.578 ± 0.060 (0.479 – 0.711)	0.568 ± 0.046 (0.499 – 0.634)
		N (%)	
Sex	Male	4 (12.5%)	2 (13.3%)
	Female	28 (87.5%)	13 (86.7%)
Race	White	25 (78.1%)	14 (93.3%)
	Black	3 (9.4%)	1 (6.7%)
	Other	4 (12.5%)	0 (0%)

a. Subject 9020404 had early termination before Week 12.
Other = Asian, Arab, North Africa, Maghreb

Of the 171 subjects enrolled in the OL LI phase of the previous study, DE038, the mean age was 11.3 years (range of 4 to 17 years). The mean weight was 42.2 kg (range of 13 to 99 kg). The mean BSA was 1.28 m2 (range of 0.57 to 2.16 m2). The majority (79.0%) of subjects was female and 95.3%

were White. The number of subjects on MTX ranged between 82 and 36 over week 0 to 16 and subjects without MTX ranged between 82 and 29.

Trough serum levels of adalimumab

Mean serum adalimumab trough concentrations in Study M10-444 were approximately 6 to 8 µg/mL at Week 12 and Week 24 in subjects who were 2 to <4 year olds and ≥4 year olds but body weight <15 kg. Steady state appeared to have been reached by week 12. The mean serum adalimumab concentrations at steady-state were observed to be higher in subjects who received concomitant methotrexate (MTX) compared to the non-MTX stratum.

Table 2 Summary of serum adalimumab trough concentrations (µg/mL) in paediatric subjects with JIA through Week 24 (N = 15) (Study M10-444)

	Mean ± SD (Min – Max), N_{nmiss}		
	Week		
Treatment Groups	**0**	**12**	**24**
Adalimumab 24 mg/m^2 BSA eow (N = 15)	0 ± 0 (0 – 0), 14	6.97 ± 5.69 (0 – 14.9), 15	7.78 ± 5.85 (0 – 14.7), 15
Adalimumab 24 mg/m^2 BSA eow with MTX (N = 11)	0 ± 0 (0 – 0), 10	7.27 ± 5.71 (0 – 14.8), 11	8.45 ± 5.69 (0 – 14.7), 11
Adalimumab 24 mg/m^2 BSA eow without MTX (N = 4)	0 ± 0 (0 – 0), 4	6.13 ± 6.41 (0 – 14.9), 4	5.95 ± 6.74 (0 – 12.7), 4

BSA = Body surface area; MTX = Methotrexate, N_{nmiss} = number of non-missing observations

Comparison of Study M10-444 and Study DE038

Study DE038 was a multicenter, Phase 3, randomized, stratified, double-blind, parallel-group study in children (ages of 4 to 17 years) with JIA. The subjects were stratified as MTX-treated or non-MTX-treated prior to study enrollment. Subjects in the MTX group were treated concomitantly with MTX during the study. Subjects who were in the non-MTX group were either naïve to MTX or had been withdrawn from MTX at least 2 weeks prior to study drug administration and were not treated concomitantly with MTX during the study. The study consisted of a 16-week open-label lead-in followed by a 32-week double-blind phase with a subsequent open-label extension (OLE) period. A total of 171 subjects were enrolled in the open-label lead-in phase and 133 subjects were randomized and dosed in the double-blind phase of Study DE038. Summary statistics of adalimumab concentrations during the open-label lead-in phase in Study DE038 are presented in Table 3.

Table 3 Summary statistics for serum adalimumab concentrations (µg/ml) by MTX treatment during the 16-week open-label phase in study DE038

	16 Week Open-Label Phase (Week)						
	0	**1[a]**	**2**	**4**	**8**	**12**	**16**
	Adalimumab 24 mg/m² BSA eow w/o MTX						
N	82	80	81	50	31	45	29
Mean	0.00	5.76	4.48	3.47	4.82	4.49	7.03
SD	0.00	2.32	1.76	3.05	4.81	5.05	6.26
%CV	--	40.3	39.3	88.0	99.8	112	89.1
Median	0.00	5.50	4.50	3.58	3.83	2.63	6.70
	Adalimumab 24 mg/m² BSA eow w/MTX						
N	82	76	85	45	37	41	36
Mean	0.00	5.77	4.77	6.40	8.45	10.5	8.85
SD	0.00	2.16	1.41	2.91	4.53	5.46	5.53
%CV	--	37.4	29.4	45.5	53.6	52.1	62.6
Median	0.00	5.75	4.70	6.70	8.80	10.0	9.60

a. Collected between Day 2 and 10, not a trough sample.

Mean (SD) serum adalimumab concentrations were compared between the current Study M10-444 by Week 24 and Study DE038 OL-LI by Week 16

Table 4 Comparison of Mean (SD) Serum Adalimumab Steady-State Concentrations in Study M10-444 and Study DE038

	Mean ± SD, N_{nmiss}
Study and Treatment Groups	**Week**
M10-444	**12**	**24**
24 mg/m² BSA eow with MTX	7.27 ± 5.71, 11	8.45 ± 5.69, 11
24 mg/m² BSA eow without MTX	6.13 ± 6.41, 4	5.95 ± 6.74, 4
DE038	**12**	**16**
24 mg/m² BSA eow with MTX	10.5 ± 5.46, 41	8.85 ± 5.53, 36
24 mg/m² BSA eow without MTX	4.49 ± 5.05, 45	7.03 ± 6.26, 29

Mean steady-state adalimumab serum concentrations in Study M10-444 (Week 24) appeared to be similar to those observed in Study DE038 (Week 16). It has been observed that concomitant MTX use results in higher serum adalimumab concentrations. While MTX administration was controlled during Study DE038, this was not the case for subjects who received MTX during Study M10-444. It is possible that subjects received MTX, but were not currently on a stable dose.

Anti-adalimumab antibodies

In Study DE038, there were 19 AAA positive (AAA+) subjects (11.1%, 19/171) during open-label phase. Among them, 4 (4.7%, 4/85) subjects were with concomitant MTX and 15 (17.4%, 15/86) subjects were without MTX. In Study M10-444, one subject became AAA+ by Week 24. Among 15 subjects who had pharmacokinetic samples analyzed, the AAA+ rate was 6.67% (1/15). Overall, the number of subjects who developed AAA was too small (N = 1) to make definitive conclusions regarding the effect of AAA on safety or efficacy in pediatric subjects with JIA. Based on DE038 no increased adverse events were reported in subjects who were AAA+.

2.3.3. Discussion on clinical pharmacology

The clinical pharmacology and immunogenicity of adalimumab have been well characterized in healthy adult subjects as well as in adult subjects with RA, PsA, AS, CD and Ps. Assay methods for serum adalimumab and AAA were modified for Study M10-444. The modified analysis methods are considered adequately validated. Thirty-two subjects were enrolled in this study and fifteen of them provided serum samples for PK analysis. The age and weight ranges in subjects included in the PK analysis of study M10-444 were 2.0-4.2 years and 11.0-16.0 kg, respectively. The weight range appears to reasonably well cover the normal weight range for this age group. The mean serum adalimumab trough concentrations achieved a steady-state of approximately 6 to 8 µg/mL at Week 12 and Week 24 in subjects treated with adalimumab 24 mg/m2 BSA eow dosing. The mean serum adalimumab concentrations at steady-state were observed to be higher in subjects who received concomitant MTX compared to the non-MTX stratum. However, due to the small number of subjects and large variability in the MTX arm as well as uncontrolled MTX use in those subjects, no firm conclusions can be made based on these data.

The PK of adalimumab in Study M10-444 was compared to a previous study (Study DE038) in children (4 to 17 years of age) with JIA. Based on a between-study comparison no differences was observed in mean steady state serum adalimumab concentrations between children 4-17 years (Week 16) and children 2-4 years old (Week 24) after a dose of 24 mg/m^2 eow. Adalimumab serum concentrations in the MTX stratum tended to be higher than the non-MTX group, which is consistent for both studies (Study DE038 and Study M10-444).

As the number of children was limited in both studies, plots showing individual plasma concentration data vs. age and body surface area, respectively, were provided by the MAH at the request of the CHMP in order to confirm the suitability of the dose throughout the BSA range. Comparisons of individual trough serum adalimumab concentrations over the body weight (kg) and body surface area (BSA) (m2) were provided for Study DE038 and Study M10-444. Adalimumab exposure based on 24 mg/m^2 dosing in paediatric JIA subjects (up to a maximum dose of 40 mg and 20 mg eow in Study DE038 and Study M10-444, respectively) was similar between the 2 studies.

Based on this data the CHMP concluded that there are no trends suggesting different serum concentrations over the studied weight and BSA ranges at administration of the BSA-adjusted dose (24 mg/m^2 eow). Thus, although the data in this age group is limited, pharmacokinetics can be considered supportive of using the same dose to the smaller children as that previously approved for children from 4 years.

2.3.4. Conclusions on clinical pharmacology

Overall, based on the PK findings, the mean steady-state adalimumab concentrations appear to be similar in JIA subjects in Study M10-444 (2 to <4 years of age and subjects 4 years of age and above who weighed <15 kg) versus JIA subjects in Study DE038 (4 to 17 years of age) over the studied weight and BSA ranges at administration of the BSA-adjusted dose (24 mg/m^2 eow). Thus, pharmacokinetics can be considered supportive of using the same dose to the smaller children as that previously approved for children from 4 years.

2.4. Clinical efficacy

2.4.1. Main study

Study M10-444

Methods

This was an open-label (OL) multicenter study for subjects 2 to <4 years and subjects ≥ 4 years and weighing <15 kg diagnosed with moderately to severely active polyarticular JIA or polyarticular course JIA, per International League of Associations for Rheumatology (ILAR) criteria, treated in a clinical setting with adalimumab.

All subjects had a screening visit, baseline visit and visits at Weeks 2, 4, 8, 12, 16, 20 and 24. Visits beyond Week 24 occurred every 12 weeks for those subjects who continued in the study. Serum samples were collected for PK analyses (including AAA analysis).

At the completion of 24 weeks in the United States, subjects could continue in the study until reaching the age of 4 and ≥15 kg. At the completion of 24 weeks in the European Union (EU), subjects could continue for a maximum of 1 year after reaching age 4 and ≥15 kg (to allow transition to an appropriate treatment).

- ***Study participants***

The main enrollment eligibility criteria required that subjects be 2 to <4 years of age, or ≥4 and weighing <15 kg and have a disease diagnosis of moderately to severely active (defined as arthritis affecting ≥ 5 joints at the time of treatment initiation) of polyarticular JIA or polyarticular course JIA. This corresponded to the ILAR categories of polyarticular RF+ disease, polyarticular RF– disease and extended oligoarthritis disease. For subjects in the EU, subject must have previously failed, had an insufficient response to, or been intolerant to ≥ 1 disease-modifying anti-rheumatic drug (DMARD).

Major exclusion criteria included prior exposure to any other biologic therapy and infection requiring treatment with intravenous anti-infectives within 30 days prior to Baseline visit or oral anti-infectives within 14 days prior to the Baseline visit.

Major exclusion criteria included:

- Subject had prior exposure to natalizumab, efalizumab or any other biologic therapy, such as abatacept. Any previous use of anti-tumor necrosis factor (TNF) agents, including etanercept, infliximab, certolizumab pegol, golimumab and adalimumab was also prohibited.
- Infection(s) requiring treatment with intravenous anti-infectives within 30 days prior to Baseline visit or oral anti-infectives within 14 days prior to the Baseline visit.
- Subject had undergone joint surgery within the 2 months preceding the Screening visit (at joints to be assessed within the study).
- Subject had a previous diagnosis of a condition that could cause arthritis other than polyarticular JIA.
- Subject had a history of an allergic reaction or significant sensitivity to constituents of the adalimumab.
- Subject had been treated with any investigational drug of chemical or biologic nature (e.g. anakinra or rituximab) within a minimum of 30 days or 5 half-lives (whichever was longer) of the drug prior to Baseline visit. If these biologics were approved, they would continue to be excluded.
- Subject had a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, recent cerebrovascular accident (CVA), seizure disorder and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.

- Subject had a history of clinically significant hematologic disorder (e.g. severe anemia, leukopenia, thrombocytopenia, clotting), renal or liver disease (e.g. fibrosis, cirrhosis, hepatitis), or active gastroenteric ulcer.
- Subject had history of moderate to severe congestive heart failure (New York Heart Association class III or IV), recent CVA or thrombotic event and any other condition which, in the opinion of the Investigator, would have put the subject at risk by participation in the protocol.
- Evidence of dysplasia or history of malignancy (including lymphoma or leukemia).
- History of demyelinating disease (including myletis) or neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease.
- History of invasive fungal infection (e.g. listeriosis, histoplasmosis), active viral disorders, human immunodeficiency virus infection.

- ***Treatments***

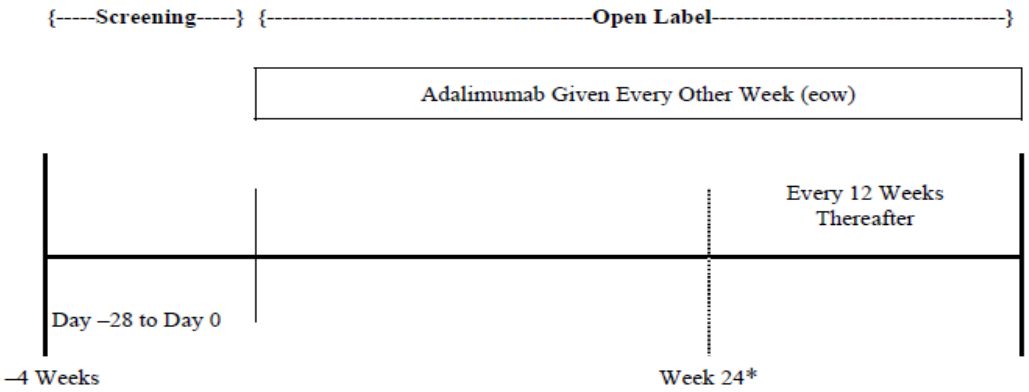
Adalimumab was administered SC by parent or designee eow at approximately the same time of day. The recommended dose of adalimumab for subjects with polyarticular JIA, aged 2 to 4 years old and those aged 4 and above weighing <15 kg, is 24 mg/m^2 BSA up to a total dose of 20 mg adalimumab administered eow as a single dose via SC injection. The volume for injection was based on the subject's height and weight as outlined in Table 5.

Table 5 Adalimumab total body dose in milliliters (mL) of 50 mg/mL injectable solution (for all subjects)

	Administered Volume (mL) eow Based on Height and Weight of Pediatric Subjects				
	Total Body Weight (kg)				
Height (cm)	10	15	20	25	30
80	0.2	0.3	0.3	0.3	0.4
90	0.2	0.3	0.3	0.4	0.4
100	0.3	0.3	0.3	0.4	0.4
110	0.3	0.3	0.4	0.4	0.4
120	0.3	0.4	0.4	0.4	

Baseline measurements of the subject's height and weight were used to determine the subject's dose of adalimumab. At the Week 12 visit, another determination of the subject's height and weight was made to determine the subject's dose of adalimumab. If a dose adjustment was required, it was done at each of the scheduled study visits, i.e. Week 12, Week 24 and every 12 weeks thereafter until the subjects reached age 4 and ≥15 kg. In the event that a subject fell in the middle of 2 ranges, the higher of the 2 dose volumes was to be utilized in order to ensure an efficacious dose. For example, if body weight was 14 kg and height was 81 cm, dose volume was 0.3 mL.

Figure 1 Study design schematic



* Subjects were treated for 24 weeks regardless of age or weight. In the US, at the completion of 24 weeks subjects could continue in the study until reaching the age of 4 and ≥ 15 kg. In the EU at the completion of 24 weeks, subjects could continue for a maximum of 1 year after reaching age 4 and ≥ 15 kg (to allow transition to an appropriate treatment).

- ***Objectives***

The primary objective of this study was to evaluate the safety of adalimumab in subjects 2 to <4 years of age and subjects age 4 and above weighing <15 kg with moderately to severely active polyarticular JIA or polyarticular course JIA. The secondary objectives of this study were to collect PK data and to evaluate the effectiveness of adalimumab in these subjects.

- ***Outcomes/endpoints***

The primary study endpoint, measured over the course of the study, was the incidence of SAEs and AEs in polyarticular JIA subjects 2 to <4 years old and subjects ≥4 years weighing < 15 kg.

Secondary endpoints, measured over the course of study, included collection of PK data, change from Baseline in laboratory findings, the individual indicators of effectiveness and the proportion of subjects with Pediatric American College of Rheumatology (PedACR)30/50/70/90 responses.

PedACR 30/50/70/90 responses are defined as follows: ≥30/50/70/90% improvement in ≥ 3 of the 6 JIA core set variables and ≥ 30% worsening in not more than 1 of the 6 JIA core set criteria. The 6 JIA criteria are:

- PGA of subject's disease activity (100 mm VAS)
- Parent's global assessment of subject's disease activity (100 mm VAS)
- Number of active joints (joints with swelling not due to deformity or joints with limitation of passive motion (LOM) and with pain on passive motion (POM), tenderness or both)
- Number of joints with LOM
- DICHAQ
- CRP

Information to evaluate the effectiveness of adalimumab was collected from the subject's parent and from the study physician. Effectiveness data were collected with clinical assessments, beginning with the baseline visit (physical function of the Disability Index of Childhood Health Assessment Questionnaire [DICHAQ], Parent's Global Assessment of Subject's Overall Disease Activity, Parent's assessment of pain, Physician's Global Assessment [PGA] of disease activity, joint assessments, C-reactive protein [CRP] and the Child's Health Questionnaire [CHQ-PF50].

- ***Sample size***

The proposed sample size for this study was approximately 30 subjects. Due to the low incidence and prevalence of JIA in subjects 2 to <4 years old, the size of the study was chosen based on expected availability of eligible subjects to be enrolled in a 3-year time frame.

- ***Randomisation***

All subjects received adalimumab. Subjects were assigned a subject number. The subject number was used for identification throughout the study.

- ***Blinding (masking)***

This was an OL study; blinding was not performed.

- ***Statistical methods***

The primary and secondary variables (including both safety and effectiveness) were to be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were enrolled and received ≥1 dose of adalimumab.

No statistical analysis has been performed to report the results of the efficacy and safety of this study. Descriptive statistics has been provided. These include the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and counts and percentages for discrete variables. To account for missing data, NRI and LOCF imputation approach have been used up to Week 24. NRI and LOCF approach have not been used for data beyond Week 24 as it may not be appropriate for imputing long term efficacy data, as some subject may reach the age/weight criteria to complete the study sooner than some other subjects.

Demographic and baseline characteristics were summarized. The number of observations, mean, standard deviation (SD), median, minimum and maximum were summarized for continuous variables; discrete variables were to be summarized via counts and percentages.

The following demographic and Baseline characteristics were summarized: age, sex, race/ethnicity, duration of JIA, severity of JIA (as measured by Physician and Parent Global Assessments, CHQ-PF50, DICHAQ), onset type JIA (oligoarticular, polyarticular, or systemic) body weight and height (including parent's height), prior therapies for JIA, concomitant JIA medications, co-morbid conditions and adalimumab dosage and exposure duration.

The number and percentage of subjects who discontinued from treatment were summarized, overall and by reason for discontinuation. Duration of treatment was to be summarized. Medical history was presented by count and percentage of subjects broken down by body system and diagnosis.

Results

- ***Participant flow***

Subject Disposition

A total of 32 subjects were enrolled. All received ≥1 dose of adalimumab (ITT population). At the time of data lock for the interim report (09 Sep 2011), 4 subjects had discontinued from the study (1 before Week 24 and 3 after Week 24) and 11 subjects had completed the study (Table 6). Thirty-one subjects completed Week 24.

Table 6 Disposition of Subjects (ITT Population)

	Adalimumab, n (%) N = 32
Discontinuation due to (all reasons)	4 (12.5)
AE	0
Withdrew consent	1 (3.1)
Lost to follow-up	1 (3.1)
Other[a]	2 (6.3)
Completed study	11 (34.4)

a. Other = 1) Humira was approved. 2) Subject was over the weight and age limit.

Mean exposure to adalimumab was 299.1 days (SD = 129.84; median = 266.0). All subjects received at least 57 days of adalimumab treatment; with a maximum exposure to adalimumab of 679 days at the time of the interim database lock (09 September2011).

- ***Recruitment***

This study was conducted at 14 sites in the in the US, France, the Czech Republic and Germany. Subjects who satisfied all eligibility criteria were enrolled into the study. One subject had entry criteria violations.

- ***Conduct of the study***

Since the original protocol for Study M10-444, 2 administrative changes have been made and the protocol has been amended 6 times (4 global amendments and 2 regional amendments).

- ***Baseline data***

Demographics characteristics

Most subjects were female, white and < 4 years of age. Mean age was 3.0 years and mean weight was 13.4 kg.

Table 7 Demographic Characteristics (ITT Population)

Characteristic	Adalimumab N = 32
Sex, n (%)	
Female	28 (87.5)
Male	4 (12.5)
Race, n (%)	
White	25 (78.1)
Black	3 (9.4)
Asian	1 (3.1)
Other	3 (9.4)
Ethnicity, n (%)	
Hispanic or Latino	1 (3.1)
No Ethnicity	31 (96.9)
Age distribution, n (%)	
< 4 years	28 (87.5)
≥ 4 years	4 (12.5)
Age, years	
Mean ± SD	3.04 ± 0.723
Median	3.15
Min – max	2.0 – 4.6
Weight, kg	
Mean ± SD	13.4 ± 1.96
Median	13.0
Min – max	10.4 – 18.9
Height, cm	
Mean ± SD	93.0 ± 6.09
Median	93.5
Min – max	83.0 – 104.0
BMI, kg/m^2	
Mean ± SD	15.5 ± 1.27
Median	15.3
Min – max	13.1 – 18.5
BSA, m^2	
Mean ± SD	0.6 ± 0.06
Median	0.6
Min – max	0.5 – 0.7

Note: Percentages calculated on non-missing values.

Baseline disease activity

Mean duration of JIA at time of first adalimumab dose was 12.3 months. Baseline disease activity was consistent with moderately to severely active JIA. Only 1 subject was RF+ at baseline and most subjects had a normal baseline CRP.

Table 8 Baseline disease activity (ITT Population)

Variable	ADA N = 32
Duration of JIA at first dose, months	
Mean ± SD	12.3 ± 9.26
Median	10.3
Min – max	2.3 – 40.8
TJC75	
Mean ± SD	3.8 ± 5.02

Variable	ADA N = 32
Median	2.0
Min – max	0 – 19
SJC66	
Mean ± SD	8.9 ± 7.37
Median	7.0
Min – max	0 – 36
LOM69	
Mean ± SD	8.5 ± 7.70
Median	6.5
Min – max	0 – 32
POM75	
Mean ± SD	5.1 ± 4.70
Median	4.0
Min – max	0 – 19
Active joint count (AJC73)	
Mean ± SD	9.8 ± 7.59
Median	7.0
Min – max	1 – 36
Parents' assessment of pain (VAS, mm)	
Mean ± SD	46.1 ± 25.73
Median	51.0
Min – max	0 – 83
Parents' global assessment of disease activity (VAS, mm)	
Mean ± SD	47.6 ± 25.91
Median	51.5
Min – max	0 – 90
PGA (VAS, mm)	
Mean ± SD	55.3 ± 19.70
Median	60.5
Min – max	9 – 84
DICHAQ	
Mean ± SD	1.2 ± 0.66
Median	1.3
Min – max	0 – 2.9
CRP, mg/dL[a]	
Mean ± SD	1.6 ± 2.43
Median	0.4
Min – max	0.4 – 12.8
Normal (< 0.9 mg/dL), n (%)	19 (61.3)
Abnormal (≥ 0.9 mg/dL), n (%)	12 (38.7)
Missing, n	1
RF, IU/mL	
Mean ± SD	10.2 ± 1.24
Median	10.0
Min – max	10.0 – 17.0
Positive (≥ 12 IU/mL), n (%)	1 (3.1)
Negative (< 12 IU/mL), n (%)	31 (96.9)

a. N = 31.

Prior medications

Prior medications are shown in Table 9. Most subjects had previously taken MTX to treat their JIA, with fewer subjects reporting prior use of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). A majority of subjects (29 subjects, 90.6%) had received a non-RA medication prior to enrolment into the study. The most frequently reported prior medications (≥4 subjects) were standard childhood vaccines including the Hepatitis B vaccine and pneumococcal vaccine, as well as folic acid and paracetamol.

Table 9 Prior JIA-related medications (ITT population)

Generic Name (WHO Q1 2011)	ADA, n (%) N = 32
Synthetic DMARDs	25 (78.1)
MTX	25 (78.1)
Biologic DMARDs	0
Systemic corticosteroids	22 (68.8)
Methylprednisolone	8 (25.0)
Prednisolone	8 (25.0)
Prednisone	6 (18.8)
Triamcinolone	1 (3.1)
Systemic NSAIDs	12 (37.5)
Ibuprofen	6 (18.8)
Naproxen	5 (15.6)
Indometacin	4 (12.5)

Note: This table includes all medications administered prior to the treatment period. Thus, all medications with a start date prior to the first adalimumab dose are included.

Concomitant medications

During the study, most subjects used concomitant MTX to treat their JIA, with fewer reporting use of corticosteroids or NSAIDs. Other than adalimumab study drug, no other biologic was used during this study, consistent with the protocol requirements. A majority of subjects (30 subjects, 93.8%) took a non-JIA medication during the study. The most frequently reported concomitant medications (≥4 subjects) were standard childhood vaccines, folic acid, paracetamol and amoxicillin.

Table 10 Concomitant JIA-related medications (ITT population)

Generic Name (WHO Q1 2011)	Adalimumab, n (%) N = 32
Synthetic DMARDs	23 (71.9)
MTX	23 (71.9)
Systemic corticosteroids	14 (43.8)
Prednisolone	7 (21.9)
Prednisone	3 (9.4)
Methylprednisolone	3 (9.4)
Cortisone	1 (3.1)
Dexamethasone	1 (3.1)
Triamcinolone	1 (3.1)
Systemic NSAIDs	10 (31.3)
Ibuprofen	7 (21.9)
Naproxen	4 (12.5)
Indometacin	1 (3.1)
Biologic DMARDs	0

Note: This table includes all medications administered during the treatment period (i.e. first adalimumab dose through 14 days after the final adalimumab dose). Thus, all medications with an end date prior to the first adalimumab dose are excluded.

- ***Numbers analysed***

All analyses were based on the ITT population, which included all subjects who were enrolled and received ≥1 dose of adalimumab (N = 32). No subjects were excluded from any analyses.

- ***Outcomes and estimation***

Primary Endpoints

The primary objective of this study was assessment of safety. No primary efficacy endpoint was defined.

Secondary Efficacy Endpoints

Efficacy endpoints, measured over the course of study, included the individual indicators of effectiveness and the proportion of subjects with Paediatric American College of Rheumatology (PedACR)30/50/70/90 responses.

PedACR Response

At Week 12 and Week 24, PedACR30 response was achieved by 93.5% and 90.0% of subjects, respectively, using the analysis of observed data. The proportions of subjects with PedACR50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Results were similar for the last observation carried forward (LOCF) analysis and slightly lower for the non-responder imputation analysis (NRI) analysis.

Observed data past Week 24 demonstrate that the majority of subjects at these study visits had a PedACR30/50/70 response and many had a PedACR90 response; however, the numbers of subjects with data from Week 60 onward were small as not all subjects have had the opportunity to complete through Week 60 and the study is still ongoing.

Table 11 PedACR30/50/70/90 Response (Observed Data; ITT Population)

		Adalimumab			
Visit	**Analysis Method**	**PedACR30 n/N1 (%)**	**PedACR50 n/N1 (%)**	**PedACR70 n/N1 (%)**	**PedACR90 n/N1 (%)**
Week 12	Observed	29/31 (93.5)	28/31 (90.3)	19/31 (61.3)	12/31 (38.7)
	NRI[a]	29/32 (90.6)	28/32 (87.5)	19/32 (59.4)	12/32 (37.5)
	LOCF[b]	29/31 (93.5)	28/31 (90.3)	19/31 (61.3)	12/31 (38.7)
Week 24	Observed	27/30 (90.0)	25/30 (83.3)	22/30 (73.3)	11/30 (36.7)
	NRI[b]	27/32 (84.4)	25/32 (78.1)	22/32 (68.8)	11/32 (34.4)
	LOCF[c]	28/31 (90.3)	26/31 (83.9)	23/31 (74.2)	11/31 (35.5)
Week 36	Observed	18/20 (90.0)	17/20 (85.0)	13/20 (65.0)	11/20 (55.0)
Week 48	Observed	12/14 (85.7)	11/14 (78.6)	10/14 (71.4)	9/14 (64.3)
Week 60	Observed	4/5 (80.0)	3/5 (60.0)	3/5 (60.0)	2/5 (40.0)
Week 72	Observed	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Week 84	Observed	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Week 96	Observed	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)

a. NRI: Missing responses are imputed as non-response.
b. LOCF: Missing responses were imputed by last non-missing post-Baseline response.
c. Note: Only responder percentages are displayed. Percentages were calculated using non-missing values. N1 represents the number of subjects for either observed or imputed methods.

Because the PedACR response requires improvement in a minimum of 3 of 6 of the JIA core set variables and worsening in not more than 1 of the 6 JIA core set variables, it is important to examine each of the core set variables individually. Each of the JIA core set variables demonstrated clinically meaningful reductions in disease activity at both Weeks 12 and 24 (Table 12). Specifically, joint swelling, pain and tenderness were reduced and limitation of motion was decreased after adalimumab treatment.

Table 12 Change from baseline in JIA core set variables (Observed) (ITT Population)

	Adalimumab, Mean Change from Baseline ± SD							
Visit	**Parent's Global Assessment of Disease Activity**	**PGA**	**DICHAQ**	**TJC75**	**SJC66**	**POM75**	**LOM69**	**CRP**
Week 0 (mean) n/N = 32/32	47.6 ± 25.91	55.3 ± 19.70	1.2 ± 0.66	3.8 ± 5.02	8.9 ± 7.37	5.1 ± 4.70	8.5 ± 7.70	1.6 ± 2.43[a]
Week 12 (change) n/N = 31/32	–28.1 ± 29.91	–41.4 ± 21.20	–0.5 ± 0.64	–2.7 ± 5.09	–6.2 ± 4.24	–4.7 ± 4.63	–5.6 ± 4.84	–0.6 ± 2.65[b]
Week 24 (change) n/N = 30/32	–32.2 ± 29.74	–45.3 ± 21.32	–0.5 ± 0.69	–3.0 ± 5.54	–6.3 ± 5.83	–3.9 ± 7.32	–5.6 ± 5.56	–0.2 ± 3.20[c]

a. n/N = 31/32. b. n/N = 28/32. c. n/N = 28/32.

In the analysis of observed data, each of the items measured in the CHQ-PF50 showed improvements (increases) from Baseline to Week 12 and from Baseline to Week 24. The greatest percent improvements were seen for bodily pain/discomfort, physical functioning and change in health. Changes tended to be greater at Week 24 than at Week 12. LOCF analysis showed results similar to the observed data analysis.

Table 13 Change from Baseline in CHQ-PF50 (Observed) (ITT Population)

	Adalimumab					
	Week 0		**Week 12**		**Week 24**	
CHQ-PF50 Domain	**n/N**	**Mean ± SD**	**n/N**	**Change from Baseline ± SD**	**n/N**	**Change from Baseline ± SD**
Global health	31/32	50.5 ± 23.46	29/32	17.1 ± 29.48	28/32	24.3 ± 25.77
Physical functioning	32/32	50.9 ± 30.82	31/32	30.6 ± 32.14	30/32	31.6 ± 31.91
Role/social limitations/emotional/behavioral	26/32	75.2 ± 30.68	23/32	20.8 ± 32.53	22/32	17.7 ± 29.43
Role/social limitations/physical	25/32	61.3 ± 37.49	21/32	28.6 ± 32.97	20/32	31.7 ± 35.00
Bodily pain/discomfort	31/32	40.0 ± 25.17	30/32	35.0 ± 30.60	29/32	36.2 ± 32.99
Behavior	31/32	70.4 ± 17.83	29/32	5.6 ± 15.78	28/32	4.2 ± 13.58
Global behavior item	24/32	68.8 ± 28.52	19/32	4.5 ± 18.17	19/32	10.8 ± 17.66
Mental health	32/32	75.6 ± 16.35	31/32	3.5 ± 11.12	30/32	3.5 ± 10.76
Self-esteem	25/32	73.4 ± 21.81	23/32	10.6 ± 23.91	22/32	10.5 ± 24.75
General health perceptions	27/32	43.1 ± 13.32	26/32	0.6 ± 14.08	25/32	3.7 ± 14.78
Change in health	31/32	2.8 ± 1.51	30/32	1.4 ± 1.75	29/32	1.7 ± 1.67
Parental impact – emotional	31/32	43.8 ± 25.27	30/32	11.4 ± 26.12	28/32	19.0 ± 28.59
Parental impact – time	31/32	69.2 ± 26.56	30/32	4.6 ± 24.50	28/32	13.5 ± 28.59
Family activities	31/32	70.6 ± 20.86	30/32	8.3 ± 28.41	28/32	17.6 ± 24.15
Family cohesion	31/32	76.8 ± 23.29	30/32	2.5 ± 14.00	28/32	4.3 ± 23.28

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted this variation to extend the indication of adalimumab to a target population of patients 2 to 4 years old, with a disease diagnosis of moderately to severely active polyarticular JIA or polyarticular course JIA that have previously failed, had an insufficient response to, or been intolerant to ≥1 DMARD. To support the application a single, still ongoing, multicenter open label study across 5 countries has been conducted: study M010-444. The study provides data from patients treated with adalimumab 24 mg/m^2 (BSA) up to a total dose of 20 mg eow, through Week 24 and subsequent data for any subjects who had continued past 24 Week. The study had a primary objective of safety, and PK and efficacy outcomes (mainly PedACR responses) were secondary objectives.

A total 32 subjects were enrolled in the study (four of the subjects were 4 years or older, but weighed <15 kg, in line with the inclusion criteria). This number is limited but considering the rarity of the disease and data already available for older age categories, the sample size of this study is considered agreeable. Another limitation of the study design is the lack of a control arm. However, considering the age-range from 2 to 4 years and the difficulties in carrying out a randomised controlled trial due to the rarity of the disease, the choice of an open label study as the pivotal study for this application is considered acceptable.

The onset types, per ILAR criteria, for the subjects enrolled in Study M10-444 were presented along with sex and anti-nuclear antibody+ (ANA) status. The majority of subjects (65.6%) had polyarticular arthritis (20 were RF- and 1 was RF+) followed by 25.0% of subjects with extended oligoarthritis. Furthermore, 2 subjects with systemic arthritis and 1 subject with undifferentiated arthritis were enrolled. Mean AJC at baseline was 9.8 joints (range 1 to 36). Out of the 32 subject enrolled, 3 did not meet this the inclusion criterion #2 requiring that subjects have a diagnosis of moderately to severely active polyarticular or polyarticular-course JIA defined as ≥5 joints affected with arthritis at the time of treatment initiation per ILAR criteria. This criterion was binding; however, the enrollment of these subjects did not negatively impact the integrity of the study data. During the procedure the MAH clarified that protocol inclusion criterion #8 required that subjects in the EU have previously failed, have had an insufficient response, or have been intolerant to ≥1 DMARD. All subjects enrolled in the EU have met this criterion. The 7 subjects who did not meet this criterion were subjects from the US, where prior DMARD treatment is not required. The MAH also clarified that dose changes for concomitant corticosteroid treatment were not specified in the protocol. This was acknowledged by the CHMP due to the compassionate nature of this study.

Subjects were followed for at least 24 months, thereafter subjects could continue until they reached age 4 and >15 kg in the Americas. EU subjects could continue in the study for up to one year thereafter. One subject discontinued the study before Week 24.

Efficacy data and additional analyses

The results presented clearly support a positive effect of adalimumab treatment in the sought indication. In terms of PedACR, the majority of subjects achieved PedACR30 (93.5%) and PedACR50 response (90.3%) by Week 12 and maintained response at Week 24; PedACR30 (90.0%) and PedACR50 response (83.3%). Furthermore, more than half of all subjects (61.3%) achieved PedACR70 at Week 12 and almost three-quarters of all subjects achieved a PedACR70 response by Week 24 (73.3%). Results were similar for the LOCF analysis and slightly lower for the NRI analysis. Each of the JIA core set variables demonstrated clinically meaningful reductions in disease activity at both Weeks 12 and 24. The CHQ-PF50 showed also improvements.

A longer term efficacy data could have provided a clearer estimate of the treatment effect, considering also the open label setting. However; taking into account the efficacy data gathered in the age category 4-12 years old and the positive PK results showing similar PK profiles of adalimumab in children from 2 to 4 years and in children above 4 years, an extrapolation of efficacy to the younger cohort of patients is considered possible and this reinforces the results of the pivotal trial. Overall, the efficacy data from this study is considered sufficient to demonstrate the effect of adalimumab in the 2-4 years old JIA population.

2.4.3. Conclusions on the clinical efficacy

The MAH submitted a single, open label study (M10-444), with a primary objective of safety, and PK and efficacy outcomes (mainly PedACR responses) as secondary objectives, to support the extension of indication of adalimumab in the paediatric population aged 2-4 years with active polyarticular course JIA that have had an inadequate response, or have been intolerant to at least 1 DMARD. The study package is considered acceptable acknowledging the particular setting. Results from study M10-444, showed efficacy of adalimumab in the paediatric population 2-4 years of age based on PedACR response as well as clinically meaningful reductions in disease activity measured with the JIA core set variables. Furthermore, given the availability of efficacy data gathered in the age category 4-12 years old and the positive PK results showing similar PK profiles of adalimumab in children from 2 to 4 years of age and in children above 4 years of age, extrapolation of efficacy to the younger cohort of patients is considered possible; this reinforces the results of the pivotal trial.

In conclusion, bearing in mind the results obtained in the previous study in older paediatric patients, the data provided by the MAH in this application are considered sufficient to demonstrate the efficacy of adalimumab in the target population aged from 2 to 4 years with active polyarticular course JIA that have had an inadequate response, or have been intolerant to at least 1 DMARD.

2.5. Clinical safety

2.5.1. Introduction

The primary study endpoint, measured over the course of the study, was the incidence of serious adverse events (SAEs) and adverse events (AEs) in polyarticular JIA subjects age 2 to <4 years old and subjects age ≥4 years weighing <15 kg. Secondary endpoints included collection of PK data and the change from baseline in laboratory findings. PK blood draws were obtained only from those who consented to this procedure. Safety analyses were to be carried out using the ITT population, defined as all subjects who were enrolled and received ≥ 1 dose of adalimumab. Treatment-emergent AEs (TEAEs) were defined as AEs that began either on or after the first dose of the adalimumab and up to within 70 days after the last dose of adalimumab if subjects terminated the study.
Because the mechanism of action of TNF antagonists, including adalimumab, is inhibition of an immunologically active cytokine, episodes of infections, malignancies, central nervous system (CNS) demyelinating disease, immunologic reactions and lupus-like illness were specifically evaluated as AEs of special interest. Congestive heart failure (CHF) has also been an event specifically examined in studies with TNF antagonists and was also evaluated as an AE of special interest.
For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 3 or higher were provided. Shift tables for changes from Baseline according to the normal range were provided for laboratory variables.

- ***Patient exposure***

A total of 32 subjects were enrolled and all subjects received ≥1 dose of adalimumab (ITT population). Mean exposure to adalimumab was 299.1 days (SD = 129.84; median = 266.0). All subjects received at least 57 days of adalimumab treatment, with a maximum exposure to adalimumab of 679 days at the time of the interim database lock (09 September 2011). During the procedure the MAH provided further exposure data (data cut-off 24 May 2012) up to Week 60 (see discussion on clinical safety).

Table 14 Duration of study drug exposure (ITT Population)

Duration interval (days)	Adalimumab N = 32 n (%)
≥ 1	32 (100)
≥ 16	32 (100)
≥ 31	32 (100)
≥ 46	32 (100)
≥ 61	31 (96.9)
≥ 76	31 (96.9)
≥ 91	31 (96.9)
≥ 106	31 (96.9)
≥ 121	31 (96.9)
≥ 136	31 (96.9)
≥ 151	31 (96.9)
≥ 166	30 (93.8)
≥ 181	27 84.4)
≥ 196	24 (75.0)
Patient years	26.2

- ***Adverse events***

Most subjects (84.4%) reported ≥1 TEAE. Most TEAEs were considered by the investigator to be not related or probably not related to adalimumab. TEAEs considered by the investigator as possibly or probably related to adalimumab occurred in 8 subjects (25.0%). Five subjects had possibly related events (1 case each of ear infection, laryngitis, pneumonia, viral pharyngitis, and upper respiratory tract congestion [2 events in 1 subject], and pyrexia [2 subjects]). Four subjects had probably related events (1 case each of injection site reaction, injection site pain, cystitis and rash); 1 of these subjects also had a TEAE (rash) considered possibly related to adalimumab. None of the at least possibly related TEAEs experienced by these subjects were severe.

Most subjects experienced TEAEs that were mild to moderate in severity; 4 subjects experienced a severe TEAE (1 case each of uveitis, otitis media, diabetes mellitus and arthritis). All of these events were considered by the Investigator as not related or probably not related to adalimumab. One subject, who had a severe TEAE of diabetes mellitus, did not have a history of diabetes, but had a family history of type 2 diabetes. This event was considered serious because it required hospitalization; the event was considered by the investigator as probably not related to study drug.

Table 15 Overview of subjects with TEAEs (ITT Population)

	Adalimumab	
Subjects with	**N (%) N = 32**	**Events (Events/100 PYs) PYS = 26.2**
Any TEAE	27 (84.4)	133 (507.6)
TEAE at least possibly drug related as assessed by the investigator	8 (25.0)	14 (53.4)
Severe TEAE	4 (12.5)	4 (15.3)
Serious TEAE	5 (15.6)	5 (19.1)
Infectious TEAE	22 (68.8)	57 (217.6)
Serious infectious TEAE	3 (9.4)	3 (11.5)
Injection site-related TEAE	2 (6.3)	2 (7.6)
Death	0	0

Of the most frequently reported TEAEs (those reported by ≥5% of subjects), pyrexia, nasopharyngitis, upper respiratory tract infection and cough were reported by the most subjects.

Table 16 Most frequently reported TEAEs (>= 5% of subjects) by PT (ITT Population)

Preferred Term	**Adalimumab N = 32 n (%)**
Any TEAE	27 (84.4)
Pyrexia	7 (21.9)
Nasopharyngitis	6 (18.8)
Upper respiratory tract infection	5 (15.6)
Cough	5 (15.6)
Vomiting	4 (12.5)
Rhinorrhea	4 (12.5)
Rash	4 (12.5)
Gastroenteritis	4 (12.5)
Bronchitis	4 (12.5)
Otitis media	3 (9.4)
Diarrhea	3 (9.4)
Cystitis	2 (6.3)
Ear infection	2 (6.3)
Rhinitis	2 (6.3)
Arthropod bite	2 (6.3)
Hepatic enzyme increased	2 (6.3)
Juvenile arthritis	2 (6.3)
Headache	2 (6.3)

- ***Serious adverse event/deaths/other significant events***

Five subjects (15.6%) reported a serious TEAE. All of the serious events were considered not related or probably not related to adalimumab by the investigator. All were mild or moderate in severity with the exception of diabetes mellitus, which was severe. No subjects prematurely discontinued from the study due to a serious TEAE.

Table 17 Listing of subjects with serious TEAEs during administration of adalimumab

Race	Onset Day	Resolution Day	Preferred Term	Severity	Reason Serious	Relationship to Adalimumab
W	144	160	Varicella	Moderate	hospitalization	Not related
W	204	204	Dental caries[a]	Mild	hospitalization	Not related
W	156	160	Gastro-enteritis rotavirus	Moderate	hospitalization	Not related
W	272		Diabetes mellitus	Severe	hospitalization, important medical or surgical intervention	Probably not related
W	252	266	Juvenile arthritis	Moderate	hospitalization	Not related

a. Due to young age, the patient's dental care required general anesthesia to be safely administered in the hospital.

No death occurred through the cutoff date (09 September 2011) in Study M10-444.
AEs of special interest, including episodes of infections, malignancies, CNS demyelinating disease, immunologic reactions, lupus-like illness and CHF, were specifically evaluated because the mechanism of action of TNF antagonists. The only reports of TEAEs of special interest were infections (serious and nonserious) and injection site-related TEAEs.

Infections

Treatment-emergent infections occurred in 22 subjects (68.8%). Of the most frequently reported infections (≥5% of subjects), nasopharyngitis, upper respiratory tract infection, bronchitis and gastroenteritis were reported by the most subjects. Most infections were mild or moderate in severity; 1 subject had a severe event (otitis media). All subjects who had an infection had events that were considered by the Investigator as not related or probably not related to study drug with the exception of 3 subjects. These 3 subjects had events that were considered to be possibly or probably related by the investigator (cystitis, ear infection, laryngitis, pneumonia, viral pharyngitis [possibly related]).

Three subjects had infections that were serious (1 case each of dental caries, gastroenteritis rotavirus and varicella). All were considered not related to adalimumab by the investigator and were mild or moderate in severity.

Through the cutoff date (09 September 2011) no subject prematurely discontinued from the study as a result of an infection.

Table 18 Most frequently reported infections (>=5% of subjects) by PT (ITT population)

Preferred Term	Adalimumab N = 32
Any infection	22 (68.8)
Nasopharyngitis	6 (18.8)
Upper respiratory tract infection	5 (15.6)
Gastroenteritis	4 (12.5)
Bronchitis	4 (12.5)
Otitis media	3 (9.4)
Cystitis	2 (6.3)
Ear infection	2 (6.3)
Rhinitis	2 (6.3)

Note: Subjects may have more than 1 event reported; therefore, the sum of the individual events may be greater than the overall number of subjects with any infection.

Injection site reaction-related TEAEs

Treatment-emergent injection site reaction-related events occurred in 2 subjects (1 case each of injection site pain and injection site reaction). Both events were mild in severity. Both subjects saw resolution of their events and continued in the study.

- ***Laboratory findings***

Clinical laboratory evaluations

Hematology and clinical chemistry parameters generally showed clinically non-significant changes from Baseline and Week 12 and Week 24.

Hematology parameters that showed both shifts from high or normal to low and from low or normal to high for individual subjects at the last available evaluation included hemoglobin, hematocrit, neutrophils and eosinophils. Hematology parameters that showed shifts from low or normal to high for individual subjects included lymphocytes (13 of 22 subjects), platelets (5 of 18 subjects), monocytes (2 of 30 subjects) and white blood cell counts (2 of 30 subjects).

Clinical chemistry parameters that showed shifts from low or normal to high for >1 subject included calcium (5 of 26 subjects), glucose (5 of 29 subjects), aspartate aminotransferase (AST) (2 of 28 subjects), cholesterol (2 of 15 subjects), CRP (2 of 18 subjects) and triglycerides (2 of 30 subjects).

In total, 4 subjects had potentially clinically significant laboratory abnormalities:

- One subject had a hematology value of CTC grade ≥3 prior to study drug administration. This subject had normal values during treatment on Day 85 and Day 169
- One subject had a serum glucose value of CTC grade ≥3 during treatment. An AE of diabetes mellitus was reported on Day 272; this event was considered by the investigator to be probably not related to adalimumab and severe in intensity.
- Two subjects, both of whom received MTX during the study, had liver function test values that were considered potentially clinically significant. One was a case of elevated AST and ALT before drug administration; both values normalized during treatment. The other case had a transient ALT and AST elevation on day 252, ALT normalized at the following visit, AST slightly elevated but declined. Bilirubin and ALP were normal.

- ***Discontinuation due to adverse events***

No subjects prematurely discontinued from the study due to a TEAE.

2.5.2. Discussion on clinical safety

Safety analyses were carried out using the ITT population, defined as all subjects who were enrolled and received ≥1 dose of ADA. Treatment-emergent AEs, SAEs and AEs were reported. Infections, malignancies, central nervous system demyelinating disease, immunologic reactions and lupus-like illness were specifically evaluated as AEs of special interest. Pyrexia, nasopharyngitis, upper respiratory tract infection and cough were reported as TEAEs in more than 5% of patients. During the first 24 weeks, infections (serious and non serious) and injection site-related TEAEs were the only reports of TEAEs of special interest. Infections are of a special concern in this population of small children. Infections were generally considered by the investigator as not related or probably not related to study drug with the exception of few cases. Three subjects had infections classified as serious (dental caries, gastroenteritis rotavirus, varicella), considered not related to adalimumab by the

investigator, mild or moderate in severity. No subject prematurely discontinued from the study as a result of an infection and no death was reported through the cutoff date of the interim report. Injection related AEs occurred in 2 patients and were mild and transient. Five subjects experienced an SAE. Of the 5 SAEs, all were mild or moderate in severity. One was diabetes mellitus, 2 virus infections, 1 worsening of studied disease and 1 dental caries, which needed general anesthesia. No subjects prematurely discontinued from the study due to a serious TEAE. Clinical laboratory evaluations were performed and 4 subjects had potentially clinically significant laboratory abnormalities, none of which raise a new safety concern. Amongst the laboratory abnormalities there were 5 cases of increased calcium presented. The MAH clarified that the severity was in all cases mild and provided corresponding data from the study DE038. Data showed that there does not seem to be a higher frequency of hypercalcemia in children 2-4 y in association with adalimumab, than in older children. There are no biologic mechanisms known that would raise the suspicion that adalimumab was the cause, thus this finding is not considered to be a safety issue related to adalimumab.

Although the safety profile of adalimumab presented at Week 24 is considered acceptable and in line with the known safety profile in the paediatric older age category, the short follow up period (24 weeks) and limited patient number (30 patients) were raised by the CHMP. In response to this point the MAH provided an interim safety analysis (data cut-off 24 May 2012) up to Week 60 for Study M10-444. With this update the mean exposure to adalimumab increased to 428.1 days (about 60 weeks) and the median exposure was 426.0 days. A majority of subjects (21/32; 65.6%) had ≥391 days (more than 1 year) of exposure to adalimumab during the study and 9 out of 32 (28%) reached at least 18 months of exposure. The longest observation for subjects with JIA, who entered the study between 2 and 4 y, is 679 days. A comparison of adalimumab safety profile up to week 24 and week 60 has been reported on ITT population. Comparative safety data showed an overall similar safety profile with an acceptable and expected increase in TEAEs. As expected with a longer duration on-study there was a very slight increase in the number of subjects who reported TEAEs up to Week 60; however, the exposure-adjusted rate of TEAEs was comparable between Week 24 and Week 60. No SAE or death was reported. In the timeframe 24-60 weeks, one subject experienced a TEAE, namely JIA flare, leading to discontinuation of study drug. This TEAE should account for a lack of efficacy. A slight increase in upper respiratory tract infections, nasopharyngitis, rhinorrhea, rhinitis, otitis media, bronchitis and cough was detected. This trend is expected considering the increased exposure to study drug. Among TEAEs reported at week 60 are 4 TEAEs (no cases where reported at week 24) classified as rheumatoid arthritis preferred term. These cases should be considered as JIA flares and thus considered as lack of efficacy cases. Overall, results up to week 60 on TEAEs were similar to those up to week 24. Most of TEAEs up to 60 week were mild or moderate in severity. When severe TEAEs are considered, one additional case at week 60 was reported (rheumatoid arthritis) when compared to those reported up to week 24 (4 cases: uveitis, otitis media, diabetes mellitus and arthritis).

Furthermore, the MAH provided comparison between the safety results from Study DE038 and Study M10-444 in order to strengthen the results of Study M10-444. Overall, the safety results from Study M10-444 were similar to those observed in Study DE038 (pivotal clinical study supporting the application for JIA 4-17 years) and demonstrated that adalimumab is generally well-tolerated in children with JIA. The comparison of safety data from study M10-444 (32 patients aged from 2 to 4 years) with those from study DE038 (171 patients >4 years old), showed a slight lower frequency of TEAEs in the 2-4 year of age category (any TEAE 91% vs 98%, SAEs 16% vs 27%, with the exception of the serious infection TEAEs that accounts respectively for 9% vs 6%). In summary, TEAEs observed in children 2 to <4 y were similar regarding type and frequency to TEAEs observed in children 4 to 17 y. Additionally, no new and/or unexpected safety concerns were identified in children 2 to <4 y.

Taking into account these additional data, the safety data from study M10-444 up to week 60 are considered in line with the known safety profile of adalimumab in JIA. No new safety signal has been identified.

To ensure further broadening of the knowledge about the safety profile, the CHMP required that a long-term observation of adalimumab treatment in children within this age range should be performed. This is to monitor AEs of special interest as infections, CNS demyelinating disease, malignancies, lupus like syndrome and others through a registry recording data for at least 10 years of observation. The MAH addressed this request by including the relevant subset of patients 2 to 4 years in the JIA Registry already in place (study P10-262 as described in the RMP), extending the inclusion criteria and the timeframe of observations. Subjects from Studies M10-444 and DE038 have the option to roll over into the P10-262 registry. Since 01 June 2012, 11 patients rolled over from Study DE038 and 9 rolled over from Study M10-444. As per the current registry protocol, safety data collected through Year 5 focuses on the collection of AEs of special interest. Starting at Year 6, patients will be followed annually for SAEs, congestive heart failure, and malignancies through Year10. The protocol will be amended to collect the AEs of special interest throughout the 10-year observation period. The JIA registry will also bring information on treatment interruptions in this added children population as the registry effectiveness and safety variables are also collected during adalimumab treatment interruption. The impact of treatment interruptions (≥70 days) on safety and effectiveness will be evaluated for the next interim analysis. Patients being prescribed and treated with MTX per the local label will be considered a reference group.

2.5.3. Conclusions on clinical safety

Adalimumab was generally well tolerated during the study M10-444. The most common AEs were pyrexia, nasopharyngitis, upper respiratory tract infection and cough.The AE pattern in this study does not differ from the known safety profile of adalimumab in JIA patients. No new safety signal has been identified in the results presented. In the study M10-444, AEs of special interest for adalimumab have been monitored and no safety signal has been detected. The only reports of TEAEs of special interest were infections (serious and nonserious) and injections site related TEAES.

Adalimumab has a well characterised safety profile in several authorised indications, including active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more DMARDs. Data submitted in this application confirm the known safety profile observed with the approved indication in the older paediatric population. Overall, the safety profile of adalimumab in the treatment of active polyarticular juvenile idiopathic arthritis in children aged 2 to 4 years appears to be similar with the one known in polyarticular JIA in children and adolescent aged 4 to 17 years and in other approved indications.

Further data will become available to further characterise the long term safety and effectiveness of adalimumab in the treatment of active polyarticular JIA, in children aged 2 to 4 years from the JIA registry P10-262. This includes safety data concerning episodic treatment in JIA. The next interim update is expected in August 2013 as detailed in the RMP.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The MAH submitted updated Risk Management Plan within this variation procedure to include the JIA population 2 to <4 years. No new important risks or safety issue have been identified. The important missing information was updated to reduce it to the children population <2years of age.

Table 19 Extract from Summary of the risk management plan (including only the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Missing Information		
Children < ~~4~~**2** years of age for JIA indication	~~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 (Study P10-262).~~ **Routine pharmacovigilance activities.** **No actions beyond routine pharmacovigilance planned for children < 2 years of age with JIA based on low prevalence in this age group and benefit/risk considerations.**	The Dosage section of the CCDS addresses the lack of information in **these** paediatric patients. ~~Data in the paediatric populations (less than 4 years) are currently collected and this information will be included in the CCDS once available. An ongoing 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 characterise 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 local labels as necessary.

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information.

Children of 2 to 4 y will be included in the ongoing JIA registry, Study P10-262 as described in the RMP. The protocol will be amended to collect the AEs of special interest throughout the 10-year observation period for these subjects. This will complement the safety experience gained from spontaneous post-marketing AE reporting for children ≥2 years of age on adalimumab.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The submission is based on a single, open label multicenter study (M10-444) to support the extension of indication of adalimumab in the paediatric population aged 2-4 years with active polyarticular course JIA that have had an inadequate response, or have been intolerant to at least 1 DMARD. The studied dose was 24 mg/m^2 BSA up to a total dose of 20 mg adalimumab administered eow as a single dose via SC injection. The currently approved dose for children 4-12 year is 24 mg/m^2 body BSA up to a total dose of 40 mg adalimumab eow. Serum concentration data were available from 15 children. The mean serum trough concentrations in the new study were comparable with steady state concentrations seen in a previous study in children >4 years and weighing >15 kg (study DE038). Plots of individual plasma concentrations from the two studies vs. weight and body surface area, respectively, stratified for MTX treatment indicated no trend in data and the individual serum concentrations appear to be similarly distributed over the studied weight and BSA ranges at administration of the BSA-adjusted dose (24 mg/m^2 eow). Thus, although the pharmacokinetic data in this age group 2 to <4 years is limited, pharmacokinetic data are considered supportive of using the same dose to the smaller children as that previously approved for children from 4 years.

Results from study M10-444 showed efficacy of adalimumab in the paediatric population of the claimed indication: at Week 12 and Week 24, PedACR30 response was achieved by 93.5% and 90.0% of subjects, respectively. At Week 12 and Week 24, PedACR50 response was achieved by 90.3% and 83.3% of subjects, respectively. Therefore; the majority of subjects achieved PedACR30 and PedACR50 response by Week 12 and maintained response at Week 24. Furthermore, more than half of all subjects (61.3%) achieved PedACR70 at Week 12 and almost three-quarters of all subjects achieved a PedACR70 response by Week 24 (73.3%). Each of the JIA core set variables demonstrated clinically meaningful reductions in disease activity at both Weeks 12 and 24. Week 24 is the time point at which efficacy was demonstrated in the previous controlled study with adalimumab in children older than 4 years of age. Furthermore, given the availability of efficacy data gathered in the age category 4-12 years old (study DE038) and the positive PK results showing similar PK profiles of adalimumab in children from 2 to 4 years of age and in children above 4 years of age, extrapolation of efficacy to the younger cohort of patients is considered possible; this reinforces the results of the pivotal trial.

Uncertainty in the knowledge about the beneficial effects

To further characterise the long term effect treatment in the 2-4 years old this population will be included in the currently ongoing JIA registry P10-262 studying the 4-17 years population. This also includes data concerning episodic treatment in JIA. The impact of treatment interruptions (≥70 days) on safety and effectiveness will be evaluated for the next interim analysis (August 2013 as detailed in the RMP).

Risks

Unfavourable effects

Adalimumab was generally well tolerated during the study M10-444. The most common AE was pyrexia, nasopharyngitis, upper respiratory tract infection and cough.The AE pattern in this study does not differ from the known safety profile of adalimumab. No new safety signal has been identified in the results presented. AEs of special interest for adalimumab have been monitored and no safety signal has been detected. All SAEs were mild or moderate in severity with the exception of diabetes mellitus, which was severe. Furthermore, the safety profile in this young age group appeared in line with the safety profile in older children based on comparison of data from studies M10-444 (2-4 years) and DE038 (4-17 years). Infections are of a special concern in this population of small children. It is important to note that through the cutoff date of the interim report, no subject prematurely discontinued from the study as a result of an infection. To further support the safety profile presented at Week 24 the MAH provided an updated interim safety analysis (data cut-off 24 May 2012) up to Week 60 for Study M10-444. Comparative safety data showed an overall similar safety profile with an exposure-adjusted rate of TEAEs comparable between Week 24 and Week 60. Comparison between the safety results from Study DE038 (pivotal clinical study supporting the application for JIA 4-17 years) and Study M10-444 showed that the safety results observed were similar between the 2 studies. Safety data up to week 60 are considered in line with the known safety profile of adalimumab in JIA.

Uncertainty in the knowledge about the unfavourable effects

Given the limited sample size and open label design of study M10-444 the CHMP required during the procedure that a long-term observation of adalimumab treatment in children below 4 years of age or <15 kg should be ensured through a registry recording data for at least 10 years of observation. This was agreed by the MAH by including the relevant subset of patients in the currently ongoing JIA registry: study P10-262 (as described in the RMP) by extending the inclusion criteria and the timeframe of observations. This registry will allow further characterisation of the long term safety of adalimumab treatment in children below 4 years of age; including safety data concerning episodic treatment. Interim data from the registry is provided on a yearly basis until August 2020. The next interim report is expected in August 2013 as detailed in the RMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Adalimumab has been used for treating paediatric patients with active polyarticular juvenile idiopathic arthritis from 4 to 17 years. Uncontrolled disease may create longstanding and severe disability also in the very young children population below 4 years old. Results from study M10-444 showed that treatment with adalimumab dosed at 24 mg/m² body surface area up to a maximum single dose of 20 mg conferred a clinical benefit to the patients. These data are considered valuable and of clinical relevance.

The safety profile of adalimumab was adequately characterised and no new treatment-related AE or safety signal was identified from the data submitted. Safety data up to week 60 are considered in line with the known safety profile of adalimumab in JIA.

Benefit-risk balance

The efficacy results presented clearly support a positive effect of adalimumab treatment. The majority of subjects achieved PedACR30 (93.5%) and PedACR50 responses (90.3%) by Week 12 and

maintained these responses at Week 24 (≥83.3%). More than half of all subjects (61.3%) achieved a PedACR70 response at Week 12, and almost three-quarters of all subjects achieved a PedACR70 response by Week 24 (73.3%). Data from ACR JIA core set variables demonstrated that adalimumab treatment was associated with reductions in joint swelling, pain, and tenderness, as well as in limitation of motion.

The safety of adalimumab treatment has been well characterized in the adult RA and JIA population. Safety data obtained in this paediatric adalimumab trial (2-4 years) are consistent with prior paediatric JIA studies with patients aged 4 to 17 years. No new safety signal has been identified in the results presented.

Updated safety data from the ongoing study up to week 60 are considered in line with the known safety profile of adalimumab in JIA. To further characterise the long term adalimumab effect, children aged 2-4 years will be included in the ongoing JIA registry Study P10-262, which will also provide information on the impact of treatment interruptions (≥70 days) on safety and effectiveness.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of adalimumab is considered positive for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 2 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

4. Recommendations

The application for the extension of indication for the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age is approvable since the major objection and the other concerns have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age. As a consequence of this new indication, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Paediatric data

The CHMP reviewed the available paediatric data of study M10-444 subject to the agreed Paediatric Investigation Plan PIP P/63/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.