Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Adalimumab (rch)

## Proprietary Product Name: Humira

## Sponsor: AbbVie Pty Ltd

**December 2015**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# Common abbreviations

| Abbreviation | Meaning |
|---|---|
| AAA | Anti-adalimumab antibody |
| ACR | American College of Rheumatology |
| AE | Adverse event |
| AESI | Adverse event(s) of special interest |
| AJC | Active joint count |
| ALT | Alanine aminotransferase |
| ANA | Anti-nuclear antibody |
| AP | Alkaline phosphatase |
| BCG | Bacille Calmette-Guérin |
| BSA | Body surface area |
| BUN | Blood urea nitrogen |
| CHQ-PF50 | Child Health Questionnaire – PF50 |
| CHF | Congestive heart failure |
| CK | Creatine phosphokinase |
| CPK | Creatine phosphokinase |
| CRF | Case report form |
| CRO | Contract research organization |
| CRP | C-reactive protein |
| CV | Coefficient of variation |
| CVA | Cerebrovascular accident |
| DICHAQ | Disability Index of Childhood Health Assessment Questionnaire |
| DMARD | Disease-modifying anti-rheumatic drug |
| dsDNA | Double stranded DNA |
| EMA | European Medicines Agency |
| eow | Every other week |

| Abbreviation | Meaning |
|---|---|
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| ET | Early termination |
| GCP | Good clinical practice |
| HCP | Health care provider |
| HSTCL | Hepatosplenic T-cell lymphoma |
| IgG1 | Human immunoglobulin |
| ICH | International Conference on Harmonisation |
| ILAR | International League of Associations for Rheumatology |
| ILD | Interstitial lung disease |
| IRB | Institutional Review Board |
| JADAS | Juvenile Arthritis Disease Activity Score |
| JIA | Juvenile idiopathic arthritis |
| JRA | Juvenile rheumatoid arthritis |
| LFT | Liver function tests |
| LOM | Limitation of Passive Motion Joint Count |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| MTX | Methotrexate |
| NMSC | Non-melanoma skin cancer |
| OL | Open-label |
| PedACR | Pediatric American College of Rheumatology |
| PGA | Physician's global assessment |
| PK | Pharmacokinetics |
| POM | Pain on Passive Motion Joint Count |
| PPD | Purified protein derivative |

| Abbreviation | Meaning |
|---|---|
| PT | Preferred Term |
| PYs | Patient-years |
| RA | Rheumatoid arthritis |
| RBC | Red blood cell |
| RF | Rheumatoid factor |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SD | Standard deviation |
| SJC | Swollen Joint Count |
| SOC | System Organ Class |
| TEAE | Treatment-emergent adverse event |
| TB | Tuberculosis |
| TI | Treatment interruption |
| TJC | Tender Joint Count |
| TNF | Tumor necrosis factor |
| ULN | Upper limit of normal |
| US | United States |
| VAS | Visual analog scale |
| WBC | White blood cell |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | Extension of indications |
| *Decision*: | Approved |
| *Date of decision:* | 14 May 2015 |
| *Date of entry onto ARTG* | 25 May 2015 |
| *Active ingredient(s):* | Adalimumab (rch) |
| *Product name(s):* | Humira |
| *Sponsor's name and address:* | AbbVie Pty Ltd<br>Locked Bag 5029, Botany NSW 1455 |
| *Dose form(s):* | Solution for Injection |
| *Strength(s):* | 40 mg/0.8 mL, 20 mg/0.4 mL or 10 mg/0.2 mL |
| *Container(s):* | 10 and 20 mg in Pre-filled syringe only and 40 mg in Vial, Pre-filled syringe or Pre-filled pen. |
| *Pack size(s):* | 10 and 20 mg in 2's and 40 mg in 1, 2, 3, 4 or 6's |
| *Approved therapeutic use:* | *Polyarticular Juvenile Idiopathic Arthritis*<br>*Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older 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.* |
| *Route(s) of administration:* | Subcutaneous (SC) injection |
| *Dosage:* | The recommended dose of Humira for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis is based on weight as shown below. Methotrexate, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with Humira. |

| Paediatric Patients (2 years of age and older) | Dose |
|---|---|
| 10 kg to <15 kg | 10 mg fortnightly (10 mg Pre-filled Syringe) |
| 15 kg to <30 kg | 20 mg fortnightly (20 mg Pre-filled Syringe) |
| ≥ 30 kg | 40 mg fortnightly (Humira 40 mg Pen or 40 mg Pre-filled Syringe) |

| | |
|---|---|
| *ARTG number (s):* | 95779, 95780, 127116, 155315, 199410, 199411, 199412 and 216038 |

## Product background

This AusPAR describes the application by AbbVie, the sponsor, to extend the indications of Humira (adalimumab rch) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) from patients 4 years of age and older to patients 2 years of age and older.

Humira (adalimumab rch) is a Tumour Necrosis Factor (TNF)-a neutralising recombinant immunoglobulin ($IgG_1$) monoclonal antibody containing only human peptide sequences. It binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface receptors. Humira is produced in a mammalian cell expression system.

The currently approved indications are:

> *Polyarticular Juvenile Idiopathic Arthritis*
>
> *Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 4 years of age and older. Humira can be given as monotherapy in case of intolerance or when continued treatment with methotrexate is inappropriate.*

The sponsor has proposed the following indications in their application:

> *Polyarticular Juvenile Idiopathic Arthritis*
>
> *Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 ~~[4]~~ years of age and older. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*

The currently recommended dose of Humira for patients 4 to 17 years of age with polyarticular juvenile idiopathic arthritis is based on weight is shown below. Methotrexate, glucocorticoids, salicylates, Non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics may be continued during treatment with Humira.

> *Paediatric Patients (4 to 17 years)*
>
> - *15kg to <30kg, 20mg fortnightly (20mg Pre-filled Syringe)*
> - *≥ 30kg, 40mg fortnightly (Humira 40mg Pen or 40mg Pre-filled Syringe)*
>
> *Limited data are available for Humira treatment in paediatric patients with a weight below 15kg.*

The sponsor has proposed the following dosage in this application for Polyarticular Juvenile Idiopathic Arthritis:

> *The recommended dose of Humira for patients 2 ~~4 to 17~~ years of age and older with polyarticular juvenile idiopathic arthritis is based on weight as shown below. Methotrexate, glucocorticoids, ~~salicylates~~, NSAIDs and/or analgesics may be continued during treatment with Humira.*
>
> *Paediatric Patients (~~4 to 17~~ 2 years of age and older)*
>
> - *10kg to <15kg, 10mg fortnightly (10mg Pre-filled Syringe)*
> - *15kg to <30kg, 20mg fortnightly (20mg Pre-filled Syringe)*
> - *≥ 30kg, 40mg fortnightly (Humira 40mg Pen or 40mg Pre-filled Syringe)*
>
> *~~Limited data are available for Humira treatment in paediatric patients with a weight below 15 kg~~. Humira has not been studied in patients with polyarticular JIA less than 2 years of age, or in patients with a weight below 10 kg.*

The sponsor originally proposed a different dosage regimen that included doses for patients weighing 10 to <12 kg of 10 mg fortnightly and patients weighing 12 to <15 kg of 15 mg fortnightly but amended this during the evaluation to a single dose covering the weight range of 10 to <15 kg of 10 mg fortnightly. The clinical evaluator has supported the amended dosage regimen.

The sponsor has also proposed updates to the corresponding sections of the Product Information (PI) with the pJIA data, however the details of this is beyond the scope of this AusPAR.

There is a European Medicines Agency (EMEA) guidance document relating specifically to the current submission:

- Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis (London, 18 October 2006; CPMP/EWP/422/04). This document was adopted by the TGA on 26 June 2009.

## Regulatory status

The first entry for Humira on the Australian Register of Therapeutic Goods (ARTG) was on 10 December 2003 for the treatment of adult rheumatoid arthritis and is currently also approved for use in psoriatic arthritis, ankylosing spondylitis, pJIA, psoriasis, Crohn's disease and ulcerative colitis.[1]

Humira in combination with methotrexate for the treatment of pJIA in patients aged 4 years of age and older was approved by the TGA in July 2009. The TGA approval for pJIA was based on the data from the previously evaluated Study DE038.

Adalimumab for pJIA has been approved in 85 countries. Similar indication in patients 2 years and older have been approved in Europe, the USA and Singapore with the following indications (Table 1):

[1] Full indications: *Rheumatoid Arthritis: Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate. Humira can be used alone or in combination with methotrexate.*
*Polyarticular Juvenile Idiopathic Arthritis: Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 4 years of age and older. Humira can be given as monotherapy in case of intolerance or when continued treatment with methotrexate is inappropriate.*
*Psoriatic Arthritis: Humira is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.*
*Ankylosing Spondylitis: Humira is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*
*Crohn's Disease: Humira is indicated for the treatment of moderate to severe Crohn's disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab.*
*Ulcerative colitis: Humira is indicated for the treatment of moderate to severe ulcerative colitis in adult patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS).*
*Psoriasis: Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.*

**Table 1: International regulatory status**

| Country/Region | Status | Approved Indications |
|---|---|---|
| EU<br>(Centralised Procedure) | Approved<br>25 February 2013 | *Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents from the age of 2 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.* |
| United States of America | Approved<br>30 September 2014 | *Humira is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Humira can be used alone or in combination with methotrexate.* |
| Canada | N/A | N/A |
| New Zealand | Under Evaluation | N/A |
| Singapore | Approved<br>19 September 2014 | *Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents from the age of 2 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 (for the efficacy in monotherapy see CLINICAL STUDIES). Humira has not been studied in children aged less than 2 years.* |
| Switzerland | N/A | N/A |

N/A=not applicable (no submission as yet).

The dosage regimen approved in the USA is the same as proposed here but the dosage regimen approved in Europe is different and based on body surface area (patient's height and weight) with more detailed dosage selection.

Four biological treatments are approved in Australia for JIA (abatacept, tocilizumab, etanercept and canakinumab) with the latter three approved from the age of 2 years onwards and canakinumab only for systemic JIA. The approved indications are as follows for JIA:

1. *Abatacept:*
   - *Orencia® is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Orencia ® may be used as monotherapy or concomitantly with methotrexate (MTX). (There is no clinical trial data for the use of*

*Orencia® subcutaneous formulation in children, therefore its use in children cannot be recommended.)*

2. *Tocilizumab:*
   - *Polyarticular Juvenile Idiopathic Arthritis*

     *Actemra is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). Actemra can be given alone or in combination with MTX.*
   - *Systemic Juvenile Idiopathic Arthritis*

     *Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*
3. *Etanercept*:
   - *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.*
   - *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*
   - *Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.*
   - *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*
   - *Enbrel has not been studied in children aged less than 2 years.*
4. *Canakinumab:*
   - *Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years or older.*

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# II. Quality findings

### Quality summary and conclusions

The validation of the methods for Determination of anti-Adalimumab-Antibodies in Human serum via Sandwich ELISA[2] ANA 04/009 (Double-antigen Technique) and Measurement of Adalimumab concentrations in serum**,** are satisfactory.

[2] ELISA=enzyme-linked immunosorbent assay

# III. Nonclinical findings

No new nonclinical data were submitted.

# IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

## Introduction

### Clinical rationale

The sponsor's Clinical Overview stated that the pivotal study (M10-444) in paediatric patients aged 2 to < 4 years of age was undertaken by AbbVie as a commitment to the United States (US) Food and Drug Administration (FDA) and as a requirement of the European Medicines Agency (Pediatric Investigation Plan). The sponsor's Clinical Overview also stated that there is an '*evident medical need for treatment of this young patient population with JIA*'.

The sponsor's clinical rationale is acceptable.

## Contents of the clinical dossier

### Scope of the clinical dossier

The submission contained the following clinical information:

- Study M10-444 - uncontrolled study of compassionate use of adalimumab for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in children aged 2 to < 4 years and aged ≥ 4 years weighing < 15 kg.
- Study P10-262 (interim report of first 4 years registry experience): A long-term, multi-Centre, longitudinal post-marketing, observational registry to assess long term safety and effectiveness of Humira (adalimumab) in children with moderately to severely active polyarticular or polyarticular-course juvenile idiopathic arthritis (JIA)–STRIVE.
- Bioanalysis validation report (ANA11-009): Partial validation of the analytical method after lot change of detection Biotin-labeled antibody (analytes = anti-adalimumab antibodies; method = sandwich ELISA [double antigen technique]).
- A Clinical Summary of Efficacy (CSE) Statistical Tables; a Clinical Summary of Safety (CSS) Statistical Tables; tabular listing of studies and literature references.

### Paediatric data

The submission provides paediatric data specifically relating to the treatment of pJIA in children aged 2 to < 4 years and aged ≥ 4 years weighing < 15 kg. The submission included a paediatric development program relating to provision of paediatric data to the EU and the USA.

### Good clinical practice

The pivotal study (M10-444) complied with requirements for good clinical practice.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Study M10-444 (the pivotal study) was a multi-centre, open label, uncontrolled study of adalimumab undertaken at 14 sites in the US (including Puerto Rico) and Europe in paediatric patients with moderately to severely active pJIA or polyarticular course JIA aged 2 to < 4 years or aged ≥ 4 years weighing < 15 kg. It was specified that the JIA diagnoses were to meet International League of Associations for Rheumatology (ILAR) criteria.

The submission included an interim pharmacokinetics (PK) report (R&D/11/1281) focusing on the pharmacokinetics (PK) and immunogenicity of adalimumab in the paediatric patients from Study M10-444 at Week 24 of treatment. The PK evaluation of adalimumab was a secondary objective of Study M10-444. The PK data from Study M10-444 have been fully evaluated. There were no other studies in the submission providing PK data in the proposed patient population.

### Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of adalimumab in the proposed patient population have been adequately characterised in 15 paediatric subjects with pJIA from Study M10-444 of mean age 3.0 years (range: 2, 4.2 years) and mean weight 13.1 kg (range: 11.0, 16.0 kg). The 15 subjects with PK data were a subset of the 32 subjects enrolled in the study. Participation in the PK analysis was not a requirement for subjects enrolled into the study. The baseline demographic characteristics of the 15 subjects with PK data were consistent with those of the 32 subjects in the study.

In Study M10-444(N=15), following treatment with adalimumab 24 mg/m$^2$ body surface area (BSA) every other week (eow) (with or without methotrexate (MTX)) the steady-state mean ± standard deviation (SD) serum adalimumab trough concentrations at Week 12 and Week 24 were 6.97 ± 5.69 µg/mL and 7.78 ± 5.85 µg/mL, respectively. The steady-state mean serum adalimumab trough concentrations at Week 12 and Week 24 were higher in subjects treated with adalimumab 24 mg/m$^2$ BSA eow with MTX (N=11) than without MTX (N=4). However, the difference between the two groups should be interpreted cautiously due to the imbalance in subject numbers between the two groups (N=11 [with MTX] versus N=4 [without MTX]), and the higher inter-subject variability in adalimumab concentration in the adalimumab without MTX group compared to the adalimumab with MTX group (coefficient of variation (CV) 105% versus CV 79%, respectively).

In subjects treated with adalimumab 24 mg/m2 eow with MTX, the mean serum ± SD adalimumab steady-state trough concentration at Week 24 in the proposed paediatric group (N=11) from Study M10-444 was similar to that at Week 16 in the approved paediatric group (N=36) from Study DE038 (8.45 ± 5.69 versus 8.85 ± 5.53 µg/mL, respectively). However, in patients treated with adalimumab 24 mg/m$^2$ eow without MTX, the mean ± SD serum adalimumab steady-state trough concentration at Week 24 in the proposed paediatric group (N=4) from Study M10-444was lower than the corresponding concentration at Week 16 in the approved paediatric group (N=29) from Study DE038 (5.95 ± 6.74 [CV = 113%] versus 7.03 ± 6.26 µg/mL [CV = 89%], respectively). The comparative data for steady-state adalimumab concentration in patients treated with adalimumab without MTX should be interpreted cautiously due to the high inter-subject variability in both studies and the marked imbalance in subject numbers between the two studies.

Of the 15 patients from Study M10-444 with Anti-adalimumab antibody (AAA) data, there was one patient who became AAA positive (AAA+) at Week 24 (6.7% [1/15]). The

imbalance in patient numbers between AAA+ and AAA- patients preclude clinically meaningful comparison of efficacy and safety between the two groups.

## Pharmacodynamics

No new data submitted.

## Dosage selection for the pivotal studies

The sponsor stated that BSA based dosing with adalimumab in M10-444 has been used in previous clinical trials in children with JIA. However, the sponsor is proposing weight based dosing, which it states is supported by clinical and PK data. The proposed weight based dosing regimen is consistent with the approved weight base regimen for polyarticular JIA patients aged 4 to 17 years. The sponsor's Clinical Overview provided a justification for the proposed weight based dosing regimen supported by clinical trial and PK data. This justification is discussed below.

In the pivotal Study M10-444, patients were administered 10, 15, or 20 mg adalimumab SC eow, based on BSA, calculated according to Table 2 below. The dose of adalimumab was determined based on height and weight at the following time points: Baseline, Week 12, Week 24, and every 12 weeks thereafter until the subjects reached the age of 4 years, and weighed 15 kg. In the event that the BSA fell between two ranges, the dose was to be rounded up to the nearest 5 kg weight and 10 cm height.

**Table 2: Study M10-444 - Adalimumab total body dose in millilitres (mL) of 50 mg/mL injectable solution given every other week (eow) based on weight and height.**

| | 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 | -- |

The currently approved Humira dosing schedule for patients aged 4 to 17 years is based on two body weight categories, with a cut-off of 30 kg (that is, 15 kg to < 30 kg; and ≥ 30 kg). In order to align with the approved dosage schedule the sponsor summarised the administered doses from Study M10-444 according to the subject's weight for three time points (Baseline, Week 12 and Week 24); see Table 3 below.

**Table 3: Study M10-444 - Body weight and adalimumab dosing.**

| | Dose (mg) at Baseline N = 32 n | | | Dose (mg) at Week 12 N = 31 n | | | Dose (mg) at Week 24 N = 30 n | | |
|---|---|---|---|---|---|---|---|---|---|
| **Subject Body Weight (kg)** | **10** | **15** | **20** | **10** | **15** | **20** | **10** | **15** | **20** |
| 10 | 1 | | | | | | | | |
| 11 | 4 | | | 3 | | | | | |
| 12 | 3 | 3 | | 1 | 4 | | 1 | 4 | |
| 13 | | 7 | | | 7 | | 1 | 6 | |
| 14 | | 5 | | | 5 | | | 3 | |
| 15 | | 4 | | | 5 | | | 7 | |
| 16 | | 3 | | | 3 | | | 6 | |
| 17 | | 1 | | | 2 | | | 2 | |
| 18 | | | | | | | | | |
| 19 | | 1 | | | | | | | |
| 20 | | | | | | | | | |
| 21 | | | | | | 1 | | | |
| Total | 8 | 24 | | 4 | 26 | 1 | 2 | 28 | |

The tabulated summary of the dose distribution for patients from Study M10-444 shows that:

- the majority of patients in the study were treated with adalimumab 15 mg: 75% (24/32) at Baseline, 84% (26/31) at Week 12, and 93% (28/30) at Week 15 mg;
- all patients weighing 10 kg or 11 kg were treated with adalimumab 10 mg at Baseline and Week 12, and no patients weighed less than 12 kg at Week 24;
- the majority of patients weighing 12 kg were treated with adalimumab 15 mg: 50% (3/6) at Baseline, 80% (4/5) at Week 12, and 80% (4/5) at Week 24;
- all subjects weighing 13 kg to 20 kg (inclusive) were treated with adalimumab 15 mg at Baseline, Week 12 and Week 24; and
- one subject weighing 21 kg was treated with adalimumab 20 mg at Week 12.

Based on the dosing data from Study M10-444 the sponsor proposes the following adalimumab treatment regimens:

- 10 mg eow in patients 2 years of age and older who weigh 10 kg to < 12 kg administered via the 40 mg/0.8 mL vial;
- 15 mg eow in patients 2 years of age and older who weigh 12 kg to < 15 kg; and
- for patients 2 years of age and older who weigh ≥ 15 kg, the currently approved dosage instructions apply (that is, 20 mg eow for patients weighing 15 kg to < 30 kg; 40 mg eow for patients weighing ≥ 30 kg).

The sponsor also compared the actual doses (n=1145) in Study M10-444 and the proposed weight based doses (see Table 4, below). Weight at Baseline, Week 12, Week 24 and every 12 weeks thereafter was used to determine the weight based dose at those visits and visits in between these time points. The comparison used data collected up until subjects reached the age of 4 years or their weight was 15 kg. The comparative data indicates that for the majority of administered doses (63.32%) the doses were identical irrespective of the dosage method used (that is, weight based or actual dose). For most of the remaining administered doses the weight based dose was greater than the actual dose

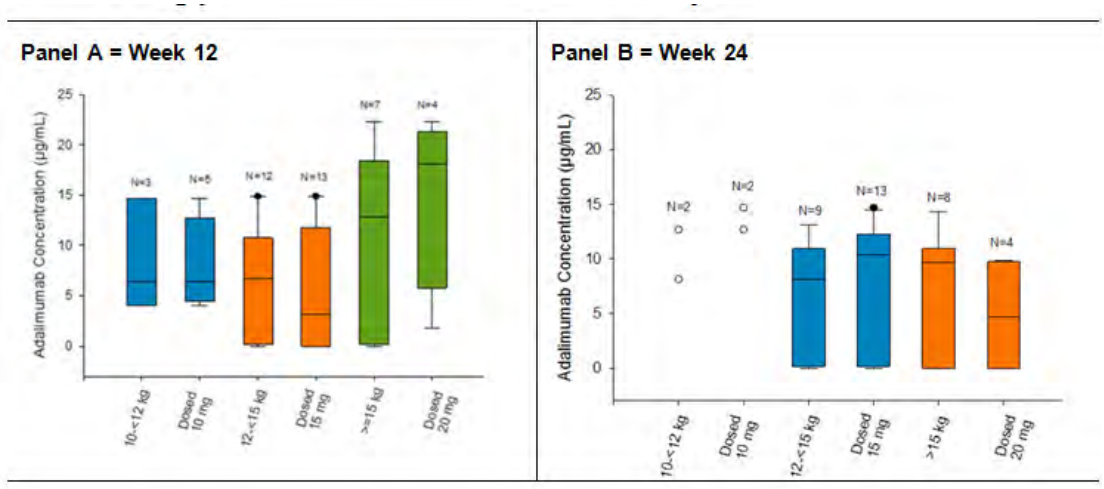
(34.67%), while the actual dose was greater than the weight based dose for only a small percentage of administered doses (2.01%)

**Table 4: Study M10-444 - Comparison of 1145 adalimumab doses administered throughout the study based on BSA (actual dose) and corresponding dose based on the proposed weight categories.**

| | Number of Doses Administered | Percent |
|---|---|---|
| Weight based dose > actual dose | 397 | 34.67 |
| Weight based dose = actual dose | 725 | 63.32 |
| Weight based dose < actual dose | 23 | 2.01 |

In order to further compare the weight based and BSA based dosing regimens the sponsor pooled the PK data from Study M10-444 (N=15) with the PK data for subjects aged 4 to 6 years treated with adalimumab 10, 15, or 20 mg from Study DE038 (N=7 for Week 12; N=4 for Week 24). The observed concentration data were plotted in two ways: subjects in the proposed body weight based dosing ranges (10 to < 12 kg; 12 to < 15 kg; and ≥ 15 kg) and subjects who received 10, 15, or 20 mg doses. The pooled exposure data from the two studies showed that the plasma concentration trough (Ctrough) levels were similar for weight based and BSA based dosing (see Figure 2, below). The high variabilities observed for Ctrough levels are likely to be due to the small sample sizes.

**Figure 2: Adalimumab concentrations (Ctrough) in JIA subjects aged 2 to 6 years from studies M10-444 and DE038 plotted by body weight based dosing and by BSA based dosing (Panel A = Week 12; Panel B = Week 24).**




The dosing data from Study M10-444 and the pooled exposure data (Ctrough) from Studies M10-444 and DE038 support the proposed weight based dosing regimens.

## Efficacy

### Studies providing efficacy data

One, pivotal study (M10-444) was submitted.

### Evaluator's conclusions on efficacy

The assessment of the clinical efficacy of adalimumab for the treatment of moderate to severe pJIA in children aged 2 to < 4 years and children age ≥ 4 years weighing < 15 kg is based on the results of the efficacy variables from a small number of subjects (N=32) enrolled in a multinational, multicentre, open label, uncontrolled study (M10-444). The

study aimed to treat all subjects for at least 24 weeks, and 30 of the 32 subjects (94%) achieved this objective. The majority of subjects (84.4%, N=27) were treated with adalimumab in combination with MTX. There were no efficacy data comparing adalimumab alone to adalimumab in combination with MTX.

The most commonly reported JIA diagnosis at Baseline in Study M10-444 was sero-negative polyarthritis (type 2 JIA) (N=20 [62.5%]) followed by extended oligoarthritis (type 5 JIA) (N=8 [25.0%]). All other JRAJIA diagnoses based on ILAR criteria were reported in ≤ 2 subjects. The majority of subjects had received treatment for pJIA prior to enrolment with MTX (N=25, 78.1%), systemic NSAIDs (N=20, 62.5%) and/or systemic corticosteroids (N=22, 68.8%). Prior to enrolment, no patients had been treated with biologics for treatment of their disease.

All subjects in Study M10-444 were treated with adalimumab 24 mg/m$^2$ (BSA) by SC injection eow and, as noted above, the majority of subjects also received concomitant treatment with MTX (N=27, 84.4%). Subjects enrolled in EU countries were required to have previously failed, had an insufficient response to, or been intolerant to ≥ 1 Disease-modifying anti-rheumatic drug (DMARD). However, this was not a requirement for non-EU subjects.

In Study M10-444, there were no primary efficacy outcomes and all efficacy outcomes were defined as secondary outcomes. Efficacy data were available on 94% of subjects (30/32) at Week 24, 53% of subjects (17/32) at Week 84 and 9% of subjects (3/32) at Week 120. There were no statistical analyses of the efficacy outcomes and all results were presented descriptively. The main efficacy outcomes were the PedACR30/50/70/90[3] responses in the Intention-to-Treat (ITT) population. The PedACR30 is a validated efficacy outcome for paediatric subjects. The Paediatric American College of Rheumatology (PedACR)50/70/90 responses do not appear to have been validated for paediatric subjects, but are commonly used clinical trial endpoints for the assessment of medications for the treatment of pJIA. The PedACR responses are considered to be acceptable efficacy endpoints for the assessment of adalimumab in the patient population studied.

The observed PedACR30 response was achieved by at least 85% of subjects from Week 12 through to Week 120. The imputed PedACR30 responses for both the last observation carried forward (LOCF) and non-responder imputation analysis (NRI) methods supported the observed PedACR30 response through to Week 24 but the NRI responses were notably lower than the observed responses at Weeks 36 and 60. The observed PedACR50 response was achieved by at least 80% of subjects from Week 12 through to Week 120, while the observed PedACR70 and PedACR90 responses were achieved by at least 61% and 36% of subjects, respectively, from Week 12 through Week 120. The observed PedACR30/50/70/90 responses at Week 24 were 90.0%, 83.3%, 73.3% and 36.7% of subjects, respectively, and the responses were consistent with the results for the LOCF and NRI analyses at this time-point. Overall, the PedACR responses indicate a clear benefit for adalimumab treatment. Due to the magnitude of the improvements in the observed PedACR responses (from Baseline) it is considered unlikely that they are due to chance alone.

[3] 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
- Disability Index of Childhood Health Assessment Questionnaire (DICHAQ)
- C-reactive protein (CRP)

The results for the JIA core set of variables showed consistent improvement from baseline over the course of treatment for each of the parameters. The results for each of the joint assessments (Tender Joint Count (TJC) 75, Swollen Joint Count (SJC) 66, Pain on Passive Motion Joint Count (POM) 75, Limitation of Passive Motion Joint Count (LOM) 69, Active joint count (AJC) 73) showed a reduction in mean score from Baseline at all visits from Week 12 through to Week 120. In general, mean reductions from Baseline for all joint assessment scores increased from Week 12 through to Week 72 to Week 84. The number of subjects with joint assessments after the Week 84 visit was notably lower than the number prior to this visit.

The results for Physician's global assessment (PGA) of disease activity, parent's global assessment of disease activity and parent's assessment of pain all showed reductions in mean Visual analogue scale (VAS) scores from Baseline at all visits from Week 12 through to Week 120. In general, the reductions from Baseline in mean VAS scores were higher from Week 72 through to Week 120 than from Week 12 through to Week 72. However, the number of patients assessed at Week 72 through to Week 120 (17 ® 3) was notably lower than the number of patients assessed at Week 12 through to Week 72 (30 ® 17). Therefore, the imbalance in patient numbers between the two time periods suggests that the difference in the observed PGA VAS scores between the two time periods should be interpreted cautiously. In addition, the Week 72 through to Week 120 group can be interpreted as being a 'survivor cohort', while the Week 12 through to Week 72 group can be interpreted as being an 'inception cohort'. Therefore, it is possible that the greater reductions in PGA VAS scores from Week 72 through to Week 120 compared to Week 12 through to Week 72 might represent 'survivor-related' bias. Consequently, in the absence of PGA VAS data on all patients in the 'inception cohort' from Week 72 through to Week 120 the significance of the observed difference in the PGA VAS scores between the two time periods is unclear.

The results for the Disability Index of Childhood Health Assessment Questionnaire (DICHAQ) and Child Health Questionnaire - PF50 (CHQ-PF50) assessments were consistent with improvement in the quality of life for both the subject and the parent(s) over the course of treatment with adalimumab. The results for the CRP showed a mean reduction from baseline at all visits from Week 12 through Week 84, with levels being in the normal range at Week 72 and Week 84. However, mean CRP levels were higher than Baseline at Week 96 through to Week 120, but subject numbers with CRP data at these visits were small. The majority of subjects (61.3%, N=19) had Baseline CRP values within the normal range (that is, < 0.9 mg/dL), with a mean ± SD value of 1.6 ± 2.43 mg/dL.

Overall, it is considered that the available open label, uncontrolled data from Study M10-444 support the efficacy of adalimumab for the treatment of subjects aged 2 to < 4 years or aged ≥ 4 years weighing < 15 kg. The results for all efficacy outcomes consistently showed clinically meaningful improvements with treatment from Baseline through to Week 120.

There were no efficacy data in Study M10-444 in the proposed patient population treated with adalimumab without MTX. The sponsor is proposing that adalimumab be administered as monotherapy in cases where subjects aged 2 to < 4 years and ≥ 4 years weighing < 15 kg are intolerant to MTX or where continuous treatment with MTX is inappropriate. The proposed approach to treatment with adalimumab without MTX is identical to the approved approach for subjects aged 4 to 17 years.

There were PK data comparing serum adalimumab trough concentrations at steady-state following treatment with adalimumab 24 mg/m$^2$ eow without MTX in the proposed and approved paediatric populations. The data showed that the mean ± SD serum adalimumab steady-state trough concentration at Week 24 in the proposed paediatric population (N=4) from Study M10-444 was lower than the corresponding adalimumab concentration at Week 16 in the approved paediatric patient population (N=29) from Study DE038 (5.95 ± 6.74 versus 7.03 ± 6.26 μg/mL, respectively). In contrast, the mean ± SD serum

adalimumab steady-state trough concentrations following treatment with adalimumab combined with MTX were similar for the proposed paediatric population (N=11) from Study M10-444 at Week 24 and the approved paediatric population (N=36) from Study DE038 at Week 16 (8.45 ± 5.69 vs 8.85 ± 5.53 µg/mL, respectively).

However, the comparative PK data in patients treated with adalimumab without MTX should be interpreted cautiously due to the high inter-subject variability in serum adalimumab steady-state trough concentrations observed in both studies (CV 113% [ M10-444/Week 24] versus CV 89% [DE038/Week 16]) and the marked imbalance in subject numbers between the two studies (N=4 [M10-444] versus N=29 [DE038]). In addition, MTX administration was controlled in Study DE038 over the 16 weeks, open label, lead-in phase but not in Study M10-444. Consequently, it is possible that the 4 patients from Study M10-444 on combination therapy might not have been taking a stable dose of MTX over the 24 weeks of treatment.

The efficacy of adalimumab in combination with MTX in the proposed paediatric population is consistent with the efficacy of the combination in the approved paediatric population. In Study M10-444, the observed PedACR30 response at Week 24 was 90.0% (27/30) in the ITT population, while in Study DE038 the PedACR30 response at the end of the 16 weeks open label, lead-in phase was 94% (80/85) in the adalimumab with MTX stratum and 74% (64/86) in the adalimumab without MTX stratum. Despite the uncertainties arising from the PK data it is considered that the lack of efficacy data for adalimumab without MTX in the proposed patient population should not preclude approval of the monotherapy option in cases where this might be required (that is, intolerance to MTX, continuous therapy with MTX is inappropriate).

## Safety

### Studies providing safety data

Pivotal Study M10-444 and Study P10-262 (Registry - interim 4-year safety data) were submitted.

### Patient exposure

#### *Study M10-444*

*Exposure*

The mean ± SD duration of exposure to adalimumab was 515.3 ± 245.33 days (median = 575.0 days). All subjects received at least 57 days of adalimumab treatment, with a maximum exposure of 910 days. Thirty (30) subjects (93.8%) were exposed for ≥ 181 days, 21 subjects (65.6%) were exposed for ≥ 391 days and 9 subjects (28.1%) were exposed for ≥ 721 days.

Adalimumab was administered at a dose of 24 mg/m$^2$ BSA, up to a total dose of 20 mg, eow by SC injection. Concomitant MTX was taken by 84.4% (N=27) of patients, concomitant systemic NSAIDs by 62.5% (N=20) of patients and systemic corticosteroids by 68.8% (N=22) of patients.

#### *Study P10-262 (Registry - interim 4 year safety data)*

*Exposure*

The observation period was defined from the Registry enrollment date up to the last date of Registry participation + 1 day (inclusive of the HCP process). The duration of Registry exposure was defined for the two treatment arms as follows: for the Humira arm, from the first Humira dose date in the Registry to the last Humira dose date in the Registry + 14

days, excluding total days of any treatment interruptions; and for the MTX arm, from the first MTX dose date in the Registry to the last MTX date in the Registry + 1 day, or the first Humira dose in the Registry + 1 day, whichever was earlier; and

As of 1 June 2013, 459 patients have received Humira, representing a cumulative exposure in the observational group of 891.3 patient years (PYs) compared to 763.7 PYs in the Registry group. All patients in the Humira Registry group (N=459) had at least 6 months of exposure, while 68% (N=312) had at least 1 year of exposure and 36.6% (N=168) had at least 2 years of exposure.

As of 1 June 2013, 306 patients have received MTX, representing a cumulative exposure in the observational group of 706.2 PYs compared to 503.1 PYs in the Registry group. All patients in the MTX Registry group (N=306) had at least 6 months of exposure, while 64.1% (N=196) of patients in this group had at least 1 year of exposure and 38.9% (N=119) had at least 2 years of exposure.

### Post-marketing data

The post-marketing experience for adalimumab for the treatment of pJIA is being collected in the Registry (Study P10-262). The sponsor commented that '*following approval in the European Union to expand the indication for Humira in the treatment of pJIA to include patients 2 to < 4 years old, the protocol for the Registry was amended to allow for enrollment of patients in this age group. However, no such patients were recruited into the registry before enrollment was completed*'. This statement appears to be inconsistent with the patient disposition for the interim 4 year Registry report which identified 1 patient aged < 4 years. The sponsor will be asked to clarify this matter (see *Clinical questions* below).

The sponsor's Clinical Overview included a brief summary of post-marketing safety data collected on children aged 2 to 4 years through AbbVie's post-marketing Pharmacovigilance system conducted from the International Birthdate (IBD) of the drug through to September 2013. In this time period, there have been 49 postmarketing reports containing 131 adverse events (AEs) reported for JIA (JIA [5 reports], pJIA [2 reports], systemic arthritis [1 report], juvenile arthritis [4 reports], chronic juvenile arthritis [1 report], juvenile rheumatoid arthritis [15 reports], and JIA reports without subtype information [21 reports]). The most frequently reported events were stated to be injection site pain (20 reports), followed by pyrexia (8 reports) and cough (6 reports).

### Evaluator's conclusions on safety

#### *Study M10-444*

No new or unexpected safety findings emerged from the pivotal study in the proposed patient population (M10-444). In this study, the safety analyses were based on the ITT population, which included all subjects who were enrolled and received at least 1 dose of adalimumab (N=32). The mean ± SD duration of exposure to adalimumab was 515±245 days (median 575 days) and all subjects were exposed for at least 57 days, with a maximum exposure of 910 days.

Adalimumab was administered at a dose of 24 mg/m$^2$ BSA, up to a total dose of 20 mg, eow by SC injection. Concomitant MTX was taken by 84.4% (N=27) of patients, concomitant systemic NSAIDs by 56.3% (N=20) of patients, and systemic corticosteroids by 62.5% (N=20) of patients.[4]

Nearly all subjects (90.6%, N=29) experienced at least 1 treatment emergent AEs (TEAE) (217 events, 481.2 events/100 PYs). The most frequently reported TEAEs in subjects (≥

[4] Prior medications included MTX taken by 78.1% (N=25) of patients, systemic NSAIDs taken by 62.5% (N=20) of patients, and systemic corticosteroids taken by 68.8% (N=22) of patients.

15%) were nasopharyngitis (25%, N=8), pyrexia (21.9%, N=7), bronchitis (18.8%, N=6), cough (18.8%, N=6), rhinorrhea (18.8%, N=6), upper respiratory tract infection (18.8%, N=6), juvenile arthritis (15.6%, N=5), otitis media (15.6%, N=5) and vomiting (15.6%, N=5). All other TEAEs were reported in < 15% of subjects.

The majority of TEAEs were considered by the investigator to be mild to moderate in severity and not related or probably not related to treatment with adalimumab. There were 18 subjects (56.3%) with TEAEs reported to be not related or probably not related to treatment with adalimumab (10 [31.3%] and 8 [25.0%], respectively). There were 11 subjects (34.4%) with events reported to be at least possibly related to treatment with adalimumab (22 events, 48.8 events/100 PYs). The only treatment-related TEAE reported in ≥ 2 subjects was rash (N=2; 6.3%). There were 5 subjects with 1 or more events reported to be possibly related to adalimumab (pyrexia, bronchitis, ear infection, laryngitis, otitis media, pharyngitis, pharyngitis streptococcal, pneumonia, viral pharyngitis, upper respiratory tract congestion and rash). There were 6 subjects with events reported to be probably related to adalimumab (injection site reaction, injection site pain, injection site pruritis, injection site rash, injection site swelling, cystitis, and juvenile arthritis).

No deaths were reported during the study. Five (5) subjects (15.6%) reported an serious AE (SAE) during the study (1 event each for dental caries, gastroenteritis rotavirus, juvenile arthritis, type 1 diabetes mellitus, and varicella). The SAE of type 1 diabetes mellitus was reported to be probably unrelated to treatment and the other 4 SAEs were reported to be unrelated to treatment. Two (2) subjects experienced a non-serious flare of juvenile arthritis during the study and were discontinued from treatment with adalimumab due to the adverse event.

A total of 25 subjects (78.1%) reported at least 1 treatment-emergent infection (93 events, 206.2/100 PYs). The most frequently occurring infections reported to be at least possibly related to study drug were nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, gastroenteritis and rhinitis. However, without a placebo control group it is difficult to assign a causative role to adalimumab for the high infection rate observed in subjects in this study due to the high background infection rate expected in children in the age group studied.

The majority of subjects who reported an infection experienced events that were considered by the investigator to be mild or moderate in severity and not related or probably not related to study drug. Three (3) subjects had serious infections (1 report each of dental caries, gastroenteritis rotavirus and varicella). These events were considered by the investigator to be mild to moderate in severity and not related to adalimumab. No subjects prematurely discontinued treatment with adalimumab due to an infection.

The study included an examination of TEAEs of special interest. Overall, 9 subjects reported 11 TEAEs of special interest (45.1 events/100 PYs). The adverse events of special interest were injection site reaction (4 subjects [12.5%] with 6 events for a rate of 13.3 events/100 PYs), allergic reaction (2 subjects [6.3%] with 2 events for a rate of 4.4 events/100 PYs), haematologic disorders (2 subjects with 2 events for a rate of 4.4 events/100 PYs), and oral candidiasis (1 subject [3.1%] with 1 event for a rate of 2.2 events/100 PYs).

The 5 injection site reactions were pain, pruritus, rash, reaction and swelling. The 2 haematologic disorders were microcytic anaemia and decreased platelet count, both considered to be unrelated to treatment with adalimumab. There were no reports of leukopenia or pancytopenia. The 2 allergic reactions were skin reactions (urticaria not related to adalimumab and rash possibly related to adalimumab). There were no reports of angioedema or anaphylaxis.

There were no reports of the following listed adverse events of special interest: malignancy; lupus like reactions or systemic lupus erythematosus; demyelinating disorder; vasculitis; hepatitis B; diverticulitis; intestinal perforation; liver failure or other liver events; myocardial infarction; cerebrovascular accident; pulmonary embolism; worsening/new onset psoriasis; adalimumab administration-related medication error; Steven's-Johnson syndrome; erythema multiforme; congestive heart failure; interstitial lung disease; pancreatitis; sarcoidosis; progressive multifocal leukoencephalopathy or reversible posterior leukoencephalopathy syndrome; amyotrophic lateral sclerosis; tuberculosis; seizure disorder; anti-phospholipid syndrome; or severe creatinine kinase (CK) elevations.

The clinical laboratory tests (haematology and clinical chemistry) showed no obvious patterns in mean change from Baseline over the course of the study. Nearly all shifts in haematology and clinical chemistry parameters observed for individual subjects were from low/normal levels at Baseline to high levels with adalimumab treatment. There was no evidence of haematologic, renal or hepatic toxicity associated with adalimumab. There were no shifts from Baseline in antinuclear antibody (ANA) or anti-double-stranded deoxyribonucleic acid DNA antibody (anti-dsDNA). There were no significant changes in vital signs of pulse rate or temperature over the course of the study. The mean weight of the subjects increased over the course of the study. There were no safety data summarising changes in blood pressure over the course of the study or abnormal electrocardiogram (ECG) findings. There were no data relating to the effects of age, weight, dose or sex on safety. There were no data investigating the effects of co-morbidities (such as hepatic or renal) on safety. There were no data on the effects of withdrawal or disease symptom rebound associated with cessation of adalimumab treatment.

### *Study P10-262 (Registry - interim 4 year safety data)*

The submission included interim 4 year safety data from a Registry for 459 enrolled patients treated with Humira and 306 enrolled patients treated with MTX. The mean ± SD duration of exposure in the observational all Humira treatment group was 891 PYs. The mean ± SD age of the 459 patients in the all Humira treatment group was 12.2 ± 3.94 years range (3, 20 years), and the mean ± SD weight was 47.8 ± 20.0 kg (range: 13, 118 kg).

The Registry included 12 patients rolled over from the pivotal study for the proposed paediatric patient population (Study M10-444) and 12 patients rolled over from the previously evaluated pivotal study (DE038) supporting the currently approved paediatric patient population. There were only two patients included in the 459 all Humira treated group who met the criteria for the proposed paediatric patient population (that is, aged > 2 years to < 4 years, or ≥ 4 years weighing < 15 kg). The interim 4 year safety data in the all Humira treatment group did not identify new or unexpected safety signals associated with Humira for the treatment of juvenile idiopathic arthritis. Overall, it is considered that all of the interim 4 year safety data from the Registry in the all Humira paediatric treatment group can be extrapolated to the proposed patient population.

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of adalimumab for the proposed usage in the proposed patient population have been satisfactorily demonstrated in one, uncontrolled, compassionate use study (M10-444) in a small number of subjects with pJIA (N=32). The majority of subjects in this study were treated with adalimumab in combination with MTX (84.4%, N=27). The benefits of adalimumab for the treatment of moderately to severely active pJIA in the proposed patient population were:

- an observed PedACR30 response was achieved by at least 90% of subjects from Week 12 through to Week 120, apart from Week 108 (88.9%);
- an observed PedACR50 response was achieved by at least 80% of subjects from Week 12 through to Week 120;
- an observed PedACR70 response was achieved by at least 61% of subjects from Week 12 through to Week 120, with a greater proportion of subjects achieving a response at later compared to earlier time-points;
- an observed PedACR90 response was achieved by at least 36% of subjects from Week 12 through to Week 120, with a greater proportion of subjects generally achieving a response at later compared to earlier time-points;
- observed PedACR30/50/70/90 responses were achieved at Week 24 by 90%, 83.3%, 73.3%, and 36.7% of subjects, respectively, and 30 of the 32 patients (94%) had observed data at this time-point for each PedACR response;
- clinically meaningful improvement was observed in each of the individual JIA core set of variables contributing to the PedACR response assessments including physician's global assessment of disease activity, parent's global assessment of disease activity, number of active joints, number of joints with loss of motion, DICHAQ score and CRP levels.

There were no efficacy data in the submission on the benefits of adalimumab alone in the proposed patient population for the proposed usage. The sponsor is proposing that adalimumab monotherapy be used in children aged 2 to < 4 years and ≥ 4 years weighing < 15 kg where patients are intolerant to MTX or continuous treatment with MTX is inappropriate. The proposed use of adalimumab monotherapy in the proposed paediatric patient population is identical to the approved use of this regimen in the approved paediatric patient population.

The efficacy of adalimumab in combination with MTX in the proposed paediatric population is consistent with the efficacy of the combination in the approved paediatric population. In Study M10-444, the observed PedACR30 response at Week 24 was 90.0% (27/30) in the ITT population, while in Study DE038 the PedACR30 response at the end of the 16 weeks open label, lead-in phase was 94% (80/85) in the adalimumab with MTX stratum and 74% (64/86) in the adalimumab without MTX stratum.

The PK data from Study M10-444 (Week 24) in the proposed paediatric population and Study DE038 (Week 16) in the approved paediatric population showed that the mean steady-state serum adalimumab trough concentration was lower in the adalimumab without MTX group in Study M10-444 (N=4) compared to Study DE038 (N=29). However, it is difficult to draw clinically meaningful conclusions from the comparative PK data in subjects treated with adalimumab without MTX due to the marked inter-subject variability in steady-state serum adalimumab concentrations in the two studies (CV 113% [M10-444/Week 24] versus CV 89% [DE038/Week 16]) and the notable imbalance in subject numbers between the two studies (N=4 [M10-444] versus N=29 [DE038]).

On balance, it is considered that the lack of specific information on the benefits of treatment with adalimumab without MTX in the proposed patient population should not preclude approval of the monotherapy option in cases where this might be required (that is, intolerance to MTX, continuous treatment with MTX not appropriate).

**First round assessment of risks**

The risks of adalimumab for the proposed usage in the proposed patient population have been adequately characterised in one, open label, uncontrolled, compassionate use study (M10-444) in a small number of subjects with pJIA (N=32). In this study, nearly all

subjects were treated with concomitant MTX (84.4%, N=27), while the majority of subjects were also treated with concomitant systemic NSAIDs (56.3%, N=18) and/or concomitant systemic corticosteroids (62.5%, N=20). There are no data on the risks of adalimumab administered without MTX in the proposed patient population. However, it can be reasonably inferred that the risks of adalimumab without MTX are likely to be similar to, or less than, the risks of adalimumab with MTX.

The risks of adalimumab in combination with MTX for the treatment of moderately to severely active pJIA in the proposed paediatric patient population are considered to be comparable to the known risks of the combination for the same indication in the currently approved paediatric patient population.

The risks of adalimumab for the proposed usage in the proposed patient population based on Study M10-444 (N=32) are summarised below:

- TEAEs reported in 90.6% of subjects (418.2 events/100 PYs); TEAEs reported by the investigator to be a least possibly related to treatment with adalimumab in 34.4% of subjects (48.8 events/100 PYs);
- serious TEAEs reported in 15.6% of subjects (11.1 events/100 PYs); TEAEs leading to discontinuation of adalimumab reported in 6.3% of subjects (4.4 events/100 PYs); no deaths reported in the study;
- TEAEs reported most frequently (≥ 15% of subjects) were nasopharyngitis (25%), pyrexia (21.9%), bronchitis (18.8%), cough (18.8%), rhinorrhea (18.8%), upper respiratory tract infection (18.8%), juvenile arthritis (15.6%), otitis media (15.6%), and vomiting (15.6%, N=5); all other TEAEs were reported by < 15% of subjects (< 5 subjects);
- 5 subjects (15.3%) with 11 TEAEs reported to be possibly related to treatment (pyrexia, bronchitis, ear infection, laryngitis, otitis media, pharyngitis, pharyngitis streptococcal, pneumonia, viral pharyngitis, upper respiratory tract congestion, and rash); 6 subjects (18.8%) with 7 TEAEs reported to be probably related to treatment (injection site reaction, injection site pain, injection site pruritis, injection site rash, injection site swelling, cystitis, and juvenile arthritis);
- 5 subjects (15.6%) reported 5 SAEs (dental caries, gastroenteritis rotavirus, juvenile arthritis, type 1 diabetes mellitus, and varicella); 1 of the 5 SAEs (type 1 diabetes mellitus) was considered to be probably not related to treatment with adalimumab while the remaining 4 of the 5 SAEs were considered not related to treatment with adalimumab; 2 subjects (6.3%) experienced TEAEs (both non-serious flare of juvenile arthritis) resulting in discontinuation of adalimumab treatment;
- 25 subjects (78.1%) reported 93 TEAEs of infection (206.2 events/100 PYs); infections reported in ≥ 10% of subjects were nasopharyngitis (25.0%), bronchitis (18.8%), upper respiratory tract infection (18.8%), otitis media (15.6%), gastroenteritis (12.5%) and rhinitis (12.5%); the majority of infections were reported by the investigator to be mild or moderate in severity and not related or probably not related to treatment with adalimumab; 3 subjects (9.3%) had serious infections considered by the investigator to be mild to moderate in severity and not related to adalimumab (1 report each of dental caries, gastroenteritis rotavirus, and varicella);
- 9 subjects (28.1%) reported 11 Adverse Event of Special Interest (AESI) (6 injection site reactions, 2 allergic reactions, 2 haematological disorders, 1 oral candidiasis); there were no other reports of AESI including anaphylaxis/angioedema;
- no clinically meaningful changes in laboratory parameters (haematological, clinical chemistry) or vital signs (temperature, pulse rate).

### First round assessment of benefit-risk balance

The benefit-risk balance of Humira (adalimumab) in the proposed patient population for the proposed usage is favourable.

## First round recommendation regarding authorisation

a. It is recommended that Humira (adalimumab) in combination with MTX be approved for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 to 4 years, and in patients aged 4 years and older weighing < 15 kg. Consequently, as proposed by the sponsor, it is recommended that the approved indication for pJIA be amended to read:

   *Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 years of age and older. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*

b. It is recommended that Humira (adalimumab) be administered subcutaneously based on weight as proposed by the sponsor.

## Clinical questions

### Efficacy

1. Serum adalimumab steady-state trough concentrations in subjects treated with adalimumab without MTX were lower in Study M10-444 (proposed paediatric population/Week 24) compared to Study DE038 (approved paediatric population/Week 16). The PK results suggest that adalimumab administered without MTX in the proposed paediatric patient population might be less effective than in the approved paediatric patient population.
2. Does the sponsor have any efficacy data from Study M10-444 comparing adalimumab without MTX to adalimumab with MTX? It is realised that such data might be limited as the majority of children in the study were administered adalimumab with MTX (84.4%, N=27). If the sponsor has no such data from Study M10-444, does the sponsor have any other efficacy data on the use of adalimumab without MTX in the proposed patient population for the treatment of pJIA?
3. In view of the PK data referred to above, if the sponsor has no efficacy data on the use of adalimumab without MTX in the proposed patient population for the proposed indication, then it should justify its proposal to use Humira monotherapy (that is, without MTX) in children aged 2 to < 4 years and ≥ 4 years weighing < 15 kg who are intolerant to MTX or when treatment with MTX is inappropriate.
4. In Study M10-444, one of the inclusion criteria required that subjects in the EU must have previously failed, had an insufficient response to, or been intolerant to ≥ 1 DMARD. This criterion did not apply to non-EU subjects. How many of the enrolled patients (N=32) had previously failed, had an insufficient response to or had been intolerant to ≥ 1 DMARD?
5. In Study M10-444, 84% (N=27) of enrolled patients were treated with MTX plus adalimumab. What was the mean ± SD, median, and range (minimum-maximum) of the administered MTX doses? What was the mean ± SD, median, and range (minimum-maximum) of the frequency of MTX dosing? Was MTX dose fixed or flexible?

6. Please provide data plots for the CRP (mg/dL) versus visit (baseline and last observation) for each individual patient in Study M10-444. In addition, please tabulate the following data for each patient (CRP mg/mL [mean, SD, minimum, Q1, median, Q3, maximum] at baseline and at time of last visit, with absolute and % change in CRP from baseline and time of last visit). The data should be tabulated using the format in Table 14.2_4.3.1 of the study report but only baseline and last visit details are required for each individual patient.

**Safety**

7. In Study M10-444, dosing was scheduled eow. If a scheduled dose was missed then parents or designees were instructed to administer the missed dose as soon as it was remembered up until the day of the next scheduled dose. Two doses were not to be administered on the same day. Please confirm that it was possible for dosing to occur on two consecutive days (that is, missed scheduled dose given on last day of 2 week period, followed the next day with dose given as scheduled on the first day of next 2 week period). Is the sponsor aware of any potential safety issues if two doses of adalimumab are administered in close proximity to each other?
8. In Section 5.3.6 of the submission (Reports of Post-marketing Experience), the sponsor stated '*that following approval in the European Union to expand the indication for Humira in the treatment of pJIA to include patients 2 to < 4 years old, the protocol for the Registry was amended to allow for enrollment of patients in this age group. However, no such patients were recruited into the registry before enrollment was completed*'. This comment appears to be inconsistent with data provided for the 4 year interim report of the pJIA registry program (Study P10-262), which identified 1 patient aged < 4 years. Please comment on this apparent discrepancy.
9. Two (2) patients were identified in the data provided for the 4 year interim report of the pJIA registry program (Study P10-262) aged < 4 years (1 patient) and < 15 kg (1 patient). Are these two patients the same patient or are they two separate patients?
10. Please summarize the data presented in Tables 27, 28 and 34 of Study M10-044 by age group (that is, 2 to 4 years, ≥ 4 years). The new summary tables for the two age groups should include the same data as that provided for the total population in the identified tables.

## Second round evaluation of clinical data submitted in response to questions

The details of the sponsor's responses to the clinical questions (above) and the evaluator's assessment of these responses are detailed in Attachment 2.

## Second round benefit-risk assessment

### Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of adalimumab in the proposed usage are unchanged from those identified in the First round evaluation.

### Second round assessment of risks

After consideration of the responses to clinical questions, the risks of adalimumab in the proposed usage are unchanged from those identified in the First round evaluation.

### Second round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, is favourable. In particular, the benefit-risk balance of the amended dose regimen proposed by the sponsor in the *Response to s31 Request (29 December 2014)* is considered to be favourable.

### Second round recommendation regarding authorisation

*a.* It is recommended that Humira (adalimumab) in combination with MTX be approved for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 to 4 years, and in patients aged 4 years and older weighing < 15 kg. Consequently, as proposed by the sponsor, it is recommended that the approved indication for pJIA be amended to read:

*Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 years of age and older. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*

b. It is recommended that Humira (adalimumab) be administered subcutaneously based on weight as proposed by the sponsor. It is recommended that the amended dose regimen proposed by the sponsor in the *Response to s31 Request (29 December 2014)* be approved.

# V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP (version 10.2 dated November 2012) + Australian-specific Annex (version 1.0, dated May 2014)) which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

**Table 5: Summary of Ongoing safety concerns**

| | |
|---|---|
| **Important Identified Risks** | · Serious infections including diverticulitis and opportunistic infections eg invasive fungal infections, parasitic infections, legionellosis and Tuberculosis (TB).<br>· Reactivation of hepatitis B<br>· Pancreatitis<br>· Lymphoma<br>· Hepatosplenic T-cell lymphoma (HSTCL)<br>· Leukaemia<br>· Non-melanoma skin cancer (NMSC)<br>· Melanoma<br>· Merkel Cell Carcinoma |

| | |
|---|---|
| | · Demyelinating disorders (including Multiple Sclerosis, Guillain Barré Syndrome and optic neuritis)<br>· Immune reactions (including lupus-like reactions and allergic reactions)<br>· Sarcoidosis<br>· Congestive Heart Failure (CHF)<br>· Myocardial Infarction (MI)<br>· Cerebrovascular accident (CVA)<br>· Interstitial lung disease (ILD)<br>· Pulmonary embolism (PE)<br>· Cutaneous vasculitis<br>· Stevens-Johnson Syndrome (SJS) and erythema multiforme<br>· Worsening and new onset of Psoriasis<br>· Haematologic disorders<br>· Intestinal perforation<br>· Intestinal strictures in Crohn's disease<br>· Liver failure<br>· Elevated ALT levels<br>· Autoimmune hepatitis<br>· Medication errors and maladministration |
| **Important Potential Risks** | · Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC and melanoma)<br>· Vasculitis (non-cutaneous)<br>· Progressive multifocal leukoencephalopathy (PML)<br>· Reversible posterior leukoencephalopathy syndrome (RPLS)<br>· Amyotrophic Lateral Sclerosis (ALS)<br>· Colon cancer in Ulcerative Colitis patients<br>· Infections in infants exposed to adalimumab in utero<br>· Medication errors with paediatric vial<br>· Off-label use |
| **Missing information** | · Subjects with immune-compromised conditions (ie subjects with HIV, post-chemotherapy, organ transplant); subjects with a history of clinically significant drug or alcohol abuse<br>· Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischaemic heart disease, CHF, recent cerebrovascular accidents<br>· Subjects with a history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals or antifungals, history of viral hepatitis<br>· Subjects with a history of cancer, lymphoma, leukaemia or |

| | |
|---|---|
| | lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of demyelinating disorders<br>· Children < 18 years of age for psoriatic arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, spondyloarthritis, hidradenitis suppurativa, enthesitis-related arthritis, and uveitis indications<br>· Children < 4 years of age for psoriasis<br>· Children < 2 years of age for juvenile idiopathic arthritis<br>· Children < 6 years of age for crohn's disease and enthesitis-related arthritis.<br>· Pregnant and lactating women<br>· Subjects with renal or liver impairment<br>· Patients taking concomitant biologic therapy<br>· Long-term rheumatoid arthritis data beyond 10 years<br>· Long-term juvenile idiopathic arthritis data beyond 7.5 years<br>· Episodic treatment in juvenile idiopathic arthritis<br>· Long-term ankylosing spondylitis data beyond 5 years<br>· Long-term axial spondyloarthritis data beyond 1 year<br>· Short and long-term peripheral spondyloarthritis data<br>· Remission-withdrawal-retreatment axial spondyloarthritis data<br>· Short and long-term paediatric enthesitis-related arthritis data<br>· Long-term psoriatic arthritis data beyond 3 years<br>· Long-term psoriasis data beyond 6 years<br>· Episodic treatment in psoriasis<br>· Short and long-term hidradenitis suppurativa data<br>· Long-term crohn's disease data beyond 5 years<br>· Episodic treatment in crohn's disease<br>· Long-term paediatric crohn's disease data beyond 2 years<br>· Long-term ulcerative colitis data<br>· Episodic treatment in ulcerative colitis<br>· Short and long-term uveitis data |

**Pharmacovigilance plan**

Routine pharmacovigilance is proposed to monitor the risks attributed to adalimumab.

The RMP and ASA describe several planned and ongoing additional pharmacovigilance activities relating to the multiple approved indications.

Of relevance to the application is the following ongoing study:

· Study P10-262: a 10 year registry of JIA patients ≥ 2 years treated with adalimumab. Interim data is reported in August annually, final report due December 2021. The sponsor has advised that enrolment has now completed.

### Risk minimisation activities

Routine risk minimisation is proposed for the safety concerns attributed to adalimumab except for potential risks *'progressive multifocal leukoencephalopathy', 'reversible posterior leukoencephalopathy', 'amyotrophic lateral sclerosis', 'colon cancer in ulcerative colitis patients', 'infection in infants exposed to adalimumab in utero'* for which no risk minimisation is proposed.

Additional risk minimisation in the form of an educational program is proposed for the following safety concerns:

- Serious infections including diverticulitis and opportunistic infections for example, invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)
- Lymphoma
- Hepatosplenic T-cell lymphoma
- Leukemia
- Non-melanoma skin cancer (NMSC)
- Melanoma
- Demyelinating disorders
- Congestive heart failure (CHF)
- Medication errors and maladministration
- Other malignancies (except lymphoma, Hepatosplenic T-cell Lymphoma (HSTCL), leukemia, NMSC and melanoma)

According to the ASA the sponsor is conducting a 'global risk minimisation program'. This includes an educational program consisting of the following:

- Safety monograph
- Patient information card (adult and paediatric versions)
- TB screening brochure
- TB screening checklist
- Safety publication

According to the ASA these risk minimisation measures '*are in the process of being implemented in Australia*'.

The ASA further stipulates that the risk minimisation program for Australia includes the following:

- Patient support program including a patient information booklet and patient alert card
- Humira safety summary sheet

The ASA also describes the following activities as '*under development*':

- Evaluation tool: an online survey to assess the effectiveness of the Australian Educational Program.

### Reconciliation of issues outlined in the RMP report

Table 6 summarises the First round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator of the sponsor's responses and the evaluator's comment(s) on the sponsor's response.

**Table 6: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)**

| Recommendation in RMP evaluation report | Sponsor's response (or summary of the response) | RMP evaluator's comment |
|---|---|---|
| 1. Safety considerations may be raised by the clinical evaluator and/or the Clinical Evaluation Report respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP. | AbbVie acknowledges that issues raised throughout the clinical evaluation process may impact on the Humira Risk Management Plan, and an assurance is provided that the RMP will be revised to include relevant information needed to address new safety considerations. No new safety signals or new trends were observed for the JIA 2-4 patient population during the M10-444 trial.<br><br>No dose-limiting toxicity for adalimumab has been observed in any of the adalimumab clinical programs undertaken to date. Treatment should be initiated and supervised by specialist physicians experienced in the treatment of RA, JIA, PsA, AS, CD, paed-CD, Ps, UC, where these indications are approved. These measures are designed to minimise the potential for medication administration errors.<br><br>Overdose of adalimumab has not shown any risk of harm based on safety surveillance to date. | This is acceptable. |
| 2. The EU-RMP has a data lock point of 6 November 2010. Therefore contemporary safety and exposure information relating to the proposed extension of indication (and other indications) has not been included. The corresponding sections of the RMP should be amended and an updated RMP provided. | Please find included as part of this response a copy of RMP Version number 11.1.2_EU, dated September 2014, which has a revised data lock point of 31 December 2012. The revised EU-RMP contains updated safety and exposure information, including data for new indications which have been approved worldwide up until the data lock point of 31 December 2012. | This is acceptable. It is recommended to the Delegate that this version is implemented as the RMP for this submission. |
| 3. Several milestones attached to additional pharmacovigilance activities suggest that the corresponding studies have concluded. The sponsor should ensure that the Pharmacovigilance plan is amended to reflect the studies which have since completed. | As indicated by the TGA RMP evaluator, milestones attached to a number of additional pharmacovigilance activities have concluded. The most recent Periodic Safety Report (PSUR) for adalimumab, for the reporting interval of 01 January 2011 through 31 December 2013, detailed the status of the studies which had concluded up until the data lock point of 31 December 2013. The Humira PSUR was submitted to the TGA on 28 March 2014 but a copy of the relevant sections of the PSUR is able to be provided to the TGA for ease of | This is acceptable. |

| Recommendation in RMP evaluation report | Sponsor's response (or summary of the response) | RMP evaluator's comment |
|---|---|---|
| | reference purposes if required.<br><br>The information in the RMP-ASA has been updated to reflect the status of the completed pharmacovigilance studies. Additional studies are expected to be completed in coming months and so the ASA will be revised again to capture these completed activities. | |
| 4. Given enrolment for Study P10-262 has completed, the sponsor is requested to confirm how many and what proportion of included JIA patients are ≥ 2 and ≤4 years. | Patients enrolled into the Study P10-262 JIA Registry were 2 to < 4 years of age at Baseline (n=28), and patients ≥ 4 years of age at Baseline (n=4). | The sponsor's response is noted. |
| 5. Ongoing study protocols are not reviewed as part of the RMP evaluation process. These studies will either generate safety data that will support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. Therefore results should be submitted to the TGA as appropriate. | AbbVie undertakes an ongoing monitoring program to ensure that safety data collected during both clinical trials and post-authorisation pharmacovigilance activities are captured and reviewed to incorporate into worldwide product information documents as appropriate. AbbVie utilises a Company Core Data Sheet program to revise the company product information documents as appropriate, with Humira subject to one Safety-Related Requests to the TGA in both 2013 and 2014 to include new safety data. There is also a Category 1 application being prepared for submission in 2015 to include results from ongoing clinical studies in ulcerative colitis and psoriasis, both indications which are currently registered in Australia. | The sponsor's response is noted. |
| 6. The sponsor should provide an update of the implementation of the global risk minimisation program in Australia including which materials are currently distributed. | The risk minimisation program tools which are currently available in Australia to educate healthcare professionals and patients about the key safety risks associated with adalimumab use, and the need to regularly and actively monitor the safety of these patients are as follows:<br><br>-Humira (adalimumab) Safety Monograph<br><br>-Humira Patient Information Card<br><br>- Tuberculosis (TB) Screening Brochure (including a TB Screening Checklist)<br><br>-A step-by-step guide to using the Humira (adalimumab) single-use pen<br><br>-A step-by-step guide to using the Humira (adalimumab) syringe | The evaluator has no particular objection to the implementation of these Australian educational materials. |

| Recommendation in RMP evaluation report | Sponsor's response (or summary of the response) | RMP evaluator's comment |
|---|---|---|
| | -A Humira (adalimumab) safety information reminder<br><br>-A Humira starter pack from the patient support program<br><br>These materials are distributed proactively by AbbVie to specialist physicians in the fields of rheumatology, gastroenterology and gastroenterology who prescribe biological medicines such as Humira, and are also available on request from AbbVie Medical Information. | |
| 7. As recommended in a previous RMP evaluation the draft versions of the educational materials for use in Australia should be attached to the updated ASA. | As requested by the TGA, the latest versions of the Humira educational materials, which are discussed in response to the question above, have been included as appendices to the updated ASA and attached to this reponse [not in this AusPAR] | The evaluator has no particular objection to the content of the Australian educational materials. |
| 8. Similarly, as previously recommended, the sponsor should provide an assurance that details of the evaluation tool to assess the effectiveness of the Australian Educational program will be provided to the TGA for review once it has been fully developed. | AbbVie provides an assurance that details of the evaluation tool to assess the effectiveness of the Australian Educational program will be provided to the TGA for review once it has been fully developed. AbbVie believes that there needs to be consistency in the evaluation tool used worldwide, and discussions are ongoing in Europe with the EMA to finalise the evaluation tool to be utilised in the European market. The sponsor has received the following advice as to the most recent activities in relation to the RMP evaluation in Europe:<br><br>In accordance with the PRAC's assessment of the RMP (versions 11.2 and 11.2.1, within procedure EMEA/H/C/481/II/134), ongoing routine Pharmacovigilance activities are considered sufficient to monitor the effectiveness of the additional risk minimisation measures. The effectiveness of the Humira risk minimisation activities in the EU was assessed annually between 2008 and 2010 in terms of the prescriber awareness of the key risks associated with use of Humira. Results of each of the annual surveys were submitted to the EMA. Currently, effectiveness of the risk minimisation plan is being assessed in terms of fidelity of program implementation: in particular the extent to which each of the risk minimisation tools is being distributed | This is acceptable. |

| Recommendation in RMP evaluation report | Sponsor's response (or summary of the response) | RMP evaluator's comment |
|---|---|---|
| | (that is,, number distributed, how distributed, when and by whom). This distribution of the risk minimisation tools will continue to be monitored. | |

RA=Rheumatoid arthritis; JIA=Juvenile idiopathic arthritis; PsA= psoriatic arthritis; AS= Atherosclerosis; CD= Crohn's disease; paed-CD= paediatric Crohn's disease; Ps=psoriasis. UC=ulcerative colitis

### Summary of recommendations

It is considered that the sponsor's response to the TGA S31 Request has adequately addressed all of the issues identified in the RMP evaluation report.

#### *Outstanding issues*

*Issues in relation to the RMP*

There are no outstanding issues in relation to the RMP for this submission.

*Advice from the Advisory Committee on the Safety of Medicines (ACSOM)*

ACSOM advice was not sought for this submission.

#### *Key changes to the updated RMP*

EU-RMP Version 10.2 (dated November 2012) and Australian Specific Annex Version 1.0 (dated May 2014) has been superseded by:

EU-RMP Version 11.1.2 (dated September 2014, DLP 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014)

Key changes from the version evaluated in the First round are summarised below (Table 7):

**Table 7: Summary of key changes to the RMP and ASA**

| Summary of key changes between EU-RMP (version 10.2)/ASA (version 1.0) and EU-RMP (version 11.1.2) and ASA (version 2.0) | |
|---|---|
| **Safety specification** | A number of items of missing information have been removed from the updated EU-RMP however these remain as missing information in the ASA. Important identified and potential risks listed in the updated EU-RMP and ASA are essentially unchanged. |
| **Pharmacovigilance activities** | Revised to reflect the status of completed studies. |
| **Risk minimisation activities** | Nil significant change. |
| **ASA** | The Australian educational materials have been attached to the latest version of the EU-RMP/ASA. |

The evaluator has no particular objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

### *Suggested wording for conditions of registration*

*RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP Version 11.1.2 (dated September 2014, DLP 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014) and any future updates as a condition of registration.

# VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Adalimumab has been considered by the TGA's Advisory Committee on Prescription Medicines (ACPM) on a number of occasions with the pJIA application for 4 years and older patients considered at the June 2009 meeting. At that meeting the committee advised that dosing should be weight based, that the indication not require failure of a previous DMARD and that both monotherapy and combination therapy with methotrexate were appropriate.

## Quality

The sponsor submitted a bioanalysis validation report which demonstrated that the assay for measuring adalimumab concentrations is validated and capable of measuring free adalimumab concentrations in serum within the limits of quantification.

## Nonclinical

There were no new nonclinical data.

## Clinical

The clinical evaluator has recommended approval of adalimumab in patients aged 2 to 4 years and in patients aged 4 years and older weighing < 15 kg. The evaluator recommended that Humira be administered SC based on weight as proposed by the sponsor and that the amended dose regimen proposed by the sponsor in the *Response to s31 Request (29 December 2014)* be approved.

### Pharmacology

The pivotal study supporting the submission was Study M10-444, a Phase IIIb, multicentre, open label, uncontrolled study of adalimumab in the US and Europe in 32 paediatric patients with moderately to severely active pJIA aged 2 to < 4 years or aged ≥ 4 years weighing < 15 kg, according to the International League of Associations for Rheumatology (ILAR) criteria. The primary objective of the study was to evaluate the safety of adalimumab and the secondary objectives were to collect PK data and to evaluate efficacy. The study provided pharmacokinetic data up to Week 24 in 15 paediatric patients (11 with methotrexate and 4 without) and used a dose of 24 mg/m$^2$ BSA up to a total dose of 20 mg administered fortnightly as a single dose via SC injection. The baseline

characteristics of the 15 patients who provided PK data were consistent with the overall study population of 32 patients. Results for the steady state adalimumab mean trough concentrations at Weeks 12 and 24 were 6.97 and 7.78 microgram/mL respectively with higher values in those on concomitant methotrexate than those without. However the patient numbers were imbalanced, small and there was a higher inter-subject variability in those not taking methotrexate to draw definitive conclusions.

One patient out of 15 in the study developed anti-adalimumab antibodies. This patient, who was on concomitant methotrexate, was a PedACR30 responder at Weeks 12 and 24 and had 8 adverse events. In comparison, 14 patients did not develop antibodies and were mostly PedACR30 responders. Given one patient developed antibodies, then no clinically meaningful comparison can be made.

The submission included a comparison of the PK data from the previously evaluated Study DE038 that supported the approval in subjects aged 4 to 17 years with pJIA treated with adalimumab, stratified by concomitant MTX use, and the PK data from this Study M10-444 (see table below). In Study DE038, treatment consisted of a 16 week, open label, lead-in phase followed by a 32 week double blind phase with a subsequent open label extension phase. A total of 171 subjects were enrolled in the open label, lead-in phase (mean age 11.3 years, range 4 to 17 years), and 133 subjects were randomised and dosed in the double blind phase. Subjects initially received adalimumab 24 mg/m$^2$ BSA fortnightly SC (up to a maximum of 40 mg total body dose), and in the open label, extension phase, fixed doses of 20 mg or 40 mg were administered. The mean adalimumab steady state trough concentrations were similar between patients treated with adalimumab with methotrexate between the two studies at Week 24 in the younger population (n=11, 8.45 µg/mL) and week 16 in the older population (n=36, 8.85 µg /mL). Adalimumab concentrations were higher in patients taking methotrexate than not in both studies. In patients not taking concomitant methotrexate, the concentrations were lower in the younger population however this should be interpreted cautiously.

**Table 8: Comparison of mean ± SD steady-state serum adalimumab trough concentrations in studies M10-444 and DE038**

| | Mean ± SD, $N_{nmiss}$ | |
|---|---|---|
| **Study and Treatment Groups** | **Week** | |
| **M10-444** | **12** | **24** |
| 24 mg/m$^2$ BSA eow with MTX | 7.27 ± 5.71, 11 | 8.45 ± 5.69, 11 |
| 24 mg/m$^2$ BSA eow without MTX | 6.13 ± 6.41, 4 | 5.95 ± 6.74, 4 |
| **DE038** | **12** | **16** |
| 24 mg/m$^2$ BSA eow with MTX | 10.5 ± 5.46, 41 | 8.85 ± 5.53, 36 |
| 24 mg/m$^2$ BSA eow without MTX | 4.49 ± 5.05, 45 | 7.03 ± 6.26, 29 |

## Efficacy

In Study M10-444, six children discontinued with two due to adverse events and 18 children had protocol deviations with most being due to single use concomitant medications. No statistical analyses were performed for the efficacy or safety results and the sample size was chosen based on expected availability of eligible subjects. Concomitant methotrexate was used by 84% of children with a mean dose of 8.1mg (range 2.5 to 17.5mg) and concomitant systemic corticosteroids were used by 63%. At baseline, subjects were 88% female, 88% <4 years of age (mean 3 years), mean weight 13.4 kg, mean duration of JIA of 12.3months, disease activity was consistent with moderate to severe pJIA, 63% had sero-negative polyarthritis and 25% had extended oligoarthritis, 78% had prior methotrexate use, 69% prior systemic corticosteroids and no patients had

received prior biological medicine treatment. All subjects had a negative PPD skin test[5] at screening. There was no primary efficacy endpoint but PedACR30/50/70/90 were used as secondary endpoints and the results showed PedACR30 was achieved by >85% from week 12 -120, PedACR50 was achieved by >80% from week 12-120, PedACR70 by at least 61% from week 12-120 and PedACR90 by >36% from week 12-120. A clinically meaningful improvement in joint swelling, pain, tenderness and movement was observed to week 24, an improvement in disability was seen and the impact of disease appeared to decrease over time. CRP levels suggested a decrease in inflammation.

**Table 9: Study M10-444 - PedACR response; ITT population**

| Adalimumab n/N1a (%) | | | | | |
|---|---|---|---|---|---|
| **Visit** | **Analysis Method** | **PedACR30** | **PedACR50** | **PedACR70** | **PedACR90** |
| Week 12 | Observed | 29/31 (93.5) | 28/31 (90.3) | 19/31 (61.3) | 12/31 (38.7) |
| | NRI[b] | 29/32 (90.6) | 28/32 (87.5) | 19/32 (59.4) | 12/32 (37.5) |
| | LOCF[c] | 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 | 25/27 (92.6) | 24/27 (88.9) | 18/27 (66.7) | 14/27 (51.9) |
| | NRI[b] | 25/32 (78.1) | 24/32 (75.0) | 18/32 (56.3) | 14/32 (43.8) |
| | LOCF[c] | 29/31 (93.5) | 28/31 (90.3) | 21/31 (67.7) | 16/31 (51.6) |
| Week 60 | Observed | 18/20 (90.0) | 16/20 (80.0) | 14/20 (70.0) | 10/20 (50.0) |
| | NRI[b] | 18/32 (56.3) | 16/32 (50.0) | 14/32 (43.8) | 10/32 (31.3) |
| | LOCF[c] | 27/31 (87.1) | 25/31 (80.6) | 22/31 (71.0) | 16/31 (51.6) |
| Week 72 | Observed | 17/17 (100) | 17/17 (100) | 13/17 (76.5) | 11/17 (64.7) |
| Week 84 | Observed | 17/17 (100) | 16/17 (94.1) | 14/17 (82.4) | 11/17 (64.7) |
| Week 96 | Observed | 12/13 (92.3) | 12/13 (92.3) | 10/13 (76.9) | 8/13 (61.5) |
| Week 108 | Observed | 8/9 (88.9) | 8/9 (88.9) | 7/9 (77.8) | 6/9 (66.7) |
| Week 120 | Observed | 3/3 (100) | 3/3 (100) | 3/3 (100) | 3/3 (100) |

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

[5]The PPD skin test is a method used to diagnose silent (latent) tuberculosis (TB) infection. PPD stands for purified protein derivative.

In patients not on concomitant methotrexate, the numbers are too small to draw definitive conclusions but suggested an improvement in joint assessment, health and quality of life assessment.

### Safety

The mean exposure to adalimumab from the pivotal study was 515 days with 91% reporting at least one treatment emergent adverse event, the most common being nasopharyngitis, pyrexia, bronchitis, cough, rhinorrhoea, upper respiratory tract infection, juvenile arthritis, otitis media and vomiting. The events were mild in 28%, moderate in 44% and severe in 19%. The severe events were 6 TEAEs of uveitis, otitis media, platelet count decreased, arthritis, type 1 diabetes and juvenile arthritis with the latter two considered probably related. Of all the TEAEs, rash was the only treatment related event that was reported in ≥ 2 subjects and 5 subjects had at least one event possibly related and 6 subjects had at least one event probably related which were mostly infections or injection site reactions. Infections were reported in 78% and were mostly mild or moderate and not related or probably not related. No subjects discontinued due to infections. There were three serious infections not considered related to adalimumab of dental caries, rotavirus gastroenteritis and varicella. There were no deaths and five serious adverse events of dental caries, rotavirus gastroenteritis, juvenile arthritis, type 1 diabetes and varicella. Two subjects had a non-serious flare of juvenile arthritis and were discontinued. Adverse events of special interest included one case of oral candidiasis, four subjects with mild injection site reactions, two subjects with mild allergic reactions (urticaria and rash) and two subjects with haematological disorders (anaemia and decreased platelet count (normal on repeat testing)). There were no malignancies or demyelinating disorders. The majority of patients had shifts from low/normal to high values for lymphocytes (81%) and platelet count (67%) with only one subject having a shift from high/normal to low value (eosinophils). Clinical chemistry parameter changes were all shifts from low/normal to high values. One subject had a small shift in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values and two subjects had abnormal liver function tests but neither subject discontinued from the study. Pulse rate changes were seen in the majority of children but most were intermittent. At the final determination, 9 children had significant decreases and 8 had significant increases. The mean change in pulse rate to week 96 was ±4 beats per minute (bpm).

The submission included interim 4 year data from a 'Long-term, Multi-center, Longitudinal Post-marketing, Observational Registry to Assess Long Term Safety and Effectiveness of Humira® (Adalimumab) in Children with Moderately to Severely Active Polyarticular or Polyarticular-course Juvenile Idiopathic Arthritis (JIA) – STRIVE'. The interim report covered 4 years of the registry and included patients from Australia and those rolling over from the current study and the previous study in older children. The registry includes patients on Humira or methotrexate. As of 1 June 2013, 778 patients had been enrolled. The sponsor has advised that enrollment has now been completed and includes 12 patients from the current study. Only one patient in the registry study was within the age of 2 to 4 years. Patients with observational adverse events are as follows.

**Table 10: Study P10-262- Patients with observational adverse events; all treated population**

| Adverse events (AEs) | All Humira (N=459) | | All MTX (N=306) | |
|---|---|---|---|---|
| | N | % | N | % |
| Any AE | 142 | 30.9 | 125 | 40.8 |
| Any serious AE | 30 | 6.5 | 16 | 5.2 |
| Any AE leading to discontinuation of study drug | 25 | 5.4 | 23 | 7.5 |
| Any severe AE | 22 | 4.8 | 12 | 3.9 |
| Any AE at least possibly drug-related | 71 | 15.5 | 63 | 20.6 |
| Any SAE at least possibly drug-related | 14 | 3.1 | 3 | 1.0 |
| Any Infection | 80 | 17.4 | 64 | 20.9 |
| Any serious infection | 12 | 2.6 | 7 | 2.3 |
| Any opportunistic infection (excluding oral candidiasis and TB) | 0 | 0 | 0 | 0 |
| Any TB | 0 | 0 | 0 | 0 |
| Any lymphoma | 0 | 0 | 0 | 0 |
| Any non-melanoma skin cancer (NMSC) | 0 | 0 | 0 | 0 |
| Any malignancy other than lymphoma, HSTCL, leukaemia, NMSC, or melanoma | 0 | 0 | 0 | 0 |
| Any demyelinating disorder | 0 | 0 | 0 | 0 |
| Any AE leading to death | 0 | 0 | 0 | 0 |
| Deaths (including non-treatment-emergent deaths) | 0 | 0 | 0 | 0 |

No deaths occurred in the registry and discontinuations of registry drug were higher on methotrexate than adalimumab (43% versus 18%). Infections were slightly higher on methotrexate (21% versus 17%), allergic reactions were slightly higher on adalimumab (1.3% versus 0.7%), injection site reactions were higher on adalimumab (4.4% versus 1%), three patients on adalimumab experienced new onset or worsening psoriasis and one patient on methotrexate had pancreatitis.

### Risk management plan

The RMP evaluator has accepted the EU Risk Management Plan for Humira (adalimumab), version 11.1.2 (dated September 2014, data lock point 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014), and any future updates as a condition of registration.

There are no outstanding matters in relation to the RMP.

## Risk-benefit analysis

### Delegate's considerations

This submission is to extend the age group for the currently approved pJIA indication from 4 years and older to 2 years and older. The proposed extension to the age group has been approved in the USA and Europe but the dosing protocol approved overseas differs between the USA and Europe. The extent of the data is limited as expected for this type of application, and the evidence supporting use without methotrexate is also limited. In Europe, the indication specifies that patients are to have failed a DMARD prior to use, however the current Australian approved indication for patients 4 years and older with pJIA or the proposed extension to the younger population does not specify this requirement.

#### *Pharmacology*

The PK data submitted indicates that the adalimumab trough concentrations at steady state are similar between the 2 to 4 years group compared to the approved 4 years and older group in those taking concomitant methotrexate. However in both studies, the concentrations were lower in those not taking methotrexate and lower again in those 2 to 4 years old. These results indicate consistency between the population age groups for those on methotrexate however the results should be interpreted with caution given the limited data and imbalanced study numbers.

#### *Efficacy*

The pivotal study had no primary efficacy endpoint or statistical analyses and the study was non-randomised, open label and uncontrolled and therefore prone to bias and confounding. The sample size was small and the majority of patients were treated with methotrexate with very little data to assess monotherapy use. The PedACR30 is a validated efficacy outcome but the other PedACR50/70/90 are not but commonly used and accepted in pJIA. Given this, the study has a number of significant limitations to draw conclusions on efficacy. However, the PK data in the younger population is consistent with the older population on methotrexate who had more robust data and the efficacy data using PedACR indicate a benefit for patients on adalimumab that was sustained. This was also supported by an improvement in joint assessments, a reduction in VAS scores for physician global assessment of disease activity, parent's global assessment of disease activity and parent's assessment of pain, an improvement in quality of life and a reduction in CRP. Thus the evidence is supportive for patients treated concomitantly with methotrexate. For monotherapy use, that is, without methotrexate, the data show a reduced adalimumab concentration exposure compared to the older children from the previous study, however there is high inter-subject variability (CV 113% in this study) and only 4 subjects in this study were not on methotrexate. There is therefore very limited data in this subgroup but the efficacy information that was available suggested an improvement in joint assessment, health and quality of life assessment. On balance, despite the limitations of the data, and considering the difficulties in recruiting and designing such a study in paediatric patients and the supportive pharmacokinetic and efficacy data that is available, the data are acceptable to support the proposed efficacy in patients with or without concomitant methotrexate.

#### *Safety*

The safety of adalimumab was assessed in the pivotal study with the majority of patients on concomitant methotrexate. Although there is very little data on the safety in patients without methotrexate, it can be inferred that any risks are likely to be similar to or

possibly less than treatment with methotrexate. The safety profile is considered to be similar to the known safety profile in children aged 4 years and older and is therefore satisfactory. There were no new or unexpected findings. The majority of adverse events were infection or injection site related as expected. The patient registry did not identify new or unexpected safety signals and it supports the overall safety of adalimumab for the proposed population.

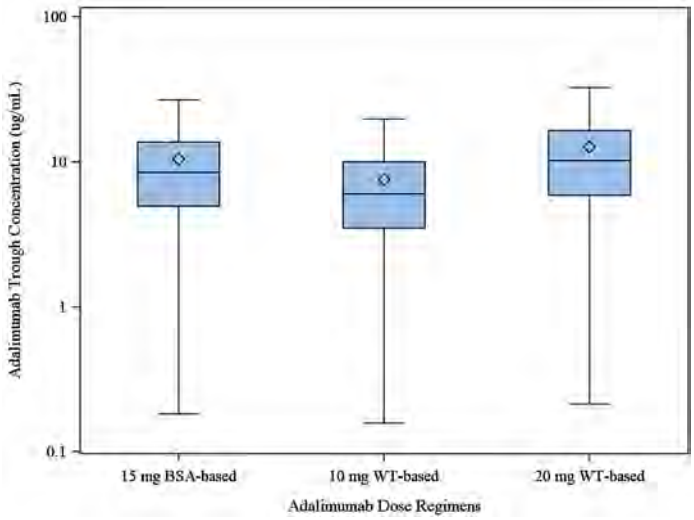
### *Indication*

The currently approved indication and the proposed indication in Australia do not require that patients are to have had an inadequate response to one or more DMARDs, whereas the approved indication in Europe requires that patients are to have had an inadequate response to one or more DMARDs. The clinical evaluator has not recommended this be included in the indication however it is noted that the approved indications for abatacept, tocilizumab and etanercept for pJIA all require that patients have had an inadequate response to one or more DMARDs or methotrexate. The submitted study required patients in Europe to have previously failed, had an insufficient response to, or been intolerant to ≥ 1 DMARD but this was not a requirement for non-EU subjects. All subjects in the EU met this requirement and 7 subjects (22%) did not meet this requirement who were from the USA. Given the current approval and ACPM's previous advice for pJIA patients 4 years and older not requiring them to have failed a DMARD and that the data included patients who did and did not meet this requirement then it appears reasonable to not include this into the indication.

### *Dosage*

The pivotal study used a body surface area approach to dosing using heights and weights which the sponsor has justified that the preferred dosing approach for the PI should be a simplified regimen based on body weight alone. The sponsor initially proposed two dose categories for pJIA patients 2 to 4 years for those patients weighing 10 to <12 kg of 10 mg fortnightly and patients weighing 12 to <15 kg of 15 mg fortnightly but amended this during the evaluation to a single dose covering the weight range of 10 to <15 kg of 10 mg fortnightly. The sponsor designed a non-linear population PK model, consistent with TGA adopted guidelines, to simulate adalimumab exposure from the BSA approach to a weight based approach and showed that adalimumab concentrations under the weight based approach using 10 mg for weight <10 kg or 20 mg for weight ≥ 15 kg substantially overlapped with concentrations from 15mg based on BSA (see figure below). For patients who would receive 10 mg fortnightly under the proposed dosing instead of 15 mg fortnightly, the exposure is expected to be approximately 30% lower, as opposed to approximately 20% higher for patients who would receive 20 mg adalimumab fortnightly instead of 15 mg fortnightly. A 10 mg dose is therefore expected to provide sufficient exposure to achieve a clinical response while maintaining a positive benefit-risk profile for patients weighing 10 kg to < 15 kg. However, 9 of the 31 subjects in Study M10-444 who received 15 mg of adalimumab based on BSA would be dosed with 20 mg from Week 12. The sponsor stated that this was not expected to pose an increased safety risk due to no relationship seen between adalimumab exposure and infectious events in both pJIA studies. This simplified dosage regimen was supported by the clinical evaluator and is consistent with that approved in the USA.

**Figure 1: RD2.1 - PK M&S - Comparison of simulated week 24 adalimumab trough concentrations (µg/mL) for pJIA patients who were dosed with either adalimumab 15 mg fortnightly based on BSA or 10 mg or 20 mg fortnightly based on body weight (kg).**




In Europe, the dose in patients aged 2 to 12 years is 24 mg/m$^2$ BSA up to a maximum of 20 mg fortnightly for patients 2 to <4 years and up to a maximum 40 mg fortnightly for patients aged 4 to 12 years. For patients 13 years and older, the dose is 40 mg fortnightly. A dosage table is provided in Europe that includes body weight and height for patients 2 to 12 years (see below) which includes more specific dosing instructions. The proposed Australian dosing is also provided for comparison. The body surface area approach is consistent with the clinical trial's design however adalimumab in Australia has been approved with a dosage regimen based on body weight alone for pJIA patients aged 4 years and older since 2009, which was supported by ACPM at the time. Given the PK modelling data and the current dosing approach, the delegate supports the sponsor's proposed dosage based on body weight for patients aged 2 years and older, consistent with that approved in the USA. ACPM's advice is requested on whether the European approach is more appropriate.

**Table 11: EU SmPC for Humira, pJIA age 2 to 12 years. Humira Dose in Millilitres (mL) by Height and Weight of Patients for pJIA and Enthesitis- related Arthritis**

| Height (cm) | Total Body Weight (kg) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 |
| 80 | 0.2 | 0.3 | 0.3 | 0.3 | | | | | | | | | |
| 90 | 0.2 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | | | | | | | |
| 100 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | | | | | |
| 110 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 0.5 | 0.6 | 0.6 | | |
| 120 | 0.3 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 |
| 130 | | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 |
| 140 | | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 | 0.7 | 0.8* |
| 150 | | | 0.5 | 0.5 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 | 0.7 | 0.8* | 0.8* |
| 160 | | | 0.5 | 0.5 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 | 0.8* | 0.8* | 0.8* | 0.8* |
| 170 | | | | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.8* | 0.8* | 0.8* | 0.8* | 0.8* |
| 180 | | | | | 0.6 | 0.7 | 0.7 | 0.8* | 0.8* | 0.8* | 0.8* | 0.8* | 0.8* |

*Maximum single dose is 40 mg (0.8 mL)

### *Proposed australian PI dosage instructions for pJIA*

**Table 12: Polyarticular JIA dosing recommendations**

**Polyarticular Juvenile Idiopathic Arthritis**

The recommended dose of Humira for patients ~~4 to 17~~2 years of age and older with polyarticular juvenile idiopathic arthritis is based on weight as shown below. Methotrexate, glucocorticoids~~, salicylates~~, NSAIDs and/or analgesics may be continued during treatment with Humira.

| Paediatric Patients (~~4 to 17~~2 years of age and older) | Dose |
|---|---|
| 10 kg to <15 kg | 10 mg~~0.2 mL~~ fortnightly (10 mg Pre-filled Syringe) |
| ~~-~~15 kg to <30 kg | 20 mg fortnightly (20 mg Pre-filled Syringe) |
| ≥ 30 kg | 40 mg fortnightly (Humira 40 mg Pen or 40 mg Pre-filled Syringe) |

~~Limited data are available for Humira treatment in paediatric patients with a weight below 15 kg.~~Humira has not been studied in patients with polyarticular JIA less than 2 years of age, or in patients with a weight below 10 kg.

### *RMP*

The sponsor's RMP is acceptable.

### *Data deficiencies or limitations*

The pivotal study was open label, uncontrolled and non-randomised, therefore prone to bias and confounding. The proposed weight based dosing is not directly supported by the trial design but from a simulation using the trial's data and adalimumab concentrations. There is limited data supporting monotherapy use. Concomitant methotrexate and systemic corticosteroid use may confound the results. There is a lack of data on growth and development and a lack of data on rebound associated with withdrawal of treatment.

### *Conditions of registration*

The following are proposed as conditions of registration and the ACPM and sponsor are invited to comment:

1. The implementation in Australia of the EU Risk Management Plan for Humira (adalimumab), version 11.1.2 (dated September 2014, data lock point 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014), included with submission PM-2014-01048-1-3, and any subsequent revisions, as agreed with the TGA.
2. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
    a. The 5 year interim study report for the STRIVE registry.

### Summary of issue/s

The primary issues with this submission are as follows:

1. Whether the data are sufficient to extend the indications to an age of 2 years and older, including with and without concomitant methotrexate.
2. Whether the appropriate dosage regimen should be based on body weight or based on body surface area (body weight and height).

### Proposed action

The Delegate had no reason to say, at this time, that the application for Humira should not be approved for registration.

### Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Is the data sufficient to support use in patients as monotherapy and with methotrexate?
2. Is the sponsor's proposed weight based dosage regimen, as approved in the USA, appropriate or is the dosage regimen based on body surface area, as approved in Europe, more appropriate?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### Response from sponsor

AbbVie Pty Ltd welcomes the opportunity to provide comments on the evaluation and proposed actions in relation to the application to extend the indications registered in Australia for Humira (adalimumab) Solution for Injection to include the treatment of polyarticular juvenile idiopathic arthritis (pJIA) to include patients 2 years of age and older.

AbbVie agrees with the assessment and proposed action of the Delegate in the Request for ACPM's Advice dated 3 March 2015. This assessment is consistent with the opinion of the clinical evaluator, who recommended that the application be approved for patients 2 years of age and older, and that Humira (adalimumab) be administered subcutaneously based on weight as proposed by the sponsor.

The committee is requested to provide advice on the following specific issues:

1. *Is the data sufficient to support use in patients as monotherapy and with methotrexate?*

### *Sponsor comment*

As indicated by the Delegate, adalimumab for the treatment of pJIA patients 4 years of age and older was considered at the July 2009 meeting of the ACPM, with approval for the indication granted, and the committee advised that dosing should be weight-based, that the indication did not require failure of a previous DMARD and that both monotherapy and combination therapy with methotrexate were appropriate. The sponsor is proposing the extension of the current approved indication for pJIA patients to include those patients 2 years of age and older.

2. *Is the sponsor's proposed weight based dosage regimen, as approved in the USA, appropriate or is the dosage regimen based on body surface area, as approved in Europe, more appropriate?*

### *Sponsor comment*

As indicated by the Delegate, adalimumab for the treatment of pJIA patients has different dosage regimens approved in the USA (weight-based dosing) and in Europe (dosing based on body surface area). The current approved dosage regimen in Australia (for pJIA patients 4 years of age and older) was considered at the July 2009 meeting of the ACPM, with the committee advised that dosing should be weight-based. The sponsor is proposing an extension of the current weight-based dosing regimen, as approved by the FDA in the USA, and consistent with the current TGA approved weight-based dosing.

### *Other Issues in the Request for ACPM's Advice*

*Conditions of registration*

3. *The implementation in Australia of the EU Risk Management Plan for Humira (adalimumab), version 11.1.2 (dated September 2014, DLP 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014), included with submission PM-2014-01048-1-3, and any subsequent revisions, as agreed with the TGA.*

*Sponsor comment*

The sponsor agrees with, and accepts, the proposed condition of registration that the EU Risk Management Plan for Humira (adalimumab), version 11.1.2 (dated September 2014, DLP 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014), be implemented in Australia. This will also include ongoing dialogue with the TGA of subsequent revisions of these documents as applicable.

4. *The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 application.*
    a. *The 5 year interim study report for the STRIVE registry.*

*Sponsor comment*

The sponsor accepts the condition of registration that the 5 year interim study report for the STRIVE registry be submitted to the TGA for evaluation as a Category 1 submission. As this interim study report is now available, the sponsor will enter into discussions with the TGA to enable evaluation of this study to begin as soon as possible following completion of this current submission.

### *Questions for the sponsor*

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. *Please advise if the planned submission to the FDA of the 5 year interim report for the registry has been submitted and reviewed and whether any changes are recommended to the safety or efficacy of adalimumab, including in the US PI, as a result.*

*Sponsor comment*

The 5 year interim report for the registry was submitted to the US FDA and the EMA in June 2014, and there have been no changes recommended to the safety or efficacy of adalimumab, including in the US PI, as a result.

2. *For Study DE038, the sponsor had previously indicated in 2009 that the final study report would be submitted to the TGA, estimated to be approximately April 2013. Please provide an update on the submission of this final study report.*

*Sponsor comment*

The final study report for Study DE038 is available, and will be submitted to the TGA as soon as possible following discussion with the TGA Delegate.

3. *Please outline any further studies or registries being conducted to assess long term safety, especially effects on growth and development, and advise when the interim 5 year report for the registry will be submitted to the TGA.*

*Sponsor comment*

There are global registries running for Humira (adalimumab) in the treatment of Crohn's Disease in adults, Crohn's Disease in paediatric patients, Ulcerative Colitis in adults and Psoriasis in adults. There are no ongoing studies to evaluate the long-term efficacy and safety of adalimumab in pJIA. As indicated above, the 5 year interim study report for the registry is available, and will be submitted to the TGA for evaluation as soon as possible following discussions with the TGA Delegate.

## Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Humira vial and pre-filled pen 40 mg; and pre-filled syringe, 10 mg, 20 mg and 40 mg of adalimumab to have an overall positive benefit–risk profile for the indication;

> *Polyarticular Juvenile Idiopathic Arthritis;*
>
> *Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 years of age and older. 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.*

### *Proposed conditions of registration*

The ACPM agreed with the Delegate on the proposed conditions of registration, including submitting to the TGA the 5 year interim study report for the STRIVE registry, as soon as possible after completion, for evaluation as a Category 1 submission.

### *Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments*

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

### *Specific advice*

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Is the data sufficient to support use in patients as monotherapy and with methotrexate (MTX)?*

Most children (78%) in the small, uncontrolled open label Study M10-444 had been pretreated with MTX and 84% received combination therapy. The data do not support a first-line indication lack of suitable untreated population in the pivotal study. The other biologicals available for pJIA can be used with or without MTX. Although the data are less supportive of monotherapy, it would be reasonable to approve it, as with the other biologicals, and leave this to be determined by prescribers.

2. *Is the sponsor's proposed weight-based dosage regimen, as approved in the USA, appropriate or is the dosage regimen based on body surface area, as approved in Europe, more appropriate?*

The limited data presented regarding trough levels and efficacy support weight-based dosing. It is less confusing and there is less risk of errors. In very small children, body surface area (BSA) dosing has a risk of overdosage. Weight-based dosing is in line with the current dosing for older children, is simpler and more convenient to use given the available pre-filled syringes and pens. BSA based dosing in the pivotal trial was simplified to 3 dose strata and few children of those chidlren would have received lower doses on a weight based strategy.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration Humira adalimumab (rch), sterile solution for subcutaneous administration, indicated for:

> *Polyarticular Juvenile Idiopathic Arthritis*
>
> *Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older 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.*

### Specific conditions of registration applying to these goods

1. The Humira (adalimumab) EU Risk Management Plan (EU-RMP), version 11.1.2, dated September 2014 (DLP 31 December 2012) and Australian Specific Annex Version 2.0 (dated December 2014), included with submission PM-2014-01048-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
   - The 5 year interim study report for the STRIVE registry.
   - The final study report for Study DE038.

# Attachment 1. Product Information

The PI approved for Humira at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# Attachment 2. Extract from the Clinical Evaluation Report

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