



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2017
EMA/CHMP/829007/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/X/0164/G

Note

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



Table of contents

1. Background information on the procedure	5
1.1. Submission of the dossier.....	5
1.2. Steps taken for the assessment of the product.....	6
2. Scientific discussion	7
2.1. Problem statement	7
2.1.1. Epidemiology and clinical presentation	7
2.1.2. Aetiology and pathogenesis	8
2.1.3. Management.....	8
2.2. The development programme/compliance with CHMP guidance/scientific advice.....	9
2.3. Quality aspects	11
2.3.1. Introduction.....	11
2.3.2. Active Substance	12
2.3.3. Finished medicinal product.....	12
2.3.4. Discussion on chemical, pharmaceutical and biological aspects.....	13
2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects	13
2.4. Non-clinical aspects	13
2.5. Clinical aspects	14
2.5.1. Introduction.....	14
2.5.2. Pharmacokinetics.....	20
2.5.3. Pharmacodynamics.....	31
2.5.4. Discussion on clinical pharmacology.....	31
2.5.5. Conclusions on clinical pharmacology	31
2.6. Clinical efficacy	32
2.6.1. Dose response studies and main studies.....	32
2.6.2. Discussion on clinical efficacy.....	42
2.6.3. Conclusions on the clinical efficacy.....	43
2.7. Clinical safety	44
2.7.1. Discussion on clinical safety	50
2.7.2. Conclusions on clinical safety	54
2.7.3. PSUR cycle	54
2.8. Pharmacovigilance.....	54
2.9. Product information	55
2.9.1. User consultation.....	55
3. Benefit-Risk Balance.....	55
3.1. Therapeutic Context	55
3.1.1. Disease or condition.....	55
3.1.2. Available therapies and unmet medical need	55
3.1.3. Main clinical studies	56
3.2. Favourable effects	58
3.3. Uncertainties and limitations about favourable effects	58
3.4. Unfavourable effects	58
3.5. Uncertainties and limitations about unfavourable effects	59

3.6. Benefit-risk assessment and discussion	60
3.6.1. Importance of favourable and unfavourable effects	60
3.6.2. Balance of benefits and risks.....	61
3.7. Conclusions	61
4. Recommendations	61

List of abbreviations

AAA	Anti-adalimumab antibodies
ADA	adalimumab
AE	adverse event
BSA	Body Surface Area
BW	Body Weight
CD	Crohn's disease
CHAQ	Childhood Health Assessment Questionnaire
CI	Confidence Interval
CNS	central nervous system
CS	corticosteroids
DB	Double-blind
eow	every other week
ERA	enthesitis-related arthritis
FD	Fixed Dose
HPLC	High Performance Liquid Chromatography
HR	hazard ratio
HS	Hidradenitis suppurativa
IC ₅₀	Half maximal inhibitory concentration
JIA	juvenile idiopathic arthritis
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
OLE	Open-Label Extension
PedACR	Paediatric American College of Rheumatology PFS
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
Ps	psoriasis
PsA	psoriatic arthritis
PSUR	Periodic Safety Update Report
PY	patient years
RA	rheumatoid arthritis
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class (MedDRA)
TNF(-α)	tumour necrosis factor (alpha)
UC	Ulcerative Colitis
USP	United states Pharmacopoeia
UV	Ultra Violet
VH	vitreous haze
	pre-filled syringe

1. Background information on the procedure

1.1. Submission of the dossier

AbbVie Limited submitted on 2 March 2017 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH applied for a new strength/potency (20 mg) for adalimumab solution for injection in pre-filled syringe. In addition, the MAH proposed an update of sections 4.2 of the SmPC in order to introduce new fixed dose regimen (posology) for the paediatric indications of Juvenile idiopathic arthritis (JIA), Paediatric plaque psoriasis, Paediatric Crohn's disease, and Paediatric Uveitis. The Package Leaflet and Labelling are updated accordingly. Furthermore, the marketing authorisation holder took the opportunity to introduce editorial changes to align wording and layout of the Product Information and to amend the statement relating to anti-adalimumab antibody development in JIA patients, which will reside in section 5.1 of the Humira SmPCs (20 mg and 40 mg presentations).

The MAH applied for the following indication for Humira 20 mg solution for injection in pre-filled syringe:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients 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 section 5.1). Humira has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Paediatric plaque psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 23 June 2016 and 2 September 2016. The Scientific Advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

- The application was received by the EMA on 2 March 2017.
- The procedure started on 23 March 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 June 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 7 June 2017.
- During the meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 20 July 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 10 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 15 September 2017.
- During the meeting on 12 October 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Humira on 12 October 2017.

2. Scientific discussion

2.1. Problem statement

This procedure concerns changes to a Fixed Dose (FD) posology for the paediatric indications JIA, ERA (currently body surface area [BSA] dependent posology) and Ps (currently body weight [BW] dependent posology). FD is proposed also for the new indication uveitis which has been evaluated in a parallel procedure (EMA/H/C/000481/II/0163). No changes are proposed in the paediatric indications for which a fixed-dose posology is already applied (CD, HS). The changes are reflected in section 4.2 of the SmPC for the new dose-strength 20 mg prefilled syringe, that is included as a line extension in this application, as well as the changes proposed in the SmPCs for the currently approved presentations. Furthermore the applicant proposes to add a statement on immunogenicity in JIA in section 5.1 of the SmPC referring to data from a previous procedure.

2.1.1. Epidemiology and clinical presentation

JIA

Chronic arthritis in childhood is a heterogeneous group of diseases. The currently used International League of Associations for Rheumatology (ILAR) classification distinguishes the following JIA categories:

- Systemic arthritis (sJIA)
- Polyarthritis rheumatoid factor (RF) negative
- Polyarthritis RF positive
- Oligoarthritis (2 subcategories based on joint count beyond 6 months)
 - Persistent (not more than 4 joints)
 - Extended (more than 4 joints)
- Psoriatic arthritis (JIA-PsA)
- Enthesitis related arthritis (ERA)
- Undifferentiated arthritis

JIA refers to arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. JIA has an annual incidence of 2-20 cases per 100 000 population and a prevalence of 16-150 cases per 100 000 population. JIA is less common than RA in adults but it is one of the most common systemic autoimmune diseases in children and adolescents. Children of all age groups may be affected although onset during the first year of life is rare and restricted predominantly to sJIA. In some of the categories girls predominate whereas in ERA boys predominate, and there are racial differences in incidence and relative frequency of JIA categories.

RA, axial spondyloarthritis, and PsA are diseases in adults that correspond most closely to individual categories of JIA with similar clinical manifestations and underlying immunologic mechanisms (i.e. polyarticular JIA, ERA and JIA-PsA, respectively). They all are covered by the overarching condition: chronic idiopathic arthritis (including RA, axial spondyloarthritis, PsA and JIA). (EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, EMA/CHMP/239770/2014).

Psoriasis

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull-red scaly plaques, particularly on extensor parts of limbs and in the scalp. Psoriasis affects 1.5 to 3% of the general population in Europe. The first manifestation of psoriasis may occur at any age. Two peaks of onset are frequently reported: in the second and third decades and about the age of 60. In 3% of patients, psoriasis begins in childhood. Patients with a family history of psoriasis tend to have an earlier age of onset. The duration may vary from a few weeks to a whole lifetime. The clinical course is unpredictable but in the majority of cases psoriasis is a chronically remitting and relapsing disease (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, (EMA/CHMP/EWP/2454/02).

2.1.2. Aetiology and pathogenesis

Although the aetiology and pathogenesis of JIA are not fully understood, it is known that JIA shares many of the pathological abnormalities that have been identified in RA. At the same time multiple differing pathogenesis and phenotypic features exist between the JIA categories. Increased production of cytokines in different forms of JIA (e.g. interleukin-1 β and interleukin-6 in sJIA, tumor necrosis factor- α (TNF- α) in polyarticular JIA) in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone. Increased knowledge of these factors including understanding their genetic background may help to redefine the classification of JIA in terms of aetiology, response to treatment, risk of relapse or prognosis. (EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, EMA/CHMP/239770/2014).

Psoriasis is considered to be caused by a genetic-environmental interaction. Smoking, alcohol consumption, diet, psychological stress, infections and physical trauma have been suggested as factors which may influence the onset of the disease and/or may affect severity or response to treatment. The pathogenesis of psoriasis is still incompletely understood. A genetically determined skin disorder as a cause of the infiltration of lesions with activated T cells, interaction between dermal antigen-presenting cells, and activation of neutrophils and T cells has been postulated. The histochemistry of psoriatic lesions and therapeutic response of chronic plaque psoriasis to T-cell targeting therapy such as ciclosporin A are also in favour of this hypothesis (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. EMA/CHMP/EWP/2454/02).

2.1.3. Management

JIA

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered a first-line treatment option in most cases of newly diagnosed JIA, followed by intra-articular glucocorticosteroids and disease modifying antirheumatic drugs (DMARDs). The latter include both synthetic (methotrexate (MTX), sulfasalazine) and biological DMARDs. The introduction of biological therapies has resulted in a significant advance in therapy for JIA. (EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, EMA/CHMP/239770/2014). Five biologic agents are approved for the treatment of pJIA: adalimumab, etanercept, golimumab, abatacept and tocilizumab.

Psoriasis

Topical therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage mild psoriasis. Practicability (time needed to apply treatment), convenience, and adverse effects such as skin irritation limit the use of topical drugs. A combination of phototherapy and systemic therapy is needed for patients with moderate-to-severe disease. Established systemic drugs for the treatment of psoriasis include methotrexate, ciclosporin, acitretin, and in some countries fumaric acid esters. In the past decade, several biologics have been developed and approved for the treatment of psoriasis. Additionally, the oral phosphodiesterase 4 inhibitor apremilast has been approved for adults. TNF α inhibitors etanercept, adalimumab, and infliximab are approved for the treatment of psoriasis and psoriatic arthritis, and golimumab has been approved for psoriatic arthritis. Ustekinumab, a drug that blocks interleukin 12 and 23, is also approved for both indications. Ustekinumab interferes with the development of Th17 lymphocytes, which are important effector cells in psoriatic inflammation. Secukinumab was approved in adults as the first biological blocking IL-17A, a key effector cytokine produced by TH17 and other cells. (Boehncke et al, Lancet. 2015 Sep 5; 386(9997):983-94).

About the product

Adalimumab is a fully human antibody that binds specifically to TNF- α and neutralizes the biological function of TNF- α by blocking its interaction with the p55 and p75 cell surface TNF- α receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF- α . After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

In the EU, the approved indications for adalimumab in paediatric patients are JIA (polyarticular JIA [pJIA] and ERA), paediatric Ps, adolescent HS, and paediatric CD, as reflected in the Humira® summary of product characteristics (SmPC).

2.2. The development programme/compliance with CHMP guidance/scientific advice

This procedure concerns changes to the posology for the paediatric indications JIA, ERA (currently BSA-dependent posology) and Ps (currently BW-dependent posology). FD is proposed also for the new indication uveitis which is currently being evaluated in a parallel procedure (EMA/H/C/000481/II/0163). No changes are proposed in the paediatric indications for which a fixed-dose posology is already applied (CD, HS). See summary of currently approved and proposed posology in the table below.

Table 1 **Posology of Adalimumab for Paediatric Indications**

Paediatric Indication	Current Approved Posology ^a			Proposed Posology ^a
	Age	BW-Dependent (Single-Use Vial)	BSA-Dependent (Single-Use Vial)	Fixed Dose (Prefilled Syringe/Vial)
pJIA	2 to 12 years		24 mg/m ² BSA in 5 mg increments	20 mg (10 kg to < 30 kg)
	≥ 13 years			40 mg (≥ 30 kg)
ERA	≥ 6 years		24 mg/m ² BSA in 5 mg increments up to 40 mg	20 mg (15 kg to < 30 kg) 40 mg (≥ 30 kg)
Ps	≥ 4 years	0.8 mg/kg BW in 5 mg increments up to 40 mg ^b		20 mg (15 kg to < 30 kg) 40 mg (≥ 30 kg)
CD	≥ 6 years			20 mg (< 40 kg BW) 40 mg (≥ 40 kg BW)
Uveitis ^c	2 to < 18 years			20 mg (< 30 kg) 40 mg (≥ 30 kg)
HS	≥ 12 years			40 mg (≥ 30 kg)
				No change

BSA = body surface area; BW = body weight; CD = Crohn's disease; ERA = enthesitis-related arthritis; HS = hidradenitis suppurativa; pJIA = polyarticular idiopathic arthritis; Ps = psoriasis

- a. Posology is for dosing every other week.
- b. Posology is weekly for the first 2 doses and every other week thereafter.
- c. Application currently under review.

No new clinical data was submitted in support of this application. Instead new analysis of existing clinical data was submitted.

A central scientific advice was given regarding the issue was received in June 2016 (EMA/SAWP/401051/2016). Several points were raised including the following:

1. The proposed posology in the SA Briefing material was for pJIA: 10 kg to < 15 kg 10 mg every other week, 15 kg to < 30 kg 20 mg every other week and ≥ 30 kg 40 mg every other week. For ERA, the proposed posology was: 15 kg to < 30 kg 20 mg every other week ≥ 30 kg 40 mg every other week. In this SA it was stated that: " CHMP acknowledges that on a population level, the proposed fixed-dose regimen will likely produce similar exposure as compared to the BSA-based dosing for patient with body weights > 15kg. However, as shown in Figure 3 of the briefing package, for the weight group < 15 kg the proposed fixed-dose regimen will decrease exposure as compared to the BSA-based dose regimen" and "PedACR30 response rate was shown to be lower in the quartile of patients with the lowest exposure (70 versus 90 percent), however, this difference is larger for the PedACR50 response ratio (50 versus 90 percent). Even if PedACR30 is the primary endpoint, all data has to be taken into account especially given the limited amount of data that is available. Based on the lower efficacy in the lower exposure quartile group and given the fact that the below 15 kg patients will have the tendency for underdosing, this should be carefully evaluated".

The currently proposed posology for pJIA differs from the posology proposed in the SA Briefing material; the dose is currently proposed to be 20 mg for children with weight 10-30 kg and 40 mg for children >30 kg.

2. The proposed posology in the SA Briefing material for Paediatric plaque psoriasis was: 15 kg to < 40 kg 20 mg every other week and \geq 40 kg 40 mg every other week. The CHMP stated that: *“From the data provided by the applicant, it appears that patients between 30 and 40 kg are expected to receive a lower FD, compared to the BW-calculated dose. This aspect was discussed during the discussion meeting and for Ps there is a pronounced correlation between clinical efficacy and exposure levels, without a significant effect on safety (for safety see below). Hence it seems advisable to revise the proposed cutoff of 40 kg and lower this to 30 kg. The applicant argued that analysis of AE rates in relation to administered adalimumab dose (0.4 mg/kg versus 0.8 mg/kg) or observed serum adalimumab concentrations in paediatric Ps patients indicated no association between AE rate and adalimumab dose or exposure. However, the possible consequences on safety of doubling of AUC exposure in the lightest children have not been sufficiently addressed by the applicant, and this will be expected to be part of the application for the variation.”*

The revision regarding cut-off proposed by the CHMP has been implemented in the posology proposed in the current application.

3. In the SA it was also stated that: *“CHMP agrees that there is enough data to support the claim that variations in adalimumab doses in individual patients, compared to doses calculated based on BSA, have a low probability to induce an increased risk of adverse events. In particular, the data provided by the applicants in their document show no increase in infectious side effects in patients exposed to higher adalimumab doses. Infectious side effects in JIA patients are related to multiple factors, including the use of corticosteroids. Because of the corticosteroid-sparing effect of adalimumab in patients with JIA, the overall risk-benefit balance still leans in favour of adalimumab, even after dose adjustments based on BW thresholds.”*

Type of Application and aspects on development

- Legal basis - Legal basis: This application is for a Line Extension to add a new dose strength (20 mg solution for injection in pre-filled syringe) grouped with type II variation, according to Article 8(3) of Directive 2001/83/EC,
- 1 year data exclusivity n/a
- Significance of paediatric studies n/a

2.3. Quality aspects

2.3.1. Introduction

The purpose of this line extension application is to introduce a 20 mg strength for the adalimumab 100 mg/mL formulation in a single-use pre-filled syringe (PFS) presentation for use in approved Humira paediatric indications.

The 100 mg/mL formulation of adalimumab solution for subcutaneous (SC) injection was first approved through variation EMEA/H/C/000481/II/138/G (40 mg in PFS) and EMEA/H/C/000481/II/145/G (40 mg in Autoinjector). Subsequently a 80 mg in PFS was approved through line extension EMEA/H/C/000481/X/0157.

The new 20 mg presentation has the same, active substance, formulation and container closure system as the approved 40 and 80 mg strengths of the 100 mg/mL formulation. The only difference is the volume of solution filled into the syringe.

2.3.2. Active Substance

There are no changes declared for the active substance part of Module 3.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical development

Adalimumab 20 mg Pre-Filled Syringe is provided as a 100 mg/mL sterile solution, ready for injection. The product is supplied in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer). The material complies with Ph. Eur. and EC requirements.

Adalimumab 20 mg Pre-Filled Syringe contains as excipients mannitol (tonicity agent) and polysorbate 80 (detergent) in water for injections (solvent). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Manufacture of the product and process controls

The finished product manufacturing process for the 20 mg PFS is comparable to the validated process for the already approved 100 mg/mL FS. Only some minor adaptations have been made to the manufacturing process (mixing speed, mixing time, fill volume and stopper position), which have been sufficiently described in the documentation.

The manufacturing, packaging and testing sites are generally the same as those established for the already approved 40 mg/0.4 mL and the 80 mg/0.8 mL PFS and no new sites have been added. The extent of specific testing performed by the registered manufacturers has been slightly changed.

The unit operations and controls comprising the finished product manufacturing process for the 20 mg/0.2 mL PFS is comparable to the validated process for the already approved 40 mg/0.4 mL and 80 mg/0.8 mL PFS, with minor adaptations. The manufacturing process for the 20 mg/0.2 mL PFS was validated. The acceptance criteria for all process validation lots were met. Reproducibility and robustness in manufacturing were demonstrated.

The 20 mg/0.2 mL PFS is supplied in a 1 mL single-use syringe for subcutaneous administration (Becton Dickinson (BD) Hypak PhysioliS Sterile, Clean, and ready-to-Fill (SCF) syringe system). This is the same container closure system as utilized by the already approved 40 mg/0.4 mL PFS and 80 mg/0.8 mL PFS.

Product specification

The specification for the 20 mg/0.2 mL PFS is identical as the one to the already approved 40 mg/0.4 mL and 80 mg/0.8 mL PFS, except it does not include measurement of the plunger breakout and gliding forces for filled syringes intended for autoinjector use, since an autoinjector presentation is not

provided for the 20 mg dose. All other tests, analytical methods and acceptance criteria are identical to the already approved 40 mg/0.4 mL and 80 mg/0.8 mL PFS. The finished product specification include tests for appearance (visual), identity, purity, potency, protein quantity, pH, osmolality, visible and sub-visible particulate contamination and extractable volume. Appropriate specifications have been set to control the active substance and finished product, both at release and at the end-of-shelf life.

Batch analysis

Batch analysis data have been provided for production scale batches for 20 mg/0.2 mL PFS. The batches are representative of the adalimumab 100 mg/mL formulation and commercial process and all are being evaluated in stability studies. The provided batch data comply with the release specifications.

Reference materials

The reference materials are identical to those already approved for the 40 mg/0.4 mL and 80 mg/0.8 mL PFS.

Stability of the product

Based on available stability data, the shelf-life (24 months) and storage conditions (Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled syringe in its outer carton in order to protect from light. A single Humira pre-filled syringe may be stored at temperatures up to a maximum of 25° C for a period of up to 14 days. The syringe must be protected from light, and discarded if not used within the 14-day period.) as stated in the SmPC are acceptable.

Real time/real condition (5°C) stability data of commercial scale batches of finished product for accelerated (25°C/60% RH) and stressed (40°C/ 75% RH) conditions according to the ICH guidelines were provided. The batches of Adalimumab 20 mg/0.2 mL PFS are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The currently available stability data for 20 mg/0.2 mL PFS batches meet the pre-defined acceptance criteria under the recommended storage conditions. The reported stability data are considered sufficient to support the application of a 24 month shelf-life at 5°C with an additional 14 days room temperature ($\leq 25^{\circ}\text{C}$) storage available to the product end-user.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided to support this line extension has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the new presentation 20 mg PFS is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.4. Non-clinical aspects

The MAH confirms that there have been no changes in the pharmaco-toxicological evaluation for Adalimumab since the last updates of Module 2.4 and Module 4 submitted with Variation

138G/Sequence Number 0229 (HC 40 mg pre-filled syringe) and Variation 146/Sequence Number 0229 (Uveitis).

The local tolerance study TE09-259 (R&D/10/297) and the conclusions from the nonclinical overview submitted with variation 138G are also valid for this application.

The CHMP deems the available non-clinical package acceptable to support this variation.

2.5. Clinical aspects

2.5.1. Introduction

The data that support the FD regimens of adalimumab are from clinical trials and from a post-approval commitment to the FDA/PIP requirement of the EMA. These studies have been conducted in patients with pJIA (Studies DE038, M10-240 [Japan], M10-444, and P10-262 [STRIVE]), ERA (Study M11-328), paediatric Ps (Study M04-717), paediatric CD (Studies M06-806, M06-807, and P11-292 [CAPE]), and paediatric uveitis (the SYCAMORE study). Study reports have been previously submitted for these studies.

GCP

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

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

Tabular overview of clinical studies

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment / Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Complete d	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
JIA (pJIA and ERA) Studies								
DE038/ 31/ US & EU/ up to 408 weeks	19 Sep 2002 completed 171/168	Phase 3, multicenter, randomized , DB, placebo- controlled study	OL LI, DB, & OLE BSA Ada 24 mg/m ² BSA eow subcutaneous (SC) (up to 40 mg) or pbo OLE FD Ada 20 mg or 40 mg FD eow SC	Assess safety, efficacy, and PK	OL LI: 171/160 DB: 133/128 OLE BSA: 128/106 OLE FD 106/62	OL LI Phase M: 17 (MTX); 19 (non-MTX) F: 68 (MTX), 67 (non-MTX) DB Phase M (MTX): 7 (pbo), 8 (ada); M (non-MTX): 8 (pbo), 7 (ada) F (MTX): 30 (pbo), 30 (ada) F (non-MTX) 20 (pbo), 23 (ada) OLE BSA M (MTX): 7 (pbo) 8 (ada); M (non-MTX): 8 (pbo), 7 (ada) F (MTX): 29 (pbo), 27 (ada), F (non-MTX): 20 (pbo), 22 (ada) OLE FD M (MTX): 8 (pbo), 6 (ada) M (non-MTX): 8 (pbo), 6 (ada) F (MTX): 20 (pbo), 25 (ada), F (non-MTX): 17 (pbo), 16 (ada) 11 years (4 – 17 years)	pJIA ≥ 5 swollen joints, ≥ 3 joints with LOM, naïve to MTX or inadequate responders to MTX or intolerant to MTX.	Proportion of ada-treated subjects in the non-MTX stratum who experienced disease flare in the DB phase.

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M10-240/ 14/Japan/at least 60 weeks	19 May 2008/ completed 25/25	Phase 3 single-arm, OL study	Ada: 20 mg or 40 mg eow SC	Assess safety, efficacy, and PK	MTX: 20/14 non-MTX: 5/2	M: 5 F: 20 13.0 years (7 – 17 years)	pJIA with SJC \geq 5 and LOM \geq 3 Disease not controlled by or patients intolerant of NSAIDs or MTX	PediACR30 response rate at Week 16.
M10-444/ 14/US, France, Czech Republic, Germany/ 24 weeks, then until 4 years of age and \geq 15 kg (US) or until 1 year after 4 years of age and \geq 15 kg (EU)	24 Mar 2009 completed 32/30	Phase 3b, multicenter, OL, postmarketing compassionate use study	Ada: 24 mg/m ² BSA (up to 20 mg) eow SC	Assess safety, efficacy, and PK	32/26	M: 4 F: 28 3.15 years (2.0 – 4.6 years)	Moderately to severely active polyarticular or polyarticular-course JIA with \geq 5 joints affected Previously failed, had an insufficient response to, or been intolerant to \geq 1 DMARD (EU)	Incidence of SAEs and AEs.

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment / Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M11-328/ 16/ Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and Switzerland/ up to 204 weeks	22 Sep 2010/ completed 46/45	Phase 3, multicenter, DB, placebo controlled study with OL period	Ada 24 mg/m ² BSA (up to 40 mg) eow SC or pbo	Assess efficacy and safety	DB: 46/39 OL: 39/29	M: 22 (ada), 9 (pbo) F: 9 (ada), 6 (pbo) 13.0 years (6.0 – 18.0 years)	ERA At least 3 active joints, enthesitis in at least 1 location, inadequate response or intolerance to at least 1 NSAID, inadequate response or intolerance to at least 1 DMARD, SSZ or MTX, no JIA, no previous biologic therapy	Percent change from Baseline to Week 12 in number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) .

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment / Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Complete d	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Paediatric Plaque Ps Studies								
M04-717/ 38/Belgium, Canada, Chile, Czech Republic, Germany, Hungary, Italy, Mexico, Netherlands, Poland, Spain, Switzerland, Turkey/ up to 120 weeks	14 Dec 2010 completed 114/111	Phase 3, multicenter, randomized, double- dummy, DB study	Ada 0.8 mg/kg (up to 40 mg) eow SC or 0.4 mg/kg (up to 20 mg) eow SC MTX: 0.1 mg/kg to 0.4 mg/kg per week (up to 25 mg/week)	Assess safety, efficacy, and PK	<u>MTX</u> 37/34 <u>0.4 mg/kg</u> 39/26 <u>0.8 mg/kg</u> 38/30	M: 11 (MTX), 21 (0.4 mg/kg), 17 (0.8 mg/kg) F: 26 (MTX), 18 (0.4 mg/kg), 21 (0.8 mg/kg) 14 years (5 – 18 years)	Psoriasis for at least 6 months Failed topical therapy and required systemic therapy to control disease with at least 1 of the following: PGA ≥ 4, BSA involved > 20% or very thick lesions with BSA > 10%, PASI > 20, or PASI > 10 and at least 1 of the following: concomitant PsA unresponsive to NSAIDs, facial involvement, genital involvement, hand and/or foot involvement, or CDLQI > 10.	Proportion of subjects achieving ≥ PASI 75 at Week 16A, ada 0.8 mg/kg versus MTX. Proportion of subjects achieving PGA 0,1 (cleared or minimal) at Week 16A, ada 0.8 mg/kg versus MTX.

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment / Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Paediatric CD Studies								
M06-806/ 45/Belgium, Canada, Czech Republic, France, Italy, Netherlands, Poland, UK, US/52 weeks	04 May 2007 completed 192 ^a /186	Phase 3, multicenter, DB study	<u>Induction</u> Ada 160 mg at Week 0/80 mg at Week 2 if ≥ 40 kg, 80 mg at Week 0/ 40 mg at Week 2 if < 40 kg <u>Maintenance</u> (starting at Week 4) High-Dose: 40 mg SC eow if ≥ 40 kg, 20 mg SC eow if < 40 kg Low Dose: 20 mg eow SC if ≥ 40 kg, 10 mg eow SC if < 40 kg	Assess safety, efficacy and PK	High-Dose: 93/66 Low Dose: 95/58	M: 108 F: 84 14.0 years (6–17 years)	CD for > 12 weeks & confirmed by endoscopy or radiologic evaluation. PCDAI > 30 with oral CS, and/or AZA or 6-MP, or MTX, unless subject had previous nonresponse or intolerance. If previously received INF, an initial response and then discontinued use for loss of response or intolerance, unless there was an initial treatment-limiting reaction.	Proportion of subjects who were in PCDAI clinical remission at Week 26.

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Total Enrollment / Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Complete d	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M06-807/ 31/US, Canada, and Europe/ up to 336 weeks	01 May 2008 ongoing, 31 Jan 2015 100/130	Phase 3, multicenter, OL study	If enrolled from DB phase of Study M06-806, received ada 40 mg eow SC if ≥ 40 kg, 20 mg eow SC if < 40 kg If enrolled from OL phase of Study M06-806, continued on same dose (either 40 mg ew SC or 20 mg ew SC)	Long-term maintenance of clinical response, safety, and tolerability	100/ ongoing	M: 52 F: 48 14.0 years (7.0 to 17.0 years)	CD Previously participated in and successfully completed Study M06-806 through Week 52.	Clinical remission and response over time; incidence of SAEs and AEs.
Paediatric Uveitis Studies								
SYCAMORE/ 14/England, Northern Ireland, and Scotland/up to 18 months for double- masked phase	27 Oct 2011 completed/ 90/114	Phase 3, multicenter, randomized, double- masked, placebo- controlled study	Ada or pbo, 20 mg if weighing < 30 kg or 40 mg if weighing ≥ 30 kg, SC, every 2 weeks	Assess effectiveness in combination with MTX	Ada: 60 Pbo: 30/ double- masked phase completed; follow-up ongoing	M: 20 F: 70 7.89 years (2.57 to 17.97 years)	Refractory mild or moderate uveitis associated with JIA.	Time to treatment failure.

ada = adalimumab; AEs = adverse events; AZA = azathioprine; CDLQI = Children's Dermatology Life Quality Index; CS = corticosteroids; DB = double-blind; DMARD = disease-modifying antirheumatic drugs; EU = European Union; eow = every other week; F = female; INF = infliximab; LI = lead-in; LOM = loss of motion; M = male; MTX = methotrexate; 6-MP = 6-mercaptopurine; NSAID = non-steroidal anti-inflammatory drugs; OL = open-label; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; pbo = placebo; PCDAI = Paediatric Crohn's Disease Activity Index; PediACR = paediatric American College of Rheumatology; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; SAEs = serious adverse events; SC = subcutaneous; SJC = swollen joint count; SSZ = sulfasalazine

- a. 4 subjects discontinued during the induction period, so they received at least 1 dose of adalimumab, but were not randomized into the Maintenance Period.

2.5.2. Pharmacokinetics

The pharmacokinetics (PK) and immunogenicity of adalimumab are well characterized in paediatric subjects in the approved indications of juvenile idiopathic arthritis (JIA; specifically the categories of polyarticular JIA [pJIA] and enthesitis-related arthritis [ERA]), paediatric psoriasis (Ps), and paediatric Crohn's disease (CD). These data have previously been assessed.

The proposed FD regimen is supported by population PK modelling and exposure response analyses evaluating multiple potential FD regimens with BW cutoffs for adalimumab in paediatric subjects with JIA (pJIA and ERA) and paediatric Ps. PK simulations were conducted using a population PK model that was developed previously based on adalimumab concentration data across different paediatric

indications in order to evaluate adalimumab PK across the paediatric age range and across the different disease populations. Exposure-response analyses for efficacy and safety were conducted in order to assess the potential clinical impact of PK differences associated with the FD regimens compared to current dosing based on BSA or BW for JIA and paediatric Ps, respectively.

A summary of paediatric studies is listed in the table below.

Table 1. Clinical Studies with PK Characterization

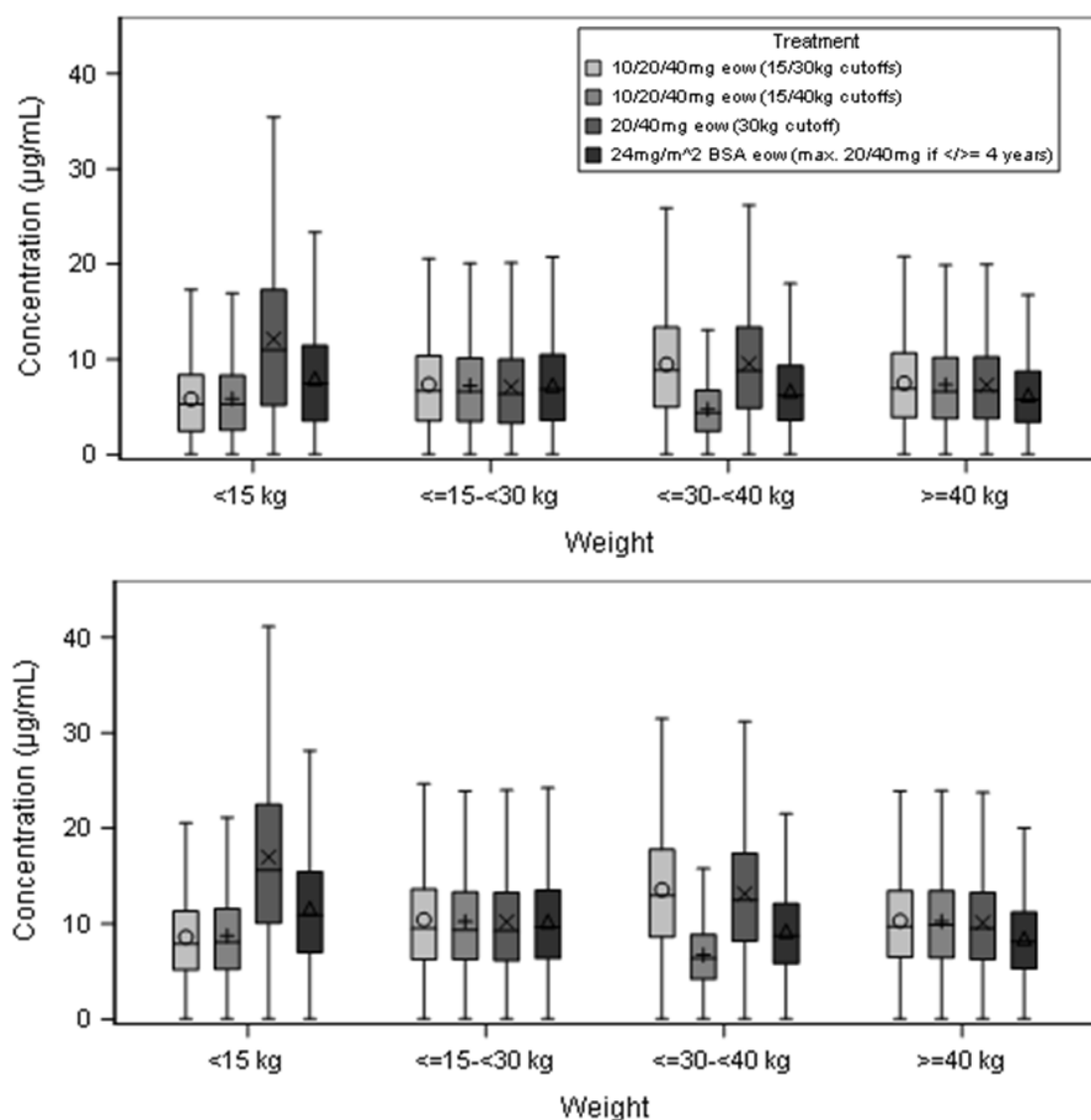
Study	Indication and Age Group	Study Drug Dosing Design
DE038	pJIA (4 – 17 years)	24 mg/m ² BSA in 5 mg increments in OL-LI and DB; fixed-dose in OLE based on body weight cutoff 30 kg
M10-444	pJIA (2 – 4 years)	24 mg/m ² BSA in 5 mg increments
M10-240	Japan pJIA (4 – 17 years)	Fixed dosing based on body weight cutoff 30 kg
M11-328	ERA (6 – < 18 years)	24 mg/m ² BSA in 5 mg increments
M04-717	Paediatric Ps (4 – < 18 years)	0.8 mg/kg or 0.4 mg/kg
M06-806	Paediatric CD (6 – 17 years)	Fixed dosing based on body weight cutoff 40 kg

A paediatric population PK model was previously developed based on adalimumab concentration data from a total of 524 paediatric subjects enrolled in studies of polyarticular JIA (Studies DE038 and M10-444), paediatric ERA (Study M11-328), psoriasis (Study M04-717), and CD (Study M06-806), as presented in PK Report, and in the EU variation procedure EMEA/H/C/481/II/134, assessing the use of adalimumab for the treatment of Ps in paediatric patients from 4 years of age and also in the EU variation procedure EMEA/H/C/000481/II/0154, supporting the use of adalimumab for the treatment of HS in adolescent patients. Subject demographics included an age range of 2 to 18 years and body weights from 11 to 120 kg. The final model parameter estimates were used to conduct PK simulations to evaluate potential fixed-dose regimens and compare expected concentrations to those using the BSA- and BW-based dosing regimens currently approved for JIA (pJIA and ERA) and paediatric Ps, respectively.

Standard methods have been used for population PK modelling and exposure simulations. The previously developed population PK model, based on data PK data in children 2-17 years old, describe the paediatric PK data sufficiently well according to the goodness-of-fit diagnostics and visual predictive checks.

In this application, serum adalimumab concentrations from each dosing regimen were compared for different BW categories in order to evaluate the potential FD options. The distribution of the simulated Week 12 pre-dose serum adalimumab concentrations by BW and dosing regimen for JIA patients are shown in Figure 1.

Figure 1. Distribution of Simulated Week 12 Serum Adalimumab Trough Concentrations by BW and Dosing Regimen (Without MTX [Top], with MTX [Bottom])



For the overall JIA population, as shown above, simulated serum adalimumab trough concentrations were also generally comparable between BSA-based dosing and the potential FD scenarios when stratified by BW categories. All observed trends were consistent regardless of concomitant use of MTX.

Additionally, to evaluate the potential FD options in the PS patient population, serum adalimumab concentrations from each dosing regimen were compared for different BW categories. The distributions of the simulated Week 11 pre-dose serum adalimumab concentrations for each dosing regimen are presented in Figures 2 and 3 by relevant BW or age category.

Figure 2. Distribution of Simulated Week 11 Serum Adalimumab Trough Concentrations by Dosing Regimen and BW (Upper) and Age (Lower) Categories Corresponding to Proposed Dosing in Paediatric Ps

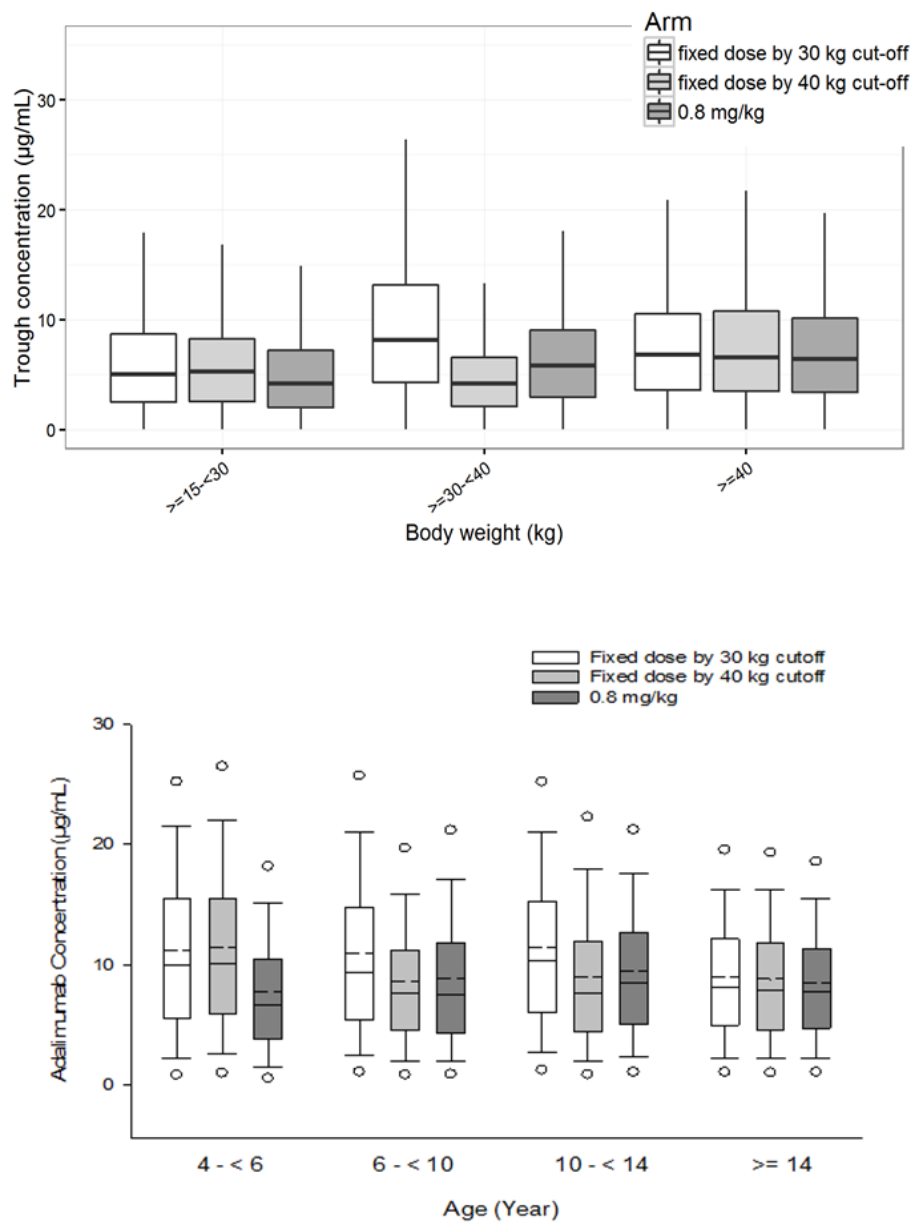
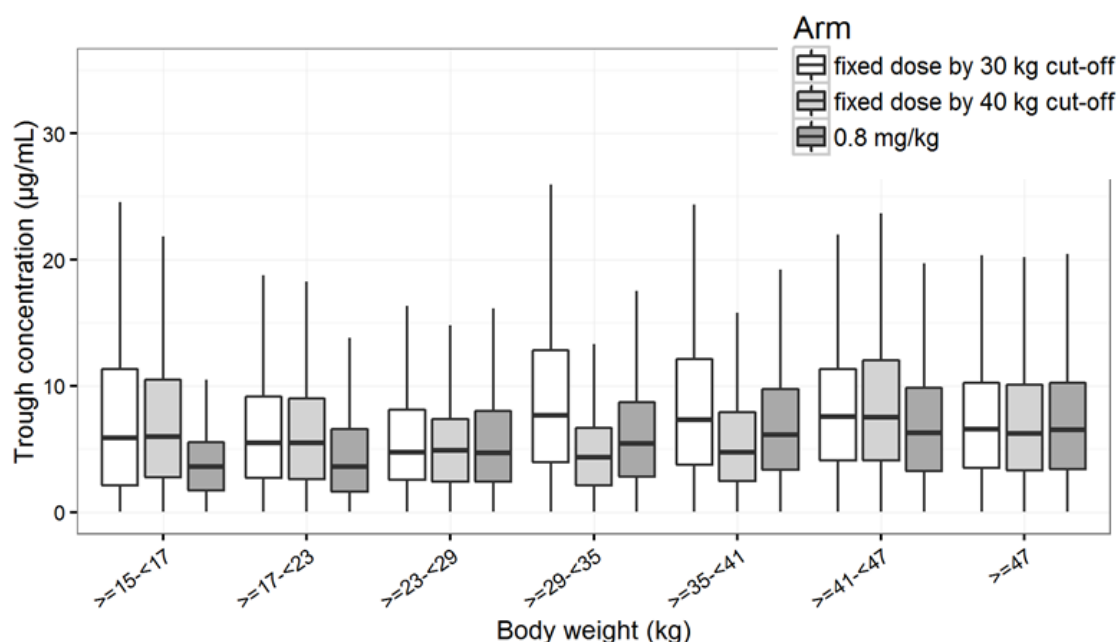


Figure 3. Distribution of Simulated Week 11 Serum Adalimumab Trough Concentrations by BW Categories Corresponding to Currently Approved 0.8 mg/kg Dosing Regimen in Paediatric Ps



The most notable differences between potential FD scenarios were observed for subjects with BW from 30 kg to 40 kg and ages 4 to < 6 years (Figure 2) and BW < 17 kg and from 29 kg to 41 kg (Figure 3). For subjects aged from 4 to < 6 years and with BW < 17 kg, both FD regimens generated approximately 2-fold higher concentrations than the 0.8 mg/kg regimen. For subjects with BW between 29 kg and 41 kg, the FD regimens with the 30-kg BW cutoff generated slightly higher adalimumab concentrations than the 0.8 mg/kg regimen and approximately 2-fold higher concentrations than the 40-kg cutoff, while the FD regimen with the 40-kg BW cutoff produced lower serum adalimumab concentrations than the 0.8 mg/kg regimen.

The slight under prediction of the observed median (which can be corrected with a more appropriate handling of LLOQ data) is considered acceptable. No differences in the adalimumab pharmacokinetics between indications were detected hence the paediatric population PK model is considered adequate for use of simulating adalimumab exposure (concentrations) for evaluating fixed-dose regimens in paediatric patients.

In JIA patients, the simulated trough concentrations given the proposed 20/40 mg dose, display higher levels in patients with body weights <15 kg, and 30 to 40 kg compared to the approved 24 mg/m² dosing regimen. Although for both weight groups there is a large overlap with the concentrations from the approved regimen. The explored alternative dosing regimen of 10/20/40 mg (15/30 kg cut-offs) display lower concentrations than the approved dosing regimen.

For Ps patients, the simulated trough concentrations display higher levels in patients with body weights <23 kg, compared to the approved 0.8 mg/kg dose. This is expected since patients <25 kg will receive a higher dose (20 mg) compared to the per body weight dosing. Also patients with body weights 30-40 kg display higher concentrations than the approved dosing regimen. However, the 40 kg cut-off provided slightly lower concentrations compared to the 0.8 mg/kg regimen.

Adalimumab Exposure-Efficacy Relationship in the Paediatric Population

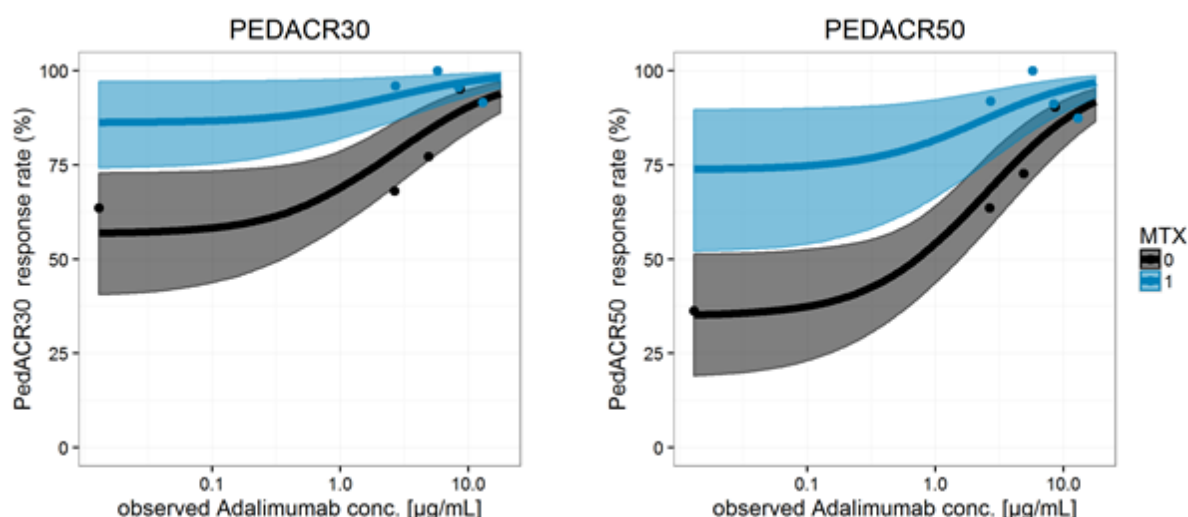
Exposure-response analyses for efficacy were conducted in order to assess the potential clinical impact of PK differences associated with the FD regimens in subjects with JIA and paediatric Ps. The

relationship between adalimumab exposure and efficacy in JIA suggests that there is a modest exposure-response relationship, whereas the relationship between adalimumab exposure and efficacy in paediatric Ps suggests that there is a clear exposure-response relationship.

Evaluation of Relationship Between Adalimumab Exposure and Efficacy Using Logistic Regression Analysis in pJIA

A logistic regression based statistical analysis was also conducted to evaluate the relationship between observed adalimumab exposure and the probability of achieving a PedACR30 or PedACR50 response. Baseline joint count and MTX co-medication were tested as covariates on minimum response and on EC₅₀. Only MTX co-medication was found to be significant on minimal response. The results of the logistic regression analysis are shown in Figure 4. There was an exposure-response relationship between adalimumab concentration and PedACR response rates in subjects with pJIA.

Figure 4. Exposure-Response and Logistic Regression Modeling Using Observed Data in pJIA Studies DE038 and M10-444

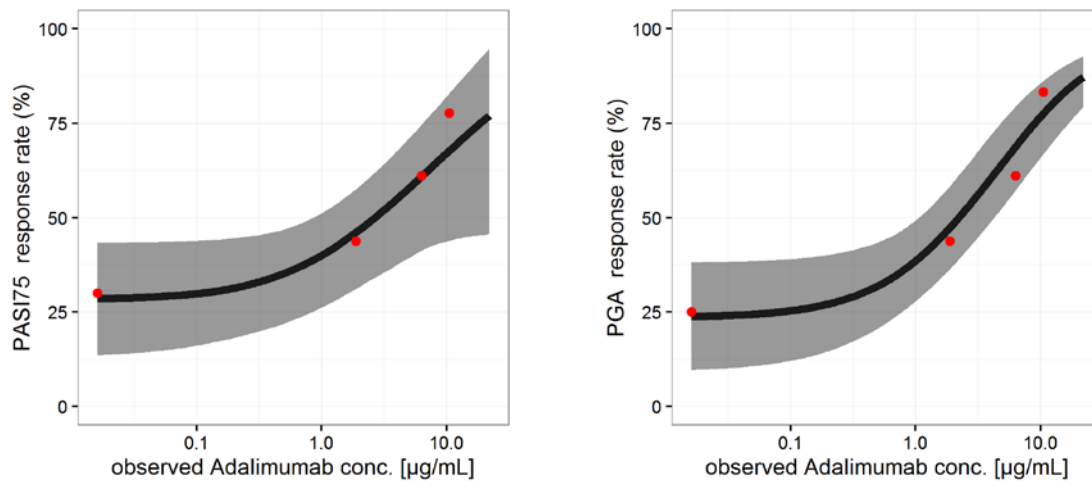


Note: solid line = predicted responder rate; shaded area = 90% prediction interval; circles = median response rate and concentration values of adalimumab trough concentration quartiles at Week 12 or 16, stratified by MTX co-medication.

Relationship Between Adalimumab Exposure and Efficacy Using Logistic Regression Analysis in Paediatric Subjects with Ps

A logistic regression based statistical analysis was also conducted to evaluate the relationship between observed adalimumab exposure and the probability of achieving a PASI 75 or PGA 0,1 response. The relationship was described with a logistic regression (with random effects) model as shown in Figure 5. Baseline PASI score was not statistically significant as an independent predictor of achieving the two ranked primary efficacy endpoints in Study M04-717.

Figure 5. Simulated PASI 75 and PGA (0,1) Using Logistic Regression Method in Paediatric Ps Subjects (Study M04-717)

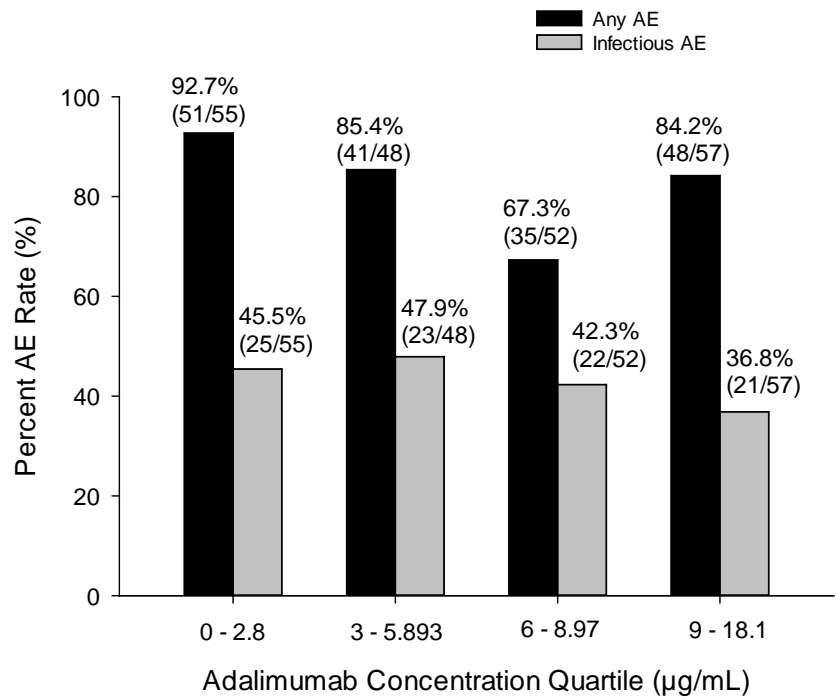


Note: black line = predicted responder rate; gray area = 90% prediction interval; red circles = median observed response rate at Week 16 and median values of Week 11 adalimumab trough concentration quartiles.

Evaluation of the Relationship Between Observed Adalimumab Concentration and Safety in Paediatric Subjects

The range of concentrations expected with the proposed FD regimens, based on population PK simulations, has been observed in paediatric subjects, with associated safety information presented in Figure 6 for JIA subjects, Figure 7 for Ps subjects, and Figure 8 for CD subjects with no apparent relationship between adalimumab concentrations and safety events. In addition, data from previous adalimumab development programs in adults includes doses up to 10 mg/kg intravenous for 6 months and 3 mg/kg for up to 2 years, plus doubling of approved sc doses in multiple indications (RA, Ps and CD), showing a similar safety profile across doses and exposures.

Figure 6. Relationship Between Adalimumab Concentrations and Adverse Events in JIA Subjects (ERA and pJIA)



Note: Data through Week 12 for Studies M10-444 and M11-328, data through Week 16 for Study DE038.

Figure 7. Relationship Between Adalimumab Concentrations and Adverse Events in Paediatric Ps Subjects During Double-Blind Treatment Phase (Through Week 16)

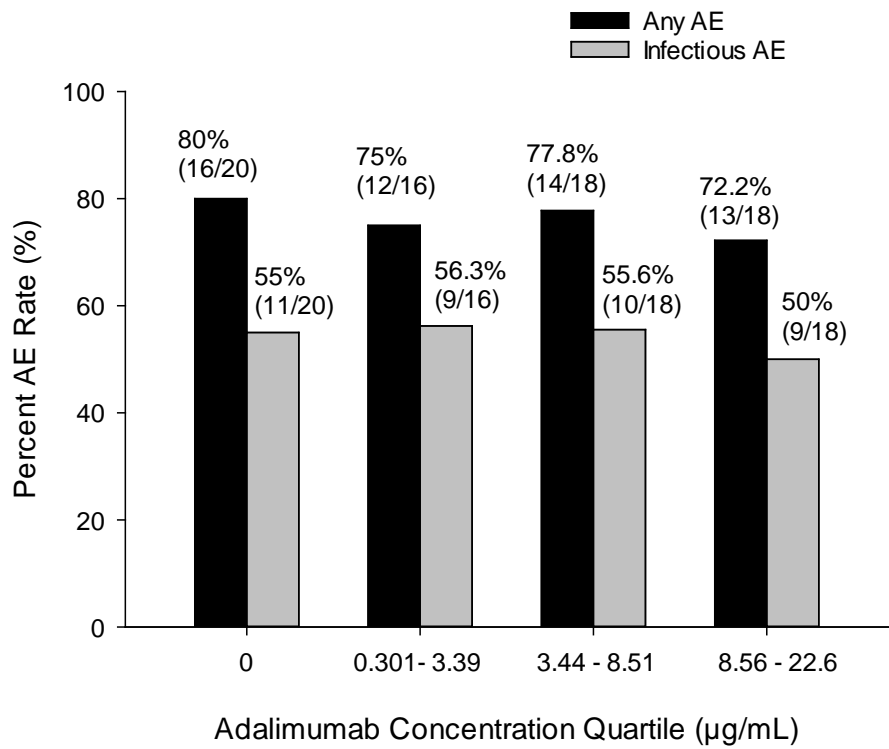
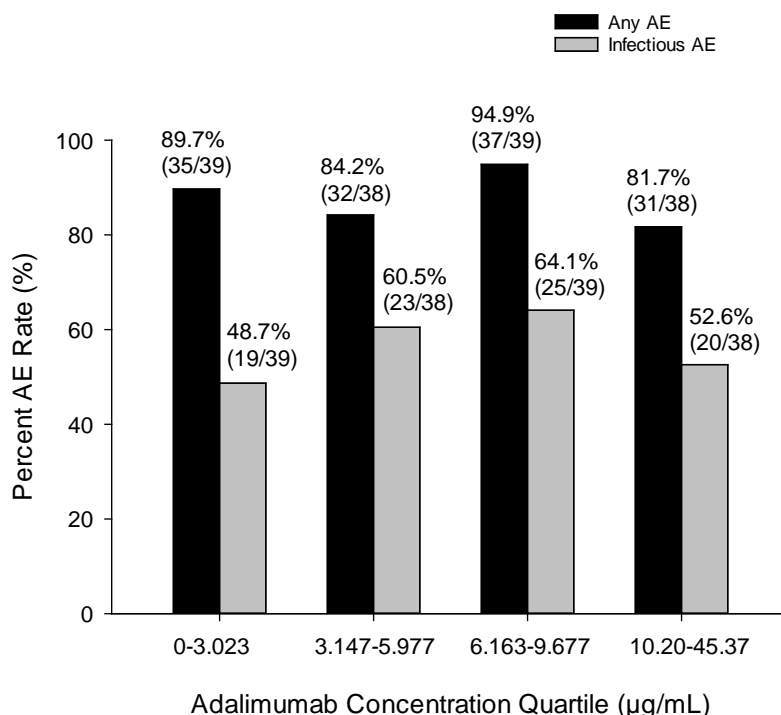


Figure 8. Relationship Between Adalimumab Concentrations and Adverse Events in Paediatric CD Subjects During Double-Blind Maintenance Phase (Week 4 to 52)



The analyses of PASI 75 and PGA 0,1 show a clear exposure-response relationship, indicating that the response increases with increasing adalimumab concentration. The PASI75 model does also indicate that a sigmoidal Emax model with a steeper slope might be more appropriate, however an improved model is not expected change the proposed dosing regimen.

The graphical analyses between adalimumab concentration and safety events display no indication of a relationship between adalimumab concentration and adverse events. However, for completeness, the applicant has been asked to provide graphs of serious infections and injection site reactions versus adalimumab concentration, respectively.

The Applicant has provided the requested graphs of serious infections in CD (Figure 9 and 10) and injection site reactions in CD, JIA and PS (Figures 9 to 12) versus adalimumab concentration. Visualisations for Serious Infections have not been generated for JIA and PS due to the very low numbers.

Figure 9. Relationship Between Adalimumab Concentrations and Serious Infectious Adverse Events and Injection Site Reaction Related Adverse Events in Pediatric CD Subjects During Open Label Induction Phase (Week 0 to 4)

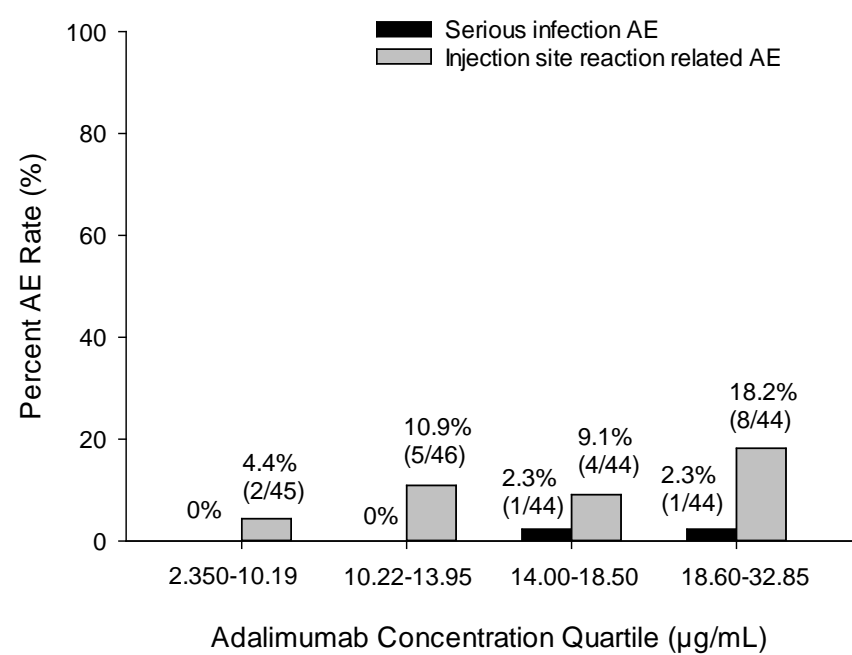


Figure 10. Relationship Between Adalimumab Concentrations and Serious Infectious Adverse Events and Injection Site Reaction Related Adverse Events in Pediatric CD Subjects During Double-Blind Maintenance Phase (Week 4 to 52)

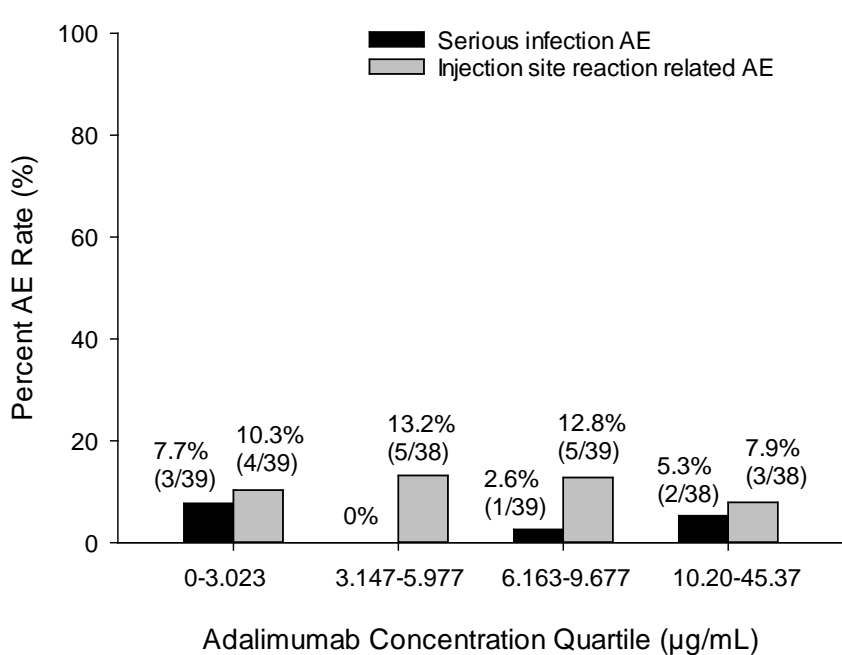


Figure 11. Relationship Between Adalimumab Concentrations and Injection Site Reaction Related Adverse Events in JIA Subjects (ERA and pJIA).

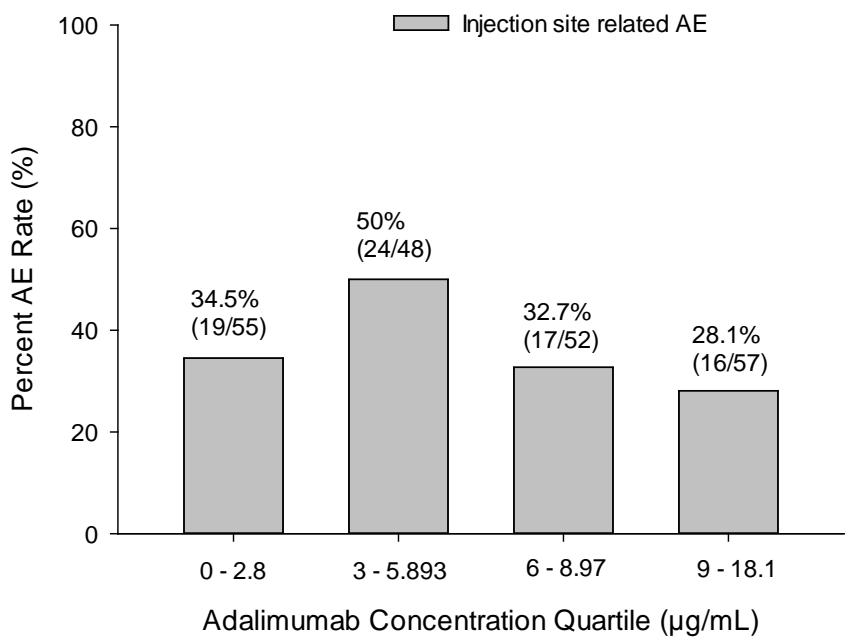
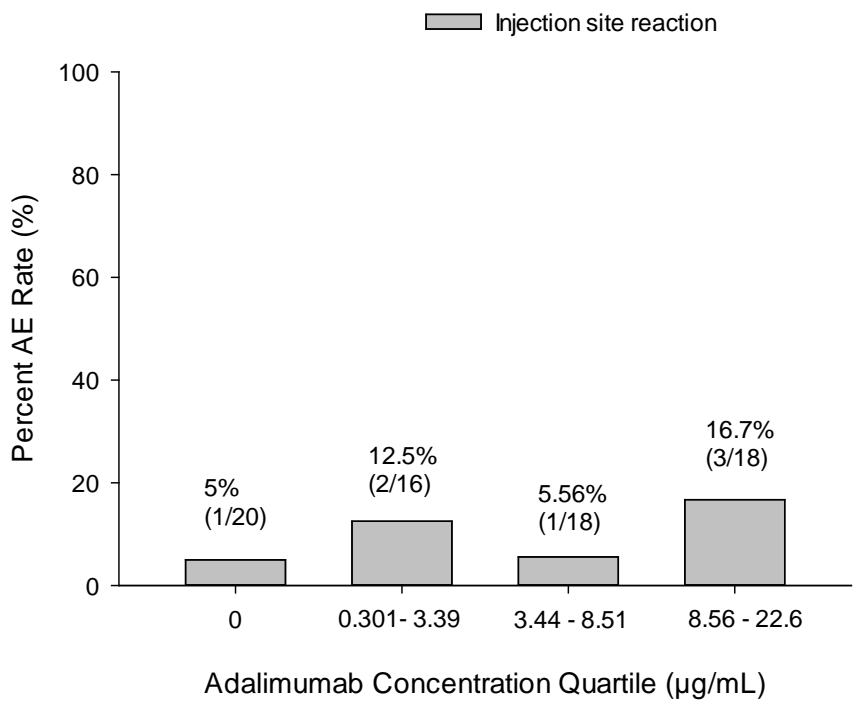


Figure 12. Relationship Between Adalimumab Concentrations and Injection Site Reaction Related Adverse Events in Pediatric Ps Subjects During Double-Blind Treatment Phase (Through Week 16)



Of note, a slight trend towards increased injection site reactions with increasing adalimumab concentrations was apparent for CD patients. However, it is agreed that overall no exposure-safety relationship of concern was detected in the present endpoints.

2.5.3. Pharmacodynamics

The application included no new PD data.

2.5.4. Discussion on clinical pharmacology

The MAH has provided adequate population PK modelling and simulations to evaluate the adalimumab exposure in the paediatric population, over several indications, given the proposed posology compared to the approved posology. Graphical display indicates that adequate functions have been used to account for the correlations between body weight and body surface area in the simulations.

In JIA patients, the simulated trough concentrations given the proposed 20/40 mg dose, display higher levels in patients with body weights < 15 kg, and 30 to 40 kg compared to the approved 24 mg/m² dosing regimen. Although for both weight groups there is a large overlap with the concentrations from the approved regimen. The explored alternative dosing regimen of 10/20/40 mg (15/30 kg cut-offs) display lower concentrations than the approved dosing regimen.

For Ps patients, the simulated trough concentrations display higher levels in patients with body weights < 23 kg, compared to the approved 0.8 mg/kg dose. This is expected since patients < 25 kg will receive a higher dose (20 mg) compared to the per body weight dosing. Also patients with body weights 30-40 kg display higher concentrations than the approved dosing regimen. However, the 40 kg cut-off provided slightly lower concentrations compared to the 0.8 mg/kg regimen.

Adequate methods have been used in the adalimumab exposure-response analysis. All investigated exposure-efficacy relationships indicate increasing effect with increasing adalimumab concentration. The PEDACR30/50 and Change in active joint count analyses suggest that the upper concentration range is approaching maximum effect (E_{max}), while there is a lower response in the lower concentration range. The PEDACR30 model (for patients without MTX) indicate that a sigmoidal E_{max} model with a steeper slope might be more appropriate, however an improved model is not expected change the proposed dosing regimen.

The analyses of PASI 75 and PGA 0,1 show a clear exposure-response relationship, indicating that the response increases with increasing adalimumab concentration. The PASI 75 model does also indicate that a sigmoidal E_{max} model with a steeper slope might be more appropriate, however an improved model is not expected change the proposed dosing regimen.

The graphical analyses between adalimumab concentration and safety events display no exposure-safety relationship of concern.

Data are consistent across indications and can be extrapolated to other indications.

2.5.5. Conclusions on clinical pharmacology

The paediatric population PK model based on adalimumab in several indications is appropriate for evaluating a potential fixed-dose regimen in paediatric patients across indications.

Some deviations between the fixed-dose regimen of 20/40 mg (30 kg cut-off) and the previous body size adjusted dosing regimens are present, with a general trend for slightly higher concentrations with the new dosing regimen.

All evaluated exposure-efficacy relationships display a general trend that increasing adalimumab concentrations lead to a beneficial response. Further, the exposure-safety relationships display no exposure-safety relationship of concern.

2.6. Clinical efficacy

2.6.1. Dose response studies and main studies

Main clinical studies with efficacy data

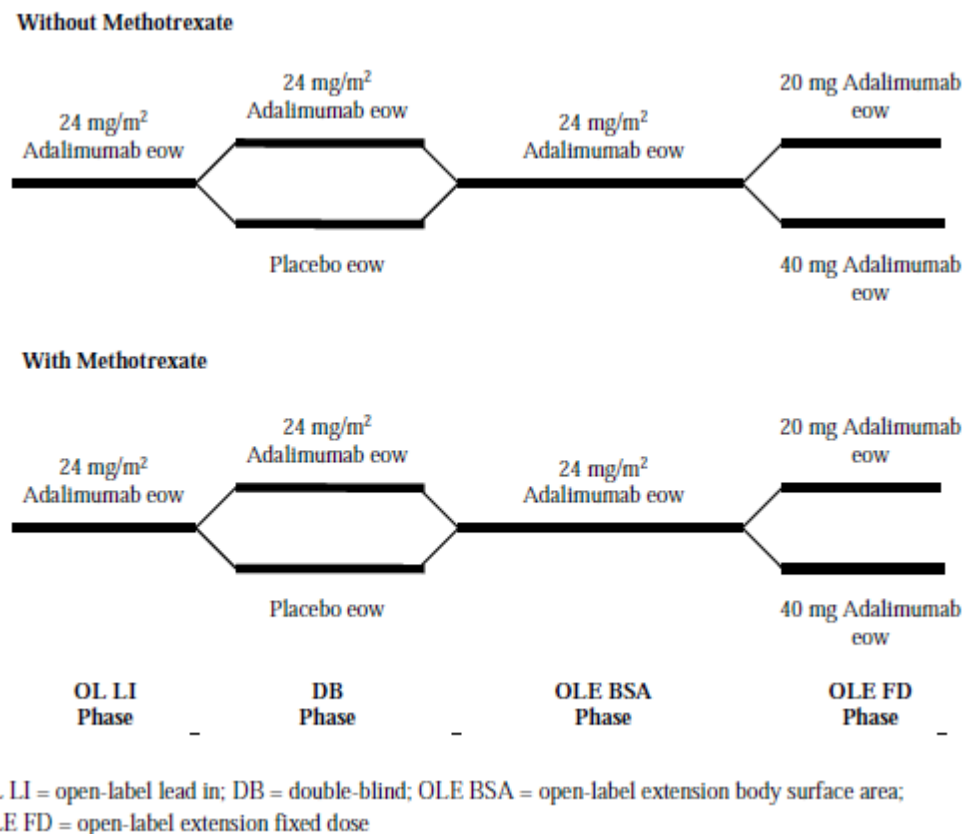
For JIA, four studies have been presented to support the variation (as described above). These are performed in patients with pJIA (DE038, M10-240 and M10-444) and enthesitis-related arthritis (ERA, study M11-328). For psoriasis, data are available from a study in paediatric plaque psoriasis (M04-717). The main clinical study to support this variation is DE038, where subjects treated with adalimumab in a BSA-based dose were transitioned to a FD, and change in PedACR 30/50/70/90 were compared between patients receiving a lowered/unchanged dose versus patients receiving a higher dose.

Clinical efficacy in pJIA, DE038:

Study DE038 was a multicenter, Phase 3, randomized, DB, stratified, parallel-group study in children (4 to 17 years old) with polyarticular JIA that were either treated or not treated with MTX. The study consisted of 4 phases: a 16-week Open-label Lead-in (OL LI), a 32-week DB phase, an up to 136-week Open-label Extension Body Surface Area (OLE BSA) phase, and an up to 224-week Open-label Extension Fixed-Dose (OLE FD) phase. Consequently, the total study duration could have been up to 408 weeks (102 months). The dosing by BSA was 24 mg of adalimumab per square meter (m²) up to a maximum of 40 mg total body dose administered SC eow. The dosing by FD in subjects weighing less than 30 kg was 20 mg of adalimumab SC eow and 40 mg SC eow in subjects weighing 30 kg or more. Non-MTX-treated subjects who were eligible for study enrollment could have been either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

A schematic presentation of the study design is found in the figure below.

Figure 13. DE038 Study Design



The open-label extension of the study allows a comparison between the BSA dose and FD. It should be noted, however, that these individuals are those who responded to adalimumab in earlier phases of the study. Subjects who did not respond to therapy in the open-label phase were discontinued from the study. A total of 128 subjects completed the DB phase and entered the OLE BSA phase. 106 subjects completed the OLE BSA phase and entered the FD phase; of these 62 subjects (58%) completed the OLE FD phase. In the OLE BSA phase, discontinuation was of the following reasons: 9 withdrew consent, 6 for 'other reasons' and 4 due to lack of efficacy. In the OLE FD phase, 44/106 (41.5%) prematurely discontinued primarily due to following reasons: lost to follow-up (13/106), 'other' reasons (13/106), withdrawal of consent (9/106), or lack of efficacy (3/106). Efficacy analyses were performed on the ITT population, however, it must be kept in mind that these patients were all primarily responders in earlier phases of the study.

Clinical efficacy in pJIA in Japanese patients, study M10-240

Study M10-240 was a Phase 3, single-arm, open-label safety, efficacy, and PK study designed to evaluate the efficacy (measured as PEDIACR30) of fixed-dose regimen of adalimumab in 25 Japanese paediatric subjects 4 through 17 years of age with active pJIA. The study was also designed to confirm the similarity between the data obtained from the Japanese subjects and those from Study DE038 in Western subjects. Adalimumab was given in combination with MTX (20 patients) or as monotherapy (5 patients). A 20-mg FD regimen with a 30-kg weight cut-off was used in Study M10-240. According to the study protocol, subjects weighing less than 30 kg were to be dosed with 20 mg of adalimumab every other week. Subjects weighing 30 kg or more were to be dosed with 40 mg of adalimumab every other week.

Clinical safety and efficacy in pJIA, study M10-444:

This was a phase 3b, open-label, postmarketing study aiming to evaluate the safety of adalimumab in subjects 2 to < 4 years of age and in subjects age 4 years and above weighing < 15 kg, with moderately to severely active polyarticular JIA or polyarticular course JIA. Primary endpoint was the incidence of SAEs and AEs. The secondary objectives of this study were to collect pharmacokinetic (PK) data (including anti-adalimumab antibody analysis [AAA]) and to evaluate the effectiveness of adalimumab in these subjects. Of the 32 subjects included, 84.4% were on concomitant MTX. The dosing was 24 mg/m² BSA (up to 20 mg) eow SC.

Clinical efficacy in ERA, study M11-328

In this phase 3, double-blind, placebo-controlled safety and efficacy study, 46 patients (6 to 17 years old) with active ERA were randomised to adalimumab in a BSA-based dose or placebo, in monotherapy or in combination with DMARDs. The dosing was 24 mg/m² BSA (up to 40 mg) eow SC.

Clinical efficacy in plaque psoriasis, study M04-717

This was a phase 3, randomized, double-blind study evaluating safety and efficacy of two dosing regimens of adalimumab versus methotrexate in 114 paediatric patients, 4 through 17 years of age, with severe chronic plaque psoriasis. All patients received a body-weight dosing regimen, either 0.8 mg/kg up to 40 mg or 0.4 mg/kg up to 20 mg. The 0.8 mg/kg dose is the approved dose. Co-primary endpoints were proportion of patients in adalimumab 0.8 mg/kg group vs MTX achieving ≥PASI 75 at week 16 and proportion of subjects achieving PGA 0.1 at week 16.

Summary of main efficacy results

Clinical efficacy in pJIA, study DE038:

Study DE038 consisted of 4 phases, including an open-label lead-in phase (OL LI), a double-blind phase, an open-label extension (OLE) BSA phase, and an OLE FD phase. For the 106 subjects enrolled in the FD phase, the transition from the OLE BSA phase to the OLE FD phase resulted in an increased (n=53), unchanged (n=50) or decreased (n=3) adalimumab dose. The paediatric American College of Rheumatology (PedACR) 30/50/70/90 response rates observed in the OLE BSA phase were, according to the MAH, maintained by greater than 90% of subjects through the duration of the OLE FD phase, regardless of whether the subjects' adalimumab dose remained the same, increased, or decreased. Results are provided in Table 4-Table 7 and Figure 14-Figure 16 below.

Table 2 PEDACR30 Responders through the OLE FD phase

Visit	MTX			Non-MTX			Overall		
	Same/Decreased N = 28	Increased N = 31	P value ^{a,b}	Same/Decreased N = 25	Increased N = 22	P value ^{a,b}	Same/Decreased N = 53	Increased N = 53	P value ^{a,b}
	N1/N2 ^c (%)	N1/N2 ^c (%)		N1/N2 ^c (%)	N1/N2 ^c (%)		N1/N2 ^c (%)	N1/N2 ^c (%)	
Week -72 (OLE BSA)	23/23 (100.0)	26/27 (96.3)	1.000	20/20 (100.0)	18/18 (100.0)	--	43/43 (100.0)	44/45 (97.8)	1.000
Week -56 (OLE BSA)	23/23 (100.0)	30/30 (100.0)	--	21/22 (95.5)	19/20 (95.0)	1.000	44/45 (97.8)	49/50 (98.0)	1.000
Week -40 (OLE BSA)	20/22 (90.9)	25/28 (89.3)	1.000	22/23 (95.7)	18/20 (90.0)	0.590	42/45 (93.3)	43/48 (89.6)	0.715
Week -24 (OLE BSA)	24/24 (100.0)	22/26 (84.6)	0.111	23/23 (100.0)	20/21 (95.2)	0.477	47/47 (100.0)	42/47 (89.4)	0.056
Week -8 (OLE BSA)	16/16 (100.0)	28/29 (96.6)	1.000	24/24 (100.0)	15/17 (88.2)	0.166	40/40 (100.0)	43/46 (93.5)	0.245
Week 0 (OLE FD)	24/24 (100.0)	29/29 (100.0)	--	24/24 (100.0)	20/21 (95.2)	0.467	48/48 (100.0)	49/50 (98.0)	1.000
Week 12 (OLE FD)	1/1 (100.0)	25/27 (92.6)	1.000	2/2 (100.0)	16/18 (88.9)	1.000	3/3 (100.0)	41/45 (91.1)	1.000
Week 16 (OLE FD)	23/24 (95.8)	28/29 (96.6)	1.000	23/24 (95.8)	18/19 (94.7)	1.000	46/48 (95.8)	46/48 (95.8)	1.000
Week 32 (OLE FD)	22/22 (100.0)	28/29 (96.6)	1.000	22/23 (95.7)	18/18 (100.0)	1.000	44/45 (97.8)	46/47 (97.9)	1.000
Week 48 (OLE FD)	20/22 (90.9)	27/29 (93.1)	1.000	23/23 (100.0)	17/17 (100.0)	--	43/45 (95.6)	44/46 (95.7)	1.000
Week 96 (OLE FD)	17/19 (89.5)	24/26 (92.3)	1.000	18/18 (100.0)	16/16 (100.0)	--	35/37 (94.6)	40/42 (95.2)	1.000
Week 112 (OLE FD)	16/16 (100.0)	23/25 (92.0)	0.512	16/16 (100.0)	15/15 (100.0)	--	32/32 (100.0)	38/40 (95.0)	0.499
Week 128 (OLE FD)	13/13 (100.0)	23/24 (95.8)	1.000	15/15 (100.0)	11/11 (100.0)	--	28/28 (100.0)	34/35 (97.1)	1.000
Week 144 (OLE FD)	8/8 (100.0)	20/21 (95.2)	1.000	13/13 (100.0)	7/7 (100.0)	--	21/21 (100.0)	27/28 (96.4)	1.000
Week 160 (OLE FD)	7/7 (100.0)	19/19 (100.0)	--	9/9 (100.0)	6/6 (100.0)	--	16/16 (100.0)	25/25 (100.0)	--
Week 176 (OLE FD)	5/5 (100.0)	19/20 (95.0)	1.000	7/7 (100.0)	6/6 (100.0)	--	12/12 (100.0)	25/26 (96.2)	1.000
Week 192 (OLE FD)	1/1 (100.0)	3/3 (100.0)	--	--	2/2 (100.0)	--	1/1 (100.0)	5/5 (100.0)	--
Week 208 (OLE FD)	--	3/3 (100.0)	--	--	2/2 (100.0)	--	--	5/5 (100.0)	--
Week 224 (OLE FD)	--	2/2 (100.0)	--	--	1/1 (100.0)	--	--	3/3 (100.0)	--
Final Visit (OLE FD) ^d	22/26 (84.6)	26/29 (89.7)	0.696	24/25 (96.0)	20/21 (95.2)	1.000	46/51 (90.2)	46/50 (92.0)	1.000

BSA = body surface area; OLE = open-label extension

a. The *P* value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's exact test was used.

b. Statistically significant, ****P* ≤ 0.001, ***P* ≤ 0.01, and **P* ≤ 0.05.

c. N1 = number of responders, N2 = number of subjects with non-missing responses.

d. Final visit = the last observation of each subject in the FD population.

Figure 12 PEDACR30 Responders through the OLE FD phase

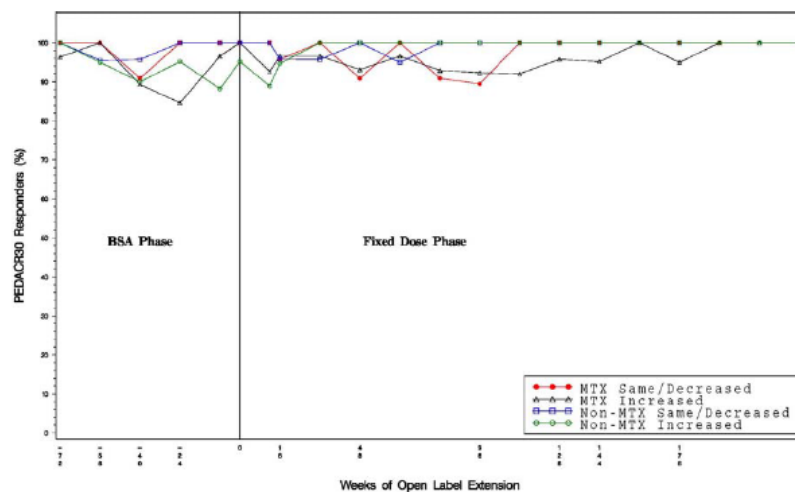


Table 3 PEDACR50 Responders through the OLE FD phase

Visit	MTX			Non-MTX			Overall		
	Same/Decreased N = 28	Increased N = 31	P value ^{a,b}	Same/Decreased N = 25	Increased N = 22	P value ^{a,b}	Same/Decreased N = 53	Increased N = 53	P value ^{a,b}
	N1/N2 ^c (%)			N1/N2 ^c (%)			N1/N2 ^c (%)		
Week -72 (OLE BSA)	23/23 (100.0)	25/27 (92.6)	0.493	20/20 (100.0)	18/18 (100.0)	--	43/43 (100.0)	43/45 (95.6)	0.495
Week -56 (OLE BSA)	22/23 (95.7)	28/30 (93.3)	1.000	21/22 (95.5)	19/20 (95.0)	1.000	43/45 (95.6)	47/50 (94.0)	1.000
Week -40 (OLE BSA)	19/22 (86.4)	25/28 (89.3)	1.000	22/23 (95.7)	18/20 (90.0)	0.590	41/45 (91.1)	43/48 (89.6)	1.000
Week -24 (OLE BSA)	23/24 (95.8)	22/26 (84.6)	0.351	23/23 (100.0)	20/21 (95.2)	0.477	46/47 (97.9)	42/47 (89.4)	0.203
Week -8 (OLE BSA)	15/16 (93.8)	26/29 (89.7)	1.000	23/24 (95.8)	15/17 (88.2)	0.560	38/40 (95.0)	41/46 (89.1)	0.442
Week 0 (OLE FD)	23/24 (95.8)	27/29 (93.1)	1.000	23/24 (95.8)	20/21 (95.2)	1.000	46/48 (95.8)	47/50 (94.0)	1.000
Week 12 (OLE FD)	1/1 (100.0)	24/27 (88.9)	1.000	2/2 (100.0)	16/18 (88.9)	1.000	3/3 (100.0)	40/45 (88.9)	1.000
Week 16 (OLE FD)	23/24 (95.8)	28/29 (96.6)	1.000	23/24 (95.8)	18/19 (94.7)	1.000	46/48 (95.8)	46/48 (95.8)	1.000
Week 32 (OLE FD)	22/22 (100.0)	27/29 (93.1)	0.500	20/23 (87.0)	18/18 (100.0)	0.243	42/45 (93.3)	45/47 (95.7)	0.674
Week 48 (OLE FD)	20/22 (90.9)	27/29 (93.1)	1.000	22/23 (95.7)	17/17 (88.2)	1.000	42/45 (93.3)	44/46 (95.7)	0.677
Week 96 (OLE FD)	17/19 (89.5)	24/26 (92.3)	1.000	18/18 (100.0)	16/16 (100.0)	--	35/37 (94.6)	40/42 (95.2)	1.000
Week 112 (OLE FD)	16/16 (100.0)	23/25 (92.0)	0.512	16/16 (100.0)	14/15 (93.3)	0.484	32/32 (100.0)	37/40 (92.5)	0.249
Week 128 (OLE FD)	12/13 (92.3)	22/24 (91.7)	1.000	15/15 (100.0)	11/11 (100.0)	--	27/28 (96.4)	33/35 (94.3)	1.000
Week 144 (OLE FD)	8/8 (100.0)	20/21 (95.2)	1.000	13/13 (100.0)	7/7 (100.0)	--	21/21 (100.0)	27/28 (96.4)	1.000
Week 160 (OLE FD)	7/7 (100.0)	19/19 (100.0)	--	9/9 (100.0)	6/6 (100.0)	--	16/16 (100.0)	25/25 (100.0)	--
Week 176 (OLE FD)	4/5 (80.0)	19/20 (95.0)	0.367	7/7 (100.0)	6/6 (100.0)	--	11/12 (91.7)	25/26 (96.2)	0.538
Week 192 (OLE FD)	0/1 (0.0)	3/3 (100.0)	0.250	--	2/2 (100.0)	--	0/1 (0.0)	5/5 (100.0)	0.167
Week 208 (OLE FD)	--	3/3 (100.0)	--	--	2/2 (100.0)	--	--	5/5 (100.0)	--
Week 224 (OLE FD)	--	2/2 (100.0)	--	--	1/1 (100.0)	--	--	3/3 (100.0)	--
Final Visit (OLE FD) ^d	19/26 (73.1)	26/29 (89.7)	0.164	23/25 (92.0)	20/21 (95.2)	1.000	42/51 (82.4)	46/50 (92.0)	0.148

BSA = body surface area; OLE = open-label extension

a. The *P* value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's exact test was used.

b. Statistically significant, ****P* ≤ 0.001, ***P* ≤ 0.01, and **P* ≤ 0.05.

c. N1 = number of responders, N2 = number of subjects with non-missing responses.

d. Final visit = the last observation of each subject in the FD population.

Figure 23 PEDACR50 Responders through the OLE FD phase

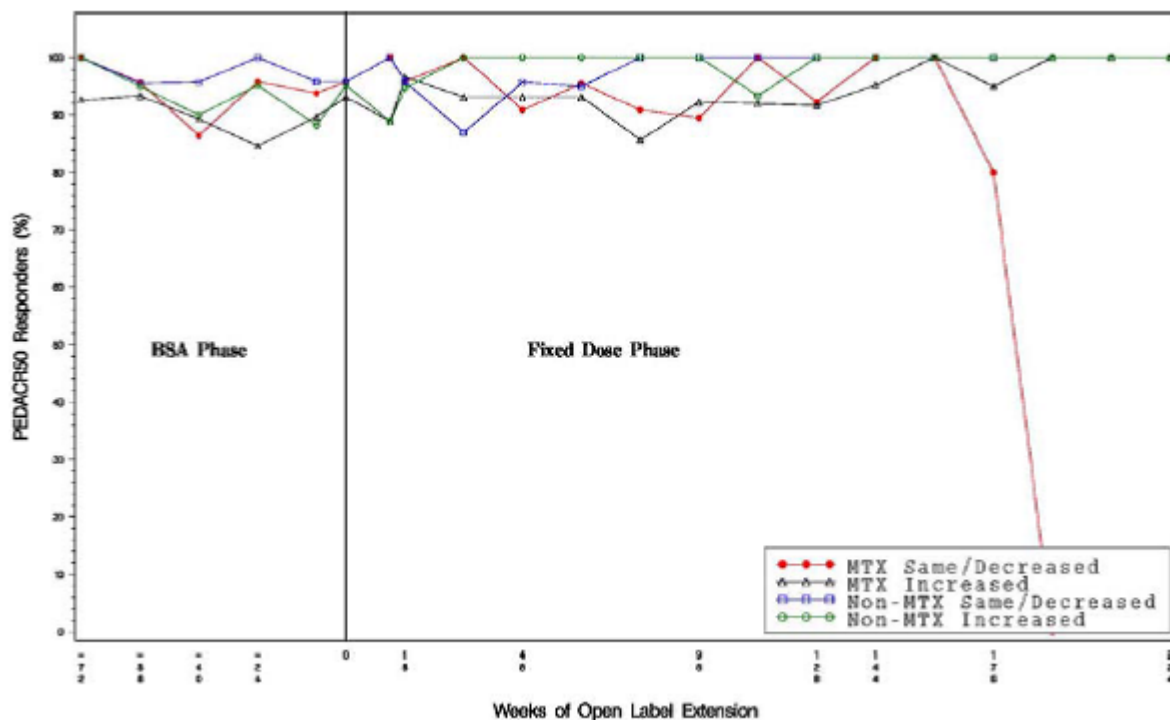


Table 4 PEDACR70 Responders through the OLE FD phase

Visit	MTX			Non-MTX			Overall		
	Same/Decreased N = 28	Increased N = 31	<i>P</i> value ^{a,b}	Same/Decreased N = 25	Increased N = 22	<i>P</i> value ^{a,b}	Same/Decreased N = 53	Increased N = 53	<i>P</i> value ^{a,b}
	N1/N2 ^c (%)			N1/N2 ^c (%)			N1/N2 ^c (%)		
Week -72 (OLE BSA)	18/23 (78.3)	21/27 (77.8)	0.967	17/20 (85.0)	15/18 (83.3)	1.000	35/43 (81.4)	36/45 (80.0)	0.868
Week -56 (OLE BSA)	20/23 (87.0)	27/30 (90.0)	1.000	17/22 (77.3)	19/20 (95.0)	0.187	37/45 (82.2)	46/50 (92.0)	0.152
Week -40 (OLE BSA)	18/22 (81.8)	24/28 (85.7)	0.718	19/23 (82.6)	17/20 (85.0)	1.000	37/45 (82.2)	41/48 (85.4)	0.676
Week -24 (OLE BSA)	22/24 (91.7)	21/26 (80.8)	0.420	22/23 (95.7)	19/21 (90.5)	0.599	44/47 (93.6)	40/47 (85.1)	0.181
Week -8 (OLE BSA)	13/16 (81.3)	22/29 (75.9)	1.000	21/24 (87.5)	15/17 (88.2)	1.000	34/40 (85.0)	37/46 (80.4)	0.578
Week 0 (OLE FD)	21/24 (87.5)	25/29 (86.2)	1.000	21/24 (87.5)	19/21 (90.5)	1.000	42/48 (87.5)	44/50 (88.0)	0.940
Week 12 (OLE FD)	1/1 (100.0)	24/27 (88.9)	1.000	1/2 (50.0)	16/18 (88.9)	0.284	2/3 (66.7)	40/45 (88.9)	0.336
Week 16 (OLE FD)	22/24 (91.7)	26/29 (89.7)	1.000	21/24 (87.5)	18/19 (94.7)	0.618	43/48 (89.6)	44/48 (91.7)	1.000
Week 32 (OLE FD)	20/22 (90.9)	25/29 (86.2)	0.688	18/23 (78.3)	18/18 (100.0)	0.056	38/45 (84.4)	43/47 (91.5)	0.298
Week 48 (OLE FD)	19/22 (86.4)	25/29 (86.2)	1.000	21/23 (91.3)	17/17 (100.0)	0.499	40/45 (88.9)	42/46 (91.3)	0.739
Week 96 (OLE FD)	15/19 (78.9)	24/26 (92.3)	0.377	18/18 (100.0)	16/16 (100.0)	--	33/37 (89.2)	40/42 (95.2)	0.411
Week 112 (OLE FD)	13/16 (81.3)	21/25 (84.0)	1.000	15/16 (93.8)	14/15 (93.3)	1.000	28/32 (87.5)	35/40 (87.5)	1.000
Week 128 (OLE FD)	11/13 (84.6)	21/24 (87.5)	1.000	15/15 (100.0)	11/11 (100.0)	--	26/28 (92.9)	32/35 (91.4)	1.000
Week 144 (OLE FD)	8/8 (100.0)	20/21 (95.2)	1.000	12/13 (92.3)	7/7 (100.0)	1.000	20/21 (95.2)	27/28 (96.4)	1.000
Week 160 (OLE FD)	7/7 (100.0)	18/19 (94.7)	1.000	9/9 (100.0)	6/6 (100.0)	--	16/16 (100.0)	24/25 (96.0)	1.000
Week 176 (OLE FD)	4/5 (80.0)	19/20 (95.0)	0.367	6/7 (85.7)	5/6 (83.3)	1.000	10/12 (83.3)	24/26 (92.3)	0.577
Week 192 (OLE FD)	0/1 (0.0)	3/3 (100.0)	0.250	--	2/2 (100.0)	--	0/1 (0.0)	5/5 (100.0)	0.167
Week 208 (OLE FD)	--	3/3 (100.0)	--	--	2/2 (100.0)	--	--	5/5 (100.0)	--
Week 224 (OLE FD)	--	2/2 (100.0)	--	--	1/1 (100.0)	--	--	3/3 (100.0)	--
Final Visit (OLE FD) ^d	18/26 (69.2)	25/29 (86.2)	0.128	21/25 (84.0)	19/21 (90.5)	0.673	39/51 (76.5)	44/50 (88.0)	0.130

BSA = body surface area; OLE = open-label extension

a. The *P* value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's exact test was used.

b. Statistically significant, ****P* ≤ 0.001, ***P* ≤ 0.01, and **P* ≤ 0.05.

c. N1 = number of responders, N2 = number of subjects with non-missing responses.

d. Final visit = the last observation of each subject in the FD population.

Figure 34 PEDACR70 Responders through the OLE FD phase

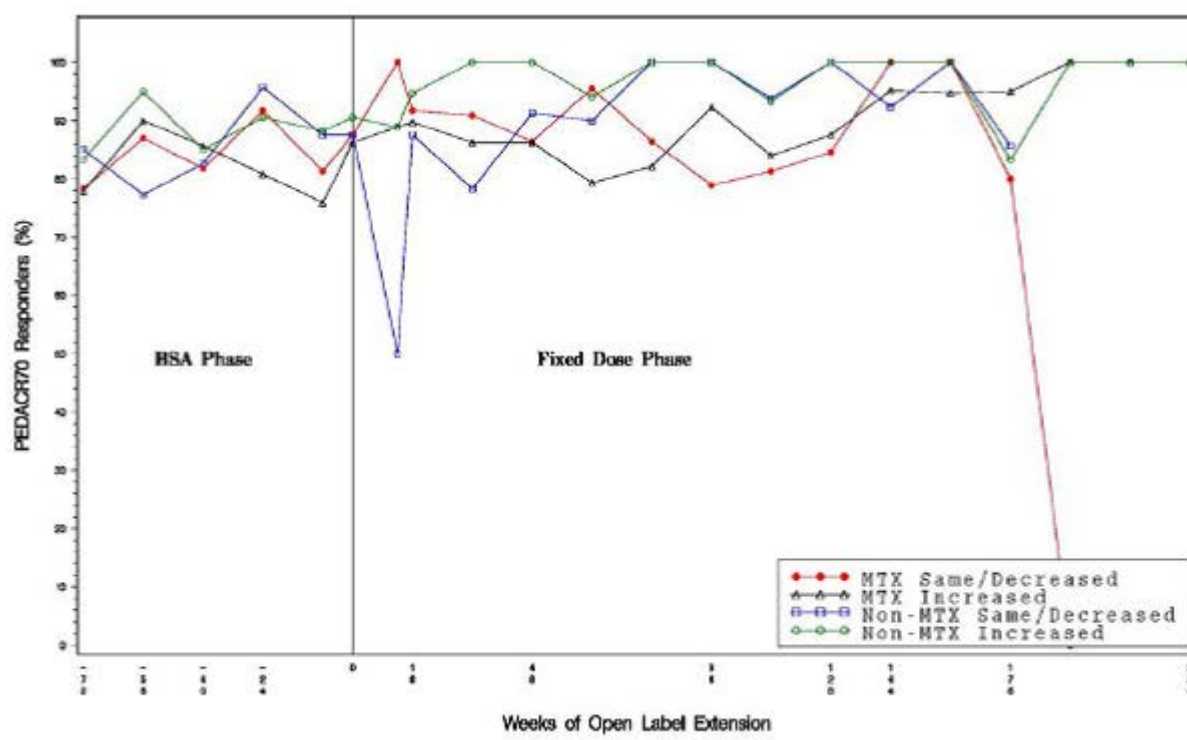


Table 5 PEDACR90 responders by dose change

VISIT	SAME/DECREASED DOSE (N=53) N1/N2 (%)	INCREASED DOSE (N=53) N1/N2 (%)	TOTAL (N=106) N1/N2 (%)	P-VALUE
WEEK (-120) (OLE BSA)	7/17 (41.2)	5/9 (55.6)	12/26 (46.2)	0.683
WEEK (-104) (OLE BSA)	11/28 (39.3)	7/17 (41.2)	18/45 (40.0)	0.900
WEEK (-88) (OLE BSA)	17/38 (44.7)	19/37 (51.4)	36/75 (48.0)	0.566
WEEK (-72) (OLE BSA)	25/43 (58.1)	26/45 (57.8)	51/88 (58.0)	0.973
WEEK (-56) (OLE BSA)	25/45 (55.6)	34/50 (68.0)	59/95 (62.1)	0.212
WEEK (-40) (OLE BSA)	28/45 (62.2)	29/48 (60.4)	57/93 (61.3)	0.858
WEEK (-24) (OLE BSA)	33/47 (70.2)	31/47 (66.0)	64/94 (68.1)	0.658
WEEK (-8) (OLE BSA)	26/40 (65.0)	29/46 (63.0)	55/86 (64.0)	0.850
BASELINE (OLE FD)	31/48 (64.6)	37/50 (74.0)	68/98 (69.4)	0.312
WEEK 12 (OLE FD)	0/3 (0.0)	32/45 (71.1)	32/48 (66.7)	0.032*
WEEK 16 (OLE FD)	36/48 (75.0)	38/48 (79.2)	74/96 (77.1)	0.627
WEEK 32 (OLE FD)	30/45 (66.7)	36/47 (76.6)	66/92 (71.7)	0.290
WEEK 48 (OLE FD)	32/45 (71.1)	37/46 (80.4)	69/91 (75.8)	0.299
WEEK 64 (OLE FD)	33/42 (78.6)	29/46 (63.0)	62/88 (70.5)	0.111
WEEK 80 (OLE FD)	31/41 (75.6)	33/44 (75.0)	64/85 (75.3)	0.948
WEEK 96 (OLE FD)	26/37 (70.3)	35/42 (83.3)	61/79 (77.2)	0.167
WEEK 112 (OLE FD)	25/32 (78.1)	29/40 (72.5)	54/72 (75.0)	0.584
WEEK 128 (OLE FD)	20/28 (71.4)	26/35 (74.3)	46/63 (73.0)	0.800
WEEK 144 (OLE FD)	18/21 (85.7)	20/28 (71.4)	38/49 (77.6)	0.311
WEEK 160 (OLE FD)	11/16 (68.8)	20/25 (80.0)	31/41 (75.6)	0.472
WEEK 176 (OLE FD)	7/12 (58.3)	19/26 (73.1)	26/38 (68.4)	0.460
WEEK 192 (OLE FD)	0/1 (0.0)	4/5 (80.0)	4/6 (66.7)	0.333
WEEK 208 (OLE FD)		4/5 (80.0)	4/5 (80.0)	
WEEK 224 (OLE FD)		3/3 (100.0)	3/3 (100.0)	
FINAL VISIT	33/51 (64.7)	35/50 (70.0)	68/101 (67.3)	0.571

When comparing outcome measures (pedACR30/50/70/90) between individuals with same/decreased dose versus increased dose, no statistically significant differences were seen in pedACR30/50/70. For pedACR90, there was a difference at Week 12 visit for patients comparing patients with an increased dose vs patients with decreased dose (66.7% vs 0%, $p=0.03$). Patients with maintained dose were not included in this analysis. When performing stratified analysis per age category, there were some differences. At Week 32 and at the Final visit, a greater proportion of subjects aged 9 to 12 years with increased doses were PedACR70 responders (100% at Week 32 and 95.7% at final visit) compared to subjects with the same/decreased doses (62.5% at Week 32 and 55.6 at final visit, $p=0.014-0.015$). At Week 48 and 96, a greater proportion of subjects aged 9 to 12 years with increased doses were PedACR90 responders (90.5 at Week 48 and Week 96) compared to subjects with the same/decreased doses (55.6% at Week 48 and 42.9% at Week 96, $p=0.049/0.021$).

Baseline characteristics differed somewhat between the groups, where more subjects in the same/decreased dose group were positive for RF than in the increased dose group. In addition, more subjects in the increased dose group had high CRP levels than in the same/decreased dose group.

Among the subjects in the same/decreased dose, only 3 received a decreased dose (2 on monotherapy and 1 on combination with MTX). Thus, only 3/106 subjects received a decreased dose, while 50/106 subjects remained on the same dose and 53/106 subjects had their dose increased.

Clinical efficacy in pJIA in Japanese patients, study M10-240

The results from this study demonstrated, according to the MAH, that a fixed-dose regimen of adalimumab 20 mg eow (<30 kg) or 40 mg eow (≥ 30 kg) was effective in reducing disease activity. PEDACR30 response rate was 92% (23/25 patients).

There were no indications of low efficacy from the study M10-240, in which a FD-regimen identical to the one currently proposed for pJIA was used. However, the number of subjects included in the study was low and there was no control group which limits the conclusions that can be drawn.

Clinical efficacy in pJIA, comparison of PedACR30/50/70/90 Results in a Subgroup Weighing 15 to < 30 kg in Studies DE038 and M10-240

In Study M10-240, Japanese subjects weighing < 30 kg (specifically, 15 to < 30 kg) received a 20-mg FD of adalimumab. Although the number of subjects in this weight category is small ($N = 8$), it allows a comparison with the matching weight category from the OL LI phase of Study DE038 in which 53 Western subjects received BSA-based dosing of adalimumab. The PedACR30/50/70/90 response at Week 16 was similar, despite different dosing regimens (Table 8).

Table 6 PedACR30/50/70/90 Responses by Visit for Subjects Weighing 15 to < 30 kg Treated with Adalimumab with Either FD (Study M10-240) or BSA-Based Dosing (Study DE038) Regimens for Initial 16 Weeks of Both Studies (NRI)

Response	Fixed Dosing Study M10-240 (Japan) n (%) Responders N = 8	BSA Dosing Study DE038 OL LI (EU/US) n (%) Responders N = 53
Week 2		
PedACR30	5 (62.5)	35 (66.0)
PedACR50	4 (50.0)	20 (37.7)
PedACR70	0	7 (13.2)
PedACR90	0	1 (1.9)
Week 4		
PedACR30	4 (50.0)	36 (67.9)
PedACR50	4 (50.0)	28 (52.8)
PedACR70	2 (25.0)	15 (28.3)
PedACR90	0	2 (3.8)
Week 8		
PedACR30	7 (87.5)	42 (79.2)
PedACR50	4 (50.0)	36 (67.9)
PedACR70	4 (50.0)	18 (34.0)
PedACR90	1 (12.5)	5 (9.4)
Week 16		
PedACR30	8 (100)	45 (84.9)
PedACR50	8 (100)	40 (75.5)
PedACR70	5 (62.5)	33 (62.3)
PedACR90	2 (25.0)	16 (30.2)

BSA = body surface area; EU = European Union; OL LI = open-label lead-in; PedACR = paediatric American College of Rheumatology; US = United States

From an efficacy perspective, individuals with weight <30 kg are of special interest since they, with the new proposed dosing regimen, will receive the lower FD of 20 mg. The number of responders in this weight group has been compared between study DE038 and M10-240. The number of patients is small and thus no safe conclusions can be drawn, however no big differences can be shown.

Clinical safety and efficacy in pJIA, study M10-444:

In this open-label study in children 2 to <4 years old or age 4 and above weighing less than 15 kg, 32 children with moderately to severe active pJIA were included. Results are shown in Table 9.

Table 7 PedACR30/50/70/90 Response at Week 12 and Week 24 (ITT Population)

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

a. NRI: Missing responses are imputed as non-response.

b. LOCF: Missing responses were imputed by last non-missing post-Baseline response.

Note: Only responder percentages are displayed. Percentages were calculated using non-missing values. N1 represents the number of subjects for either observed or imputed methods.

This was primarily a safety study as part of a submission for an extended indication for adalimumab, from 4 to 17 years of age to 2 to 17 years of age. All patients in this study were of <15 kg weight and the maximal given dose was 20 mg. Therefore, the efficacy is not expected to be negatively affected in this population when applying the FD regimen, since all subjects will receive a FD of 20 mg.

Overall, the clinical efficacy results from this study, which used BSA-dosing, are of limited interest for the current application.

Clinical efficacy in ERA, study M11-328

The primary endpoint was the percent change from baseline to week 12 in the number of active joints with arthritis, which was achieved with mean percent decrease of -62.6% in adalimumab patient compared to -11.6 in subjects in the placebo group (P = 0.039). Results are shown in Table 10 below, where results are compared across studies.

This study demonstrates the efficacy of adalimumab in ERA, but all patients were given a BSA-based dose and no direct conclusions can be drawn on the clinically efficacy of a fixed-dose regimen.

Clinical efficacy in paediatric plaque psoriasis (M04-717)

Proportion of subjects achieving \geq PASI 75 was significantly higher in adalimumab treated subjects compared to placebo, which was one of the primary endpoints. The other primary endpoint, proportion of subjects achieving PGA 0.1, was not met.

No results are available to compare clinical efficacy in paediatric psoriasis between the current (0.8 mg/kg BW in 5 mg increments up to 40 mg) and proposed (20 mg (15 kg to < 30 kg) and 40 mg (\geq 30 kg)) posologies. The proposed change in posology must therefore be supported only by PK data/simulations. PK-simulations demonstrated similar adalimumab concentrations for FD regimens and BW-based regimens see data above.

Summary of efficacy endpoints across indications

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8 Summary of Efficacy Endpoint Results from Studies M11-328, DE038, M10-444, and M10-240

Endpoint ^a	Study M11-328		Study DE038				Study M10-444		Study M10-240	
	Week 12 (DB)	Week 156	Week 16	Week 48 (DB)	Week 72 (OL BSA)	Final Visit (OL FD)	Week 12 (OL)	Week 120 (OL)	Week 24	Week 120
		(OL)	(OL LI)							
		BSA	BSA							
		BSA	BSA							
PBO/ADA	Total	Total	PBO/ADA	PBO/ADA	Total	Total	Total	Total		
Percent change from Baseline in AJC (0 – 68 ^b)	–11.6/–62.6 ^c	–88.3	–64.11	–80.85/–87.16	–82.0/–92.8	–87.8	–78.7	–100.0	-	-
Change from Baseline in AJC (0 – 68 ^b)	–2.5/–4.4	–6.9	–11.04	–11.33/–14.56	–13.6/–15.5	–14.3	–7.3	–7.3	–8.7	–9.5
Change from Baseline in SJC (0 – 68 ^d)	–2.4/–3.5	–5.5	–9.61	–10.38/–12.63	–12.3/–13.2	–12.5	–6.2	–7.3	–7.8	–8.4
Change from Baseline in TJC (0 – 72 ^e)	–4.5/–7.9	–10.8	–8.17	–7.42/–9.83	–9.2/–13.8	–11.4	–2.7	–1.3	–6.2	–6.8
Change from Baseline in Physician's Global Assessment of disease activity (0 – 100)	–22.1/–31.4	–44.3	–40.63	–46.75/–49.98	–45.2/–51.1	–47.0	–41.4	–56.3	–37.9	–45.4
Change from Baseline in Parent's Global Assessment–well being ^f (0 – 100)	–16.5/–29.2	–33.5	–29.63	–35.75/–38.54	–29.4/–42.8	–37.8	–28.1	–47.7	–20.7	–28.5
Change from Baseline in Parent's Global Assessment–pain (0 – 100)	–19.9/–32.5	–37.6	–31.63	–38.13/–38.61	–32.9/–38.7	–39.5	–27.2	–50.0	-	-
Change from Baseline in CHAQ (0 – 3)	–0.1/–0.2	–0.4	–0.59	–0.85/–0.75	–0.64/–0.86	–0.80	–0.5	–0.8	–0.3	–0.5

a. All endpoint change and percent change are mean values from Baseline.

b. For Study M10-444 and M10-240, AJC range was 0 – 73.

c. $P = 0.039$ for difference between treatment groups from ANCOVA with treatment group and baseline AJC in the model.

d. For Studies DE038, M10-444, and M10-240, SJC range was 0 – 66.

e. For Studies DE038, M10-444, and M10-240, TJC range was 0 – 75.

f. In Study M10-444, Parent's Global Assessment–Disease Activity and in Study M10-240, Patient's Global Assessment–Disease Activity.

Note: Data shown for Study M11-328 is LOCF and for Studies DE038 and M10-444 is as observed.

2.6.2. Discussion on clinical efficacy

Design and conduct of clinical studies

No new studies have been conducted to support this variation. Data has been obtained from previously submitted studies in pJIA, ERA and psoriasis. In study DE038, subjects with pJIA who were started on a BSA dose were switched to a FD and efficacy outcomes were compared between the two regimens. In study M10-240, 25 Japanese subjects with pJIA were treated with a FD adalimumab (20 or 40 mg).

In study M10-444, 32 subjects with pJIA with a body weight of <15 kg were treated with a BSA dose of adalimumab. Study M11-328 included 46 subjects with ERA treated with a BSA dose or placebo. Finally, in study M04-717, 114 subjects with paediatric plaque psoriasis were treated with BW-based adalimumab dose.

Efficacy data and additional analyses

The analysis of pharmacokinetic data and pharmacokinetic modelling is considered pivotal in this assessment, while clinical data is considered supportive. The clinical efficacy of the new proposed FD regimen is mainly supported by the results of the DE038 study in pJIA and the small study M10-240 in Japanese patients. In DE038, PED ACR30/50/70 responses were maintained after transition from BSA dose to FD, which is a direct comparison of the present and proposed regimens.

It is agreed with the MAH that response rates observed in the OLE BSA phase and the OLE FD phase of DE038 were generally similar. However, the design of the study makes the interpretation of the efficacy results difficult. All patients included in this open-label extension of the study had responded to adalimumab in earlier phases of the study. As stated in the advice given by CHMP, dose requirements in patients having already responded to a drug are less stringent than in patients initiating the treatment, and this must be taken into account when interpreting the results. Given the small number of patients actually receiving a lower dose with the FD regimen, it is not expected to have a major negative impact on the efficacy outcomes. The fact that of the 106 subjects who completed the OLE BSA phase, only 62 subjects (58%) completed the OLE FD phase is to be taken into account for the interpretation of data.

In summary, the outcome of the DE038 does not point to decreased efficacy for a FD dosing in which subjects weighing less than 30 kg was dosed 20 mg of adalimumab SC eow and subjects weighing 30 kg or more was dosed 40 mg SC eow compared to dosing by BSA; 24 mg of adalimumab per square meter (m²) up to a maximum of 40 mg SC eow. The study design clearly limits the conclusions that can be drawn from the data on clinical efficacy outcomes under the different dosing regimens. Still, this is probably not a major issue since in DE038, only 3/106 subjects received a decreased dose with the FD dosing compared with the BSA dosing and a similar outcome is expected if the FD dosing is to be introduced in clinical practice. I.e. one would expect that only a minority of JIA subjects would receive a lower dose with the proposed FD regimen compared to the current BSA regimen and thus reduced efficacy is not expected.

Regarding psoriasis, no results are available to compare clinical efficacy between the current (0.8 mg/kg BW in 5 mg increments up to 40 mg) and proposed (20 mg (15 kg to < 30 kg) 40 mg (\geq 30 kg)) posologies. The proposed change in posology must therefore be supported based on PK data.

Data is also obtained from a small study in Japanese patients with pJIA, a study in pJIA subjects of <15 kg weight and from studies in ERA. In these studies, no direct comparison has been made between the two dosing regimens. Thus for ERA, similarly as for psoriasis, the new dosing cannot be supported by clinical efficacy data but only by PK modelling and simulations.

2.6.3. Conclusions on the clinical efficacy

In summary no big differences in efficacy can be expected, since with the proposed FD posology, the majority of subjects are expected to increase dose and exposure (see pharmacokinetic section). The

advantage with a more uniform posology across indications can thus be endorsed from a clinical efficacy perspective.

2.7. Clinical safety

Patient exposure

Exposure to the FD regimen derives from the open-label phase of the placebo-controlled study DE038 in JIA, the Japanese open label study M10-240 in JIA, the post marketing observational registry study P10-262 in JIA, the phase 3 double blind study M06-806 in CD, the open label study M06-807 in CD, the post marketing observational registry study P11-292 in CD and the placebo-controlled, double masked study SYCAMORE in uveitis. Mean cumulative dose and mean duration of exposure for the studies referred to, are summarized by the applicant, see table below.

Table 9 Adalimumab Exposure

Dosing Regimen	Body Weight		Body Surface Area		Fixed Dose	
	Mean Cumulative Dose (mg)	Mean Duration of Exposure (Days)	Mean Cumulative Dose (mg)	Mean Duration of Exposure (Days)	Mean Cumulative Dose (mg)	Mean Duration of Exposure (Days)
Study DE038 ^a						
OL LI	–	–	232.4	95.1	–	–
DB	–	–	369.1	156.6	–	–
OLE BSA	–	–	1417.8	626.6	–	–
OLE FD	–	–	–	–	2475.6	922.6
Study M10-240 ^b	–	–	–	–	1852.8	721.8
Study M10-444 ^c	–	–	–	515.3	–	–
Study P10-262 (STRIVE) ^d	–	–	–	955.3	–	1146.5
Study M11-328 ^e	–	–	–	1147.1	–	–
Study M04-717 ^f	–	418.4	–	–	–	–
Study M06-806 ^g	–	–	–	–	796.3	288.7
Study M06-807 ^{h,i}	–	–	–	–	4355.2	1631.9
Study P11-292 (CAPE) ^{j,k}	–	–	–	–	–	129.1
SYCAMORE	–	–	–	–	– ^l	345.03

BSA = body surface area; DB = double blind; FD = fixed dose; LI = lead-in; OL = open label; OLE = open-label extension

a. Study DE038

b. Study M10-240

c. Study M10-444

d. RD160431

e. Study M11-328

f. Study M04-717

g. Study M06-806

h. Study M06-807 3rd Interim Report

i. Through 31 January 2015.

j. Study P11-292 2nd Interim Report

k. As of 31 May 2016 data cutoff date.

l. Mean cumulative dose (mg) not available. As of 01 June 2016, a mean total of 23.17 doses of adalimumab have been administered (SYCAMORE)

Overall, it should be kept in mind that the analysis of pharmacokinetic data and pharmacokinetic modelling is considered pivotal in the assessment of the new proposed FD-regimen while clinical data is considered complementary.

Relevant safety data for the present application stem primarily from JIA study DE038 and uveitis study SYCAMORE. Data from the other mentioned studies are considered supportive but of limited value due various reasons such as small study population, dosing that differs from the proposed dosing that this

procedure pertains to and difficulties to interpret comparisons between studies and geographical regions.

Of note, there are specific exposure and clinical safety data for the proposed FD-dose regimen for only two of the paediatric indications, pJIA and uveitis, for which the applicant aims to introduce the new dosing regimen. The uveitis indication is the focus of a parallel procedure (EMA/H/C/000481/II/0163) but the data from the uveitis population provide some support for the JIA indication as the populations overlap. There are no specific clinical safety data from FD-dosing for the ERA and the Ps population, instead the assessment entirely dependent on the PK analysis and modelling and extrapolations from the other indications. This is acceptable given the similarities of the populations but still a limitation.

Adverse events

Data from pJIA study DE038

DE038 (Art46), the study was a multicenter, Phase 3, randomized, DB, stratified, parallel-group study in children (4 to 17 years old) with pJIA that were either treated or not treated with MTX. The primary endpoint was the proportion of disease flare in the adalimumab-treated subjects compared to placebo treated subjects in the non-MTX stratum during the DB phase, occurred at Week 48. One of the secondary pharmacokinetic objectives of study DE038 was to compare the pharmacokinetics of FD eow based on body weight to variable eow dosing based on BSA of subjects rolled-over into the OLE FD phase of the trial whose pharmacokinetic samples were drawn. The study consisted of 4 phases: a 16-week Open-label Lead-in (OLLI), a 32-week DB phase, an up to 136-week Open-label Extension Body Surface Area (OLE BSA) phase, and an up to 224-week OLE FD phase. In the OLE BSA phase of Study DE038, subjects received OL adalimumab SC eow based on their BSA (i.e., 24 mg/m² BSA up to a maximum of 40 mg total body dose). In the OLE FD phase, subjects received either 20 mg of adalimumab SC eow (if weighed < 30 kg) or 40 mg of adalimumab SC eow (if weighed ≥ 30 kg), which is the posology being proposed in this submission. Subjects who met all entry criteria were enrolled into one of the 2 strata; with or without concomitant MTX). Subjects who responded positively to the OL therapy, as determined by PedACR30 response, entered the DB period. Subjects who experienced disease flare during the DB period or subjects who completed the DB period were given the option to enter the OLE period. Of the 171 subjects enrolled in the study, 128 entered the OLE BSA phase, 106 entered the OLE FD phase and 62 completed the OLE FD phase. The majority of subjects either remained on the same dose (50/106 subjects) or had their dose increased (53/106) in the OLE FD phase compared to the OLE BSA phase.

A side-by-side comparison of the exposure-adjusted rates for subjects in the OLE BSA and OLE FD phases of Study DE038 who received at least 1 dose of OLE FD study drug were presented by the applicant. The incidence rates for any AEs was 512.4/100 PYs in the BSA phase and 287.6/100 PYs in the FD phase. Incidence rates for serious AEs was 12.6/100 PYs in the BSA phase and 8.2/100 PYs in the FD phase. Incidence rates for infections was 146.4/100 PYs in the BSA phase and 99.4/100 PYs in the FD phase. Incidence rates for serious infections was 2.5/100 PYs in the BSA phase and 0.7 in the FD phase.

The most frequently reported TEAEs in both study phases were upper respiratory tract infection and viral infections. Injection site reactions and injection site pain was more frequent in the OLE BSA dosing phase than in the OLE FD dosing phase while symptoms from the joints appeared to be somewhat more frequent in the OLE FD phase. The incidence rates for injection site reaction related AEs were 148.4 E/100 PYs in the BSA phase and 9.3E/100 PYs in the FD phase. No deaths were reported.

The applicant presented an analysis of the TEAEs reported by subjects weighing 15 to < 30 kg in the OLE BSA phase (378.6 AEs/100 PYs, n=12) and OLE FD phases of Study DE038 (229.2 AEs/100 PYs, n=12). AEs were also presented according to whether the subjects increased their dose in the FD phase. In study DE038 (94.3% had any AE) or received the same/decreased dose in the FD phase compared to the BSA phase (90.6% had any AE).

The incidence rates for total number of AEs were lower during the OLE FD phase compared to the OLE BSA phase in study DE038. The incidence rates for serious AEs was also lower in the OLE FD phase as well as the number of infections, serious infections, injection site related reactions and hepatic-related AEs. The incidence rates for AEs in the BSA phase was comparable to the incidence rates for the overall treatment program for Humira for the JIA indication while the incidence rates for the FD phase was lower. The pattern of AEs in the two respective phases of the study does not cause any additional concern.

The applicant presented an analysis of the TEAEs in the OLE BSA and OLE FD phases of Study DE038 reported by subjects weighing 15 to < 30 kg as the applicant considers that this weight group is representative of the age group of 4 to 12 years of age who would be primarily affected by a dose change from a BSA-based dosing regimen to a FD regimen. There was no apparent increase in the frequency of AEs, serious AEs, infections, serious infections or injection site reactions in the FD phase compared to the BSA phase for these subjects.

It is noted that more subjects reported injection site reactions in the group that increased their dose in the FD phase of study DE038 compared to the group that received the same/decreased dose in the FD phase compared to the BSA phase. It is however acknowledged that overall, these events were rather few.

Overall, judging from the data presented above, the safety profile of the FD dosing appears more benign than the BSA dosing despite the fact that the vast majority of subjects either remained on the same dose (50/106 subjects) or had their dose increased (53/106) in the OLE FD phase compared to the OLE BSA phase. It should however be acknowledged that both subjects in the OLA BSA dosing phase and subjects in the OLE FD phase constituted very selected groups since the design of DE038 meant that subject that did not benefit from adalimumab or did not tolerate adalimumab were excluded earlier on in the study. Of note, 44 of the 106 subjects (42%) that entered the FD phase did not complete this phase while 22 of 128 subjects (17%) that entered the BSA phase did not complete this phase. Although a variety of reasons for the discontinuations were given, it is reasonable to assume that it was the patients that did best on and tolerated the treatment remained in the study which affects the comparison of AEs between the two dosing regimens.

Data from the pJIA study M10-240

In the summary of clinical safety included in the current application, the presentation of data from M10-240 was focused on the eight subjects that received the 20 mg FD i.e. subjects <30 kg and the comparison with 53 weight-matched BSA-dosed subjects in DE038. The percentage of subjects that had any AEs were 87.5% in the FD-group of the M10-240 study and 86.8% in the BSA-based dosing group in the DE38 study, the frequency for serious AEs was 12.5% vs 9.4% and the frequency for infections were 50.0% vs 50.9%. There were no serious infections reported for this time period for the two groups.

It is noted that according to the study report of M10-240, subjects weighing 30 kg or more were to be dosed with 40 mg of adalimumab eow which is also consistent with the proposed FD posology of this application. It is thus not clear why the focus in the presentation of data from M10-240 is entirely on the eight subjects <30 kg that received the 20 mg FD, discarding the safety data from rest of the 17 subjects in the study. This safety data was thus retrieved from the study protocol of study M10-240. In

total 25 Japanese pJIA subjects were included in study M10-240 and safety data up to week 60 was presented in the study report. Up to week 60, 25/25 subjects experienced any AE, 6/25 (24%) experienced any serious AE, 24 (96%) experienced any infection, 4 (16%) experienced any serious infectious AE, 6 (24%) experienced injection site reaction related AEs. Incidence rates (events/100 PY) were 655.9 for any AE, 22.3 for any serious AE, 275.3 for any infectious AE, 8.1 for any serious infectious AE, 16.2 for injection related AE. Thus overall, the incidence rates for AEs, SAEs, infections and serious infections are higher than the corresponding figures that was presented by the applicant for the overall treatment program for JIA. The reasons for this are not clear. However, as the study included only 25 subjects the conclusions that can be drawn from the safety data are limited.

Data from pJIA registry study P10-262

The applicant presented an overview of TEAEs reported as of 01 June 2015 by patients in post marketing registry Study P10-262 who received adalimumab dosing by either a BSA-based dosing regimen or a FD regimen as per local label. Incidence rates for any AE were 46.4/100 PYs for subjects dosed with FD regimen and 40.5/100 PYs for subjects dosed with BSA-based dosing while the corresponding figures for any serious AEs were 4.8/100 PYs and 10.7/100 PYs.

The comparison between FD-dosing and BSA-dosing based on registry data has to be interpreted with caution due to its many limitations including the fact that two different geographic regions with possible differences in treatment praxis and proneness to report AEs were compared. It is also not explicitly stated that the FD dosing in US and Australia is identical (including identical bodyweight-cut offs) to the FD-dosing proposed in this application. That being said, a rough assessment of total number of AEs, serious AEs, infections and serious infections for the whole population did not point at any clear safety advantage for any of the two dosing regimens. Also for the subgroup of patients weighing 15 kg to <30 kg, the safety profile for the two dosing-regimens appeared comparable.

Data from JIA-associated uveitis study SYCAMORE

The SYCAMORE study was a randomized, controlled Phase 3 study assessing the safety and effectiveness of adalimumab in combination with MTX for the treatment of JIA-associated uveitis. A total of 90 subjects were randomized to adalimumab (N = 60) or placebo (N = 30). Treatment was administered concomitantly as a FD regimen with a stable dose of MTX (10 mg/m² up to a maximum dose of 25 mg).

The overall incidence rate of AEs was for the adalimumab group 1007 events per 100 patient years [E/100 PYs] and for the placebo group (651 E/100 PYs). The rate of SAEs was in the adalimumab group 29 E/100 PY and in the placebo group 19 E/100 PY. The most common AEs in the adalimumab group were classified as infections and infestations (76.7% in the adalimumab group, 40% in the placebo group), respiratory, thoracic and mediastinal disorders (51.7% in the adalimumab group, 20% in the placebo group; most frequently reported events were cough and oropharyngeal pain), general disorders and administration site conditions (50% in the adalimumab group and 23.3% in the placebo group; including 33 events of pyrexia reported in 12 patients in the adalimumab arm) gastrointestinal disorders (43.3% in the adalimumab group and 26.7% in the placebo group; most frequent events were diarrhoea and vomiting), nervous system disorders (26.7% in the adalimumab group and 13.3% in the placebo group; including 21 events of headache in 12 adalimumab patients), musculoskeletal and connective tissue disorders (25% in the adalimumab group and 20% in the placebo group), investigations (25% in the adalimumab group, 10% in the placebo group), and eye disorders (23.3% in the adalimumab group and 26.7% in the placebo group). The 5 severe AEs in the adalimumab group were cataract, injection site reaction, tonsillitis, arthralgia and arthritis. The 3 severe AEs in the

placebo group were anterior chamber flare (2 events in the same subject) and uveitis. No death were reported. The most frequently reported SAEs in the adalimumab group were infections.

The safety results from the SYCAMORE Study is of interest as the study population is at least overlapping with the target population of this application and the dosing according to weight is identical to the proposed FD dosing in this application. Compared to the overall AE and SAE incidence rate from Humira JIA treatment program data, the SYCAMORE AE and SAE incidence rates in the Humira treatment group appear surprisingly high. It is acknowledged that also the incidence rate for AEs and SAEs were rather high also in the placebo group which could be interpreted as this specific population being more prone to develop AEs or be a reflection of the effectiveness of the AE reporting system in this trial. One reason for this population being more prone to develop AEs than the overall adalimumab treated population could be that in the SYCAMORE study adalimumab for all subjects was to be administered on top of Methotrexate which was not the case in the overall adalimumab programme. An explanation for a potentially increased proneness to report AEs in the SYCAMORE study compared to the overall programme could be that the SYCAMORE study was an investigator-initiated study.

The results from the SYCAMORE study have been reviewed in EMEA/H/C/000481/II/0163 within which the study report was submitted. The current application included a reference to the parallel uveitis procedure and the SYCAMORE study report. In this study the incidence rates of infections and serious infections were higher in the adalimumab arm of the SYCAMORE study than in previous adalimumab JIA studies. Some of the AEs that were not classified as infections could be related to infections; this concern for example cough, oropharyngeal pain, pyrexia, diarrhoea etc. However, the incidence rate of infections in the placebo arm in SYCAMORE was also comparable to the incidence rates of infections for adalimumab-treated subjects in previous JIA-studies strengthening the previous suspicion that the study population in SYCAMORE could consist of a population being more prone to develop AEs (including infections) or that the safety outcome could reflect the relative effectiveness of the AE reporting system in this trial.

Serious adverse event and deaths

As previously noted, exposure to the FD regimen derives from the open-label phase of the placebo-controlled study DE038 in pJIA, the Japanese open label study M10-240 in pJIA, the post marketing observational registry study P10-262 in pJIA, the phase 3 double blind study M06-806 in CD, the open label study M06-807 in CD, the post marketing observational registry study P11-292 in CD and the placebo-controlled, double-masked study SYCAMORE in uveitis. In addition to these studies, data from other pediatric studies using different dosing regimens were also included and discussed in the present application.

No deaths were reported in Studies DE038, M10-240, M10-444, P10-262, M11-328, M06-806, M06-807, P11-292 or SYCAMORE i.e. there were no deaths in the studies in which a FD-dosing was used.

A summary of SAEs across paediatric indications were presented by the Applicant:

- **JIA:** In the OLE phases of Study DE038, SAEs were more common for subjects receiving a BSA-based dosing regimen than subjects receiving a FD regimen of adalimumab. For the subgroup of subjects weighing 15 to < 30 kg in the OLE of Study DE038, more subjects receiving a BSA-based dosing regimen of adalimumab reported SAEs than subjects receiving a FD of adalimumab (no subjects receiving a FD regimen reported). The rate of SAEs in Study P10-262 was higher in countries using a BSA-based dosing of adalimumab than in countries using a FD regimen

- CD: The applicant summarized the SAE data from the CD population (see more information in the clinical AR)
- Uveitis: In the SYCAMORE study, the rate of SAEs was in the adalimumab group (29 E/100 PY) and in the placebo group (19 E/100 PY). There were a total of 17 SAEs reports in the adalimumab group and 3 SAEs in the placebo group during the course of the trial.

Judging from the pJIA data derived from study DE038 and P10-262 that the applicant have presented, SAEs do not occur more frequently with the FD dosing compared to BSA based dosing. However, the data presented need to be interpreted with caution due to several limitations.

The applicant also summarized the SAE data from the CD population but this data have poor relevance for this procedure, primarily since the investigated posology and analysis conducted were not coherent with the focus of this variation.

The safety results from the Uveitis SYCAMORE Study is of interest as the study population is at least overlapping with the target population of this application and the dosing according to weight is identical to the proposed FD dosing in this application. In this study, the incidence rate for SAEs was higher than in previous studies on similar populations. According to the SYCAMORE study report, there were a total of 17 SAEs reports in the adalimumab group and 3 SAEs in the placebo group during the course of the trial. Overall 13 (21.7%) and 2 (6.7%) of the patients in the adalimumab and placebo groups respectively, had at least one SAE. The SAEs reported in the 13 patients in the adalimumab group were varicella, streptococcal infection, diarrhoea, syncope (reported together with diarrhoea) viral infection, scarlet fever, cellulitis, infected bites, lower respiratory tract infection, cataract, testes exploration, antiviral prophylaxis, food poisoning, and tonsillar hypertrophy. The SAEs reported in the two patients in the placebo group were anterior chamber flare and uveitis. The most frequently reported SAEs in the adalimumab group were infections (10 events in 8 patients).

As previously stated, specific clinical safety data concerning from the proposed FD dos regimen are lacking for the ERA and Ps indications, instead the safety assessment for these indications has to rely on the PK analysis and modelling and extrapolations from the other indications. Although probably acceptable given the similarities between the populations, this is still considered a limitation.

Discontinuation due to adverse events

JIA

In Study DE038, no subjects discontinued study drug due to an AE from the OLE BSA phase, while 5 subjects discontinued from the FD phase. Of the subjects who discontinued because of an AE, 4 subjects had a dose decrease or their dose remained the same and 1 subject had a dose increase. Among the subgroup of subjects in Study DE038 weighing 15 kg to < 30 kg, no subjects discontinued due to an AE from the OLE BSA phase, while 2 subjects discontinued from the OLE FD phase.

No subjects in Study M10-240 discontinued due to an AE.

As of 01 June 2015, the rate of TEAEs leading to discontinuation of study drug in Study P10-262 (STRIVE) was according to the applicant slightly higher in countries using BSA-based dosing regimens of adalimumab than in countries using FD regimens of adalimumab (please see details in above sections of this AR). Among subjects weighing 15 kg to < 30 kg, only 1 subject receiving BSA-based dosing discontinued study drug.

Uveitis

In the SYCAMORE study, 9 subjects (15%) in the adalimumab group discontinued treatment prematurely during the course of the trial.

Discontinuations due to AEs generally appeared quite rare independently of dosing regimens.

2.7.1. Discussion on clinical safety

Introduction

This procedure concerns changes to a FD posology for the paediatric indications JIA, ERA (currently BSA-dependent posology) and Ps (currently BW-dependent posology). FD-dosing is proposed also for the new indication uveitis which has been evaluated in a parallel procedure (EMA/H/C/000481/II/0163). No changes are proposed in the paediatric indications for which a fixed-dose posology is already applied (CD, HS). The changes are reflected in section 4.2 of the SmPC for the new dose-strength 20 mg prefilled syringe, that is included as a line extension in this application, as well as the changes proposed in the SmPCs for the currently approved presentations. Furthermore the applicant proposes to add a statement on immunogenicity in JIA in section 5.1 of the SmPC referring to data from a previous procedure, this short addendum is accepted.

The pharmacokinetic data and pharmacokinetic modelling are considered pivotal for the proposed FD-regimen while the clinical efficacy and safety data is regarded as complementary.

The safety data that the applicant refers to as support for the proposed FD regimens of adalimumab are from clinical trials and from a post-approval commitment to the FDA/PIP requirement of the EMA. These studies have been conducted in patients with pJIA (phase 3 studies DE038 and M10-240 [Japan], post-marketing compassionate use study M10-444, and registry study P10-262 [STRIVE]), ERA (Study M11-328), paediatric Ps (Study M04-717), paediatric CD (Studies M06-806, M06-807, and P11-292 [CAPE]), and paediatric uveitis (the SYCAMORE study). Study reports have been previously submitted for these studies. A central scientific advice was given regarding the issue was received in June 2016 (EMA/SAWP/401051/2016). Some points were raised by the SAWP/CHMP and appear to have been generally addressed/ implemented.

In the Summary of Safety submitted with this application, an overview of AEs in the treatment programs for Humira across indications was provided. The overall incidence rates of AEs for the adalimumab paediatric indications of JIA, Ps, and CD were reported to be 525.3 E/100 PYs, 518.5 E/100 PYs, and 566.5 E/100 PYs, respectively. The overall incidence of SAEs were 13.5/100 PYs, 7.4/100 PYs and 32.2 /100 PYs respectively. The overall incidence of infections were 150.7/100 PYs, 168.7/100 PYs, 132.0/100 PYs respectively. The overall incidence of serious infection was 2.7/100 PYs, 0.8/100 PYs, 6.6/100 PYs respectively. The overall incidence of injection site reactions were 104.6/100 PYs, 14.0/100 PYs and 20.3/100 PYs.

Exposure

Exposure to the FD regimen derives from the open-label phase of the placebo-controlled study DE038 in JIA, the Japanese open label study M10-240 in JIA, the post marketing observational registry study P10-262 in JIA, the phase 3 double blind study M06-806 in CD, the open label study M06-807 in CD, the post marketing observational registry study P11-292 in CD and the placebo-controlled, double-masked study SYCAMORE in uveitis.

In total, the number of subjects with exposure to Adalimumab Fixed Dose regimen was 727 and the number of subjects with ≥ 6 month' s exposure for this regimen was 524.

Safety data generated in JIA (study DE038) and uveitis (study SYCAMORE) are of primarily relevance for the present application. Data from the other studies are considered supportive but of limited value due various reasons (small study population, dosing different from the proposed FD dosing) . Additionally, comparisons between studies and between geographical regions are difficult to interpret. There are specific exposure and clinical safety data for the proposed FD-dose regimen for only two of the paediatric indications, pJIA and uveitis, for which the applicant aims to introduce the new FD-dosing regimen. The uveitis indication is the focus of a parallel procedure (EMA/H/C/000481/II/0163), but the current application included a cross reference to the SYCAMORE study report and the SYCAMORE study data does indeed provide some support also for the JIA indication as the populations overlap. There are no specific clinical safety data from FD-dosing for the ERA and the Ps population, instead the assessment is entirely dependent on the PK analysis and modelling and extrapolations from the other indications. This is acceptable given the similarities of the populations but still a limitation.

Data from pJIA study DE038

DE038 (Art46), the study was a multicenter, Phase 3, randomized, DB, stratified, parallel-group study in children (4 to 17 years old) with pJIA that were either treated or not treated with MTX. A side-by-side comparison of the exposure-adjusted rates for subjects in the OLE BSA and OLE FD phases of Study DE038 who received at least 1 dose of OLE FD study drug were presented by the applicant. The incidence rates for any AEs was 512.4/100 PYs in the BSA phase and 287.6/100 PYs in the FD phase. Incidence rates for serious AEs was 12.6/100 PYs in the BSA phase and 8.2/100 PYs in the FD phase. Incidence rates for infections was 146.4/100 PYs in the BSA phase and 99.4/100 PYs in the FD phase. Incidence rates for serious infections was 2.5/100 PYs in the BSA phase and 0.7 in the FD phase. The incidence rates for total number of AEs were thus lower during the OLE FD phase compared to the OLE BSA phase in study DE038. The incidence rates for serious AEs was also lower in the OLE FD phase as well as the number of infections, serious infections, injection site related reactions and hepatic-related AEs. The incidence rates for AEs in the BSA phase was comparable to the incidence rates for the overall treatment program for Humira for the JIA indication while the incidence rates for the FD phase was lower.

The most frequently reported TEAEs in both study phases were upper respiratory tract infection and viral infections. Injection site reactions and injection site pain was more frequent in the OLE BSA dosing phase than in the OLE FD dosing phase while symptoms from the joints (lack of efficacy?) appeared to be somewhat more frequent in the OLE FD phase. No deaths were reported.

The applicant presented an analysis of the TEAEs in the OLE BSA and OLE FD phases of Study DE038 reported by subjects weighing 15 to < 30 kg as the applicant considers that this weight group is representative of the age group of 4 to 12 years of age who would be primarily affected by a dose change from a BSA-based dosing regimen to a FD regimen. There was no apparent increase in the frequency of AEs, serious AEs, infections, serious infections or injection site reactions in the FD phase compared to the BSA phase for these subjects.

It is noted that more subjects reported injection site reactions in the group that increased their dose in the FD phase of study DE038 compared to the group that received the same/decreased dose in the FD phase compared to the BSA phase. However, overall, these events were rather few and the conclusions that can be drawn from this data are limited.

Overall, judging from the data presented above, the safety profile of the FD dosing appears more benign than the BSA dosing despite the fact that the vast majority of subjects either remained on the same dose (50/106 subjects) or had their dose increased (53/106) in the OLE FD phase compared to the OLE BSA phase. However, it has to be acknowledged that both subjects in the OLA BSA dosing phase and subjects in the OLE FD phase constituted very selected groups since the design of DE038

meant that subject that did not benefit from adalimumab or did not tolerate adalimumab were excluded earlier on in the study. Of note, 44 of the 106 subjects (42%) that entered the FD phase did not complete this phase while 22 of 128 subjects (17%) that entered the BSA phase did not complete this phase. Although a variety of reasons for the discontinuations were given, it is reasonable to assume that it was the subjects that did best on the treatment that remained in the study which affects the comparison of AEs between the two dosing regimens.

Twenty-seven subjects (27/171, 15.8%) with JIA had at least 1 anti-adalimumab antibody (AAA)-positive on treatment sample during the OL and DB phases of the study DE-038 where BSA-based dosing was administered. For the 56 subjects included in the PK analyses from the OLE FD phase, 12 subjects (12/56, 21.4%) were identified with at least 1 AAA-positive result on treatment sample during Study DE038. None of the subjects developed AAA after the switch to a FD.

Data from the pJIA study M10-240

In the summary of clinical safety included in the current application, the presentation of data from M10-240 was focused on the eight subjects that received the 20 mg FD i.e. subjects <30 kg and the comparison with the weight-matched BSA-dosed subjects in DE038. The conclusions that can be drawn from the inter study-comparison presented by the applicant are very limited. It is noted that according to the study report of M10-240, subjects weighing 30 kg or more were to be dosed with 40 mg of adalimumab eow which is also consistent with the proposed FD posology of this application. It is thus not clear why the focus in the presentation of data from M10-240 is entirely on the eight subjects <30 kg that received the 20 mg FD, discarding the safety data from rest of the 17 subjects in the study. This safety data was thus retrieved from the study protocol of study M10-240. In total 25 Japanese pJIA subjects were included in study M10-240 and safety data up to week 60 was presented in the study report. Overall, the incidence rates for AEs, SAEs, infections and serious infections are higher than the corresponding figures that were presented by the applicant for the overall treatment program for JIA. The reasons for this are not clear. However, as the study included only 25 subjects, the conclusion that can be drawn from the safety data it generated is limited.

Data from pJIA registry study P10-262

The comparison between FD-dosing and BSA-dosing based on registry data has to be interpreted with caution due to its many limitations including the fact that two different geographic regions with possible differences in treatment praxis and proneness to report AEs were compared. It is also not explicitly stated that the FD dosing in US and Australia is identical (including identical bodyweight-cut offs) to the FD-dosing proposed in this application. That being said, a rough assessment of total number of AEs, serious AEs, infections and serious infections for the whole population did not point at any clear safety advantage for any of the two dosing regimens. Also for the subgroup of patients weighing 15 kg to <30 kg, the safety profile for the two dosing-regimens appeared was comparable.

Data from JIA-associated uveitis study SYCAMORE

The overall incidence rate of AEs was for the adalimumab group 1007 events per 100 patient years [E/100 PYs]) and for the placebo group (651 E/100 PYs). The rate of SAEs was in the adalimumab group 29 E/100 PY and in the placebo group 19 E/100 PY. The most common AEs in the adalimumab group were classified as infections and infestations (76.7% in the adalimumab group, 40% in the placebo group), respiratory, thoracic and mediastinal disorders (51.7% in the adalimumab group, 20% in the placebo group; most frequently reported events were cough and oropharyngeal pain), general disorders and administration site conditions (50% in the adalimumab group and 23.3% in the placebo group; including 33 events of pyrexia reported in 12 patients in the adalimumab arm) gastrointestinal disorders (43.3% in the adalimumab group and 26.7% in the placebo group; most frequent events were diarrhoea and vomiting), nervous system disorders (26.7% in the adalimumab group and 13.3%

in the placebo group; including 21 events of headache in 12 adalimumab patients), musculoskeletal and connective tissue disorders (25% in the adalimumab group and 20% in the placebo group), investigations (25% in the adalimumab group, 10% in the placebo group), and eye disorders (23.3% in the adalimumab group and 26.7% in the placebo group). The 5 severe AEs in the adalimumab group were cataract, injection site reaction, tonsillitis, arthralgia and arthritis. The 3 severe AEs in the placebo group were anterior chamber flare (2 events in the same subject) and uveitis. No deaths were reported. The most frequently reported SAEs in the adalimumab group were infections.

The safety results from the SYCAMORE Study is of interest as the study population is at least overlapping with the target population of this application and the dosing according to weight is identical to the proposed FD dosing in this application. Compared to the overall AE and SAE incidence rate from Humira JIA treatment program data, the SYCAMORE AE and SAE incidence rates in the Humira treatment group appear surprisingly high. It is acknowledged that also the incidence rate for AEs and SAEs were rather high also in the placebo group which could be interpreted as this specific population being more prone to develop AEs or be a reflection of the effectiveness of the AE reporting system in this trial. One reason for this population being more prone to develop AEs than the overall adalimumab treated population could be that in the SYCAMORE study, adalimumab for all subjects was to be administered on top of Methotrexate which was not the case in the overall adalimumab program. An explanation for a potentially increased proneness to report AEs in the SYCAMORE study compared to the overall program could be that the SYCAMORE study was an investigator-initiated study." The SYCAMORE study is currently under review in EMEA/H/C/000481/II/0163 within which the study report was submitted. According to the response to the first round of questions in EMEA/H/C/000481/II/0163, also the incidence rates of infections and serious infections were higher in the adalimumab arm of the SYCAMORE study than in previous adalimumab JIA studies. Some of the AEs that were not classified as infections could in fact still be related to infections; this concern for example cough, oropharyngeal pain, pyrexia, diarrhoea etc. However, the incidence rate of infections in the placebo arm in SYCAMORE was comparable to the incidence rates of infections for adalimumab-treated subjects in previous JIA-studies strengthening the previous suspicion that the study population in SYCAMORE could consist of a population being more prone to develop AEs (including infections) or that the safety outcome could reflect the relative effectiveness of the AE reporting system in this trial.

Issues relating to the FD regimen across studies

Given that the pharmacokinetic analysis/modelling indicate that exposure will be somewhat higher with the proposed FD dosing compared with previous dosing regimens in particularly subjects with BW < 15 kg, the applicant was encouraged provide a summary of the safety profile (i.e. the total number of AEs, serious AEs, infections, serious infections and injection site related AEs) in the different studies in which the proposed FD dosing was applied.

The applicant responded that among the studies presented across the indications of JIA, pediatric CD, and pediatric Ps, there were no subjects weighing < 15 kg who received a FD regimen of 20 mg. Only 1 study, Study P10-262 (STRIVE), reported subjects with a body weight < 15 kg and a FD regimen; however, these subjects received a 10 mg dose of adalimumab consistent with the local label (United States). Clinical safety data from subjects from this study and from within the same country, who weighed \geq 15 kg but < 17.5 kg and thus did receive a 20 mg FD regimen were presented. The applicant concluded that for subjects who received adalimumab 20 mg FD and weighing 15 kg to < 17.5 kg at baseline, a similar safety profile was observed compared to subjects weighing < 15 kg who received adalimumab 10 mg FD. The applicant also argues that these results are consistent with the safety profile for the overall patient population in the registry.

Thus, the data requested is not available. However, the arguments put forward by the applicant why the slightly higher exposure under the FD regimen for subjects < 15 kg does not create any safety

issues and, thus, are supportive of the modelling/simulation results are acknowledged. Moreover, as concluded in the CHMP AR for the paediatric Uveitis variation EMEA/H/C/000481/II/0163 with CHMP opinion adopted in July 2017, the exposure-safety analyses did not reveal an increase in the incidence of AEs with raised exposure levels within the analysed concentration range which included concentrations larger than the simulated range in paediatric uveitis patients <15 kg.

2.7.2. Conclusions on clinical safety

Given that transition from BSA-dosing to the proposed FD-dosing in the pJIA study DE038 for most subjects meant that they would either remain on the same dose (50/106 subjects) or have their dose increased (53/106) and that the pharmacokinetic analysis/modelling, which is considered pivotal for this application, indicates that exposure will be higher rather than lower with the proposed FD dosing compared with previous dosing regimen, analysis of the clinical safety data is of interest.

It is reassuring that the pharmacokinetic analyses appear to indicate that the differences in exposure for the proposed FD-posology are not large compared to the approved dosing for the indications of interest and that the exposure-safety data does not demonstrate a clear relationship between exposure and AEs.

In the light of the totality of data submitted by the applicant and the benefits associated with a fixed dose regimen that is consistent across indications, the posology proposed by the applicant is thus accepted.

There are no findings among the clinical safety data that would warrant changes to the RMP.

2.7.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 31 December 2019.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This procedure concerns changes to a FD posology for the paediatric indications JIA, ERA (currently BSA-dependent posology) and Ps (currently BW-dependent posology). FD is proposed also for the new indication uveitis which has been evaluated in a parallel procedure (EMA/H/C/000481/II/0163). No changes are proposed in the paediatric indications for which a fixed-dose posology is already applied (CD, HS). The changes are reflected in section 4.2 of the SmPC for the new dose-strength 20 mg prefilled syringe; that is included as a line extension in this application, as well as the changes proposed in the SmPCs for the currently approved presentations. Furthermore the applicant proposes to add a statement on immunogenicity in JIA in section 5.1 of the SmPC referring to data from a previous procedure.

JIA is an autoimmune disease with a complex genetic predisposition that has been observed in children under the age of 16 years. It is the most common rheumatic disease of childhood and an important cause of disability in children. The onset of JIA is characterized by 3 primary modes:

Oligoarthritis/pauciarticular arthritis (< 5 joints) is most common, occurring in 50% of patients, followed by polyarticular (\geq 5 joints) in 30% of patients, and systemic arthritis (at least one joint with fever and rash) in 10% to 20% of patients.

Ps is a chronic immunologic disease in infants, children, adolescents, and adults, that is characterized by marked inflammation and thickening of the epidermis, resulting in thick, scaly plaques on the skin. It affects 1% to 3% of the general population.

The aim of therapy for these conditions is both to prevent symptomatic relief and to modify the underlying disease and thereby prevent joint destruction and disabilities (JIA).

3.1.2. Available therapies and unmet medical need

For JIA, NSAIDs are the usual first-line treatment, since they are considered to be the least toxic agent in children. They provide symptomatic relief, but are not considered to be disease-modifying.

Methotrexate (MTX) is considered to have an acceptable level of toxicity relative to its efficacy; most children demonstrate at least some response to MTX therapy, although remission is rare. Other types of traditional medications commonly used to treat rheumatoid arthritis (RA) in adults are less

preferable for use in paediatric subjects. Five biologic agents are approved for the treatment of pJIA: adalimumab, etanercept, golimumab, abatacept and tocilizumab.

For paediatric Ps, treatment options are similar, but more limited than treatment options for adults. The most commonly used topical therapies in children include corticosteroids, steroid-sparing agents like calcipotriol and tazarotene, salicylic acid, tar, and anthralin. Regular use of emollients can be applied in mild Ps. Particularly effective is tar and anthralin when prescribed in combination with ultraviolet B (UVB) light. The calcineurin inhibitors, tacrolimus and pimecrolimus, are currently under investigation for Ps and are indicated for the treatment of atopic dermatitis. Systemic nonbiologic treatments, such as retinoid acitretin, cyclosporine A, methotrexate (MTX) and dapsone, are described in the literature and are used when patients are not adequately responsive to other forms of therapy. These treatments are also used for rare forms of Ps, such as pustular Ps and erythrodermic Ps in children. Four biologic agents are currently approved for adult patients with moderate to severe Ps. These include the tumor necrosis factor alpha (TNF- α) antagonists adalimumab, etanercept and infliximab and the IL 12/23 antagonist, ustekinumab. In addition, the TNF- α antagonist, golimumab, is approved for PsA.

The rationale behind the proposed the switch from the BSA/BW-dependent Humira paediatric posology to the FD-posology is to provide a simplified and more convenient use by the patient, physician, and caregiver.

3.1.3. Main clinical studies

Pharmacokinetics

The pharmacokinetics (PK) and immunogenicity of adalimumab are well characterized in paediatric subjects in the approved indications of juvenile idiopathic arthritis (JIA; specifically the categories of polyarticular JIA [pJIA] and enthesitis-related arthritis [ERA]), paediatric psoriasis (Ps), and paediatric Crohn's disease (CD). These data were provided in previous submissions.

The proposed FD regimen is supported by population PK modelling and exposure response analyses evaluating multiple potential FD regimens with BW cutoffs for adalimumab in paediatric subjects with JIA (pJIA and ERA) and paediatric Ps. PK simulations were conducted using a population PK model that was developed previously based on adalimumab concentration data across different paediatric indications in order to evaluate adalimumab PK across the paediatric age range and across the different disease populations. Exposure-response analyses for efficacy and safety were conducted in order to assess the potential clinical impact of PK differences associated with the FD regimens compared to current dosing based on BSA or BW for JIA and paediatric Ps, respectively.

A summary of paediatric studies is listed in Table 12.

Table 10 Clinical Studies with Pharmacokinetic Characterization

Study	Indication and Age Group	Study Drug Dosing Design
DE038	pJIA (4 – 17 years)	24 mg/m ² BSA in 5 mg increments in OL-LI and DB; fixed-dose in OLE based on body weight cutoff 30 kg
M10-444	pJIA (2 – 4 years)	24 mg/m ² BSA in 5 mg increments
M10-240	Japan pJIA (4 – 17 years)	Fixed dosing based on body weight cutoff 30 kg
M11-328	ERA (6 – < 18 years)	24 mg/m ² BSA in 5 mg increments
M04-717	Paediatric Ps (4 – < 18 years)	0.8 mg/kg or 0.4 mg/kg
M06-806	Paediatric CD (6 – 17 years)	Fixed dosing based on body weight cutoff 40 kg

OLLI = Open-label lead in; DB = Double-blind; OLE = Open-label extension

Clinical Efficacy

For JIA, four studies have been presented to support the variation (as described in 2.3). These are performed in patients with pJIA (DE038, M10-240 and M10-444) and enthesitis-related arthritis (ERA, study M11-328). For psoriasis, data are available from a study in paediatric plaque psoriasis (M04-717). The main clinical study to support this variation is DE038, where subjects treated with adalimumab in a BSA-based dose were transitioned to a FD, and change in PedACR 30/50/70/90 were compared between patients receiving a lowered/unchanged dose versus patients receiving a higher dose. Data from the other studies are of limited interest for this variation, due to usage of other dosing regimens than the proposed or inclusion of a low number of patients.

Clinical Safety

The safety data that the applicant refers to as support for the proposed FD regimens of adalimumab are from clinical trials and from a post-approval commitment to the FDA/PIP requirement of the EMA. Study reports have been previously submitted for these studies. Exposure to the FD regimen derives from the open-label phase of the placebo-controlled study DE038 in JIA, the Japanese open label study M10-240 in JIA, the post marketing observational registry study P10-262 in JIA, the phase 3 double blind study M06-806 in CD, the open label study M06-807 in CD, the post marketing observational registry study P11-292 in CD and the placebo-controlled, double masked study SYCAMORE in uveitis. Relevant safety data for the present application stem primarily from JIA study DE038 and uveitis study SYCAMORE. Data from the other mentioned studies are considered supportive but of limited value due various reasons.

In total, the number of subjects with exposure to adalimumab FD-regimen was 727 and the number of subjects with ≥ 6 month's exposure for this regimen was 524.

Of note, there are specific exposure and clinical safety data for the proposed FD-dose regimen for only two of the paediatric indications, pJIA and uveitis, for which the applicant aims to introduce the new dosing regimen. The uveitis indication is the focus of a parallel procedure (EMA/H/C/000481/II/0163) but the SYCAMORE safety data provide some support also for the JIA indication as the populations overlap. There are no specific clinical safety data from FD-dosing for the ERA and the Ps population, instead the assessment is entirely dependent on the PK analysis and modelling and extrapolations from the other indications. This is probably acceptable given the similarities of the populations but still a limitation.

3.2. Favourable effects

Of the 106 subjects enrolled in the open-label fixed-dose extension of study DE038, only 3 subjects received a lower dose with the FD regime compared to BSA based dosing. 50 subjects maintained the same dose and 53 got an increased dose. When comparing outcome measures (pedACR30/50/70/90) between individuals with same/decreased dose versus increased dose, no statistically significant differences were seen in pedACR30/50/70. For pedACR90, there was a difference at Week 12 visit for patients comparing patients with an increased dose vs patients with decreased dose (66.7% vs 0%, $p=0.03$). Patients with maintained dose were not included in this analysis. When performing stratified analysis per age category, there were some differences. At Week 32 and at the Final visit, a greater proportion of subjects aged 9 to 12 years with increased doses were PedACR70 responders (100% at Week 32 and 95.7% at final visit) compared to subjects with the same/decreased doses (62.5% at Week 32 and 55.6 at final visit, $p=0.014-0.015$). At Week 48 and 96, a greater proportion of subjects aged 9 to 12 years with increased doses were PedACR90 responders (90.5 at Week 48 and Week 96) compared to subjects with the same/decreased doses (55.6% at Week 48 and 42.9% at Week 96, $p=0.049/0.021$).

Furthermore, all evaluated exposure-efficacy relationships display a general trend that increasing adalimumab concentrations lead to a beneficial response.

3.3. Uncertainties and limitations about favourable effects

In study DE038, 44 of the 106 subjects (42%) that entered the FD phase did not complete this phase while 22 of 128 subjects (17%) that entered the BSA phase did not complete this phase. Also, all patients enrolled in the OLE were primarily adalimumab responders.

Since a substantial proportion of subjects discontinued the study for various reasons, the number of subjects analysed at the latter visits are few .

There are no specific clinical efficacy data from FD-dosing for the ERA and the Ps population, instead the assessment is dependent on the PK analysis and modelling and extrapolations from the other indications.

However, the totality of data with the pharmacokinetic analysis/modelling in mind, it is considered that the current level of knowledge about the favourable effects is sufficient for a positive benefit-risk evaluation.

3.4. Unfavourable effects

Given that transition from BSA-dosing to the proposed FD-dosing in the pJIA study DE038 for most subjects meant that they would either remain on the same dose (50/106 subjects) or have their dose increased (53/106) and that the pharmacokinetic analysis/modelling indicate that exposure will be higher rather than lower with the proposed FD dosing compared with previous dosing regimens; especially in subjects with BW<15 kg (see section 2 of this AR), analysis of the clinical safety data is of interest.

In the Summary of Safety submitted with this application, an overview of AEs in the treatment programs for Humira across indications was provided. The overall incidence rates of AEs for the adalimumab paediatric indications of JIA, Ps, and CD were reported to be 525.3 E/100 PYs, 518.5 E/100 PYs, and 566.5 E/100 PYs, respectively. The overall incidence of SAEs were 13.5/100 PYs,

7.4/100 PYs and 32.2 /100 PYs respectively. The overall incidence of infections were 150.7/100 PYs, 168.7/100 PYs, 132.0/100 PYs respectively. The overall incidence of serious infection was 2.7/100 PYs, 0.8/100 PYs, 6.6/100 PYs respectively.

A side-by-side comparison of the exposure-adjusted rates for subjects in the OLE BSA and OLE FD phases of Study DE038 who received at least 1 dose of OLE FD study drug were presented by the applicant. The incidence rates for any AEs was 512.4/100 PYs in the BSA phase and 287.6/100 PYs in the FD phase. Incidence rates for serious AEs was 12.6/100 PYs in the BSA phase and 8.2/100 PYs in the FD phase. Incidence rates for infections was 146.4/100 PYs in the BSA phase and 99.4/100 PYs in the FD phase. Incidence rates for serious infections was 2.5/100 PYs in the BSA phase and 0.7 in the FD phase. The most frequently reported TEAEs in both study phases were upper respiratory tract infection and viral infections. Injection site reactions and injection site pain was more frequent in the OLE BSA dosing phase than in the OLE FD dosing phase. No deaths were reported.

In the SYCAMORE study, in which the dosing according to weight was identical to the proposed FD dosing in this application, the overall incidence rate of AEs was for the adalimumab group 1007 events per 100 patient years [E/100 PYs] and for the placebo group 651 E/100 PYs. The rate of SAEs was in the adalimumab group 29 E/100 PY and in the placebo group 19 E/100 PY. The most common AEs in the adalimumab group were classified as infections and infestations (76.7% in the adalimumab group, 40% in the placebo group), respiratory, thoracic and mediastinal disorders (51.7% in the adalimumab group, 20% in the placebo group; most frequently reported events were cough and oropharyngeal pain), general disorders and administration site conditions (50% in the adalimumab group and 23.3% in the placebo group; including 33 events of pyrexia reported in 12 patients in the adalimumab arm) gastrointestinal disorders (43.3% in the adalimumab group and 26.7% in the placebo group; most frequent events were diarrhoea and vomiting), nervous system disorders (26.7% in the adalimumab group and 13.3% in the placebo group; including 21 events of headache in 12 adalimumab patients), musculoskeletal and connective tissue disorders (25% in the adalimumab group and 20% in the placebo group), investigations (25% in the adalimumab group, 10% in the placebo group), and eye disorders (23.3% in the adalimumab group and 26.7% in the placebo group). The 5 severe AEs in the adalimumab group were cataract, injection site reaction, tonsillitis, arthralgia and arthritis. The 3 severe AEs in the placebo group were anterior chamber flare (2 events in the same subject) and uveitis. No deaths were reported. The most frequently reported SAEs in the adalimumab group were infections.

There were generally few discontinuations due to AEs independently of dosing regimens.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties

Across the indications of JIA, pediatric CD, and pediatric Ps, there were no subjects weighing < 15 kg who received a FD regimen of 20 mg. Only 1 study, Study P10-262 (STRIVE), reported subjects with a body weight < 15 kg and a FD regimen; however, these subjects received a 10 mg dose of adalimumab consistent with the local label. Clinical safety data from subjects from this study and from within the same country, who weighed \geq 15 kg but < 17.5 kg and thus did receive a 20 mg FD regimen were presented. The applicant concluded that for subjects who received adalimumab 20 mg FD and weighing 15 kg to < 17.5 kg at Baseline, a similar safety profile was observed compared to subjects weighing < 15 kg who received adalimumab 10 mg FD. The applicant also argues that these results are consistent with the safety profile for the overall patient population in the registry. The arguments put forward by the applicant why the slightly higher exposure under the FD regimen for subjects < 15 kg does not create any safety issues and, thus, are supportive of the

modelling/simulation results are acknowledged. Moreover, as concluded in the CHMP AR for the paediatric Uveitis variation EMEA/H/C/000481/II/0163 with CHMP opinion adopted in July 2017, the exposure-safety analyses did not reveal an increase in the incidence of AEs with raised exposure levels within the analysed concentration range which included concentrations larger than the simulated range in paediatric uveitis patients <15 kg.

Limitations

As stated for the favourable effects, there are no specific clinical safety data from FD-dosing for the ERA and the Ps population, instead the assessment is dependent on the PK analysis and modelling and extrapolations from the other indications.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

A previously developed paediatric population PK model based on adalimumab in several indications and subsequent simulations have been used for evaluating a potential fixed-dose regimen in paediatric patients across indications. Appropriate methods have been used for model development and simulations, and adequate exposure predictions have been produced to compare exposure ranges between the FD regimen and the approved dose regimens.

Some deviations between the FD regimen of 20/40 mg (30 kg cut-off) and the previous body size adjusted dosing regimens are present, with an overall trend of slightly higher concentrations with the new dosing regimen. The largest deviations are seen in children <15 kg (<20kg for Ps patients), and in patients with a body weight of 30-40 kg. However, the presented exposure-efficacy analyses display clear exposure-response relationships where the effect increases with increasing exposure. Furthermore, the graphical analysis of exposure-safety relationships indicates that there is no trend between exposure and adverse events.

The efficacy data obtained from study DE038 demonstrate overall maintained PEDACR30/50/70 responses when shifting from BSA based dose to FD. When stratifying for age, there are some differences at individual visits for PEDACR70/90 responses indicating the effect with a FD might be lower in individuals aged 9-12 compared to a BSA based dose. However, the numbers were small in the analysed groups and since only 3 subjects actually received a lower dose, it is not expected that this variation will overall have a negative impact on clinical efficacy and the advantage with a more uniform posology is endorsed.

Relevant safety data for the present application stem primarily from pJIA study DE038 and uveitis study SYCAMORE. The uveitis indication is the focus of a parallel procedure (EMA/H/C/000481/II/0163) but the SYCAMORE safety data provide some support for the JIA indication as the populations overlap and the dosing according to weight is identical to the proposed FD dosing in this application. There are no specific clinical safety data from FD-dosing for the ERA and the Ps population, instead the assessments pertaining to these indications are dependent on the PK analysis and modelling and extrapolations from the other indications.

Judging from the pJIA DE038 data, the safety profile of the FD dosing appears overall more benign than the BSA dosing despite the fact that the vast majority of subjects either remained on the same dose (50/106 subjects) or had their dose increased (53/106) in the OLE FD phase compared to the OLE BSA phase. It should however be acknowledged that both subjects in the OLA BSA dosing phase and subjects in the OLE FD phase constituted very selected groups since the design of DE038 meant

that subject that did not benefit from adalimumab or did not tolerate adalimumab were excluded earlier on in the study.

Regarding uveitis SYCAMORE study, the AE and SAE incidence rates in the Humira treatment group were higher than the overall AE and SAE incidence rates in the Humira JIA treatment program data. It is however acknowledged that also the incidence rate for AEs and SAEs in the placebo group of SYCAMORE were rather high, which could be interpreted as the SYCAMORE study population being more prone to develop AEs or be a reflection of the effectiveness of the AE reporting system in this trial.

The FD dosing can be considered simplified and more convenient, being a positive contribution to patient care.

3.6.2. Balance of benefits and risks

The new proposed FD-dosing appears to translate into a slightly higher dosing and exposure, especially for subjects with BW < 15 kg. Given this knowledge, efficacy is expected to be maintained or even improved. The benefit with a posology that is more uniform across indications and simplified for health providers/patients is acknowledged. Regarding risks, the totality of data indicates that the safety profile can be expected to be similar with the new proposed FD-dosing compared to the currently approved. The Benefit risk is regarded as positive.

3.7. Conclusions

The overall B/R of Humira is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Humira 20 mg is favourable in the following indication:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients 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 section 5.1). Humira has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Paediatric plaque psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate. The CHMP therefore recommends the extension(s) of the marketing authorisation for Humira.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Humira subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall ensure that the Educational programme is implemented for currently authorised indications. This programme shall ensure that physicians who intend to prescribe Humira are aware of:

- the risk of serious infections, sepsis, tuberculosis and other opportunistic infections
- the risk of heart failure
- the risk of central nervous system demyelination
- the risk of malignancies
- the Patient Alert Card is to be given to patients using Humira

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2 of the SmPC in order to introduce a new fixed dose regimen (posology) for the paediatric indications of Juvenile idiopathic arthritis (JIA), Paediatric plaque psoriasis, Paediatric Crohn's disease, and Paediatric Uveitis. The Package Leaflet and Labelling are updated accordingly. Furthermore, the marketing authorisation holder took the opportunity to introduce editorial changes to align wording and layout of the Product Information and to amend the statement relating to anti-adalimumab antibody development in JIA patients, which will reside in section 5.1 of the Humira SmPCs (20 mg and 40 mg presentations).