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Human Medicines Development and Evaluation

Assessment report for

Humira

Common name: adalimumab

Procedure No. EMEA/H/C/000481/II/00081-G

Assessment Report as adopted by the CHMP with

all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

About the product

Adalimumab is a recombinant human immunoglobulin monoclonal antibody containing only human peptide sequences. Adalimumab binds specifically to tumour necrosis factor (TNF) and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

Humira is indicated for treatment of moderate to severe active rheumatoid arthritis when response to Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is inadequate or in severe, active, and progressive RA in adults no previously treated with methotrexate (in combination with methotrexate or as monotherapy), polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years, active and progressive psoriatic arthritis, active ankylosing spondylitis, and severe active Crohn's disease, and moderate to severe chronic plaque psoriasis.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis (JIA), aged 13 years and above is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

Scope of the variation

When the use of adalimumab in the JIA indication was initially approved (EMEA/H/C/000481/H/C/39 in August 2008), the CHMP concluded that there was a lack of an appropriate presentation to allow adequate dosing in children below 13 years of age. Thus, approval was only granted from the age of 13 years, where the fixed dose of 40 mg was considered appropriate. In the present submission, the MAH has developed a possibility to deliver an adequate dose for children below 13 years of age. No new controlled clinical study data have been submitted in this application. Thus, the clinical data have been reviewed previously, and the assessment presented below is mainly based on the CHMP assessment report of the data submitted in the previous application.

In this variation the MAH applies for a dosing by Body Surface Area (BSA) i.e. a flexible dosing with a single-use vial ("partial use") in JIA patients aged 4- 12 years. The product is still presented as 40 mg per 0.8 ml vial but only some of the contents of the vial may be used as it is dedicated to the JIA paediatric indication only. The existing registered vial presentation is amended to reflect "partial use" to support paediatric BSA dosing. The product name is amended as follows: "Humira 40 mg/0.8 ml Solution for injection paediatric vial".

In the above the "concentration (mg/ml)" is expressed as opposed to the "quantity (mg)", to aid the prescriber with BSA dosing. There is no change in the strength but in the expression of the strength (i.e. the contents of the vial have not changed). The qualifier "Paediatric vial" is added to the product name because only the vial fully supports the paediatric dosing. The other existing presentations of pen and pre-filled syringe support only total-use, i.e. administration of the full 40 mg single dose, and therefore are not suitable to support the BSA dosing.

A number of quality changes support the "partial-use" vial. These changes have been grouped with the clinical extension of the indication. The following variation applications are grouped in this submission:

Clinical:

Variation requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Quality:

See section 1.2 below.

Available safety data up to at least 2 years are also assessed within the current variation.

Product information changes:

The SmPC for the vial is amended to reflect only the JIA paediatric indication. The other indications, which are adult indications requiring 40 mg single-dose, have been removed from the vial presentation SmPC. The vial presentation will support the paediatric dosing only whereas the existing presentation of pen and pre-filled syringe will only support the adult dose posology, i.e. total use 40 mg single-dose. The vial is therefore the only presentation that supports "partial-use", i.e. is the presentation that will fully support the paediatric JIA indication. The SmPC for the vial contains the full safety information within sections 4.3, 4.4 and 4.8 as applicable to all the indications.

The MAH took the opportunity to correct typographical errors throughout the PI and also to remove the Patient Alert Card section from the annex III A.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No. 1901/2006 as amended, the application included an EMA decision (P/102/2010) on a paediatric investigation plan with a deferral.

The following conditions are covered in the paediatric investigation plan:

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Crohn's Disease
- Psoriasis
- Psoriatic arthritis
- Ankylosing spondylitis

The PIP is not yet completed.

1.2. Quality aspects

1.2.1. Drug substance

N/A

1.2.2. Drug Product

As already mentioned above, Humira 40 mg - vial is currently approved for marketing in Europe. However, in order to enable appropriate dosing out of the "partial-use" vial, the MAH proposes to introduce the use of the following dose administration devices (accessories): a vial adapter, a 1 mL graduated syringe and an injection needle. Furthermore, to assure the delivery of the maximum dose

(0.8 mL adalimumab solution for injection) from the vial using the provided accessories, it was found that the vial fill volume needs to be increased.

In conjunction with the introduction of the "partial-use" vial, Abbott proposes to transfer the site of manufacture for the 0.8 mL/40 mg bulk vial dosage form/presentation. Consequential changes to the change in manufacturing site of the bulk vials include:

1) changes to the vial manufacturing process (and batch size) to align the process with that approved for the bulk pre-filled syringe dosage/presentation;
2) a change to the rubber vial stopper; and
3) increase in shelf-life

The current variation application does not include any changes to the sections in the approved Humira dossier referring to drug substance.

Transfer of the manufacture and the introduction of changes to manufacturing process to align the process with that approved for the bulk pre-filled syringe dosage/presentation

The Manufacturing site performing the commercial scale qualification and validation of the manufacturing process for adalimumab solution for injection in vials has been changed.

The validated manufacturing process for adalimumab 50 mg/mL solution for injection in 40 mg/0.8 mL vials was transferred to the proposed facility. The manufacturing of the bulk drug product solution for filling the vial presentation was qualified at the new facility using the same basic process as validated at the previous facility and the manufacturing process was also harmonized with the approved bulk drug product solution manufacturing process used for filling pre-filled syringes. The thawing, pooling and compounding steps, as well as the equipment used in these steps, are identical for the pre-filled syringe and vial manufacturing processes.

Discussion:

Data on three process validation runs are provided supporting adequate performance of the adalimumab manufacturing process to fill 40 mg/0.8 mL vials at the site. The bulk solution manufacturing process was identical to that already validated previously for manufacture of adalimumab 40 mg/0.8 mL pre-filled syringes. Vials for these first three process validation runs were filled to a target volume per vial, and drug product from all three batches conformed to specifications and acceptance criteria. Although the MAH did not challenged the maximum batch size proposed in these studies, the data reported are considered satisfactory to support the transfer of production to the new site, taking into consideration that the thawing, pooling and compounding steps, and equipment are identical for the pre-filled syringe and vial, and that production of syringes in a batch size proposed is approved.

Change to the rubber vial stopper

Upon transferring the bulk vial manufacturing process, the same 2R glass vial quality has been preserved, and the vial rubber stopper is still coated on the product contact side with teflon, although the original rubber stopper elastomer has been changed. In order to support this change, as well as to develop supporting data to register an alternate adalimumab pre-filled syringe primary packaging system, a forced extraction studies were done with syringe plunger stoppers made of the same rubber

and the same coating (on the product contact side of the syringe plunger stopper) as for the vial rubber stoppers used to manufacture bulk pre-filled vials.

Forced extraction studies of the coated syringe plunger stoppers, utilizing solvents in a range of polarities, were performed to determine which extractables from the stoppers could potentially migrate into the final product during storage. The rubber stoppers were extracted independently with three different solvents using reflux conditions. The extracts were evaluated using high performance liquid chromatography and other analytical methods.

A risk-based approach was employed to select a subset of the extractable substances detected after forced extraction for method validation and potentially leachable impurities evaluation in actual (pre-filled syringe) product samples. This risk assessment utilised a ranking system for each extractable compound based on the relevance of the solvent in which it was extracted, the amount of the extractable detected, and the relative toxicological properties of the compound as indicated by its acceptable daily intake (ADI) value.

The methods used to detect the extractable substances were validated according to ICH Q2 (R1) guidelines so that these compounds could be tracked as potentially leachable impurities in the drug product during real-time storage. Additional compounds and metal ions were included in the validation of the methods.

Samples from pre-filled syringe batches with 29 G x ½ inch needles which were filled using the proposed, coated plunger stoppers and stored at the recommended storage temperature of 2° to 8°C, were evaluated for the detection of any leachables at timepoints ranging from Time 0 through 18 months. All results indicated that there was no change to the potentially leachable impurities from the initial timepoint to the 18 month timepoint. All results were below the method detection limits or the method quantitation limits.

A separate stability study was performed to evaluate the potential impact of extractables from the proposed coated plunger stoppers and the (thermoplastic elastomer – TPE) soft needle shield on adalimumab drug product. The extractables/leachables profile for a combined extract of this pre-filled syringe stopper and soft needle shield formulation could be considered a worst case surrogate for extractables/leachables that might be present in the vial rubber stopper only. Solutions containing forced extracts from the stoppers and soft needle shields were used to prepare adalimumab drug product solution which was filled into syringes and placed on stability at the recommended storage temperature (2° to 8°C) for 24 months and at short term accelerated conditions (25°C/60%RH and 40°C/75%RH, respectively) for 6 months. The stability testing results indicated that the extractables from the coated plunger stoppers and soft needle shields had no adverse effects on the adalimumab shelf life stability.

Discussion:

Studies reported from the control for leachables are satisfactory supporting the change of stoppers.

Increase in the nominal fill volume for the bulk vial

To enable appropriate dosing out of the vial for administering the product to juvenile patients, the following dose administration devices (accessories) are provided: a vial adapter, a 1 mL graduated syringe and an injection needle. To assure delivery of the maximum dose (0.8 mL adalimumab solution for injection) from the vial using the provided accessories, the vial fill volume needs to be greater than the vial fill volume used for the first three process validation batches manufactured. Laboratory studies

demonstrated that the increased target fill volume assures that the maximum prescribed dose of 0.8 mL can be withdrawn from the vial and administered using the provided dose administration accessories. To demonstrate that the vial filling process is able to fill vials with to the increased nominal fill volume, a fourth process validation run following the same study protocol as the three earlier runs, was performed at the target fill volume. Vials from this additional process validation run conformed to specifications and acceptance criteria.

Discussion:

Considering the marginal difference in volume, production of only one additional validation batch is considered sufficient to support the increase in fill volume.

Increase in shelf-life

Supporting the proposed extension of the shelf-life for product in vials, the following documentation is presented:

- Stability testing results through 36 months storage for primary vial stability batches results for the process validation batches
- Stability data through three months for the three process validation lots of adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vial
- Supportive stability data for two pre-filled syringe batches manufactured using the same rubber, coated stopper material that will be used for all vial batches filled
- Results of stability studies on the Extraction Stress Testing of Stability results include data from pre-filled syringe batches that were spiked with extractables from the coated stoppers and needle guard and the controls.

The available real time data of the stability studies for the primary vial batches the process validation vial batches, the process validation vial as well as for the supportive pre-filled syringe batches with the new grey rubber stopper composition (still coated on the product contact side) support the conclusion that adalimumab 40 mg solution for injection 0.8 mL is stable for at least 24 months when stored at 2 to 8°C in 2R glass vials (or syringes) with a stopper enclosure of rubber elastomer, coated on the product contact side of the stopper.

This conclusion is supported by the statistical analyses of data.

The results of these stability studies also reveal that the storage position of the vials (stored upright or upside down) is not relevant as to stability.

Discussion:

A comprehensive data package is submitted supporting stability of product in the paediatric vial. Although the individual studies do not fulfil all requirements, being either conducted on batches produced at another site, equipped with the "old" stoppers, representative of the syringe presentation or covering too short time in storage, the studies together provide a satisfactory base for conclusion on the shelf-life. The production of drug product has adhered to basically the same procedure since obtaining license for Humira on the EU-market, and the early production date of the batches is therefore not considered critical. As refers to the change in stoppers, both the new and the old were Teflon coated. Furthermore, the stability studies performed on the syringe can be considered representative "worst case" conditions.

The stability data as tabulated in the reports and subjected to statistical evaluation, reveal no significant differences between batches, irrespectively of whether they have been stoppered with the old or new stoppers, the vials were stored upright or upside down, or presented as a vial or a syringe.

Conclusion

The proposed extension of the pre-filled vial shelf life is acceptable.

The ongoing stability studies will continue, and stability data for subsequent time points will be submitted if any trends toward divergence from previous results are observed.

Suitability of Dose Administration Devices (Accessories)

The adalimumab drug product solution contained in the pre-filled vial dosage presentation will be transferred and administered using three CE-marked and 510(k) cleared dose administration devices (accessories), which will be included for the patient/caregiver in the commercially distributed procedure pack (kit); each accessory component will be individually packaged to protect sterility and inserted, along with the pre-filled vial, into the procedure pack (kit) carton for each dose.

Various vial adapter designs from different suppliers were evaluated. The vial adapter was selected based on criteria that included residual volume in the vial after aspiration, force to penetrate the vial stopper and the potential to maintain sterility during user handling due to the blister package design. The vial adapter is made of polycarbonate and consists of a spike that is siliconized to facilitate penetration through the rubber stopper of the vial. The vial adapter design enables gripping over the neck of the vial and also has a female Luer Lock hub that is designed to be compatible with male Luer Lock syringes designed to the ISO 594-1 and ISO 594-2 standards. Biocompatibility of materials of construction meets ISO 10993 standards.

Drug volume delivery results were evaluated for adalimumab 50 mg/ml, solution for injection in 2R glass vials.

Also evaluated were adalimumab drug product content (extractable volume) and uniformity (mass variation) for variable dosing. Solution was aspirated and dispensed using the accessories for adalimumab drug product when filled, stoppered and capped into a glass vial. In this study, vials filled from the fourth process validation run were used. The extractable volume results confirm that 0.8 mL (maximum dose) can be delivered, using the accessories, from vials filled with a target fill volume. Uniformity of dosage was also evaluated at using the 1mL BD syringe and needle accessories with the same vials from process validation batch. Each target dosage volume was expelled into a tared glass vial for mass determination. The uniformity of dosage was calculated as described in Ph. Eur. 2.9.40 and results met the Ph. Eur. acceptance criteria.

A short-term stability study was performed to assess adalimumab drug product stability and adsorption "in-use", upon exposure to the accessory components at room temperature. Drug product from representative adalimumab vials was drawn into the 1 mL disposable graduated plastic syringe, using the vial adapter, to approximately 0.8 mL. After attaching the needle, the filled syringe was exposed to ~~the~~ elevated room temperature. The sample showed essentially no change in adalimumab characteristics. The change observed for the sample followed the typical adalimumab degradation kinetics, with approximately 0.5% reduced adalimumab purity in terms of sum of lysine variants per cation exchange HPLC, which was comparable to the corresponding control. These results indicated that the observed change is mainly due to the temperature effect but not the accessory device. Changes observed have no significant impact on product quality. In addition, no significant protein

adsorption was observed upon short term exposure to the dose administration device components at an accelerated temperature storage condition.

Discussion:

The suitability of dose administration devices has been satisfactorily supported.

Conclusions on the chemical, pharmaceutical and biological aspects

The proposed re-labelling of the currently approved vial presentation, and the changes introduced in conjunction with the transfer of the production are satisfactorily supported. The proposed extension of the shelf-life for the vial presentation is acceptable. The suitability of dose administration devices has been satisfactorily supported.

1.3. Clinical aspects

General Comments on Compliance with GCP

The Clinical trial submitted in support of this variation was performed in accordance with GCP. Furthermore, the applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.3.1. Clinical pharmacology

Pharmacokinetics

The pharmacokinetic and immunogenicity data of adalimumab were evaluated in paediatric (4 – 17 years) subjects with polyarticular JIA in study DE038 (for details of the studies referred in this section, please see section Clinical efficacy). Subjects were dosed based on BSA during the first three phases of the study, and received a fixed dose based on body weight in the fourth phase. Samples for pharmacokinetic analysis and immunogenicity assessment were taken during the first 48 weeks of the study (open-label lead-in [OL LI] and double-blind [DB] phases) during which subjects received a BSA-based dose. The pharmacokinetics of adalimumab were also evaluated during the first 16 weeks of the open-label extension fixed dose (OLE FD) phase, but only in subjects who had their dose changed (increased or decreased) when switched to the FD regimen. No new pharmacokinetic data were collected after Week 16 of the OLE FD phase.

In the 16-week OL LI phase and the 32-week DB phase the dosing regimen was 24 mg per m^2 (max 40 mg) subcutaneously eow, with or without concomitant methotrexate (MTX). The OLE comprised the same dosing based on BSA (OLE BSA) and a period with fixed dosing (OLE FD) treatment (20 mg for subjects with body weights < 30 kg and 40 mg for subjects with body weights >30 kg).

Pharmacokinetics during open-label lead-in and double-blind phases

The pharmacokinetics of adalimumab were evaluated in 171 pediatric subjects with polyarticular JIA in the OL LI and DB phases of Study DE038. Steady-state serum adalimumab concentrations were achieved by Week 20 for subjects who received adalimumab during both the OL LI and DB phases. Mean (± SD) steady-state serum adalimumab trough concentrations of 10.9 ± 5.2 µg/mL and 5.5 ± 5.6 µg/mL were observed in subjects on concomitant MTX and in subjects not on concomitant MTX, respectively. The inter-individual variability was very large, in particular in patients without concomitant MTX treatment. These systemic exposures were in the range of steady-state serum

adalimumab trough concentrations previously observed in adult subjects, both during monotherapy and concomitant MTX treatment. There was a tendency for a higher inter-individual variability and higher immunogenicity rate in juvenile subjects. During concomitant MTX treatment the serum levels were on average higher and the variability was lower.

Serum adalimumab concentration data from the OL LI and DB phases of Study DE038 were combined with data from the Phase 2 Study DE009 (MTX) and Phase 3 Study DE011 (non-MTX) in adult subjects with RA and modeled using population pharmacokinetic modeling. The purpose of the analysis was to compare adalimumab pharmacokinetics in adults to those in pediatric subjects with JIA. A one-compartment model with exponential inter-individual random effect terms on apparent clearance (CL/F) and apparent volume of distribution (V/F), with significant covariates of body weight, MTX, and rheumatoid factor (RF) on CL/F and body weight on V/F, and a combined residual error model, was identified as the final population pharmacokinetic model. The results of the analysis showed body weight normalized CL/F and V/F values to similar levels between juvenile and adult subjects.

Pharmacokinetics during the open-label extension fixed dose phase

There were 106 subjects who entered the OLE FD phase of Study DE038. Of these subjects, 56 subjects had a change in their dose upon entering the OLE FD phase and 50 did not have a change in their dose.

Serum adalimumab trough concentrations were measured only in subjects who had a change in dose upon switching to the FD regimen (N = 56). Of these 56 subjects, 53 subjects had an increase in dose and 3 subjects had a decrease in dose. Serum adalimumab trough concentrations were near steady state by Week 12 of the OLE FD phase in subjects who increased dose. The average steady state trough concentrations with the FD regimen were calculated as the arithmetic mean of pre-dose concentrations from both Week 12 and Week 16 of the OLE FD phase. For subjects who had dose increases in the OLE FD phase, serum adalimumab trough concentrations increased correspondingly. The increase in serum adalimumab trough concentrations was modest, at about 20% for the MTX stratum and 30% for the non-MTX stratum. However, these concentrations are still in the range observed previously in adalimumab-treated adults with RA, AS, PsA, and CD. In subjects who had dose decreases, 1 subject had serum adalimumab concentrations increase by Week 16 of the OLE FD phase and 2 subjects had serum concentrations that did not change.

Serum adalimumab trough concentrations were also examined stratified by weight-adjusted dose quartiles for subjects in the OLE FD phase compared to subjects in the OL LI and DB phases. The subjects who entered the OL LI phase received adalimumab doses (normalized by body weight) ranging from 0.4 mg/kg to 1.11 mg/kg (median – 0.78 mg/kg). By comparison, subjects who entered the OLE FD phase received adalimumab doses (normalized by body weight) ranging from 0.37 mg/kg to 1.31 mg/kg (median – 0.78 mg/kg). These data demonstrate that the dose range for subjects receiving the FD in the OLE FD phase was fairly comparable to that of the subjects receiving the BSA-based dose in the OL LI phase. The serum adalimumab trough concentrations analyzed by normalized dose quartiles are also fairly comparable for the two regimens.

Discussion on clinical pharmacology

Overall, following the BSA-based dosing in juvenile subjects (24 mg/m^2 with a maximum dose of 40 mg eow) steady-state serum concentrations obtained in subjects with JIA appeared to be within the range of those previously observed in adult subjects (40 mg eow in RA, AS and PsA patients), both during monotherapy and concomitant MTX treatment. There was a tendency for a higher inter-individual variability in juvenile subjects compared with adults. An initial approach to support a fixed

dose regimen on the basis of data from study DE038 PK modelling was previously not considered appropriate due to deficiencies in the model building and also in assessing how well the model simulates data.

Therefore, under the assumption of similar exposure-response relationships, with respect to safety and efficacy, for children, adolescents and adults the available pharmacokinetic data support the studied dosing based on BSA, since the systemic exposure is in the same range as that observed in adults.

Conclusions on clinical pharmacology

The available pharmacokinetic data suggest that the systemic exposure in children of the age of 4 years, and adolescents using a dosing based on body surface area is similar to the obtained in adults following treatment with adalimumab.

1.3.2. Clinical efficacy

Main study

Study DE038 was the pivotal clinical study to evaluate efficacy and safety with adalimumab for pediatric subjects with polyarticular JRA, who were either MTX-naïve, inadequate responders or intolerant to MTX.

Methods

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

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

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

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

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

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

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

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

Subject Population

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

Efficacy Variables

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

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

- Physician's Global Assessment of subject's disease severity by VAS (Visual analog scales)
- Parent's Global Assessment of subject's overall well-being by VAS
- Number of active joints (joints with swelling not due to deformity or joints with LOM and with pain, tenderness or both)
- Number of joints with LOM
- DICHAQ (disability Index of the Childhood Health Assessment Questionnaire)

- CRP (C-reactive protein) - Change in CRP from baseline was evaluated for clinical improvement or worsening only if at least one of the CRP values, baseline value, or the visit value was outside the normal reference range.

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

Statistical Methods

The efficacy analyses were performed on an intent-to-treat (ITT) population. The ITT population was defined as all subjects who received at least one dose of study drug in the OL LI phase.

The four analysis sets that were used for different phases in this study report are mentioned below:

- The OL LI phase includes any ITT subject that received at least one dose of adalimumab in the OL LI period of the trial (initial 16 weeks)
- The DB phase includes any ITT subject that received at least one dose of DB medication (32-week period)
- The OLE BSA phase includes any ITT subject that received at least one OLE dose of adalimumab (32 to 136 weeks)
- The OLE FD phase includes any ITT subject that received at least one dose of adalimumab at a FD of 20 mg or 40 mg (176 weeks)

The primary efficacy variable was the proportion of subjects in the non-MTX stratum who experienced disease flare in the DB phase.

The analyses of the PedACR response from all four phases of the study were used to demonstrate the efficacy of adalimumab treatment. Data from the OLE BSA phase were used to demonstrate the safety and efficacy of long-term adalimumab dosing with the BSA dosing regimen, and data from the OLE FD phase were used to support the efficacy of the FD adalimumab regimen. For the OLE FD phase, this report includes data from Week 0 through Week 176 visits.

For categorical efficacy data, Pearson's Chi-square test was used or, in instances where at least one cell had the expected value of cell count < 5, Fisher's exact test was used. Continuous efficacy variables were summarized using n (sample size), mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum for continuous variables. For continuous variables, comparisons between groups were conducted using an analysis of covariance (ANCOVA), with the OL LI Baseline as the covariate.

Overall the statistical methods used were considered as appropriate.

Results

Patient flow

Table 2 presents the number of subjects in each phase of the study.

Table 2 Number of subjects in each respective phase of the study

Disposition of patients in Study DE038
Open label lead in phase (171 enrolled)

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

Baseline disease characteristics

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

Main efficacy endpoints

Open label lead in phase (OLE LI)

A total of 171 subjects enrolled in the OL LI phase: 86 subjects in the non-MTX stratum and 85 subjects in the MTX stratum. Response was measured at selected time points during the 16 week OL LI phase and subjects who achieved a PedACR30 response were eligible to enroll in the DB phase. At Week 16, 144 of 171 (84.2%) subjects were PedACR30 responders. A greater proportion of subjects (94.1%) in the MTX stratum achieved a PedACR30 response compared to the non-MTX stratum (74.4%). Six patients in the non-MTX stratum discontinued treatment due to lack of efficacy, but none in the MTX group. Of those who completed the OLE LI, 8 (9%) from the MTX group and 19 (22%) from the non-MTX group did not continue into the DB phase. This indicates that monotherapy was insufficient to achieve adequate response in certain individuals. Of the 144 subjects who achieved a PedACR30 response, 133 subjects continued on to the DB phase of the study.

Double blind phase

The primary efficacy endpoint was the proportion of adalimumab-treated subjects in the non-MTX stratum with disease flare during the DB phase, Week 16 to Week 48, compared to the proportion of placebo-treated subjects in the non-MTX stratum with disease flare.

Adalimumab treatment significantly decreased the proportion of subjects with disease flares compared to placebo treatment (P = 0.031) in the non-MTX stratum at Week 48. Disease flare was experienced by 43.3% of subjects in the adalimumab treatment group and by 71.4% of subjects in the placebo treatment group. In addition, adalimumab monotherapy demonstrated a significant delay (P = 0.029) in time to disease flare compared to placebo treatment. Median time to flare in the placebo group was

~14 weeks from the first dose of blinded treatment compared to > 32 weeks for the adalimumab group.

Significant differences in the proportion of subjects (36.8% adalimumab-treated subjects and 64.9% of placebo-treated subjects) with disease flare by Week 48 were also seen for subjects treated in the MTX stratum (P = 0.015). Adalimumab was also superior in delaying the onset of disease flare compared to placebo in the MTX stratum (P = 0.031). Median time to disease flare in the MTX stratum from the first dose of DB treatment was > 32 weeks for subjects receiving adalimumab and ~20 weeks for subjects receiving placebo.

Additional secondary analyses of PedACR30/50/70/90 response at the end of the DB phase (imputing subjects with flare as non-responders) demonstrated that:

- In combined strata, subjects treated with adalimumab demonstrated statistically significant different (P = 0.048) proportions of PedACR30 responses as early as Week 36. PedACR30 responses were achieved by 64.7% of adalimumab-treated subjects versus 47.7% of placebo-treated subjects.
- A greater proportion of placebo-treated subjects in the non-MTX stratum lost their PedACR70 response compared to adalimumab-treated subjects. Specifically at Week 48, 46.7% of adalimumab-treated subjects were PedACR70 responders versus 60.0% at Week 16. For the placebo-treated subjects 28.6% were PedACR70 responders at Week 48 versus 71.4% at Week 16. The difference between treatment groups was not statistically significant.
- In the MTX stratum, adalimumab treatment was statistically superior to placebo in achieving PedACR30/50/70 responses (P = 0.028; P = 0.028, and P = 0.002, respectively) at Week 48.

Among patients with no flare during the DB phase, a tendency towards more injection site reactions was found, but also a lower number of infections. These data are however, very limited due to a low number of patients. More knowledge on the risks and/or loss of efficacy in patients who interrupt treatment and restart again was considered important and should be collected in e.g. the registry. Clarifications that data from week 36 to week 48 in the adalimumab arm were not based on LOCF were provided.

Open-Label Extension Data

The continued benefit of adalimumab treatment was assessed during the OLE phases of the study. At the time of flare during the DB phase, subjects were immediately eligible to enter the OLE BSA phase. Subjects who completed the DB phase were also eligible to enter the OLE BSA phase.

The results demonstrate that the proportion of subjects with a PedACR30/50/70/90 response significantly increased by Week 8 of the OLE BSA phase (100% of subjects were PedACR30 responders) from the last value of the DB phase in those subjects who received placebo during the DB phase, and the high response rate was maintained during the OLE BSA phase.

In those subjects who received adalimumab during the DB phase, the proportion of subjects achieving a PedACR30 response by Week 8 of the OLE BSA phase was similar to the response at the last value of the DB phase, and was maintained during the OLE BSA phase.

Long-term efficacy

All subjects who completed 32 weeks of DB phase or experienced a flare were eligible to receive OL adalimumab during the OLE BSA phase. Due to the study design, subjects had different durations of

exposure during the OLE BSA phase. There were only five subjects with exposure of 136 weeks. The CHMP noted this limited amount of data following longer term treatment, and that the numbers of treated patients decreased over time in the open BSA phase, partly due to recruitment of patients into the FD regimen.

The OLE FD phase includes any ITT subject who received at least one dose of adalimumab at a fixed dose of 20 mg or 40 mg, and could continue for up to 240-weeks. In total 106 entered this phase. The number of subjects with efficacy results reported by week 176 was 38, and by week 102, 6 subjects. In these subjects, vast majority still responded. The overall long-term efficacy in this study remains limited.

Immunogenicity

Only samples with low adalimumab concentrations (<2 microg/ml) were analysed for anti-adalimumab antibodies (AAA). Positive values were defined as an apparent antibody concentration >20 ng/ml, with <50% suppression of antibody concentrations by normal human serum and that developed within 30 days of the preceding dose of adalimumab.

In Study DE038, 27 of 171 subjects (15.8%) had at least one anti-adalimumab antibody (AAA) positive sample during the OL LI and DB phases. The percentages of AAA positive subjects were 5.9% (5/85) in the MTX stratum and 25.6% (22/86) in the non-MTX stratum. The overall rate of AAA positive subjects was higher than seen in clinical trials in adults with RA while there was no obvious difference in the antibody incidence between juvenile and adult subjects on concomitant MTX. No subjects developed AAA for the first time upon switching to the FD regimen during the OLE FD phase.

The overall proportion of subjects achieving a PedACR30[2] response at Week 16 in the OL LI phase was lower in subjects who were AAA positive (12 of 19, 63.2%) compared to subjects who were AAA negative (132 of 152, 86.8%). Similarly, at Week 48 of the DB phase, the overall proportion of subjects achieving a PedACR30 response was lower in subjects who were AAA positive (6 of 14, 42.9%) compared to subjects who were AAA negative (35 of 54, 64.8%). Although the response rate was lower in AAA-positive subjects, a substantial proportion of these subjects were responders. Reduced efficacy in the presence of AAAs has also been observed in adults with RA; however, the development of AAAs in this patient population does not appear to impact efficacy to the same extent as in adult subjects with RA.

16 of the 30 (53%) subjects in the OLE FD phase were AAA positive at some point in time during the previous phases of the study. Despite their antibody status, these subjects remained in the study through the OLE FD phase and had PedACR responses during the OLE BSA and OLE FD phases that were fairly comparable to AAA negative subjects. At Week 16 of the OLE FD phase, 12 of 17 (70.6%) of AAA positive subjects achieved a PedACR30 response compared to 79 of 89 (88.8%) of AAA negative subjects. Although the response rate was slightly lower in AAA positive subjects, a substantial proportion of these subjects were responders.

Discussion on clinical efficacy

One pivotal trial was performed to study efficacy and safety in children aged 4-17 years, with polyarticular JIA. An open initial phase study design, including two strata (non-MTX and MTX), followed

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

by a double-blind withdrawal phase was chosen mainly from the ethical point of view. The study population was adequate as well as the chosen clinical endpoints.

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

The primary endpoint, proportion of subjects with disease flare in the non-MTX stratum during the DB phase, was statistically significantly in favour of adalimumab. The same result was shown in the MTX stratum. The low threshold for flare and the use of imputation have to be taken into account when analysing the results of the primary efficacy. It was considered that in the DB phase, a proportion of patients who were in the placebo arm may improve, also after a flare. The imputation assumes there will be no further improvement and could weaken the control arm. Because more patients drop out of the placebo condition than the adalimumab arm, imputation (particularly LOCF) results in a bias in favour of the alternative hypothesis. Overall, it can be concluded that adalimumab prevents disease flares compared to placebo but due to the complex trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. Appropriate wording in section 4.2 of the SmPC was added in the framework of EMEA/H/C/000481/H/C/39. It reduces the risk of patients not responding to receive continued treatment: "*Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period*".

In addition, it was considered of importance to collect efficacy data in "real-world" practice. The MAH agreed to set up a registry in JIA patients in the framework of EMEA/H/C/000481/H/C/39. A first report from this study was assessed recently (FUM 046 in December 2010). The secondary objective of this registry will be to evaluate the long-term effectiveness of Humira in JIA patients who are treated as recommended in the approved product information. Patients treated with MTX will be considered a reference group. Conclusion on the first report informed that there is only very limited data available at the time of the report, and thus no firm conclusions can be drawn. (see clinical safety section).

The MAH now applies with dosing instructions to allow for dosing according to the BSA posology used in the clinical study for children younger than 13 years. The reason is that only BSA dosing has been adequately documented for those children. Thus, with this new option, it is possible to administer an appropriate dose also to the age range from 4-12 years.

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

Anti-adalimumab antibodies developed in a higher number in the non-MTX group, 25.6% versus 5.9%, which also raised concerns regarding long term efficacy. Further, the pharmacokinetic data indicate a higher adalimumab plasma level in the combination group. Overall, these data support combination therapy with MTX, and therefore combination therapy is the primary recommendation for this indication.

1.3.3. Clinical safety

The safety of adalimumab was determined through evaluation of AEs (adverse events), clinical laboratory evaluations, physical examinations, and vital signs. In addition, TNF – inhibitor related AEs

of interest were evaluated: infections, serious infections, malignancies, opportunistic infections, tuberculosis (TB), demyelinating disorders, lupus – like syndrome, congestive heart failure (CHF), allergic reactions, injection site reactions, haematologic events, and hepatic events.

Patient exposure

In the OL LI phase and the DB phase, there were 55 subjects exposed to adalimumab, corresponding the 44 patients years (PYs). During the subsequent open label phases, exposure corresponded to 118 PYs.

Adverse events

An overview of treatment emergent AEs in the three phases of the study where patients received a dose based upon BSA (OL LI, DB and OLE BSA) is shown in tables 3-5 below.

Table 3 Overview of treatment emergent adverse events (ITT population, open label lead in phase)

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

Table 4 Overview of treatment emergent adverse events (ITT population, double blind phase)

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

infections including TB						
Death	0	0	0	0	0	0

The percentage of subjects with any AE was higher (88.2%) in the adalimumab group versus the placebo group (73.8%). Few subjects reported SAEs; 5 in the MTX stratum (2 placebo-treated subjects and 3 adalimumab-treated subjects) and 1 treated with adalimumab in the non-MTX stratum. The proportion of subjects presenting with infections, AEs at least possibly related to study drug, and injection site reactions was

Table 5 Overview of treatment emergent adverse events (ITT population, OLE BSA phase)

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

	MTX		non-MTX		Overall	
	Adalimumab (placebo during DB phase)	adalimumab	Adalimumab (placebo during DB phase)	adalimumab	Adalimumab (placebo during DB phase)	adalimumab
	N=36	N=35	N=28	N=29	N=64	N=64
Adverse event	n (%)					
Allergic reaction related	0	1 (2.9)	1 (3.6)	0	1 (1.6)	1 (1.6)
Lupus-like syndrome	0	0	0	0	0	0
Hematologic related	1 (2.8)	1 (2.9)	0	0	1 (1.6)	1 (1.6)
Serious blood dyscrasias	0	0	0	0	0	0
Non-serious blood dyscrasias	2 (5.6)	1 (2.9)	0	0	2 (3.1)	1 (1.6)
Fatal adverse event	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

The percentage of subjects with any AE was similar (58 [90.6%]) in the adalimumab group versus the placebo (61 [95.3%]). The proportion of subjects with any AE in the adalimumab group (58 [90.6%]) was comparable to the proportion in the placebo group (61 [95.3%]). Similarly, the proportions of subjects experiencing specific types of AEs (e.g., serious, severe, infections) were comparable for the subjects previously treated with placebo versus adalimumab. The only notable difference was the incidence rate of infections reported for the adalimumab-treated subjects in the MTX stratum compared to adalimumab-treated subjects in the non-MTX stratum (29 [82.9%] versus 20 [69.0%], respectively). In this case, the concomitant use of MTX with adalimumab may have resulted in a higher frequency of infectious AEs compared to adalimumab treatment without concomitant MTX. There were no deaths, opportunistic infections, malignancies, lymphomas, non-melanoma skin cancer, congestive heart failure (CHF), CNS demyelinating disease, lupus-like syndromes, or serious blood dyscrasias reported in the OLE BSA phase of this study. In addition, no cases of TB were found in this study phase.

Most common adverse events

The most common AEs across the trial included injection site reactions (injection site pain and injection site reactions), viral infections, upper respiratory infections, and nasopharyngitis. This pattern is consistent with that reported in adult RA studies.

Adverse Events At Least Possibly Related to Study Drug

The most common AEs at least possibly related to study drug across all phases of the study included injection site reactions (injection site pain, injection site reactions) and upper respiratory infections.

Serious adverse events, deaths and other events of interest

No deaths were reported in any phase of this study.

A total of 48 subjects reported SAEs. Most were mild to moderate in severity. Four subjects had SAEs that were reported as severe and at least possibly related to study drug. A larger proportion of subjects reporting severe SAEs were in the MTX stratum (9 of 15 subjects). The most frequently reported severe SAEs were juvenile arthritis (4 subjects) and appendicitis (3 subjects). Pneumonia was reported during the OL LI phase and bronchopneumonia was reported during the OLE BSA phase; both

events were reported for subjects in the non- MTX stratum. The third event, herpes zoster was reported for a subject in the MTX stratum during the OLE BSA phase. These events were resolved and the subjects continued in the study.

With regard to special AEs of interest, no events of CHF, CNS demyelination, lymphomas, non-melanoma skin cancer, drug-induced lupus, or malignancies were reported during the trial. Serious infectious AEs were reported in 11 subjects

Adverse events leading to discontinuation of study drug

During the 4 phases of the trial, 16 treatment-emergent AEs led to study drug discontinuation; 9 occurred during the OL LI phase or the post-OL LI phase. The most common event (in 10 of 16 subjects) was disease flare. One had leucopenia, two infections (pneumoniae), one dizziness, one abortion, one arthralgia. The majority of subjects with AEs leading to study drug discontinuation were in the non-MTX stratum (all but 5 subjects).

Laboratory findings

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

Immunogenicity

The overall percentage of adverse events was slightly lower in AAA-negative subjects than AAA-positive subjects, while the percentage of adverse events with and without MTX treatment for AAA positive (both 100%) and AAA negative (86.4% *vs*. 78.9%) subjects was similar. The rate of serious adverse events, severe adverse events, adverse events leading to discontinuation of study drug, and serious infectious adverse events was less than 10% in both AAA negative and positive groups. The rates of adverse events leading to discontinuation of study drug and infectious adverse events were lower in the AAA-positive than AAA-negative subjects. Injection site reactions reported as adverse events were similar among the groups. There were no reported adverse events of malignant neoplasms, opportunistic infection (including TB), or death during the OL LI phase.

In the DB phase the overall percentage of adverse events was slightly lower in AAA-negative subjects in the adalimumab group without MTX treatment compared to the AAA-positive subjects in the same treatment group. The rate of serious adverse events, severe adverse events, and serious infectious adverse events was less than 10% in both AAA-negative and positive groups. There were no reported adverse events leading to discontinuation of study drug, adverse events of malignant neoplasms, opportunistic infection (including TB), or death during the DB phase.

In the OLE FD phase, the percentage of adverse events with and without MTX treatment for AAA positive (80% *vs.* 83.3%) and AAA negative (57.4% *vs.* 45.7%) subjects was similar. Only one subject discontinued study drug due to an adverse event, and this subject was AAA negative. There were no reported adverse events of malignant neoplasms, opportunistic infection, or death during the first 16 weeks of the OLE FD phase. In the OLE FD phase, the percentages of adverse events were higher for AAA positive subjects compared to AAA negative subjects in both MTX (80% for AAA positive *vs.* 57.4% for AAA negative) and non-MTX groups (83.3% for AAA positive *vs*. 45.7% for AAA negative). However, the number of AAA positive subjects in each group (MTX or Non-MTX) was too small to enable a meaningful assessment.

Overall no increased safety risk was observed in subjects who were AAA positive versus those who were AAA negative.

Other sources for safety data

Within the recently circulated FUM 46 (registry in JIA patients) the first report from the ongoing long-term registry follow up in this indication was assessed. This registry (Study P10-262) is a long-term, multi-center, longitudinal post-marketing, observational registry to assess long term safety and effectiveness of Humira (adalimumab) in children with moderate to severe active polyarticular or polyarticular course juvenile idiopathic arthritis (JIA) – STRIVE

The primary objective of this registry is to evaluate the long-term safety of adalimumab in patients with moderate to severe active polyarticular or polyarticular course JIA who are prescribed and treated in accordance with the local adalimumab product label under the conditions of a routine clinical setting. The secondary objective of this registry is to evaluate the long-term effectiveness of adalimumab in patients with moderate to severe active polyarticular or polyarticular course JIA who are prescribed and treated in accordance with the local adalimumab product label under the conditions of routine clinical setting. Patients being prescribed and treated with MTX per the local product label will be considered a reference group for both, the primary and secondary objective of the registry.

The registry was established in 2008, and the first subject was recruited in June 2008. Approximately 800 patients with JIA will be enrolled in the US, EU and Australia. Approximately 500 patients will receive adalimumab (alone or in combination with MTX) and be followed and 300 patients will receive MTX without concomitant adalimumab and be followed. Recruitment is estimated to be complete by June 2011. Study progress through 01 June 2010 was presented in this first interim report. A total of 202 patients have been enrolled.

At this early point of the registry, due to the small number of patients and the limited observation period for most of the enrolled patients, a thorough discussion is limited. However, no trends of clinical concern have been established with regard to the incidence of SAEs or AEs of interest, and no new safety signals have been observed. Safety data are comparable to those observed in previous adalimumab trials

Discussion on clinical safety

The CHMP concluded that there were no new safety signals in the treated children/adolescents compared with the already well known safety profile in adults. Infections were the most common events, as for adults. No cases of death, malignancies, CHF, CNS demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions were reported. However, it is noted that the database is small, and long-term safety cannot be assessed. In this regard, the main concerns are the development of malignancies.

The MAH provided some further comparisons on the safety profile in patients with or without disease flare during the double-blind phase. There was a tendency towards more injection site reactions in subjects without flare, but also a lower number of infections. These data are very limited. More knowledge on risks and/or loss of efficacy from patients who interrupt treatment and restart again is of importance, and is followed in the ongoing registry. Within the recently circulated FUM 46, the first report from the ongoing long-term registry follow up in this indication was assessed. Currently, experience is limited. However, there were no signals of unexpected safety findings so far. Continued monitoring within this study is of importance.

Risk Management Plan

The MAH submitted a new version of the RMP. The following are the main changes made: Version 8.0 has added information regarding the spondyloarthritis (SpA), paediatric enthesitis-related arthritis (pedERA), hidradenitis suppurativa (HS), and uveitis indications under development.

The MAH proposed to add in addition to the existing educational programme an educational programme for the paediatric vial. The CHMP did not consider that there was a need for additional pharmacovigilance or risk minimisation activities, beyond those already in place. Thus, it is not considered that this additional education activity should be part of the required risk minimisation plan or the already agreed education programme. The current education activities are sufficient to cover main issues of the safety profile.

Furthermore, the MAH took the opportunity to harmonize the important identified and important potential risk definition applied in previous procedures. Important AEs with adequate evidence of an association with adalimumab treatment are categorized as important identified risks. Important AEs for which there is some basis for suspicion of an association with adalimumab or other TNF-antagonists treatment, but where association has not been confirmed, are categorized as important potential risks. The following has been changed:

- Pulmonary embolism, melanoma, erythema multiforme, and sarcoidosis were newly added to the important identified risks.
- Stevens Johnson Syndrome (SJS), congestive heart failure (CHF), reactivation of hepatitis B, interstitial lung disease (ILD), intestinal stricture in CD, and pancreatitis were moved from the important potential risks to the important identified risks
- The risk category for central nervous system (CNS) demyelinating disorders was broadened to demyelinating disorders, including both peripheral and central demyelinating disorders.
- The risk for elevated Alanine aminotransferase (ALT) was expanded to cover all indications instead of PsA only.
- The important identified risk of vasculitis was specified as cutaneous vasculitis;
- Vasculitis (non-cutaneous); medication errors with paediatric vial; progressive multifocal leukoencephalopathy; reversible posterior leukoencephalopathy syndrome; off-label use; and amyotrophic lateral sclerosis (ALS) will be added as important potential risks.

These changes and updates are endorsed by the CHMP.

Change to the Product information

Further to the assessment of the proposals of the Marketing Authorisation Holder to amend the Product Information and in the light of the assessment of the submitted data, the following sections of the SmPC were amended: sections 1, 4.1, 4.2, 5.1, 5.2, 6.3, 6.5.

The expression of the product name is amended to reflect the new paediatric vial in section 1. The extended therapeutic indication in JIA and corresponding posology and method of administration are reflected in section 4.1 and 4.2 respectively. Section 5.1 and 5.2 are amended to reflect the results of study conducted in JIA patients. Section 5.1 is also amended to bring it in line with the QRD template. Section 6.3 reflects the updated shelf-life. Section 6.5 is amended to reflect the updated nature and contents of container. Minor editorial corrections are also made throughout the SmPC. Annex II is updated to reflect the last version of the RMP. The PL was updated in accordance with the changes of the SmPC. The labelling is also updated to reflect changes to this presentation. The MAH also took the opportunity to remove the alert card from the labelling. Details on the amendment of the PI can be found in Attachment 1.

User consultation

The applicant presented a bridging to a full user test carried out on the product Humira Pre-filled Pen 40 mg solution for injection in pre-filled pen (Adalimumab), which was assessed and accepted in 2006. The results showed 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.

1.3.4. BENEFIT RISK ASSESSMENT

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

After the blinded phase, patients could continue on open label BSA dosing. Thereafter, patients were switched to open label fixed dosing of 20 mg (subjects up to 30 kg body weight) or 40 mg ($\geq$ 30 kg) eow. The data presented allowed fixed dose of 40 mg from the age of 13 years. For younger children, dosing based on BSA was recommended. The MAH has now developed a presentation which allows for the accurate dosing according to BSA.

Benefit

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

During the blinded withdrawal phase, the primary endpoint, proportion of subjects with disease flare in the non-MTX stratum, as well as the same endpoint in the MTX stratum, was statistically significantly in favour of adalimumab. The low threshold for flare and the use of imputation have to be taken into account when analysing the results of the primary efficacy. Overall, it is accepted that adalimumab prevents disease flares compared to placebo but due to the complex trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. Appropriate wording in the SmPC reduces the risk of patients not responding to receive continued treatment: the product information advises caution if a patient does not respond within 12 weeks of treatment; furthermore, a registry aiming to collect more data in this regard has been set up following the previous procedure (EMEA/H/C/000481/H/C/39). It was considered of importance to collect efficacy data in the registry setting, which the MAH agreed to undertake. The registry is ongoing.

In addition to the higher percentage of responders in the lead-in phase, the number of discontinuations was higher in the non-MTX during the initial phase, and there was a higher number of responders achieving the more stricter Ped ARC50/70 criteria in the combination group. Anti-adalimumab antibodies developed in a higher number in the non-MTX group, 25.6% versus 5.9%, which justifies follow-up on the long term efficacy (registry ongoing) also raises concerns regarding long term efficacy. Finally, the pharmacokinetic data indicate a higher adalimumab plasma level in the combination group.

Overall, these data support combination therapy with MTX. Combination therapy is the primary recommendation in the indication.

Risks

The safety profile of an anti-TNF agent is well established, with infections as one main concern. No new safety signals were found in the performed study. The three most frequently reported AEs by MedDRA preferred term included upper respiratory tract infection, viral infection, and injection site reactions. No cases of death, malignancies, CHF, CNS demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions were reported. To further assess the long-term safety, for which at present the database is limited, a registry has been set up, which also monitors the development of malignancies. Safety data obtained during the OL LI, DB, and OLE BSA phases, during which dosing was based on BSA (24 mg/m2 up to a total dose of 40 mg eow), were comparable to the safety data obtained during the OLE FD phase. No apparent difference in type or rate of AEs was observed in those subjects who were determined to be AAA positive compared to those that were AAA negative. Overall, safety data obtained in this adalimumab trial in pediatric JIA subjects are consistent with those expected in the adult RA population.

The RMP is acceptable, the proposed Paediatric vial educational programme has not considered necessary for inclusion in the RMP. The MAH has a registry ongoing where both safety and effectiveness data are collected. The MAH will follow subjects for 5 years for all events specified in the Registry protocol and additional 5-years on an annual basis to collect events of CHF and Malignancies.

The MAH took the opportunity to remove the Alert Card from the annexe III-A. This is acceptable as the Alert Card is not part of the pack and is not included in the carton. Nevertheless the patient alert card must remain in use and is part of the RMP.

Benefit-risk balance

The MAH applies with dosing instructions to allow for dosing according to the BSA posology used in the clinical study for children younger than 13 years. The reason is that only BSA dosing has been adequately documented for those children. Thus, with this new option, it is possible to administer an appropriate dose also to this age group.

Efficacy has been sufficiently demonstrated with the body surface area dosing of 24 mg/m^2. There are tendencies of better efficacy with a combination of adalimumab and MTX. The indication was revised and combination therapy with MTX is the primary option. A fixed dose of 40 mg from the age of 13 years was agreed. With the availability of an option to use BSA dosing in the younger children, also adequate dosing of children aged 4-12 years is ensured.

The safety profile demonstrated in the study shows no unexpected findings, but long-term safety remains a concern to be followed in the ongoing registry. To conclude, the benefit / risk balance for the treatment of subjects aged 4-12 years, with active polyarticular juvenile idiopathic arthritis, who have inadequate response to one or more DMARDs, is positive.

2. Conclusion

On 17 February 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.