20 July 2017
EMA/CHMP/505087/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0163

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

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# List of abbreviations

| | |
|---|---|
| AAA | Anti-adalimumab antibodies |
| AC | anterior chamber |
| ADA | adalimumab |
| AE | adverse event |
| AESI | adverse event of special interest |
| ANA | Antinuclear Antibodies |
| BCVA | best corrected visual acuity |
| BD | Behçet's disease |
| BSA | Body Surface Area |
| CD | Crohn's disease |
| CHAQ | Childhood Health Assessment Questionnaire |
| CHQ | Childhood Health Questionnaire |
| CI | Confidence Interval |
| CINCA/NOMID | chronic infantile neurological cutaneous and articular/neonatal-onset multi-system inflammatory disease syndrome |
| CNS | central nervous system |
| CS | corticosteroids |
| DsDNA | anti-double-stranded DNA antibodies |
| EEA | European Economic Area |
| eow | every other week |
| ERA | enthesitis-related arthritis |
| EU | European Union |
| HR | hazard ratio |
| $IC_{50}$ | Half maximal inhibitory concentration |
| IMM | immunomodulators |
| IOP | intraocular pressure |
| ITT | intention to treat |
| JIA | juvenile idiopathic arthritis |
| JIAU | juvenile idiopathic arthritis associated anterior uveitis |
| LogMar | Logarithm of the Minimum Angle of Resolution |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | methotrexate |
| 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 |
| SOC | System Organ Class (MedDRA) |
| SUN | Standardisation of Uveitis Nomenclature |
| TINU | tubulointestinal nephritis associated uveitis |
| TNF(-α) | tumour necrosis factor (alpha) |
| UC | ulcerative colitis |
| UK | United Kingdom |
| USA | United States of America |
| VH | vitreous haze |
| VKH | Vogt-Koyanagi-Harada |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 2 December 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include new indication for treatment of chronic non-infectious uveitis in paediatric patients for Humira; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement an alternative format statement for blind/partially sighted patients into the Package Leaflet which was introduced with procedure EMEA/H/C/000481/N/0155. Furthermore, the MAH has made some editorial changes to the Package leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0200/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0200/2016 was completed. The PDCO issued an opinion on compliance for the PIP P/0200/2016.

## *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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Scientific advice*

The applicant did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

| Timetable | Actual dates |
|---|---|
| Submission date | 2 December 2016 |
| Start of procedure | 24 December 2016 |
| CHMP Rapporteur's preliminary assessment report circulated on | 16 February 2017 |
| PRAC Rapporteur's preliminary assessment report circulated on | 16 February 2017 |
| PRAC RMP advice and assessment overview adopted by PRAC on | 9 March 2017 |
| Updated CHMP Rapporteur's assessment report circulated on | 16 March 2017 |
| Request for supplementary information and extension of timetable adopted by the CHMP on | 23 March 2017 |
| MAH's responses submitted to the CHMP on | 17 May 2017 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on | 19 June 2016 |
| PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on | 22 June 2016 |
| PRAC RMP advice and assessment overview adopted by PRAC on | 6 July 2017 |
| CHMP Rapporteur's updated assessment report on the MAH's responses circulated on | 13 July 2017 |
| CHMP opinion | 20 July 2017 |

# 2. Scientific discussion

## *2.1. Introduction*

Humira contains the active substance adalimumab, a recombinant human immunoglobulin 1 monoclonal antibody specific for human tumour necrosis factor-alpha (TNF-α). Adalimumab is a 1,330 amino acid macromolecule containing exclusively human sequences. It binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF-α receptors. As a consequence, adalimumab modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration. TNF is a naturally occurring cytokine involved in normal inflammatory and immune responses. Elevated levels of TNF-α are thought to play an important role in autoimmune disorders and immune-mediated disorders.

Humira was first approved in the European Union (EU)/European Economic Area (EEA) through the centralised procedure by Commission Decision in September 2003 for the treatment of rheumatoid arthritis (RA). Since then, Humira was approved in a number of other (adult and paediatric) autoimmune conditions including psoriasis (Ps), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), Crohn's disease (CD) and ulcerative colitis (UC). In June 2016, Humira was also approved for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.

This variation application seeks to extend the indication to *"the treatment of chronic non-infectious uveitis in paediatric 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".* During the course of the procedure, in light of concerns raised by the CHMP, the MAH agreed to limit the indication to non-infectious anterior uveitis.

The application is based on the following:

- an 18-month, double-masked, placebo-controlled study (SYCAMORE) of paediatric patients with JIA-associated non-infectious anterior uveitis (JIAU),
- extrapolation of efficacy data from studies M10-877 and M10-880 (VISUAL I and II) in adults with uveitis involving the posterior segment,
- extrapolation of pharmacokinetic (PK) data from other paediatric populations,
- literature data, and
- safety data from the MAH's adalimumab database for JIA and other paediatric data.

Non new quality or preclinical data were presented.

The proposed posology for patients weighing <30kg consists of a subcutaneous (sc) dose of 20 mg every other week (eow) with the option to administer a loading dose of 40 mg one week prior to the start of maintenance therapy. Patients weighing ≥30kg are proposed to receive 40 mg sc eow and an optional loading dose of 80 mg. Humira is recommended to be used in combination with methotrexate (MTX).

***Background information on the disease***

Uveitis is a serious and debilitating disease concerning some or all ocular tissues comprising the uveal tract (iris, ciliary body, and choroid). It involves severe intraocular inflammation, vision impairment and pain. According to the Standardization of Uveitis Nomenclature (SUN) working group (Jabs et al., 2005), uveitis can be classified according to the primary anatomical location of the inflammation into anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis (affecting all 3 eye segments). The location of the inflammation dictates the prognosis and therapy for the disease and there is a higher risk of vision loss and blindness in subjects with posterior and pan-uveitis. Uveitis can also be categorised by the aetiology of the inflammatory process into infectious or non-infectious uveitis. Non-infectious uveitis can be further classified as to whether it is an isolated ocular syndrome or if there is accompanying extra-ocular or systemic inflammation. Subjects with non-infectious uveitis, who have no characteristic disease pattern, or systemic involvement that indicates a specific diagnosis, are often referred to as having 'idiopathic' uveitis.

The prevalence of paediatric non-infectious uveitis in North America and Europe is approximately 30 cases per 100,000 children (Foster et al., 2013). Besides being rare, uveitis is a highly heterogeneous disease with a varied spectrum of clinical presentation (see above and below) and difficulties in diagnosis as well as in treatment. Difficulties performing full eye examinations (especially in young non-compliant children), delays in diagnosis and limited management options together with the prolonged duration and increased risks of complications can results in significant ocular morbidity and severe vision loss or blindness. The most commonly observed complications of non-infectious uveitis in paediatric patients include increased intraocular pressure (IOP), corneal opacities, cataracts, posterior synechiae of the iris to the lens, retinal detachment, vitreous opacities, and macular oedema. These complications are usually associated with delayed diagnosis and treatment because the disease is often without symptoms until vision loss occurs. The likelihood of progression to severe visual impairment if left untreated, with a substantial impact on day-to-day functioning and overall quality of life adds to the socioeconomic burden of the disease.

Non-infectious anterior uveitis is the most common type of paediatric uveitis, accounting for more than 50% of all cases. JIA associated anterior uveitis (JIAU) is unique for children and the leading cause in case series reported from Northern European countries and from the USA, whereas it is less frequent in Mediterranean countries. The onset of the disease is commonly at the age of 2-4 years and it occurs more common in girls. The activity of uveitis usually does not parallel the joint inflammation and in the majority of cases, the arthritis is diagnosed before the eyes are involved. Likewise, the severity of the arthritis does not correlate with the severity of the uveitis.

Behçet's disease (BD) and Vogt-Koyanagi-Harada (VKH) syndrome are very rare in paediatric patients from Northern Europe and the USA but more frequent in Middle Eastern countries. Other forms of paediatric non-infectious uveitis include (but are not limited to) pars planitis/intermediate uveitis, sarcoidosis, sympathetic ophthalmia (often secondary to trauma), Fuchs' iridocyclitis and tubulointestinal nephritis associated uveitis (TINU), the latter occurring mainly in children and young adults. There are also some additional syndromes unique to children: Kawasaki's syndrome, chronic infantile neurological cutaneous and articular/neonatal-onset multi-system inflammatory disease syndrome (CINCA/NOMID) and familial juvenile systemic granulomatosis (Blau syndrome).

For some uveitis subsets, the aetiology, clinical course and severity are similar in the adult and the paediatric population while other forms differ. For example, anterior uveitis would be expected to be similar independent on the presence or absence of associated systemic conditions. Although intermediate uveitis can develop at any age, it is more commonly developed in children and young adults. In paediatric subjects, there are reports suggesting an association with a worse visual acuity

outcome compared to adults, potentially due to delayed diagnosis, but there are also reports indicating a more aggressive disease course in children and adolescents compared to adults.

***Current treatment options***

At the time of this report, the mainstay of treatment early in the course of non-infectious uveitis was corticosteroids (CS, either topical, oral, periocular or intraocular). The type and severity of the disease dictate the route of administration of CS and the likelihood of requiring other immunosuppressive therapy to control the disease. Topical CS eye drops are often sufficient to control milder forms of anterior uveitis, including JIAU, but in patients who require prolonged therapy or fail to respond to topical CS, immunomodulators (IMMs), such as MTX, are the standard of care for paediatric patients. Periocular or sub-tenon CS injections are also used for the treatment of chronic anterior, intermediate or posterior uveitis. Systemic CS can be used as a short-term bridge to immunosuppressive therapy in patients not controlled with local therapy.

Prolonged use of topical CS is associated with ocular complications, mainly progressive cataracts, IOP elevation and glaucoma which occur more rapidly and may be difficult to treat in children compared to adults. Long-term use of systemic CS should be avoided in children who are more vulnerable to their side effects, in particular growth inhibition, immunosuppression and related increased susceptibility of infections as well as adrenal suppression. Other side effects include cataract development, osteoporosis, and glucose intolerance, deposition of body fat, thinning of skin and weight gain.

IMMs such as MTX are poorly tolerated in a subset of children. In the EU, ciclosporin is also approved for the treatment of uveitis, however its onset of action is rather slow and its use is associated with substantial side effects. In general, use of immunosuppressive agents has limitations related to safety.

There is also a subset of patients, in whom the disease is not sufficiently controlled with CS and non-biologic IMMs. As a result, there is an unmet medical need in paediatric patients with uveitis who do not tolerate treatment with CS or IMMs or in whom those treatments are inappropriate or do not sufficiently control the disease.

In some of these patients, biologics including anti-TNF agents are used in clinical practice. A number of studies suggest that TNFα blockers may be beneficial in the treatment of uveitis, particularly infliximab and adalimumab. At the time of this report, several local commissioning and clinical guidelines for the treatment of severe, refractory anterior uveitis in paediatric patients were available. Typical treatment algorithms agreed by national health services, e.g. United Kingdom and Germany, recommend 3 phases of treatment:

1) treatment with topical CS,
2) treatment with non-biologic IMMs, and
3) addition of a second non-biologic IMM (e.g., MTX or ciclosporine) or a biologic IMM (e.g., infliximab or adalimumab).

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

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

Non-clinical data available at the time of this report revealed no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity. In a previous application for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients, the MAH submitted the results of a study in an Experimental Autoimmune Uveoretinitis mouse model. The data showed that murine anti-mouse TNF monoclonal antibody is able to reduce inflammation in the model.

### 2.2.2. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00), proteins are unlikely to result in a significant risk to the environment. Hence, the CHMP agreed that no environmental risk assessment studies were needed.

### 2.2.3. Conclusion on the non-clinical aspects

Given that the pharmaco-toxicological profile of adalimumab has been well established, the CHMP agreed that no non-clinical data were needed to support this application.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH provided the results from one randomised placebo-controlled Phase 3 trial (SYCAMORE) investigating adalimumab in combination with MTX for the treatment of JIAU. Reference was also made to previous studies in adult patients with active and inactive uveitis. In addition, population PK modelling was performed to simulate adalimumab exposure in paediatric uveitis patients. Finally, data from the adalimumab database for JIA and other related paediatric indications were provided to support the safety assessment.

**Table 1 – Tabular Overview of Clinical Studies**

| Study Objective | Study ID | No. of study centres/ locations | Design | Study Posology | Subjs. ADA/ placebo | Duration | Age (years) | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| Efficacy, safety | SYCAMORE | 17/UK | Double-masked, randomised, placebo-controlled, superiority | ADA: <30kg: 20 mg, ≥30 kg: 40 mg eow (sc) + MTX 10-20 mg/m$^2$ (max 25 mg) versus placebo + MTX | 60/30 | Up to 18 month | 2.6-18 | Refractory mild or moderate JIAU |
| Paediatric population PK model – for extra-polation | M04-717<br>DE038<br>M10-444<br>M11-328<br>M06-806 | Several | One-compartment model | various | 524 | | 2-18 | Ps<br>JIA<br>ERA<br>CD |
| Efficacy, safety – for extra-polation | M10-877 | 67/ global incl. EU | Double-masked, randomised, controlled, superiority | ADA: 80 mg loading, 40 mg eow vs. placebo. Initial | Main study: 111/112 | Up to 80 weeks | adults | Active uveitis involving posterior segment |

| Study Objective | Study ID | No. of study centres/ locations | Design | Study Posology | Subjs. ADA/ placebo | Duration | Age (years) | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | | | prednisone 60 mg/day in both arms | | | | despite CS 10-60 mg/day |
| Efficacy, safety - for extra-polation | M10-880 | 62/ global incl. EU | Double-masked, randomised, controlled, superiority | ADA: 80 mg loading, 40 mg eow vs. placebo | Main study: 115/114 | Up to 80 weeks | adults | Inactive uveitis involving posterior segment on CS 10 -35 mg/day |

ADA=adalimumab; CD= Crohn's disease; CS=corticosteroids; eow=every other week; ERA=enthesitis-related arthritis; EU=European Union; JIA=juvenile idiopathic arthritis; JIAU=juvenile idiopathic arthritis associated anterior uveitis; MTX=methotrexate; PK=Pharmacokinetic; Ps=psoriasis; UK=United Kingdom

## Good Clinical Practice (GCP)

The MAH confirmed that the clinical trial was performed in accordance with GCP.

## 2.3.2. PK modelling

The paediatric population PK model has previously been developed using data from 5 paediatric studies in paediatric Ps (Study M04-717), polyarticular JIA (studies DE038 and M10-444), paediatric ERA (study M11-328), and paediatric CD (study M06-806). Overall, the model includes data from 524 paediatric patients covering an age range from 2 to less than 18 years.

A summary of the demographic characteristics of subjects included in the paediatric population PK model stratified by indication is presented in Table 2.

**Table 2 - Summary of Demographic Data for Paediatric Population PK Analysis**

| Characteristics | | RA (N = 226) | CD (N = 189) | Ps (N = 109) | Total (N = 524) |
|---|---|---|---|---|---|
| AAA Status | AAA– [n (%)] | 194 (85.8) | 183 (96.8) | 83 (76.1) | 460 (87.8) |
| | AAA+ [n (%)] | 32 (14.2) | 6 (3.2) | 26 (23.9) | 64 (12.2) |
| Concomitant MTX | No [n (%)] | 10 (47.8) | 189 (100) | 109 (100) | 406 (77.5) |
| | Yes [n (%)] | 118 (52.2) | 0 | 0 | 118 (22.5) |
| Race | White [n (%)] | 208 (92.0) | 166 (87.8) | 98 (89.9) | 472 (90.1) |
| | Black [n (%)] | 4 (1.8) | 11 (5.8) | -- | 15 (2.9) |
| | Other [n (%)] | 14 (6.2) | 12 (6.3) | 11 (10.1) | 37 (7.1) |
| Sex | Male [n (%)] | 67 (29.6) | 105 (55.6) | 48 (44.0) | 220 (42.0) |
| | Female [n (%)] | 159 (70.4) | 84 (44.4) | 61 (56.0) | 304 (58.0) |
| Age (Year) | Mean (SD) | 11.2 (3.97) | 13.6 (2.49) | 13.0 (3.79) | 12.4 (3.64) |
| | Median | 12.0 | 14.0 | 14.0 | 13.0 |
| | Range | 2.0 – 18.0 | 6.0 – 17.0 | 5.0 – 18.0 | 2.0 – 18.0 |
| Albumin (g/dL) | Mean (SD) | 4.3 (0.44) | 4.0 (0.55) | 4.7 (0.27) | 4.3 (0.53) |
| | Median | 4.30 | 4.10 | 4.80 | 4.35 |
| | Range | 2.5 – 5.4 | 2.4 – 5.3 | 3.9 – 5.4 | 2.4 – 5.4 |
| BSA ($m^2$) | Mean (SD) | 1.3 (0.38) | 1.4 (0.28) | 1.5 (0.37) | 1.4 (0.35) |
| | Median | 1.27 | 1.40 | 1.52 | 1.38 |
| | Range | 0.5 – 2.2 | 0.7 – 2.2 | 0.7 – 2.3 | 0.5 – 2.3 |

AAA= Anti-adalimumab antibodies; BSA=Body Surface Area, CD= Crohn's disease; MTX=methotrexate; Ps=psoriasis; RA=Rheumatoid Arthritis; SD=Standard Deviation

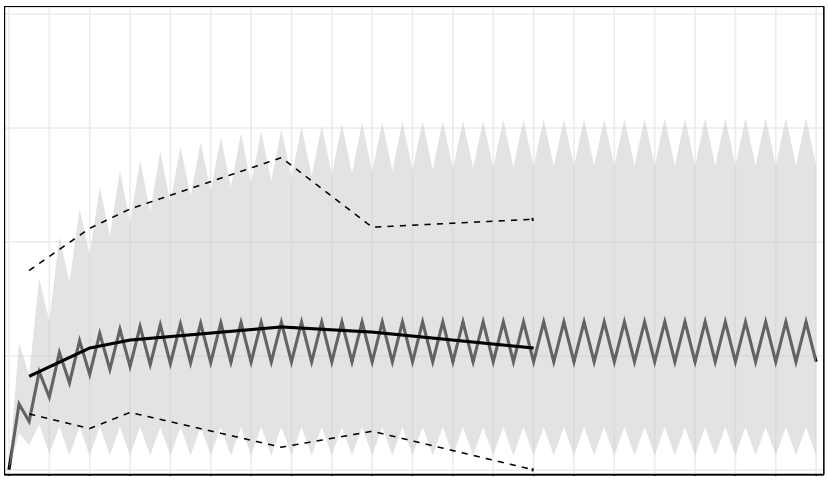
Details of the paediatric model development have been previously presented and were discussed during the evaluation of the application for use of adalimumab in the treatment of paediatric plaque Ps. The final model was a one-compartment model with first-order absorption and elimination, combined additive and proportional residual error model, and exponential inter-individual variability terms on apparent clearance and apparent volume of distribution. According to the goodness-of-fit diagnostics and visual predictive checks, the model described the paediatric PK data across indications sufficiently well. A stepwise forward selection backward elimination covariate selection process resulted in anti-adalimumab antibody (AAA) status, body surface area (BSA), baseline albumin, and methotrexate co-administration as significant covariates on adalimumab apparent clearance and BSA as a significant covariate on adalimumab apparent volume of distribution. PK parameters were not different between disease indications, when adjusted for the significant covariates.

**Simulation of Adalimumab Exposure in Paediatric Uveitis Subjects**

The paediatric population PK model was used to simulate adalimumab exposure in paediatric uveitis subjects following fixed-dose regimens consisting of 20 mg adalimumab sc eow for subjects weighing <30 kg and 40 mg sc eow for subjects weighing ≥30 kg, which was the dosing used in the SYCAMORE study. Simulated serum concentrations were calculated based on individual body weight and corresponding individual BSA values, in the presence or absence of MTX, and were compared to those observed in adult uveitis subjects in the Phase 3 studies M10-877 and M10-880 (VISUAL I and II) in the presence or absence of MTX, respectively, as shown in Figure 1. In the adult studies M10-877 and M10-880, patients in the adalimumab arm received a loading dose of 80 mg adalimumab at baseline followed by a 40 mg dose eow starting at Week 1.

Adalimumab concentrations were also simulated in paediatric uveitis subjects given a loading dose in the presence or absence of MTX and were compared to those observed in adult uveitis subjects as shown in Figure 2.

**A: Presence of MTX**



**B: Absence of MTX**

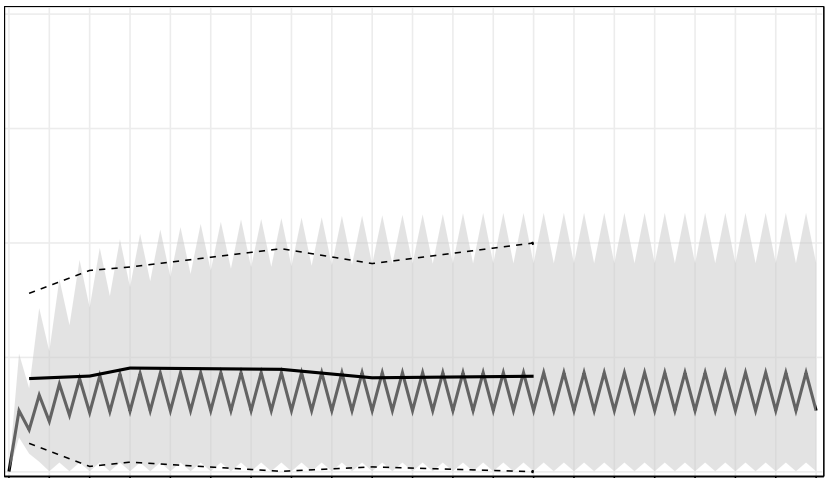
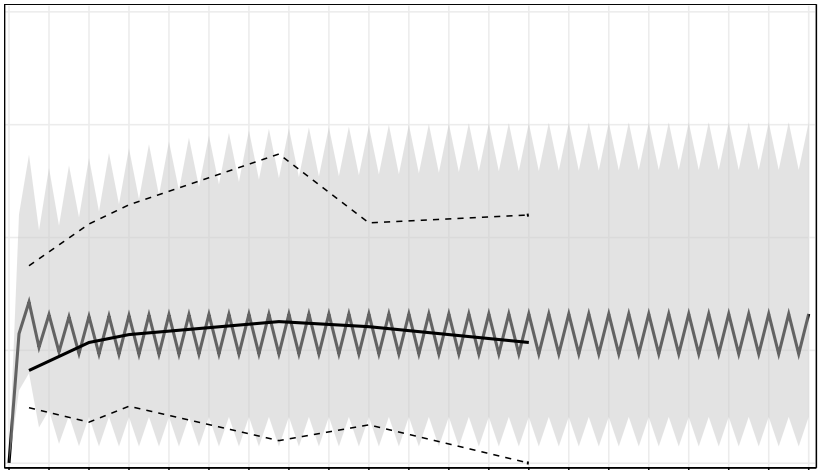


**Figure 1 – Serum Adalimumab Concentrations in Adult (Observed) and Paediatric (Simulated) Uveitis Subjects in the Presence and Absence of MTX Under Fixed Dose Regimen Without Loading Dose**

Note: Grey solid line and shaded area represent the median and 90% prediction interval for simulated concentrations in pediatric subjects with uveitis. Black solid and dashed line represents mean and 90% confidence interval (CI) of observed adalimumab concentrations in adult subjects with uveitis in Phase 3 studies (Studies M10-877 and M10-880).

**A: Presence of MTX**



**B: Absence of MTX**

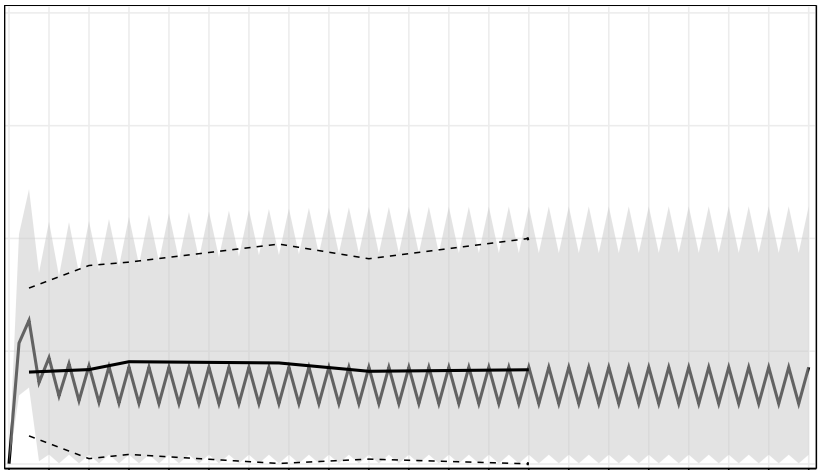


**Figure 2 - Serum Adalimumab Concentrations in Adult (Observed) and Paediatric (Simulated) Uveitis Subjects in the Presence and Absence of MTX Using a Fixed-Dose Regimen with a Loading Dose**

Loading dose: 40 mg sc for subjects with a body weight <30 kg or 80 mg sc for subjects with a body weight of ≥30 kg at Week 0 followed by 20/40 mg eow dosing beginning at Week 1.
Grey solid line and shaded area represent the median and 90% prediction interval for simulated concentrations in pediatric subjects with uveitis. Black solid and dashed line represents mean and 90% CI of observed adalimumab concentrations in adult subjects with uveitis in Phase 3 studies (Studies M10-877 and M10-880).

Upon request by the CHMP, simulations of concentration profiles over time for the fixed-dose regimen with a weight cut-off (20 mg eow sc for subjects weighing <30 kg or 40 mg eow sc for subjects weighing ≥30 kg) were compared with a BSA-based dosing regimen similar to the one recommended for patients from 2 to 12 years with JIA (24 mg/m$^2$ up to a maximum of 40 mg) with or without MTX and with or without a loading dose. The comparison showed that the fixed-dose and BSA-based dose regimens result in largely overlapping concentration-time profiles. The median and 90$^{th}$ percentile values of simulated adalimumab concentrations were slightly higher with the fixed-dose regimen than the BSA-based dosing regimen.

Steady-state serum adalimumab concentrations achieved in adults and in paediatric patients stratified by body weight (with and without MTX) using both the fixed-dose regimen and the BSA-based dosing regimen are shown in Figure 3. Simulated adalimumab concentrations in paediatric uveitis at Week 13 and observed adalimumab concentrations in adult uveitis at Week 12 represent non-trough levels.

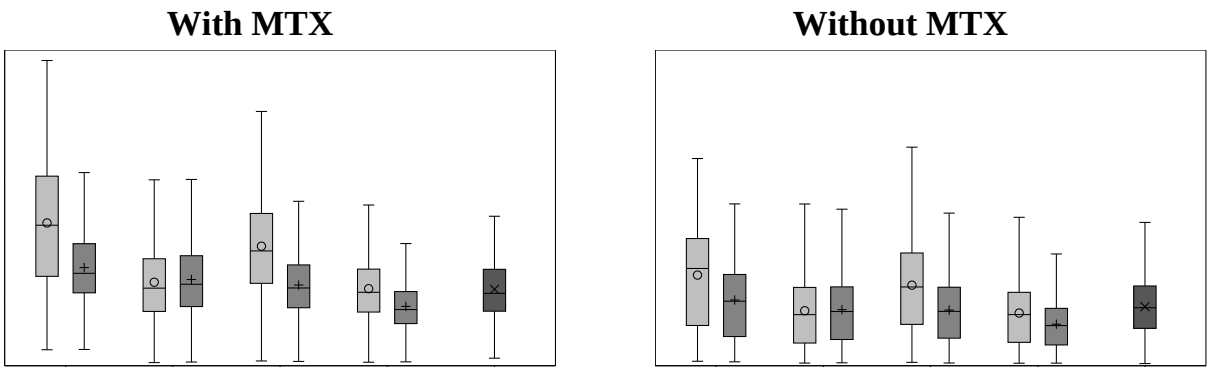



**Figure 3 - Simulated Steady-State Adalimumab Serum Concentrations Stratified By Body Weight Categories in Paediatric Uveitis Patients and Adults in the Presence and Absence of MTX Using Fixed-Dose and BSA-Based Dosing Regimens**

The most notable differences between the fixed-dose and the BSA-based regimen were observed for subjects weighing <15 kg and subjects weighing 30 to 40 kg. For these 2 weight ranges, the fixed-dose regimen with a 30 kg body weight cut-off generated higher adalimumab serum concentrations than the BSA-based regimen. Simulated concentrations using the fixed-dose regimen were within the concentration range observed across adalimumab studies in JIA, paediatric CD, and paediatric Ps.

**Exposure-safety relationship within the simulated exposure range**

In light of the observed differences in exposure with the fixed-dose regimen and the BSA-based regimen, the MAH also evaluated the relationship between adalimumab concentrations and adverse events (AEs) based on data from studies in other paediatric indications. There was no apparent relationship between adalimumab concentrations and AE rates in paediatric patients with JIA (studies M10-444, M11-328 and DE038), psoriasis (study M04-717), and CD, including both the induction and maintenance phases (study M06-806). Higher adalimumab doses and corresponding serum concentrations than those observed or expected in paediatric subjects with uveitis were observed in the paediatric CD Study M06-806 in which subjects received open-label induction of adalimumab at Weeks 0/2, based on body weight (160/80 mg for subjects ≥40 kg or 80/40 mg for subjects <40 kg).

## 2.3.3. Discussion on clinical pharmacology

No clinical PK or pharmacodynamic studies have been conducted in support of this application, which was considered acceptable by the CHMP given that the clinical pharmacology and immunogenicity of adalimumab are well characterised in healthy subjects as well as in patients in the approved indications.

As has previously been shown, the model describes the paediatric PK data across indications sufficiently well and no differences in the adalimumab PK between indications were observed. Therefore, the use of the paediatric population PK model was considered adequate for simulating adalimumab exposure in order to support dose recommendations in paediatric patients with uveitis.

According to visual inspection of the simulated exposure profiles, a lower median serum concentration is apparent in absence of MTX in children receiving the proposed fixed-dose regimen (20 mg adalimumab sc eow for subjects weighing <30 kg and 40 mg sc eow for subjects weighing ≥30 kg) compared to adult uveitis patients receiving the approved dose regimen (loading dose of 80 mg adalimumab at baseline followed by 40 mg eow starting at Week 1). Also, when comparing the exposure simulations with the $IC_{50}$ value of 9.7 µg/mL, estimated for the inhibition of treatment failure in adult uveitis patients based on exposure-response analyses with data from study M10-877, the median serum concentration in children without MTX appear slightly low. In contrast, comparison between paediatric and adult exposure in presence of MTX revealed similar serum concentration levels. Given that adalimumab is only recommended to be used in combination with MTX for the treatment of paediatric uveitis (see section 2.4.3. ), the issue in relation to the differences observed in absence of MTX were not further pursued.

The CHMP furthermore noted that the posology in children with JIA aged 2 to 12 years at the time of this report was based on BSA (24 mg/$m^2$ up to a maximum of 40 mg), whereas the proposed dosing regimen for paediatric uveitis patients was based on fixed doses with an age cut-off at 30 kg. When comparing these two regimens slightly higher simulated adalimumab concentrations were achieved with the fixed-dose regimen compared to the BSA-based regimen. Stratification by age showed differences (increased exposure with the fixed dose regimen) mainly for subjects weighing <15 kg and subjects weighing 30 to 40 kg. In particular, an increased adalimumab exposure with the fixed dose regimen compared to the BSA-based regimen was observed in the smallest children <15 kg receiving concomitant MTX and the estimated serum concentration was also higher than in adults. However, the predicted exposure range in children <15 kg (as well as 30 to 40 kg) with the fixed dose regimen largely overlaps with the observed exposure range in other paediatric indications of adalimumab. Furthermore, 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. In any event, the CHMP encouraged further simplification and harmonisation of the dose regimens across indications in the future. In particular with regards to JIA and JIAU, use of different dose regimens based on BSA and fixed-doses with a weight cut-off, respectively, could cause confusion in clinical practice.

Finally, use of a loading dose (40 mg for subjects with a body weight <30 kg or 80 mg for subjects with a body weight of ≥30 kg) at Week 0 followed by eow dosing starting at week 1 was explored. Notably, use of a loading dose was not studied in SYCAMORE. Some experience was available from studies in children with CD aged 6 years and older (studies M06-806 and M06-807, see also section 2.5.1. for a discussion of clinical safety). No clinical data were available for the use of a loading dose in patients <6 years in any indication. Simulated concentration-time profiles showed that the exposure immediately after the initial loading dose did not exceed the steady-state concentration in presence of MTX. However, in absence of MTX the initial concentration after administration of a loading dose

exceeded the steady-state concentration. The simulations furthermore showed that steady-state was achieved more rapidly with a loading dose. Taken together, the population PK analyses supported the use of a loading dose for adalimumab + MTX.

### 2.3.4. Conclusions on clinical pharmacology

The CHMP agreed that no clinical PK or pharmacodynamic studies were needed to support the present application. The paediatric population PK model was considered appropriate for evaluating drug exposure in paediatric patients with uveitis. Overall, the population PK analyses supported the proposed use of adalimumab in combination with MTX based on the proposed fixed-dose regimen with or without a loading dose and a weight cut-off at 30 kg. Relevant information on the simulations was included in SmPC section 5.2.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

No dose response studies were provided.

According to the MAH, the choice of the dose in the pivotal study SYCAMORE was based on a successful trial by Lovell et al. (N Engl J Med, 2008) investigating adalimumab with or without MTX in patients aged 4 to 17 years of age with polyarticular-course juvenile rheumatoid arthritis. In this trial a dose of 20 mg adalimumab was used for patient weighing < 30 kg and 40 mg for patients weighing ≥ 30kg.

### 2.4.2. Main study(ies)

#### A Randomised Controlled Trial of the Clinical Effectiveness, SafetY and Cost Effectiveness of Adalimumab in Combination with MethOtRExate for the Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis (SYCAMORE)

##### *Methods*

This study was a randomised, parallel, double-masked, placebo-controlled, multicentre Phase 3 trial of adalimumab or placebo in combination with MTX in patients with active uveitis in association with JIA refractory to MTX monotherapy. This investigator-initiated study was sponsored by the University Hospitals Bristol National Health Service Foundation Trust (Bristol, UK). Participants were randomised at a ratio of 2:1 (adalimumab:placebo) stratified by centre. Treatment was administered every 2 weeks (eow) for up to 18 months. The treatment period was followed by a 6 months post-treatment follow-up during which no study treatment was intended (physicians were allowed to treat at their discretion).

Visits were scheduled at baseline, months 1, 2, 3 and thereafter every 3 months.

#### Study participants

The main inclusion criteria were:

- children and adolescents aged ≥2 to less than 18 years fulfilling the International League of Associations for Rheumatology diagnostic criteria for JIA,

- active uveitis defined as a sustained anterior chamber (AC) cellular infiltrates of ≥ 1+ as per the SUN criteria during the preceding 12 weeks therapy despite treatment with MTX and CS (both systemic and topical),
- failed MTX (minimum dose of 10-20 mg/m$^2$, with a maximum dose of 25 mg/participant) after treatment for at least 12 weeks and have been on a stable dose for 4 weeks prior,
- no other IMMs but MTX,
- informed consent,
- non-pregnant and reliable means of contraception for women of childbearing potential.

The main exclusion criteria included:

- uveitis without JIA,
- current of previous use of adalimumab,
- on other biologic agent within previous 5 half-lives of agent,
- ≥ 6 topical steroid eye drops per eye/day,
- not on stable prednisone (or equivalent), i.e. change of dose within 30 days prior to screening,
- >0.2 mg/kg per day of prednisone,
- ongoing chronic or active infections or recent major infections requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to the screening evaluation,
- history of active TB of less than 6 months treatment or untreated latent TB
- CNS disease (neoplasm, active infection, demyelinating disease, or any progressive or degenerative neurological disease)
- poorly controlled diabetes or severe hypertension,
- previous malignancy,
- intraocular surgery,
- peri- or intraocular CS,
- pregnant or nursing,
- IOP < 6 mmHg or > 25 mmHg or IOP control requiring more than one topical pressure-lowering therapy or systemic acetazolamide.

### Treatments

Adalimumab sc eow: 20 mg for participants weighing <30 kg or 40 mg for participants weighing ≥ 30 kg. Dose modifications were not permitted in subjects whose body weight changed from < 30 kg to > 30 kg or from > 30 kg to < 30 kg during the treatment period.

Placebo sc eow.

Both active and placebo treatment was provided as single-use vial for SC injection in volumes of 0.8 mL.

All patients in both arms received a stable dose of MTX at a minimum of 10 mg/m$^2$ and a maximum dose of 25 mg.

CS (≤ 0.2 mg/kg/day of prednisone or prednisolone equivalent medication orally) and topical CS (maximum of 6 drops/day) that must have been stable the prior month were permitted. Either within the first three months of the trial, or at the 3-month assessment visit, topical CS were to be reduced to a maximum of 2 drops/day. Tapering of CS was at the discretion of the treating clinician.

### Objectives

The primary objective was to compare the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA.

Secondary objectives included the evaluation of short term safety and tolerability of adalimumab in combination with MTX versus MTX alone, the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission, the long term safety of adalimumab in combination with MTX versus MTX alone, and the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids.

### Outcomes/endpoints

The primary efficacy endpoint was the time to treatment failure defined as one or more of the following:

1) Anterior segment inflammatory score grade (SUN criteria)

   Following at least 3 months of therapy:

   - 2-Step increase from baseline in SUN cell activity score (AC cells) over 2 consecutive readings;
   - Sustained non-improvement with entry grade of ≥3 for 2 consecutive readings;
   - Only partial improvement (1 grade) or no improvement, from baseline, with development of other ocular co-morbidity* which is sustained;
   - Worsening of existing (on enrolment) ocular co-morbidity* after 3 months;
   - Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 1 to 2) still present after 6 months of therapy.

2) Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria, or any of the concomitant medications not allowed.

3) Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks.

* *Ocular co-morbidities were defined as:*

   *i) Disc swelling and/or Cystoid Macular Oedema, and/or*

   *ii) Raised IOP (> 25 mmHg) sustained over 2 consecutive visits not responding to single ocular hypotensive agent, and/or*

   *iii) Hypotony (< 6 mmHg) sustained over 2 consecutive visits, and/or*

*iv) Development of unexplained reduction in vision over two consecutive visits of 0.3 LogMar units (in the event of cataract, participants remain in trial, also if cataract surgery is required. Failure will still remain as described in endpoints above).*

If both of the subject's eyes were eligible, both were to be evaluated for the purpose of assessing treatment failure. In case of analyses at patient level, both results for their 'best' eye and for the 'worst' eye were considered. If only one eye was eligible, treatment failure was based on the eligible eye alone.

Secondary outcome parameters included:

1) Number of participants failing treatment.
2) Use of oral and topical CS over duration of study period and throughout follow-up.
3) Optic and ocular parameters:
    a. Number of participants having disease flares (as defined by worsening on SUN criteria) following minimum 3 months disease control (defined as zero cells for 3 months from randomisation and has at least one topical treatment during this time);
    b. Number of participants having disease flares (increase in AC cells ≥2 at 2 consecutive visits at least 4 weeks apart) within the first 3 months;
    c. Visual acuity measured by age-appropriate LogMar assessment;
    d. Number of participants with resolution of associated optic nerve or macular oedema;
    e. Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months);
    f. Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months);
    g. Duration of sustaining inactive disease (zero cells in AC, with or without topical treatment).
4) JIA-related evaluations included evaluations of American College of Rheumatology Pedi core set criteria, evaluations of disease flare, change in anti-rheumatic drugs and the Juvenile Arthritis Disease Activity Score.

Quality of life was evaluated with the Childhood Health Questionnaire (CHQ) and the Childhood Health Assessment Questionnaire (CHAQ).

Finally, *post hoc* analyses for time to treatment response and proportions of patients responding, failing or showing no change after 3 and 6 months as well as AUC of AC cells were conducted.

## Sample size

Original sample size calculation

The calculation was based on data on treatment failure rates from 62 patients on MTX in a comparable population (Great Ormond Street Hospital for Children NHS Trust). To detect a relative reduction of 50% between a failure rate of 60-30% with 90% power at a 5% significance level, using a 2:1 randomisation, a total of 140 patients (93 adalimumab, 47 placebo) were required. Assuming a 10 % estimated loss to follow-up, the sample size was set at 154 patients (102 adalimumab, and 52 placebo).

Revised sample size calculation for the primary outcome

Given challenges during recruitment, the power was reduced from 90% to 80%. Due to the very low withdrawal rate, approximately 11 months after first subject first visit, the adjustment to account for missing data was reduced to 5%. The total sample size that was required to detect the difference between a placebo proportion of 0.6 and treatment group proportion of 0.3 (with 0.05 two-sided significance level) was revised to 114.

### Randomisation

Participants were randomised using a web-based randomisation system controlled. Randomisation lists were generated in a 2:1 ratio in favour of the active therapy. Randomisation lists were stratified by centre but in order to reduce the predictability of the randomisation sequence, the randomisation numbers were sequential across all sites (rather than within site) to make it appear that there was no stratification by centre. For smaller sites (expected recruitment less than 10), a block size of 3 was used. For larger sites (expected recruitment of at least 10), block sizes of 3 and 6 were used utilising the Pascal's triangle arrangement.

### Blinding (masking)

Patients (or parents/carers), investigators, study personnel, trial co-ordinator, statisticians and data management were all masked to the patient's treatment allocation. Pharmacy department staff was not masked. The placebo solution for sc injection was created to match active treatment and consisted of a clear, colourless solution with a composition and pH identical to that of the active vials and also packaging were identical.

### Statistical methods

There were two Statistical Analysis Plans (SAPs) written for the final analysis of study results. The first SAP was written by the trial statistician and only contained the detail of the analyses for the primary outcome and the safety data of the blinded phase of the trial. The second SAP was written after the completion of the primary analysis (after masking to treatment allocation had been broken) and, therefore, written by an independent statistician who was masked to the allocation of the trial. A third SAP detailing the analysis plan for the data collected on participants during the unmasked phase of the study as well as the follow up period was written by statisticians who had had no involvement in the SYCAMORE study.

The primary analysis used the principle of intention to treat (ITT). The ITT data set was to include all patients who were randomised. The safety set was to consist of all subjects who received at least one dose of the study drug (adalimumab or placebo). No per protocol analysis were planned.

The primary outcome, time to treatment failure, was analysed as a time-to-event outcome. Patients who did not observe an event were censored. Survival estimates were calculated using the Kaplan and Meier method with curves for each treatment group presented graphically with numbers at risk. The p-value obtained from the log-rank test and the hazard ratios (HRs) with 95% CI were used to assess differences in failure estimates across treatment groups. The statistical test for the primary endpoint was performed at a 2-sided significance level of 0.05. Missing data were handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions; this was informed by data collected on the reasons for missing data. The sensitivity analyses included best case (all patients who withdrew were censored) and worst case (all patients who withdrew considered as treatment failures) scenarios as well as considerations for loss to follow-up and missing data.

Interim analyses of the primary outcome were performed, applying the Peto-Haybittle stopping rule, which required an extreme p-value of $p < 0.001$ as evidence to stop for benefit. This approach was

used to allow flexibility with the number and timings of further analyses based on current safety and efficacy data as it had the added benefit of preserving an overall two-sided type I error of 0.05 for the final analysis.

The secondary outcomes were analysed using the following methods: number of patients failing treatment, the need for pulsed corticosteroids, number of participants having uveitis disease flares, resolution of associated optic nerve and macular oedema, number of participants with disease control, number of participants entering disease remission, number of participants undergoing flare, number of participants with minimum disease activity and those requiring a change in biologic due to failure to respond from arthritis will be analysed using the chi-squared test laboratory parameters and compliance data are presented with summary statistics by time point (t-tests were used to calculate the difference between treatment groups in change from baseline to each time point for each lab parameter, no other statistical testing was carried out), total oral CS dose and systemic CS dose were analysed using Poisson regression, the reduction in systemic CS dose and topical CS use compared to baseline were analysed using a competing risk model, visual acuity, CHAQ, CHQ and American College of Rheumatology Pedi core set criteria were analysed using joint modelling of longitudinal and time to treatment failure data and the duration of sustaining inactive disease using a random intercept model.

### *Results*

### Participant flow

A total of 332 patients were assessed for eligibility at 14 centres. Of these, 130 patients were eligible to participate in the trial. Reasons for ineligibility included for example intolerance to MTX, too mild or severe uveitis, not on stable background medication and started other treatment.

There were furthermore 45 patients who did not consent to participating in the trial, resulting in a total of 90 subjects who were randomized to the active or placebo arm.

Overall 16 participants (9 adalimumab, 7 placebo) discontinued treatment prematurely. The main reasons for adalimumab were intolerance to MTX (n=4) and for placebo it was worsening of uveitis and felt no benefit (n=3). Others withdrew consent or refused injections. One subject in each group withdrew due to AEs. All but 3 subjects agreed to continue in the follow-up period, but the 3 subjects did consent for data that had already been collected to be used in the trial.

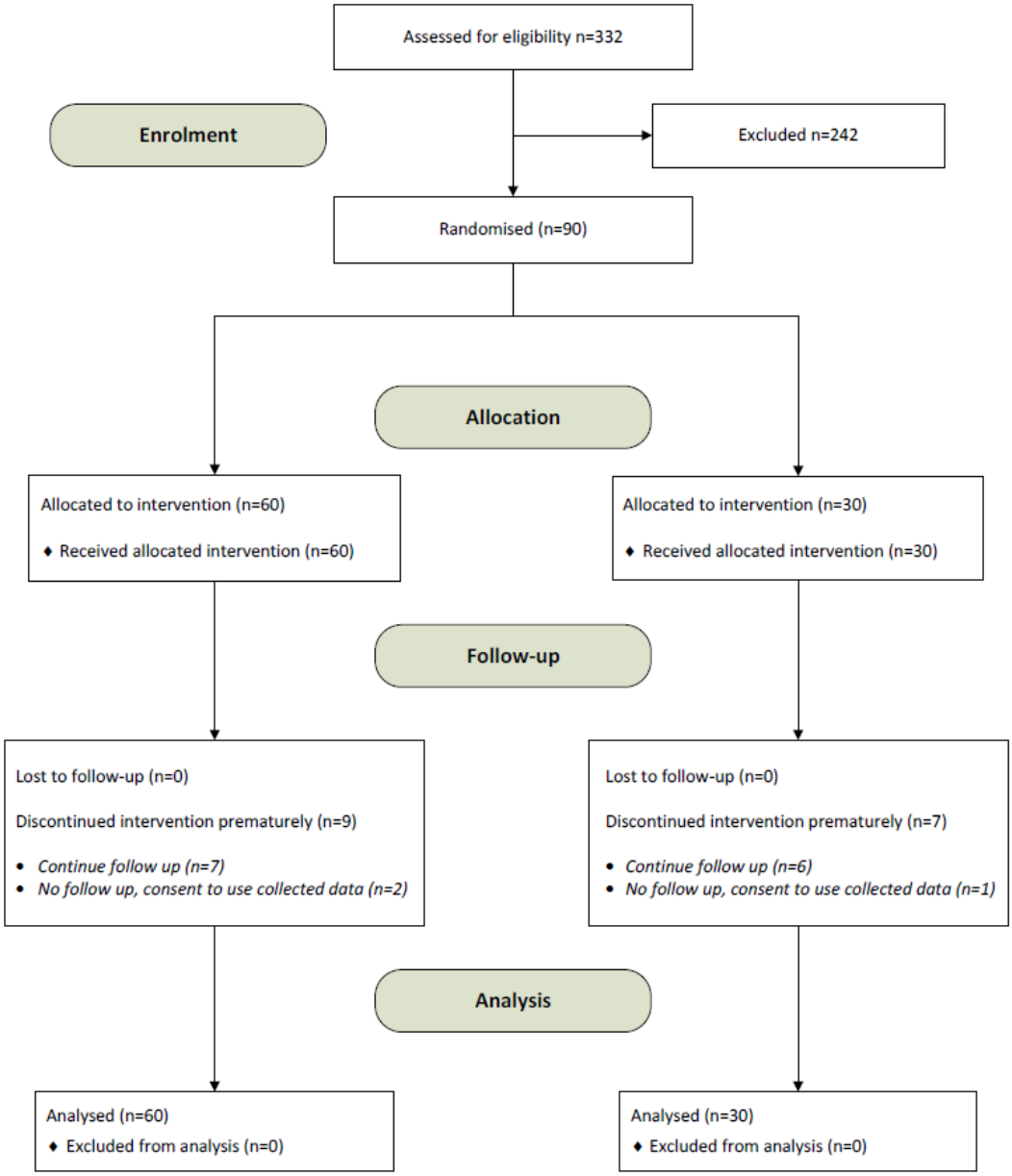



**Figure 4 – SYCAMORE Flow Diagram**

## Recruitment

The study was conducted between 27 October 2011 (first subject visit) and 16 June 2015 (last subject, last visit during double-masked phase). Subjects were enrolled at 14 study sites located in the UK. The sites recruited a range of 1 - 28 subjects each.

## Conduct of the study

Fifteen substantial amendments were made to the protocol or to procedures outside the trial (e.g. patient's newsletter). Major amendments related to patient treatment diary to collect more detailed information regarding MTX administration (Amendment 3.0) and information to use LogMar assessment for assessment of visual acuity instead of Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Amendment 10.0).

Major protocol deviations were reported for 74 subjects (82%). One participant was randomised to adalimumab, but in error was dispensed and administered one placebo kit containing two treatments. The participant went on to complete a further 5 months of allocated treatment. Corrective and preventative actions were undertaken. The majority of the other deviations related to missing study assessments.

Two interim analyses were performed by an independent data and safety monitoring committee. Open reports, available to all who attended the committee meeting, included data on recruitment and pooled data on eligibility violations, baseline characteristics, completeness of follow-up and compliance. Closed reports were available to the independent committee members attending the closed sessions of the meetings and the trial statistical team producing the reports. The trial statistical team prepared these open and the closed reports. The 1st interim analysis (29 September 2014) was made for the purpose of safety, futility and success. Treatment effects across the groups were evaluated in the closed report. The committee made the recommendation that the trial should continue. From the 2nd interim analysis (25 March 2015), data from 85 subjects were analysed. The statistical significance of the beneficial effect of the investigational medicinal product in the interim analysis exceeded substantially the predetermined requirement for consideration of stopping the trial on the basis of a powerful positive treatment effect. No immediate recommendation was made. After meeting with the trial steering committee, who remained unmasked to the trial results, the decision was taken to recommend that recruitment should be stopped, the patients should be unmasked and that the results should be made public.

## Baseline data

Main baseline demographics and ocular disease characteristics are summarised in the below tables.

**Table 3 - Key Baseline Demographics**

| | **Adalimumab n=60** | **Placebo n=30** |
|---|---|---|
| Age (year) | | |
| Mean ± SD | 9.1 ± 3.9 | 8.6 ± 3.8 |
| Range | 3.0 – 18.0 | 2.6 – 16.9 |
| Sex, n (%) | | |
| Female | 47 (78.3%) | 23 (76.7%) |
| Male | 13 (21.7%) | 7 (23.3%) |
| Weight, n (%) | | |
| <30 kg | 33 (55.9%) | 17 (56.7%) |
| ≥30 kg | 26 (44.1%) | 13 (43.3%) |
| Missing | 1 | 0 |

**Table 4 - Main Ocular Disease Characteristics at Baseline**

| **Ocular characteristics - eye level** | **Adalimumab n=77** | **Placebo n=38** |
|---|---|---|
| *Number of study eyes* | | |
| Unilateral | 43 (71.7%) | 22 (73.3%) |
| Bilateral | 17 (28.3%) | 8 (26.7%) |
| *Topical CS eye drops* | | |
| Mean ± SD | 2.3±1.4 | 2.2±1.5 |

| | | |
|---|---|---|
| Median (Range) | 2 (0-6) | 2 (0-6) |
| *BCVA* | | |
| LogMAR ± SD | 0.04±0-15 | 0.07±0.12 |
| Median (Range) | 0 (-0.23-0.56) | 0.05 (-0.13-0.4) |
| *AC cell grade* | | |
| 1+ | 52 (67.5%) | 24 (63.2%) |
| 2+ | 18 (23.4%) | 11 (28.9%) |
| 3+ | 6 (7.8%) | 3 (7.9%) |
| 4+ | 1 (1.3%) | 0 (0%) |
| *Flare score (SUN)* | | |
| 0 | 18 (23.4%) | 12 (31.6%) |
| 0.5+ | 0 (0%) | 0 (0%) |
| 1+ | 49 (63.6%) | 23 (60.5%) |
| 2+ | 10 (13%) | 3 (7.9%) |
| *Synechiae* | | |
| No | 59 (76.6%) | 32 (84.2%) |
| Yes | 18 (23.4%) | 6 (15.8%) |
| *IOP* | | |
| Mean ± SD | 14.8±3.8 | 14.1±4.3 |
| Median (Range) | 15 (7-24) | 14,2 (6.24) |
| *VH grade* | | |
| 0 | 65 (84.4%) | 32 (84.2%) |
| 0.5+ | 8 (10.4%) | 4 (10.5%) |
| 1+ | 3 (3.9%) | 2 (5.3%) |
| 2+ | 1 (1.3%) | 0 (0%) |
| 3+ | 0 (0%) | 0 (0%) |
| 4+ | 0 (%) | 0 (0%) |

AC=Anterior Chamber, ANA=Antinuclear Antibodies, BCVA=best corrected visual acuity, CS=Corticosteroids, DsDNA=DsDNA anti-double-stranded DNA antibodies, IOP=Intraocular Pressure, SD=Standard Deviation, VH=vitreous haze.

Participants ranged in age between 2.57 years and 17.97 years, with the mean age in the placebo group being slightly lower. The proportion of females and males were approximately the same in the two treatment groups, with more females than males in either group. Ethnicity data were not collected from study subjects, but according to the principal investigator, the large majority of patients in this study were Caucasian.

A total of 65 (72.2%) participants entered the trial with one eye that was eligible for evaluation and 25 (27.8%) participants with two eligible eyes. Therefore there was a total of 115 eligible eyes (77 adalimumab, 38 placebo) entered into the study.

Concomitant medication

In the adalimumab treatment group, 6 subjects received permitted topical/ocular CS at 7 occasions, but against defined acceptable criteria. Non-permitted CS was given to 3 subjects at 5 occasions for reasons that included increased cells, uveitis or cataract surgery. In the placebo treatment group, 2 subjects received topical/ocular CS against acceptable criteria also due to increased cells and uveitis. Four placebo-treated subjects also received non-permitted CS (oral, ophthalmic [assumed

subconjunctival or sub-tenon], topical) and adalimumab at 14 occasions, mainly due to worsening of uveitis, but also due to joint flares.

Treatment compliance

Treatment compliance was on average 81.0% and 93.9% (patient diaries vs. accountability logs), and 74.6% and 83.4% (patient diaries vs. accountability logs) for the adalimumab and placebo groups, respectively. Four patients in the adalimumab group and one in the placebo group failed treatment due to missing more than the required number of doses whilst on treatment.

The overall compliance for MTX (according to patient diaries) was 60.5% and 49.8% for the adalimumab and placebo groups, respectively. There were four patients on adalimumab who had their study medication stopped due to missed doses of MTX.

### Numbers analysed

The ITT and safety analysis populations were identical with the randomised patient sets, i.e. 60 patients in the adalimumab arm and 30 patients in the placebo arm. No per protocol set was defined.

### Outcomes and estimation

The extent of exposure is summarised below. Further details are given in the safety section.

**Table 5 - Extent of Exposure to Study Treatment**

| | **Placebo n=30** | **Adalimumab n=60** |
|---|---|---|
| Total number of doses | | |
| Mean (SD) | 10.2 (10.09) | 23.2 (11.49) |
| Median (Range) | 6 (1 - 39) | 24.50 (1 – 40) |
| Duration of treatment (days) | | |
| Mean ± SD | 159 (154) | 345 (165) |
| Median (Range) | 87 (14 - 571) | 352.50 (14 – 561) |

The main efficacy results as relevant to the assessment are summarised below.

Primary efficacy endpoint: Time to treatment failure

The primary efficacy endpoint, time to treatment failure (composite of increase in AC cells or failure to improve or worsening and/or presence of co-morbidities after 3 months, and/or use of non-allowed concomitant medication, and/or intermittent or continuous suspension of study treatment) demonstrated that adalimumab plus MTX significantly delayed the time to treatment failure compared to placebo and MTX (see table and figure below). Notably, less than 50% of patients experienced treatment failure in the adalimumab group and hence, median time to treatment failure was not estimable.

**Table 6 - Median time to treatment failure (ITT)**

| Treatment Group | N | Failure N (%) | Median Time to Failure in weeks (95% CI) | HR | 95% CI | *p* value |
|---|---|---|---|---|---|---|
| Placebo | 30 | 18 (60) | 24.1 (12.4, 26) | 0.25 | 0.12, 0.49 | <0.0001 |
| Adalimumab | 60 | 16 (26.7) | Not estimable[a] (-, 72.0) | | | |
| **Quartile Estimates Time to Failure in weeks (95% CI)** | | | | | | |
| Placebo | 75 % | 81.0 (24.1, 81) | | | | |
| | 25 % | 12.1 (8.0, 22.3) | | | | |
| Adalimumab | 75 % | Not reached (-, -) | | | | |
| | 25 % | 59.0 (28.9, -) | | | | |

CI=Confidence Interval, HR=Hazard Ratio
[a] Not estimable as less than half of the subjects in the adalimumab group experienced treatment failure during the double-masked period of the study.

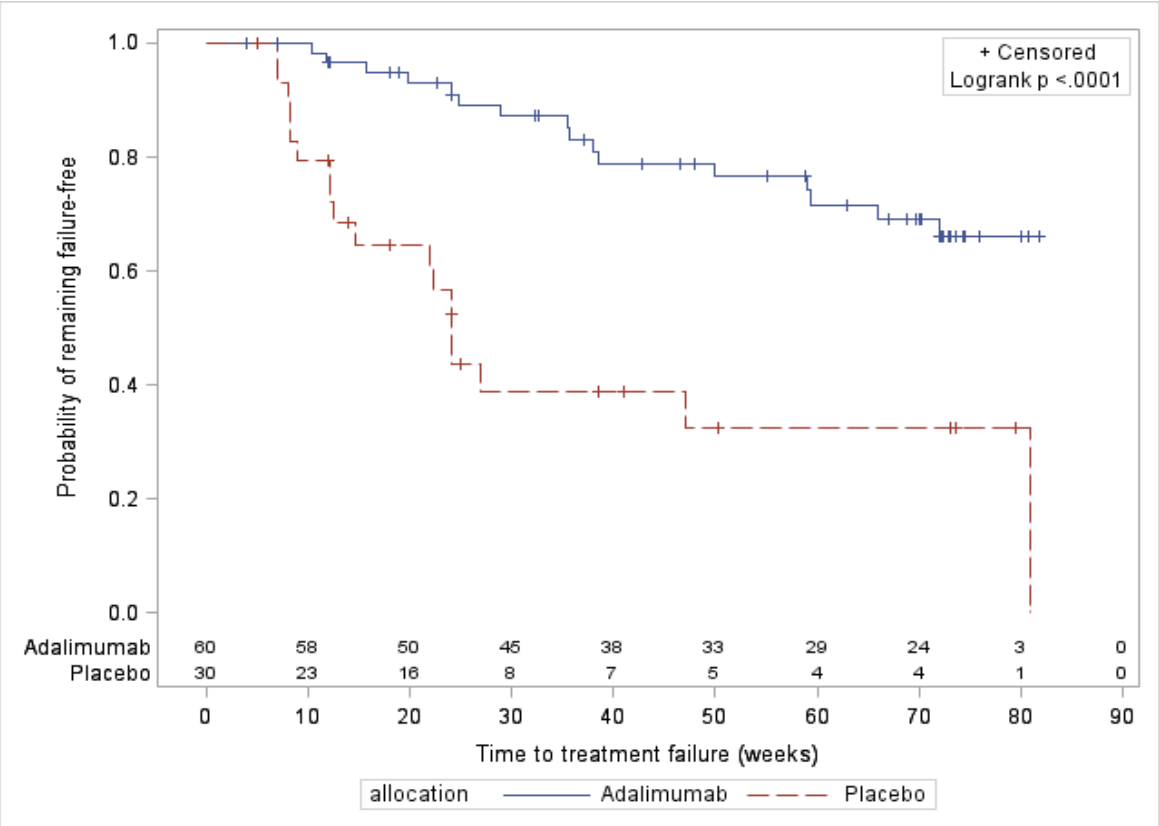



**Figure 5 - Kaplan Meier Plot for time to treatment failure**

The results of the sensitivity analyses were in line with the primary analysis: the risk for treatment failure over the double-blind period was reduced by 78 to 66 % (HR: 0.22-0.34) with active treatment compared to placebo. P-values ranged from <0.0001 to 0.001.

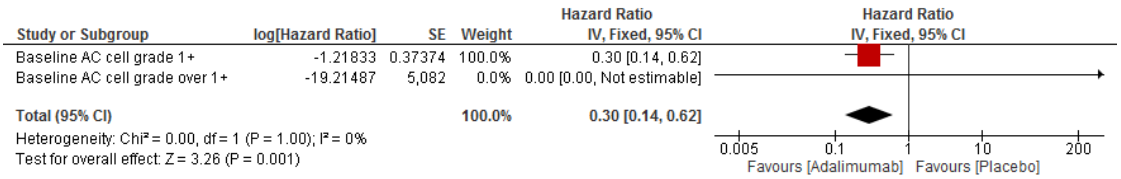
Amongst the sixteen cases of treatment failures in the adalimumab group were seven cases classified as treatment failures due to the fact that they had taken permitted concomitant medications against the acceptable criteria, three participants who were given non-permitted concomitant medications, three participants who had missed doses that met the failure criteria, two participants with sustained scores (as recorded at entry grade) that were still present after six months of therapy and one

participant had both taken permitted concomitant medications against the acceptable criteria and missed doses that met the failure criteria.

In the placebo group, three participants received permitted concomitant medications against the acceptable criteria, seven participants were given non-permitted concomitant medications, one participant had missed doses that met the failure criteria and seven participants had sustained scores (as recorded at entry grade) that were still present after six months of therapy.

Upon request by the CHMP subgroup analyses subgroup analyses by AC cell grade (1 + vs. ≥ 2+) and flare (0 vs. ≥ 0.5 +) were performed. Analyses were considered both a best-case and worst-case scenario. The best-case scenario handled participants who had both eyes eligible for the trial by considering only the eye with the best (lowest) score in the analysis. The worst-case scenario considered the inverse. The results are presented below in form of forest plots.

**A: Best-Case**




**B: Worst-Case**

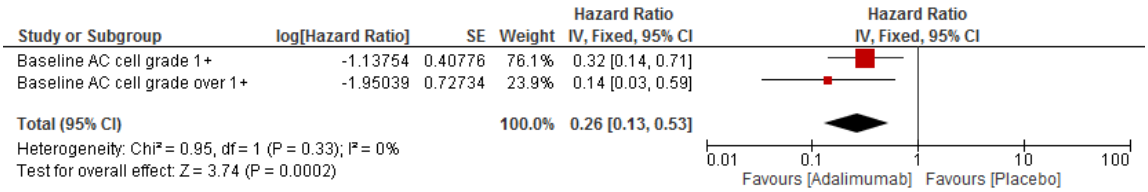
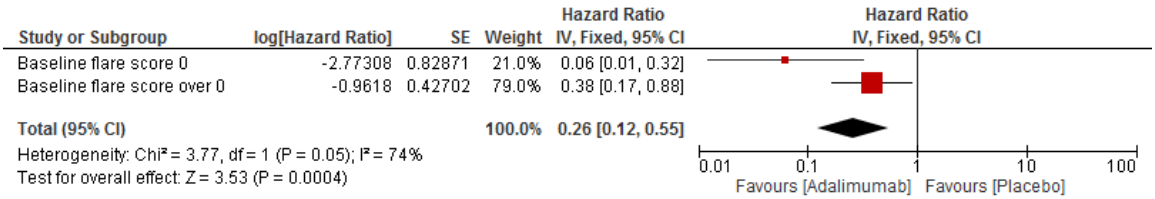



**Figure 6 - Forest Plot of Baseline AC Cell Grade 1+ Versus > 1+**

**A: Best-Case**




**B: Worst-Case**

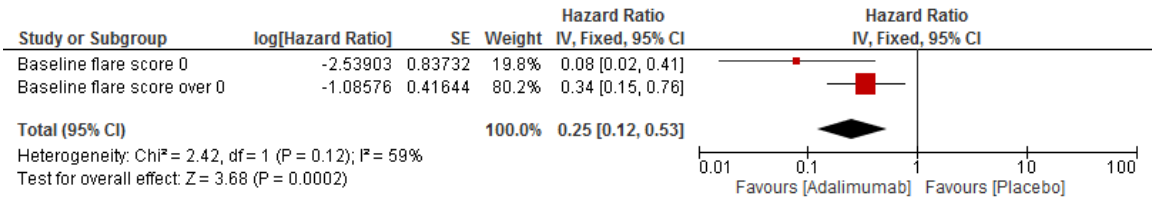



**Figure 7 - Forest Plot of Baseline Flare Score 0 Versus > 0**

Secondary efficacy endpoints

- Number of Subjects Failing Treatment

A lower proportion of subjects treated with adalimumab (16 of 60 subjects [26.7%]) failed treatment than subjects treated with placebo (18 of 30 subjects [60%]). The risk of having a treatment failure was statistically significantly reduced by 56% (risk ratio [RR] = 0.44; 95%CI: 0.27, 0.74; p=0.002) with adalimumab, as compared to placebo.

- Use of CS

The results for secondary efficacy variables related to CS use are summarised below.

**Table 7 - Summary of Systemic and Topical CS Use**

| | **Placebo n=30** | **Adalimumab n=60** |
|---|---|---|
| **Systemic CS use** | | |
| Use of oral CS (<0.2 mg/kg/day) at baseline, n | 1 | 5 |
| Reduction in systemic CS dose to 0 mg/day, n | 1 | 3 |
| Reduction in systemic CS dose to <5 mg/day, n/N[a] | 1/1 | 1/3[b] |
| **Topical CS use (frequency) compared to entry use** | | |
| Use of topical CS at baseline, n | 25 | 49 |
| Reduction to < 2 drops in topical corticosteroids, n/N[c] (%) | 3/18 (13.3%) | 22/45 (48.9) |
| p-value<br>HR for time to reduction to < 2 drops (95% CI) | 0.049<br>3.47 (1.01, 11.95) | |
| Reduction to 0 drops in topical corticosteroids, n/N[d] (%) | 4/25 (16.0%) | 23/49 (46.9) |
| p-value<br>HR for time to reduction to 0 drops (95% CI) | 0.018<br>3.38 (124, 10.32) | |

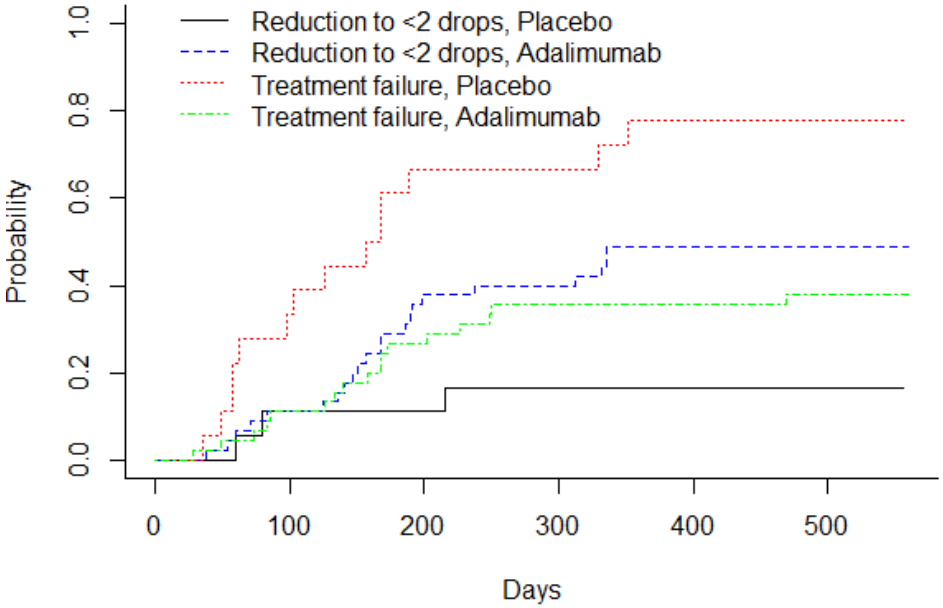
n=number of patients fulfilling criteria of the endpoint; N=Sample size/denominator (see below)
Note: Doses in mg refer to prednisone or prednisolone equivalent.
[a] for subjects on > 5 mg/day at study entry
[b] included 1 subject that ended treatment before reaching < 5 mg/day
[c] subjects at ≥2 drops/day at baseline
[d] subjects on any dose of topical CS

Systemic CS use

The total oral dose, standardised per patient year, was 3767.74 mg in the placebo group and 804.31 mg in the adalimumab group. A total of 1 participant in the placebo group and 5 participants in the adalimumab group received oral CS during the course of the blinded treatment phase. The 5 participants in the adalimumab group were on study treatment for a total of 5.28 years and the placebo participant was on study treatment for 0.17 years. A rate ratio of 0.21 (95% CI [0.20, 0.23]) indicated that patients on placebo required more oral CS per patient year than those on adalimumab (p<0.0001).

Topical CS use

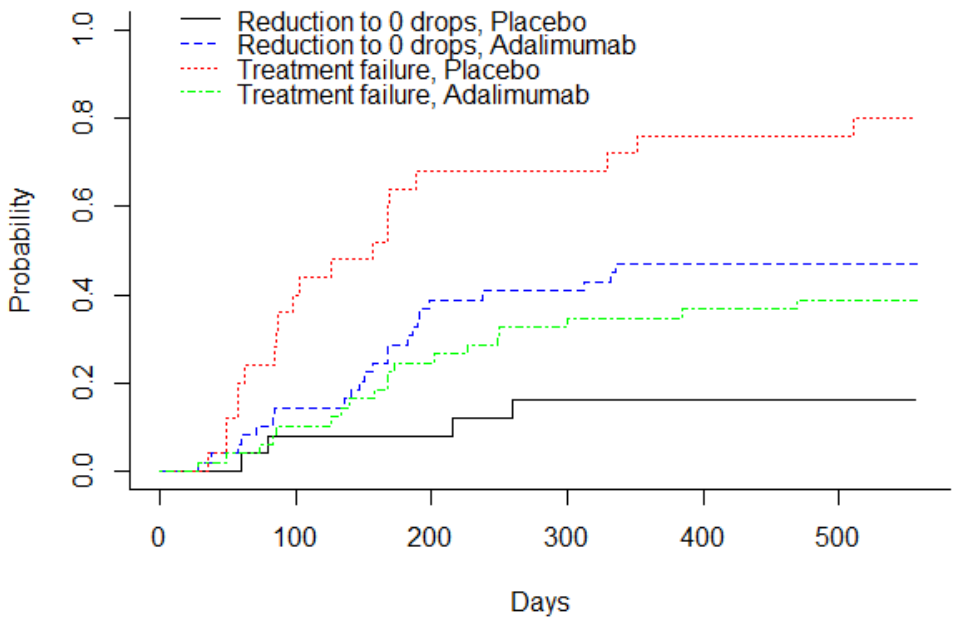
A total of 74 participants were using topical CS at randomisation. Of these, 63 participants took ≥ 2 drops/day. The incidence plots of time to reduction of topical CS to <2 (already at ≥ 2 drops at baseline) and 0 drops are shown in the below figures.




**Numbers at risk**

| Days | 0 | 100 | 200 | 300 | 400 | 500 |
|---|---|---|---|---|---|---|
| Adalimumab | 45 | 35 | 16 | 11 | 7 | 6 |
| Placebo | 18 | 10 | 4 | 3 | 3 | 2 |

**Figure 8 - Incidence Plot for Time to Reduction of Topical CS to <2 Drops**




**Numbers at risk**

| Days | 0 | 100 | 200 | 300 | 400 | 500 |
|---|---|---|---|---|---|---|
| Adalimumab | 49 | 37 | 19 | 13 | 8 | 7 |
| Placebo | 25 | 13 | 6 | 4 | 4 | 2 |

**Figure 9 - Incidence Plot for Time to Reduction of Topical CS to 0 Drops**

Overall, 22/45 (48.9%) patients on adalimumab and 3/18 (16.7%) patients on placebo reached < 2 drops before treatment failure (or the 18 months treatment visit), 6 patients (13.3%) on adalimumab and 1 (5.6%) patient on placebo reached the 18 month visit before reaching < 2 drops and 17 (37.8%) patients in the adalimumab group and 14 (78%) in the placebo group had a treatment failure before reaching < 2 drops. The HR for treatment failure with < 2 drops/day CS (95% CI) was 0.32 (0.16, 0.64), p= 0.0013.

Overall, 23/49 (46.9%) patients on adalimumab and 4/25 (16%) patients on placebo reached 0 drops before treatment failure (or the 18-month treatment visit), 7 participants (14.3%) on adalimumab and 1 participant (4%) on placebo reached the 18 month visit before reaching 0 drops and 19 (38.8%) of the adalimumab group and 20 (80%) of the placebo group had a treatment failure before reaching 0 drops. The HR for treatment failure without topical CS use was 0.31 (0.16, 0.57), p= 0.0002.

- Visual acuity

The treatment effect on LogMar is –0.01 (95% CI: –0.06 to 0.03) for the best LogMar scores and –0.02 (95% CI: –0.07 to 0.03) for the worst LogMar scores. There were essentially no differences in BCVA between treatment arms, but BCVA was only minimally or moderately impaired at baseline.

- Number of participants entering disease remission (zero AC cells), without topical treatment for 3 and 6 months

At 3 months, 2 participants in the placebo group (6.67%) and 15 in the adalimumab group (25%) had entered disease remission in at least one of their eligible eyes (RR = 3.75, 95% CI [0.92, 15.34]; p=0.05).

At 6 months, no participants in the placebo group and 14 in the adalimumab group (23.33%) had entered disease remission in at least one of their eligible eyes (RR = 14.74, 95% CI [0.91, 238.95], p=0.004).

- Number of participants with resolution of associated optic nerve or macular oedema

Five participants in the adalimumab group (8.33%) had associated optic nerve at baseline or developed it at some point during the study, 3 (60%) of these cases were resolved during the study. There were no participants who had associated optic nerve at baseline or developed this during the course of the study in the placebo group. It was, therefore, not possible to carry out the planned statistical test of these data.

Two participants in the placebo group (6.67%) had macular oedema at baseline or developed it during the course of the study and three participants in the adalimumab group (5.00%). Two participants in the adalimumab group (66.67%) and no participants in the placebo group had resolution of the macular oedema (RR=3.75, 95% CI [0.27, 52.64]).

- Quality of Life

The Quality of Life data indicate no relevant differences between the treatment arms.

- JIA-related evaluations

Most of the children entered the study with minimal arthritis. American College of Rheumatology Criteria only changed minimally during the course of the study and most of the between group analyses were not statistically significant due to the small numbers. Similar results were obtained for other JOA-related evaluations.

### *Ancillary Analyses*

Further to a request by the CHMP, the MAH provided additional analyses for AC flares. The SUN working group grading scheme for AC flare was used at each time point during the course of the study.

**Table 8 - SUN Criteria for Grading the Presence of AC Flare**

| Grade | Description |
|---|---|
| 0 | None |
| 1+ | Faint |
| 2+ | Moderate (iris and lens details clear) |
| 3+ | Marked (iris and lens details hazy) |
| 4+ | Intense (fibrin or plastic aqueous) |

The mean profile plots of the SUN flare score for the best score and the worst score are presented in Figure 8 and Figure 9, respectively.

During the first three months of treatment, the flare score for patients in the adalimumab group (baseline mean = 0.83, 3-month mean = 0.21 for best score and 0.90 to 0.21 for worst score) was reduced to a greater extent than for patients in the placebo group (baseline mean = 0.73, 3-month mean = 0.63 for best case and 0.80 to 0.74 for worst case). Due to the number of treatment failures after 3 months in the placebo group, it was difficult to draw any conclusions from data beyond this time point.

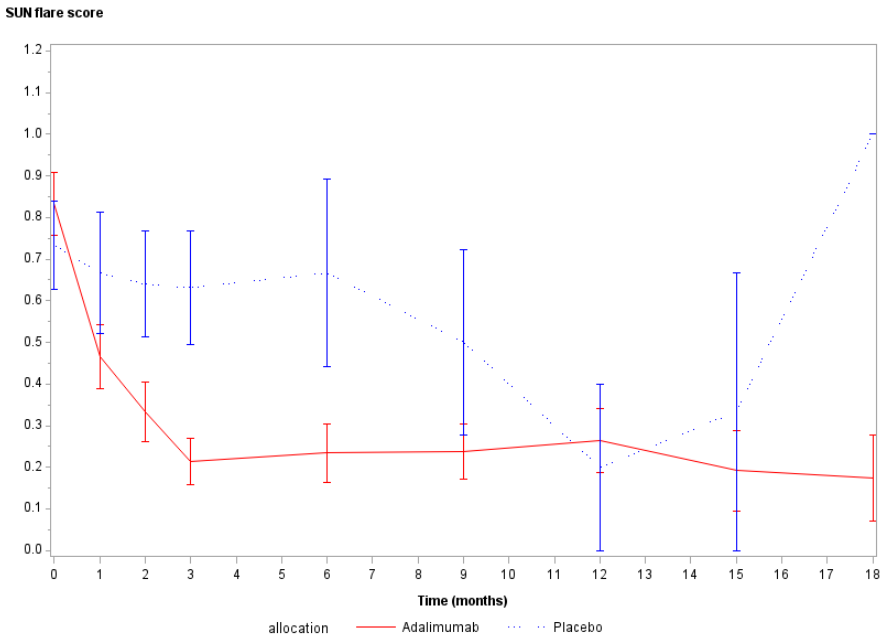



**Figure 10 - Mean Profile Plot for SUN Flare Best Score**

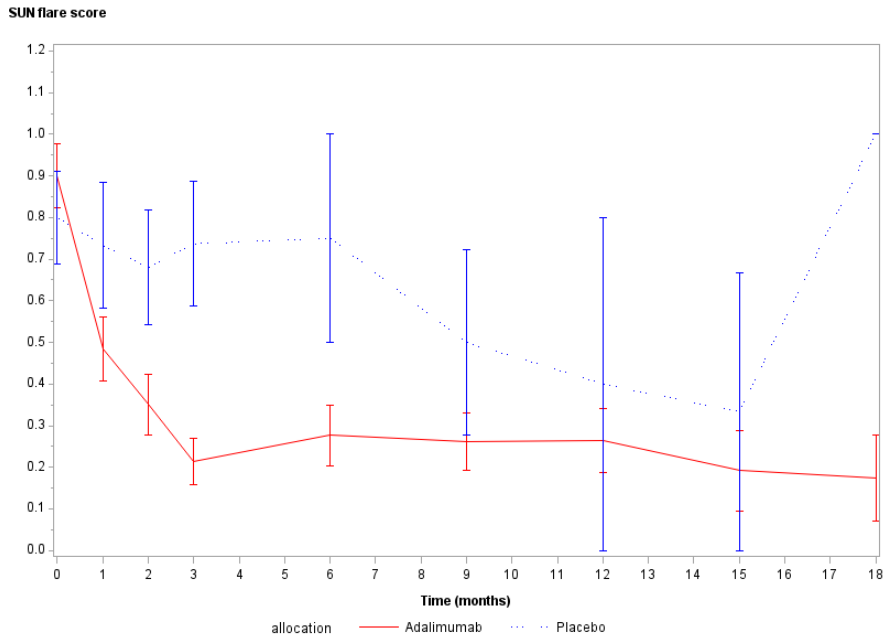



**Figure 11 - Mean Profile Plot for SUN Flare Worst Score**

To further investigate patients with low-grade inflammation, the results of 3 additional analyses were presented. The first 2 analyses were performed on patients who have had a 'persistent response' on the AC cell count (defined as a score of 0 or 0.5+ over 2 consecutive visits) and either a flare score of ≥ 1+ or ≥ 2+ over the same visits. The third analyses was performed on patients who had an 'excellent response' (defined as a having non-active uveitis and a flare score of less than 1).

One patient in the adalimumab group (2%) had a persistent flare score of ≥ 2+ and non-active uveitis and 1 patient in the placebo group (3%) had a persistent flare score of ≥ 2+ and non-active uveitis.

When considering those patients with a flare score of ≥ 1+, the results showed that a slightly higher number of patients in the adalimumab group (11 patients [18%]) than in the placebo group (3 patients [10%]) had a persistent flare score of ≥ 1+ and non-active uveitis.

The results of the analysis from patients who had an excellent response showed that there were a greater number of patients in the adalimumab arm (48 patients [80%]) who had at least 1 occurrence of a flare score of < 1 and also non-active uveitis, as compared to 13 subjects (43%) in the placebo group.

### *Summary of main study*

The following tables 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 9 - Summary of Efficacy for SYCAMORE**

| **Title: A Randomised Controlled Trial of the Clinical Effectiveness, SafetY and Cost Effectiveness of Adalimumab in Combination with MethOtRExate for the Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis** | | | |
|---|---|---|---|
| Study identifier | EudraCT number: 2010-021141-41 | | |
| Design | Randomised, parallel, double-masked, placebo-controlled, multicentre Phase 3 trial | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 18 months<br>not applicable<br>6 months (off treatment) |
| Hypothesis | Superiority | | |
| Treatments groups | Adalimumab (+MTX) | | Adalimumab sc eow for up to 18 months:<br><30 kg: 20 mg,<br>≥ 30 kg: 40 mg.<br>A total of 60 patients were randomised. |
| | Placebo (+MTX) | | Placebo sc eow up to 18 months<br>A total of 30 patients were randomised. |
| Endpoints and definitions | Primary endpoint | Time to treatment failure | Time to treatment failure defined as one or more of the following components:<br>(1) anterior segment inflammation after ≥ 3 months of therapy: Increased AC cell score, sustained non-improvement, no or partial improvement with ocular co-morbidities, or worsening of ocular co-morbidities;<br>(2) use of concomitant medication;<br>(3) suspension of study treatment for >4 weeks. |
| | Secondary endpoint | Patients failing treatment | Number of participants failing treatment (as per above criteria) |
| | Secondary endpoint | Topical CS use <2 drops/day | Use of oral and topical CS over duration of study period and throughout follow-up: Reduction in topical CS use before treatment failure (or the 18 months treatment visit) in patients receiving ≥2 drops/day at baseline to <2 drops/day. |
| | Secondary endpoint | No topical CS use | Use of oral and topical CS over duration of study period and throughout follow-up: Reduction in topical CS use before treatment failure (or the 18 months treatment visit) in patients receiving topical CS at baseline to 0 drops/day. |
| | Secondary endpoint | Disease remission for 3 months | Number of participants entering disease remission (zero AC cells), without topical treatment for 3 months |
| | Secondary endpoint | Disease remission for 6 months | Number of participants entering disease remission (zero AC cells), without topical treatment for 6 months |
| Database lock | 11 September 2015 | | |

| **Results and Analysis** | | | | |
|---|---|---|---|---|
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | Intent to treat<br>Duration: 18 months | | | |
| Descriptive statistics and estimate variability | Treatment group | | Adalimumab (+MTX) | Placebo (+MTX) |
| | Number of subject | | 60 | 30 |
| | Time to treatment failure<br>Median, weeks (95%CI) | | Not estimable<br>(-, 72.0) | 24.1<br>(12.4, 26) |
| | 75% percentile (95%CI) | | Not estimable<br>(-, -) | 81.0<br>(24.1, 81) |
| | Patients failing treatment, n (%) | | 16 (26.7) | 18 (60) |
| | Topical CS use <2 drops/day, n/N[#] (%) | | 22/45 (48.9) | 3/18 (13.3%) |
| | No topical CS use, n/N[#] (%) | | 23/49 (46.9) | 4/25 (16.0%) |
| | Disease remission for 3 months, n (%) | | 15 (25.0) | 2 (6.7) |
| | Disease remission for 6 months, n (%) | | 14 (23.3) | 0 |
| Effect estimate per comparison | Time to treatment failure | Comparison groups | Adalimumab vs. placebo | |
| | | HR | 0.25 | |
| | | 95% CI | 0.12, 0.74 | |
| | | P-value | <0.0001 | |
| | Patients failing treatment | Comparison groups | Adalimumab vs. placebo | |
| | | RR | 0.44 | |
| | | 95% CI | 0.27, 0.74 | |
| | | P-value | 0.002 | |
| | CS use <2 drops/day | Comparison groups | Adalimumab vs. placebo | |
| | | HR | 0.32 | |
| | | 95% CI | 0.16, 0.64 | |
| | | P-value | 0.0013 | |
| | No topical CS use | Comparison groups | Adalimumab vs. placebo | |
| | | HR | 0.31 | |
| | | 95% CI | 0.16, 0.57 | |
| | | P-value | 0.0002 | |
| | Disease remission for 3 months | Comparison groups | Adalimumab vs. placebo | |
| | | RR | 3.75 | |
| | | 95% CI | 0.92, 15.34 | |
| | | P-value | 0.05 | |
| | Disease remission for 6 months | Comparison groups | Adalimumab vs. placebo | |
| | | RR | 14.74 | |
| | | 95% CI | 0.91, 238.95 | |
| | | P-value | 0.004 | |
| Notes | [#] Number (N) of patients using topical CS at baseline (≥2 drops/day or any, i.e. >0) | | | |

### *Supportive study(ies)*

The 7th interim report of the STRIVE registry (study P10-262) provides limited data of 42 patients with JIA associated uveitis for a duration of up to 60 month. The report was assessed in a separate procedure. Both at baseline and through Month 60, uveitis appeared more common in the All MTX treatment group compared to the All Humira treatment group, which could reflect baseline differences

in disease severity and proneness to systemic organ manifestations between the two groups. Additional data and further discussions in relation to uveitis were requested for the next interim report.

Reference was also made to the scientific literature to support the following:

- Extrapolation of anterior uveitis to other types and anatomical locations of uveitis

Malik & Pavesio (2005) reported that MTX, used in the treatment of 10 paediatric patients with non-JIA uveitis (6 patients with idiopathic uveitis and 3 patients with sarcoidosis), improved the anterior chamber inflammation in 60% of the patients and all patients had an improvement in visual acuity. Soheilan et al (2006) reported the use of MTX in 7 of 10 patients with VKH-associated panuveitis who had an inadequate response to CS or had CS-related side effects. In this report, MTX decreased anterior chamber inflammation and preserved or improved vision in these patients.

In a systematic review (Simonini et al., 2014) of the available literature databases from the years 2000 to 2012, anti-TNF-α agents were administered to a total of 229 paediatric patients with JIA associated uveitis, Blau syndrome, sarcoidosis, VKH disease, pars planitis, BD, and idiopathic uveitis. Pooled data from eligible studies showed 87% of these patients had an improvement in intraocular inflammation when treated with adalimumab.

A prospective open label adalimumab study (Vazquez-Cobian et al., 2006) in 14 paediatric patients (5 patients with idiopathic uveitis and 9 patients with JIA-associated uveitis) who were nonresponsive to standard therapy, showed adalimumab decreased ocular inflammation over an average of 18.1 months of treatment. The proportion of affected eyes that had a decrease in ocular inflammation was 80.8% with 65.3% of the affected eyes demonstrating a sustained resolution of inflammation. Improved visual acuity was noted in 10 of 26 affected eyes (7 patients).

In a recently published retrospective case series, 12 paediatric patients with severe uveitis (6 patients with JIA-associated uveitis, 4 patients with idiopathic panuveitis, 1 patient with early-onset sarcoidosis-associated panuveitis, and 1 patient with intermediate uveitis) were treated with adalimumab (Muñoz-Gallego et al., 2016). Results showed that adalimumab improved the SUN criteria and visual acuity in these patients.

A report was also published regarding an adolescent patient with insulin-dependent diabetes mellitus who had bilateral granulomatous panuveitis and other symptoms characteristic of VKH disease (Jeroudi et al., 2014). Six weeks of adalimumab in combination with MTX (tapered and maintained at 15 mg per week) resolved the inflammation. The patient remained stable after 26 months.

In addition, in a case cohort interventional study of 17 patients (12 patients with JIA, 2 patients with Blau syndrome, and 1 patient each with sarcoidosis, panuveitis, and idiopathic uveitis) who were refractory to CS, IMMs, and in 9 subjects, other anti-TNF-α agents, adalimumab was shown to improve visual acuity and reduce ocular inflammation (Sen et al., 2012). Anterior chamber inflammation improved in 50% of eyes after 3 months on adalimumab.

- Extrapolation from adults to paediatric patients with uveitis

The MAH argued that there is no evidence to suggest that the aetiologies or anatomical locations of non-infectious uveitis are significantly different between adult and paediatric patients or between different paediatric age groups, with the exception that JIA-associated uveitis, which is an anterior uveitis, occurs only in paediatric patients: The manifestations of different types of uveitis vary, but the manifestations in paediatric patients include many of the same manifestations observed in adults with the same type of uveitis. For example, 2 of the most common types of uveitis, Behçet's disease and VKH syndrome, manifest similarly amongst adults and children. In Behçet's disease, the majority of adult and paediatric patients have bilateral involvement and recurrent panuveitis with retinal vasculitis.

Cataract, IOP elevation, macular oedema or maculopathy, and optic atrophy are the most common complications. Similar to adult-onset Behçet's disease, there is a male predominance in paediatric patients. VKH syndrome is characterized by bilateral posterior uveitis with retinal oedema and optic disc hyperaemia/oedema that eventually lead to retinal detachment (Berker 2007). Often, there is also an anterior uveitis component characterized by mutton-fat keratic precipitates, iris nodules, and increased IOP. Although sometimes more aggressive than in adults, VKH in paediatric patients manifests similarly. Complications are also similar in adults and paediatric patients, including cataract, glaucoma, subretinal fibrosis, choroidal neovascularization, neovascularization of the disc, pigmentary changes of the fundus, optic atrophy, leading to reversible and irreversible vision loss.

The MAH furthermore argued that adults and paediatric individual uveitides respond similarly to therapy. Treatment usually starts with topical and local CS, followed by systemic CS, disease-modifying anti-rheumatic drugs, and then biologic IMMs. CS are the first-line treatment for most non-infectious uveitis in adult and paediatric patients because they are potent and rapidly effective. IMMs (most commonly MTX, especially in JIA-associated uveitis) are used for the treatment of persistent or recurring uveitis in adult and paediatric patients and are used to minimize the toxicities associated with high doses and prolonged use of CS. Biologic IMMs (infliximab and adalimumab) are used in adult and paediatric patients when IMMs do not provide adequate control or result in intolerance.

## 2.4.3. Discussion on clinical efficacy

The main basis for the assessment of efficacy in the present application was the pivotal investigator-initiated Phase 3 trial SYCAMORE in 90 paediatric patients with active JIAU.

No dose-response studies have been conducted. The choice of dose in SYCAMORE of 20 mg SC eow in patients weighing <30kg and 40 mg SC eow for patients weighing ≥ 30 kg was based on a previous study in patients with JIA (Lovell et al., 2008). The results of SYCAMORE (see below) together with population PK modelling and exposure data from other paediatric indications (see section 2.3.2) supported the proposal for use of this dose regimen in clinical practice, which was in principle regarded acceptable by the CHMP. However, the CHMP noted that the approved posology for children with JIA down to 12 years of age was based on BSA and thus differed substantially from the proposed fixed dose regimen in paediatric uveitis. This has the potential to cause confusion in clinical practice in particular for children with JIA and uveitis who already receive treatment with Humira. The CHMP therefore encouraged further simplification and harmonisation of the dose regimens across indications in the future.

Furthermore, the option of a loading dose (40 and 80 mg in the respective weight categories one week prior to start of maintenance therapy) while not studied in SYCAMORE, was supported by the population PK analyses as well as data from clinical studies in patients with CD aged 6 years and older. In addition to section 2.3.2, this is further discussed in the context of safety in section 2.5.1. From an efficacy perspective, rapid attainment of steady state serum concentration of adalimumab by means of a loading dose would be expected to result in an earlier onset of action with a potential to obtain a more rapid disease control, and hence is acceptable.

### Design and conduct of clinical studies

SYCAMORE was a randomised, parallel, double-masked, placebo-controlled, trial comparing adalimumab or placebo in combination with MTX in patients with active uveitis in association with JIA refractory to MTX monotherapy. Patients had active anterior uveitis in accordance with the SUN criteria. The effects of treatment with adalimumab SC eow were compared over a period of up to 18

months to placebo in 60 and 30 patients, respectively, aged 2 to less than 18 years. The treatment period was followed by a 6 months post-treatment follow-up during which no study treatment was administered (physicians were allowed to treat at their discretion). The follow-up period was ongoing at the time of this report. The CHMP recommended that the final data be provided as soon as available.

The overall study design was considered acceptable by the CHMP. The addition of adalimumab on top of standard of care, i.e. MTX, and the use of MTX as comparator were endorsed as was the fact that the study covered induction as well as maintenance treatment. The selection criteria were adequate and allowed the identification of a MTX-refractory patient population with JIAU. The fact that CS use, especially systemic CS, was restricted and no other disease-modifying IMMs than MTX were allowed, suggests moderate disease severity in the study population.

The primary efficacy endpoint was the median time to treatment failure. Treatment failure was defined by multiple components that included increase in AC cell score, sustained non-improvement, partial or no improvement, or development or worsening of comorbidities after ≥ 3 months of therapy and/or use of concomitant medication and/or suspension of study treatment for >4 weeks. This endpoint was regarded by the CHMP to be appropriate and likely sensitive to detect a treatment failure. Consideration of ocular co-morbidities was agreed to be relevant.

However, for children with JIAU it has been reported that up to 25 % develop significant visual impairment and up to 12% very slowly progress to permanent blindness as a result of low-grade chronic intraocular inflammation. The ultimate treatment goal would thus be to completely eliminate the inflammatory reaction. Therefore, secondary endpoints addressing disease control and disease remission (no AC cells with or without topical CS and no AC cells without topical treatment, respectively) were regarded important. Overall, the range of endpoints was expected to give a comprehensive picture of the effect of adalimumab on inflammation. Further analyses were however requested by the CHMP to better capture patients with low-grade inflammation and consequently at risk for vision loss in the long term. For example, elevated anterior chamber flare has shown to be predictive of complications and vision loss in children with chronic anterior uveitis (with or without JIA). Secondary endpoints addressing the CS-sparing effect were also considered relevant.

With regards to the conduct of the study, some questions were raised in relation to the two interim analyses conducted for which the trial statistical team prepared reports to an independent trial steering committee. Although critical data seemed not to have been disclosed, treatment effects across the groups were obviously clear to the trial statisticians. However, given that study recruitment was already stopped and the study unmasked after the second interim analysis, the involvement of the trial statistical team in the interim analyses was not considered a major issue, especially as another, independent statistical team authored a late SAP update for the secondary endpoints. Some uncertainties remained regarding the lack of clearly pre-specified interim analyses (number and timing). However, keeping in mind that the results of the interim and final analyses consistently showed a beneficial effect of adalimumab and since stopping boundaries had been pre-defined, the issue was not further pursued.

## Efficacy data and additional analyses

Amongst the 90 randomised patients, 16 study participants (9 adalimumab, 7 placebo) prematurely discontinuing treatment. The main reasons for discontinuing adalimumab were intolerance to MTX (4) and for placebo it was worsening of uveitis and felt no benefit (3). Data from all patients were however captured during the main analyses and no concern arose from the early withdrawals.

Baseline demographics and ocular characteristics were generally balanced between treatment arms. The majority of patients were Caucasian as they were recruited from the UK. In the adult uveitis studies, subgroup analyses by race indicated no impact of treatment, but the size of the subgroups was small. In other indications of Humira, population PK analyses previously indicated no ethnicity-related sensitivity of adalimumab or significant race-related differences in adalimumab PK. Limited information in the published literature indicated no significant differences with regards to risk factors and rates of JIAU amongst people of different ethnicities. Although the information is limited, taken together, ethnicity was not believed to have a major impact on the outcome of treatment with adalimumab, in particular with a view to anterior uveitis.

The present application targets use in children from 2 years of age. While this was in line with the inclusion criteria (≥2-18 years) of SYCAMORE, the youngest subject randomised to the adalimumab treatment arm in this study was 3 years. Given that most of the growth of the eye occurs within the first 2 years of life and since there are no major differences in the eye of a 2- and 3-year-old child, the lower cut-off age of 2 years was nevertheless considered acceptable by the CHMP. This also took into account the large paediatric database in support of the use of adalimumab in patients with JIA as young as 2 years of age (see also discussion on clinical safety in section 2.5.1. ). Since a significant subset of paediatric patients with JIA also has uveitis, those receiving Humira are in practice also treated for their uveitis. In children with JIAU, it would thus be inconsistent to set the age limit to 3 years.

In SYCAMORE, the median duration of treatment in the adalimumab and placebo-treated groups, respectively, were 352 and 87 days. This already clearly indicates that adalimumab treated subjects had a longer time to treatment failure. This was confirmed in the primary efficacy analysis. In the placebo+MTX treated group, the median time to treatment failure was 24 weeks. In the adalimumab+MTX group, less than 50% of subjects experienced treatment failure during the 18 month treatment period and thus time to treatment failure could not be estimated ($p<0.0001$). A 75% risk reduction was demonstrated (HR=0.25; 95% CI: 0.12, 0.49; $p<0.0001$). The main reasons for treatment failures in both treatment groups were related to use of concomitant medications. Fewer subjects in the adalimumab treatment arm (compared to placebo) failed treatment due to sustained AC cell scores. The outcome is further supported by several sensitivity analyses and was regarded by the CHMP convincing, both from a clinical and statistical view.

Subgroup analyses on the primary endpoint by AC cell grade (+1 versus ≥2) and flare score (0 versus ≥0.5) also showed a convincing treatment effect in favour of adalimumab. A clear risk reduction in failure rates compared to placebo and strong p-values were shown for subjects with an AC grade of 1+ or an AC flare of 0 at baseline, as well as for those with a higher degree of disease activity.

In the context of the review of the primary endpoint, it was noted that potential uveitis-associated complications such as macular oedema, cataracts and increased IOP (besides those likely related to CS) were very few. This was however to be expected and many years of follow-up and a large sample size would be needed to adequately capture any reduction of such complications.

Secondary efficacy outcomes supported the results for the primary endpoint. Compared to placebo, in the adalimumab treatment arm, the risk of having a treatment failure was statistically significantly reduced by 56% ($p=0.002$) with a failure rate of 60% (18/30) and 26.7% (16/60) in the placebo and adalimumab groups, respectively. Amongst the subjects using ≥ 2 drops/day of topical CS at baseline, more patients in the adalimumab arm (22/45, 48.9%) than in the placebo arm (3/18, 16.7%) reduced the use before treatment failure or the 18 months treatment visit ($p=0.049$). Similarly, a higher proportion of subjects on any topical CS dose at baseline in the adalimumab group (23/49, 46.9%) discontinued topical CS use compared to placebo (4/25, 16%) ($p=0.018$). Very few subjects were on oral CS at baseline (1 participant in the placebo group and 5 participants in the adalimumab group)

and although the use was decreased with adalimumab, no conclusion could be drawn from these data. With regards to topical CS, a steroid-sparing effect was clearly demonstrated for adalimumab. The HR for treatment failure without topical CS was 0.31 (p= 0.0002), which provided further support on this aspect.

With regards to disease control (zero AC cells with topical CS allowed) and remission (zero AC cells without topical CS), a convincing effect of adalimumab over placebo was shown. Close to 25% of patients on adalimumab were in disease remission at month 6 compared to none of the patients in the placebo group (RR = 14.74, 95% CI: 0.91, 238.95, p=0.004).

The MAH has further presented data on AC flare scores, that if high have been associated with an increased risk of vision loss and development of vision-threatening complications. The additional analyses showed that the score for patients in the adalimumab group was reduced to a greater extent (e.g. from 0.83 at baseline to 0.21 at 3 month [best case]) than for patients in the placebo group (e.g. from 0.73 at baseline to 0.63 at 3 month [best case]) with mean flare scores of approximately 0.2 in the adalimumab treatment group as of Month 3 until then end of the double-blind treatment period at Month 18.

There were no relevant differences in BCVA between treatment arms, but this was not surprising as the mean BCVA was essentially normal in both treatment groups at baseline. Of importance is that there was, on average, no relevant loss of BCVA in any treatment arm and the majority of patients had a stable BCVA during the study. Responder analyses performed in response to a CHMP requested showed a small numerical trend with regards to gain or loss of BCVA by Month 6 in favour of adalimumab, but due to the very limited number of subjects fulfilling responder criteria (e.g. 4, 2, and 1 patient in the adalimumab arm and zero patients on placebo had an improvement of logMar ≤-0.10, -0.20, and -0.30, corresponding to a gain of 5, 10, and 15 letters), no firm conclusions could be drawn.

No conclusions can be drawn from the analysis of ocular co-morbidities such as associated optic nerve (assumed disc oedema) and macular oedema due to the few subjects concerned.

Analyses of quality of life indicate no relevant differences between the treatment arms.

With regards to the arthritis disease activity, there were small differences between treatment arms, however, baseline disease activity of the underlying JIA was very low, and all subjects received MTX.

Overall, the results of SYCAMORE convincingly demonstrate a clinically relevant treatment benefit of adalimumab in addition to MTX in paediatric patients with JIAU. However, the MAH applied for the approval of Humira for the treatment of *chronic non-infectious uveitis in paediatric 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.* To support such broad indication, the MAH presented justifications for the extrapolation of the available data for anterior uveitis to other types and anatomical locations of uveitis and for extrapolation from adults to paediatric patients including a summary of supportive scientific literature. It is recognised, that due to the rarity and diversity of the many different forms of uveitis that affects the paediatric population, standard clinical studies covering all different settings would be extremely difficult to conduct. It was furthermore reasonable to accept an indication including anterior uveitis irrespective of the presence or absence of associated systemic (arthritic) conditions, since these would be expected to have a similar clinical expression and responsiveness to treatment. E.g. in JIA, uveitis does not parallel joint inflammation and although arthritis is generally diagnosed before the eye is involved, the severity of the arthritis does not correlate with the severity of the uveitis. However, there was insufficient evidence to support extrapolation to non-anterior uveitides.

Even if the immunological basis of uveitis could well be similar in paediatric and adult patients, and while there is some support in the literature suggesting an effect of adalimumab on other inflammatory markers than AC cells and uveitis conditions affecting the posterior segment of the eye, overall these very limited data were not considered by the CHMP sufficiently reassuring to support use of adalimumab in paediatric patients with intermediate, posterior, or pan-uveitis. In particular for intermediate uveitis, reports exist that this form may be more aggressive in children compared to adults, although this may, at least in part, be due to a later diagnosis. Furthermore, and although there may be some exceptions (e.g. Behçet's disease), there was insufficient evidence available supporting that paediatric intermediate and posterior uveitis has a similar disease course and response to treatment compared to adult forms. Uncertainties also existed in relation to VKH, sarcoidosis as well as idiopathic uveitis affecting the posterior segment and subjects with Blau syndrome, Kawasaki's syndrome, TINU and CINCA/NOMID. In view of these concerns, the MAH agreed to limit the indication to the treatment of paediatric chronic non-infectious anterior uveitis. This restriction was considered adequate by the CHMP.

However, as a consequence, a clear unmet need remains in paediatric patients with non-anterior uveitides. Due to the difficulties conducting standard clinical trials in this group of patients, the CHMP encouraged the MAH to consider alternative strategies to generate data that could at least cover uveitis of some additional aetiologies that involves also the intermediate and posterior segment of the eye. To provide additional support for an extrapolation exercise, the MAH may explore the option of an open label (registry) trial where uveitis aetiology, dosing, detailed uveitis outcomes (e.g. as defined in SYCAMORE) and safety are recorded. In such setting, the loading dose could also be further evaluated.

Finally, in SYCAMORE, adalimumab was administered together with MTX. Initially, the MAH proposed the option to give adalimumab as monotherapy which was not agreed by the CHMP, since without MTX, the median concentration of adalimumab might be on the low side in children (see also exposure simulations in section 2.3.2. ) and no clinical data for this setting were available. Concomitant treatment with MTX was also likely to reduce the risk of antibody development with a subsequent risk for a reduced effect. Furthermore, whilst in the adult uveitis studies, subjects were treated in combination with different non-biologic IMMs, there was insufficient support for the safe and effective use of such combinations in children and adolescents. Altogether, the available evidence was considered adequate to support use of adalimumab in combination with MTX only, which was reflected in SmPC section 4.2. Use in combination with MTX in patients who are otherwise intolerant to conventional therapy, or in whom conventional therapy is inappropriate was also considered adequate and in line with current clinical practice.

### 2.4.4. Conclusions on the clinical efficacy

Overall, the CHMP considered that a beneficial effect of adalimumab in combination with MTX in paediatric patients with JIAU who are refractory to MTX monotherapy has been convincingly demonstrated. Data from the pivotal SYCAMORE trial showed both a clinically relevant effect in reducing the risk of treatment failures as well as a steroid-sparing effect. Overall, the available clinical efficacy data were considered adequate to support the use of Humira in 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.

## 2.5. Clinical safety

### Introduction

From the previous clinical development programmes as well as post-marketing reporting, the AE profile of Humira has been extensively characterised:

The most commonly reported adverse reactions of Humira are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira. In addition, serious haematological, neurological and autoimmune reactions have been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome. Finally, in controlled clinical trials, more cases of malignancies including lymphoma have been observed among patients receiving TNF-α antagonists compared to control. Overall, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with TNF-α antagonists.

The safety of adalimumab in paediatric uveitis was evaluated based on data from the Phase 3 SYCAMORE study investigating the adalimumab compared to placebo in addition to MTX in paediatric patients from 2 years of age with JIAU who were refractory to MTX monotherapy (see section 2.4.2. for a detailed description of the study design and conduct). Additional supportive data were provided from the JIA registry STRIVE (study P10-262, 7$^{th}$ interim report). Furthermore, reference was made to data from a total of 21 subjects with a reported medical history of uveitis in three previous Phase 3 studies (2 studies in polyarticular JIA and 1 study in ERA). This section will focus on the data from SYCAMORE and STRIVE.

Safety in SYCAMORE was assessed by adverse events (AEs) including Tanner score and history of tuberculosis, vital signs, and laboratory data. Causality of AEs to study treatment was judged by the investigator responsible for the care of the study participant. Frequencies were presented as events per 100 patient years (E/100 PYs) to account for the difference in duration on trial.

### Patient exposure

SYCAMORE included 90 paediatric patients. Of these, 60 were randomised into the adalimumab group and 30 into the placebo group. Treatment was administered concomitantly with a stable dose of MTX (10 mg/m$^2$ up to a maximum dose of 25 mg). Subjects in the adalimumab group received a mean total of 23 doses of adalimumab for a median duration of 352.5 days (range 14 – 561 days), compared with subjects in the placebo group who received a mean total of 10 doses of placebo for a median duration of 87 days (range 14 – 571 days).

Discontinuation rate in the SYCAMORE study was 15% and almost solely related to non-safety reasons, including intolerance to MTX in four patients. Baseline demographics and disease history/characteristics were generally balanced between placebo and adalimumab. Further details are summarised in section 2.4.2. including use of concomitant medication.

The STRIVE registry included 42 paediatric JIA patients with uveitis. Overall, by the cut-off date of 01 June 2016, 849 patients had been enrolled in the registry and 838 patients were dosed and analysed (537 patients in the adalimumab group and 301 patients in the MTX group). The median

duration of registry exposure was 2.48 years (range 0.04-7.81). Of the 42 patients who had uveitis at baseline, the median observational duration was 1164.5 days (range 1 – 2855 days) or 3.19 years (range 0 – 7.82 years), with a cumulative observational duration of 135.5 patient years (PYs). Twenty of the 42 patients who had uveitis at baseline (47.6%) were exposed to adalimumab for 912 – 1093 days (up to Week 156), with 10 patients (23.8%) continuing in the study for 1276 – 1457 days (up to Week 208).

### *Adverse events*

In SYCAMORE, there were a total of 588 AEs reported in 53 subjects (88.3%) in the adalimumab group and 103 AEs reported in 25 subjects (83.3%) in the placebo group. The overall incidence rate of AEs was higher for the adalimumab group (1007 events per 100 patient years [E/100 PYs]) than for the placebo group (651 E/100 PYs).

The most common AEs by MedDRA System Organ Class (SOC) in the adalimumab group were infections and infestations (76.7%), respirator, thoracic and mediastinal disorders (51.7%), general disorders including administration site conditions (50%), gastrointestinal disorders (43.3%), nervous system disorders (26.7%), musculoskeletal and connective tissue disorders (25%), investigations (25%), and eye disorders (23.3%). Aside from eye disorders (26.7%), common AEs reported in the placebo group were consistently lower.

The most frequently reported AEs in ≥ 5% of subjects are summarised in Table 10.

The most frequently reported AEs in the adalimumab group, occurring in >10% of patients and 1.5 times more often compared to placebo were diarrhoea (n=8, 13.3%), injection site reaction (n=7, 11.7%), lower respiratory tract infection (n=8, 13.3%), tonsillitis (n=12, 20%), viral infection (n=13, 21.7%), arthralgia (n=12, 20%), cough (n=22, 36.7%) and oropharyngeal pain (n=16, 26.7%).

The majority of AEs in both treatment groups were deemed to be mild or moderate in severity. Overall, 8.3% of subjects (5 events in 5 subjects) in the adalimumab group had at least 1 severe AE and 6.7% of subjects (3 events in 2 subjects) in the placebo group had 1 severe AE. 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. The majority of AEs in both groups were judged by the investigators to be unrelated to the treatment.

**Table 10 - Number and Percentage of Subjects with Adverse Events in the Adalimumab Group ≥ 5% (SYCAMORE Study)**

| System Organ Class<br>Preferred Term | Adalimumab<br>N = 60<br>n (%) | Placebo<br>N = 30<br>n (%) |
|---|---|---|
| Blood and lymphatic system disorders | | |
| Lymphadenopathy | 3 (5) | 0 |
| Eye disorders | | |
| Eye pain | 4 (6.7) | 0 |
| Gastrointestinal disorders | | |
| Abdominal pain | 3 (5) | 0 |
| Diarrhoea | 8 (13.3) | 1 (3.3) |

| System Organ Class<br>Preferred Term | Adalimumab<br>N = 60<br>n (%) | Placebo<br>N = 30<br>n (%) |
|---|---|---|
| Nausea | 5 (8.3) | 2 (6.7) |
| Vomiting | 18 (30) | 5 (16.7) |
| General disorders and administration site conditions | | |
| Injection site erythema | 3 (5) | 1 (3.3) |
| Injection site mass | 3 (5) | 0 (0) |
| Injection site pain | 5 (8.3) | 2 (6.7) |
| Injection site pruritus | 3 (5) | 0 |
| Injection site reaction | 7 (11.7) | 0 |
| Injection site swelling | 4 (6.7) | 1 (3.3) |
| Pyrexia | 12 (20) | 2 (6.7) |
| Infections and infestations | | |
| Ear infection | 6 (10) | 2 (6.7) |
| Impetigo | 3 (5) | 1 (3.3) |
| Lower respiratory tract infection | 8 (13.3) | 2 (6.7) |
| Nasopharyngitis | 15 (25) | 7 (23.3) |
| Oral herpes | 3 (5) | 1 (3.3) |
| Paronychia | 3 (5) | 1 (3.3) |
| Pharyngitis | 4 (6.7) | 0 |
| Tonsillitis | 12 (20) | 0 |
| Upper respiratory tract infection | 4 (6.7) | 1 (3.3) |
| Urinary tract infection | 9 (15) | 3 (10) |
| Varicella | 3 (5) | 0 |
| Viral infection | 13 (21.7) | 1 (3.3) |
| Injury, poisoning and procedural complications | | |
| Fall | 3 (5) | 0 |
| Investigations | | |
| Alanine aminotransferase increased | 4 (6.7) | 1 (3.3) |
| Aspartate aminotransferase increased | 3 (5) | 1 (3.3) |
| Intraocular pressure increased | 4 (6.7) | 0 (0) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | 12 (20) | 2 (6.7) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | |
| Skin papilloma | 5 (8.3) | 0 |
| Nervous system disorders | | |
| Headache | 12 (20) | 4 (13.3) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 22 (36.7) | 3 (10) |
| Epistaxis | 3 (5) | 0 (0) |
| Oropharyngeal pain | 16 (26.7) | 2 (6.7) |
| Skin and subcutaneous tissue disorders | | |

| System Organ Class<br>Preferred Term | Adalimumab<br>N = 60<br>n (%) | Placebo<br>N = 30<br>n (%) |
|---|---|---|
| Rash | 3 (5) | 1 (3.3) |

Among the 42 patients in the STRIVE registry who had uveitis at Baseline, 15 patients (35.7%) in the adalimumab group reported observational AEs (defined as any AE with onset on or after the first day in the registry through the last contact in registry). The observation-time adjusted rate for any AE was 25.1 E/100 PY. The most commonly reported AE was arthritis, reported by 3 patients (7.1%) (3.0 E/100 PY). AEs reported by 2 patients (4.8%) (1.5 E/100 PY) each were uveitis, bronchitis, pharyngitis streptococcal, scarlet fever, and urinary tract infection. Overall, 8 patients (19.0%) (11.1 E/100 PY) reported infections and 1 patient reported 2 serious infections (1.5 E/100 PY).

No incidents of subjects experiencing withdrawal or rebound were reported in any of the studies.

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

In SYCAMORE, 13 subjects (21.7%, 29 E/100 PY) in the adalimumab group reported 17 serious adverse events (SAEs), and 2 subjects (6.7%, 19 E/100 PY) in the placebo groups reported 3 SAEs. SAEs in the adalimumab group were mainly different kinds of infections (including 2 cases of varicella, viral infection and streptococcal infection, each, as well as 1 case of lower respiratory tract infection), and of mild or moderate intensity. The SAEs in the placebo group were related to the underlying disease (2 cases of anterior chamber flare, and 1 case of uveitis).

Among the 42 patients with uveitis at Baseline in the STRIVE registry, 3 patients (7.1%) reported 6 SAEs. Two SAEs (pyrexia, histoplasmosis) were reported in one patient and were considered severe and not related to adalimumab by the investigator. Instead, they were attributed to the patient being on immunosuppressant.

No fatal events were reported.

Adverse events of special interest (AESIs) of concern for anti-TNF agents included infections, malignancies, immune reactions, demyelinating disorders, and cardiovascular events. Of these, only injection site reactions and infections were reported in SYCAMORE and STRIVE.

In SYCAMORE, injection site-related events reported by ≥ 5% of subjects were injection site reaction (7 subjects [11.7%]), injection site pain (5 subjects [8.3%]), injection site swelling (4 subjects [6.7%]), injection site erythema (3 subjects [5%]), injection site mass (3 subjects [5%]), and injection site pruritus (3 subjects [5%]). All except 1 of these events were mild to moderate in severity and the investigator considered most of them to be related to study drug.

Infection and infestations were reported in 46 subjects (76.7%, 236.4 E/100PY) in the adalimumab group compared to 12 subjects (40%, 164.4 E/100PY) in the placebo group in SYCAMORE. Ten (10) serious infections were reported by 8 subjects (13.3%) in the adalimumab group compared to no serious infections reported in the placebo group; all of these events were mild or moderate in severity. Two (2) serious infections were considered by the investigator to be unrelated or unlikely related and the rest to be at least possibly related to adalimumab therapy. No cases of opportunistic infections including tuberculosis were reported.

Among the 42 patients with uveitis at Baseline in STRIVE, 1 patient (2.4%) reported an AESI of injection site reaction. Eight (19.0%) of the 42 patients reported at least 1 infection, including 1

patient (2.4%) with 2 serious infections (pyelonephritis and histoplasmosis), also assessed as SAEs. Pyelonephritis was considered by the investigator to be possibly related and histoplasmosis to be not related to adalimumab.

### *Laboratory findings*

None of the laboratory values in SYCAMORE were of concern.

A shift in alanine aminotransferase from Baseline (low/normal to high) was reported for 11.54% of subjects at 2 months and 18.52% of subjects at 15 months for subjects in the adalimumab group; no subjects in the placebo group reported this shift at these time points. In terms of AEs, 4 (6.7%) of the patients in the adalimumab group and 1 (3.3%) in the placebo group had alanine aminotransferase increased. Overall, the observed rate of alanine aminotransferase elevations was in line with what has been observed in other paediatric adalimumab studies. This is already adequately described in the SmPC of Humira in the context of hepato-biliary disorders.

### *Safety in special populations*

There were no pregnancies or lactating subjects in the SYCAMORE study. In the JIA Registry (STRIVE), no pregnancies were reported among the uveitis patient population.

### *Safety related to drug-drug interactions and other interactions*

Drug-drug and drug-disease interactions were not specifically evaluated in SYCAMORE or STRIVE.

### *Discontinuation due to adverse events*

In the SYCAMORE study, one subject in the adalimumab group withdrew from the study due to a mild AE of raised erythrocyte sedimentation rate and C-reactive protein, and the events resolved during follow-up. The subject in the placebo group withdrew due to an SAE of uveitis deterioration, classified as severe by the investigator and the event resolved. All other discontinuations in the study were due to non-safety reasons.

No subject discontinued in the registry study due to an AE.

### *Post marketing experience*

As of 31 December 2015, the estimated worldwide post-marketing adalimumab exposure since approval for paediatric patients (< 18 years old) was 30,426 PY for JIA, 8,677 PY for Ps, and 41,256 PY for CD. No new safety signals were identified in the most recent review of cumulative safety data in the paediatric population (Periodic Safety Update Report for 01 January 2015 through 31 December 2015).

## 2.5.1. Discussion on clinical safety

The SYCAMORE study with 90 paediatric JIAU patients provided the main basis for the assessment of the safety of Humira in paediatric uveitis patients. Notably, in SYCAMORE patients were treated with adalimumab or placebo in combination with MTX. The study size was rather small with only 60 patients being exposed to adalimumab. The limited number of patients is explained by the rarity of the

condition and thus acceptable. However, as a result, rare adverse reactions may not have occurred and frequency estimations were impacted.

Additional supportive data were available from the JIA registry STRIVE, which contributed data from 42 JIA patients diagnosed with uveitis as baseline. The CHMP furthermore considered the experience gained from the use of Humira in JIA and other paediatric indications. As of 31 December 2015, a total of 577 paediatric patients were studied in clinical trials for JIA, CD, and Ps and post-marketing exposure amounted to more than 80,000 PY.

In SYCAMORE, patients on adalimumab stayed on average longer on adalimumab treatment (median 352.5 days) compared to placebo (median 87 days). Treatment discontinuation (other than in case of treatment failure) occurred in 15% of patients and was mostly related to non-safety reasons. The most common AEs by MedDRA SOC in the adalimumab group were infections and infestations (76.7%), and general disorders including administration site conditions (50%). The most frequently reported AEs in the adalimumab group that occurred in more than 10% of patients and 1.5 times more often compared to placebo were diarrhoea (13.3%), injection site reaction (11.7%), lower respiratory tract infection (13.3%), tonsillitis (20%), viral infection (21.7%), arthralgia (20%), cough (36.7%) and oropharyngeal pain (26.7%).

SAEs in the adalimumab group in SYCAMORE were dominantly different kinds of infections (see further discussion below), mainly of mild or moderate intensity. In contrast, in patients receiving placebo, all 3 SAEs reported were potentially related to the underlying diseases. No fatal events were reported.

The limited data for uveitis patients in the JIA registry showed a similar AE profile with uveitis, bronchitis, pharyngitis streptococcal, scarlet fever, and urinary tract infection reported by 2 (4.8%) patients each, and arthritis, which was the most commonly reported event reported by 3 patients (7.1%).

Infection and infestations AEs were reported by 46 subjects (76.7%, 236.4 E/100PY) in the adalimumab group in SYCAMORE compared to 12 subjects (40%, 164.4 E/100PY) in the placebo group. While the absolute reporting rate of infections was similar to that reported for other paediatric indications (81.8% for JIA, 75.5% for CD, and 73.9% for Ps), the reporting of serious infections was higher in the SYCAMORE trials (13.3%) compared to JIA (7.7%) and Ps (0.9%), but similar to that reported in CD (13%). Furthermore, after adjusting for exposure, the incidence rates of both infections and serious infections in paediatric uveitis patients were higher (236.4 E/100 PY and 17.1 E/100 PY) compared to the other paediatric indications (JIA: 150.7 E/100 PY and 2.7 E/100 PY; CD: 132.2 E/100 PY and 6.6 E/100 PY, Ps: 168.7 E/100 PY and 0.8 E/100 PY). Notably, the reporting of infections was high also in the placebo-treated subjects. Plausible explanations for the observed discrepancy across indications include differences in clinical practice, and increased vigilance over the JIAU patients. It may furthermore be explained by the characteristics of the SYCAMORE trial e.g. increased reporting in an investigator initiated trial, methotrexate treatment, and the small sample size. Given that serious infection is already an important identified risk in the RMP and relevant safety information is included in the SmPC, no further action was considered necessary by the CHMP. A follow-up is expected in future periodic safety update reports (PSURs) and a focus should be set on paediatric patients.

Overall, the types and pattern of AEs reported in SYCAMORE for adalimumab were in agreement with the safety profile previously observed in the other approved paediatric indications as well as in adult uveitis patients. The only difference to other paediatric indications was the occurrence of ocular AEs, which were however considered to be likely related to the underlying disease. Four cases each of ocular pain and IOP increased were reported in the adalimumab group compared to no such reports in

the placebo arm. At the same time, AEs within the MedDRA SOC of eye disorders were reported slightly less frequent with adalimumab compared to placebo (23.3% versus 26.7%).

The data from SYCAMORE thus supported the use of adalimumab in combination with MTX. However, given that in SYCAMORE no other disease-modifying IMMs than MTX were allowed, the CHMP was of the view that there were insufficient data to support the combination of adalimumab with other IMMs for the treatment of paediatric uveitis.

With regards to the proposal of an optional loading dose (40 mg and 80 mg in patients weighing <30 kg and ≥30 kg, respectively) one week prior to start of maintenance therapy in order to more rapidly achieve steady sate concentrations, the CHMP noted that the safety of such loading had not been studied in SYCAMORE. Uncertainties arose due to the potential impact on the systemic exposure and risk for AEs, especially in the youngest children. Some experience with the use of a loading dose was however available from studies in children with CD aged 6 years and older (studies M06-806 and M06-807. No new safety findings arose from these studies and there was no evidence that the use of a loading dose would increase the risk of adverse reactions. Use of a loading dose (80mg and 160 mg for patients <40 kg and ≥40 kg, respectively) is approved for CD in case there is a need for a more rapid response to therapy. Population PK modelling furthermore showed that in presence of MTX, adalimumab serum concentrations immediately after the initial loading dose did not exceed the steady-state concentration (see section 2.3.2. ). Furthermore, exposure-safety analyses did not reveal an increase in the incidence of AEs with increasing exposure. Thus, while safety data remain limited in the youngest age groups, the option of a loading dose in patients with paediatric uveitis down to the age of 2 years was considered acceptable by the CHMP. Information on the absence of clinical data on the loading dose in children < 6 years of age was reflected in relevant sections of the SmPC.

Generally, the CHMP was of the view that the safety of adalimumab in the paediatric population should be reviewed in future PSURs. The MAH was furthermore encouraged to explore possibilities to study patients outside the agreed indication of paediatric chronic non-infectious anterior uveitis, e.g. by means of open-label study including collection of safety data. In such setting, use of a loading dose in particular in the younger children could also be further evaluated.

## 2.5.2. Conclusions on clinical safety

The CHMP concluded that the available clinical safety data were adequate to support the application for Humira in 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. While the data were limited, overall, the safety data from paediatric uveitis patients were consistent with the safety profile previously observed in other paediatric indications as well as in adult uveitis patients.

In addition, the MAH should review the safety of adalimumab in the paediatric population in future PSURs. To this end, separate tabulations for the paediatric population should be provided.

## 2.5.3. PSUR cycle

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.

## *2.6. Risk management plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.0.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 13.0.1 with the following content:

## *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | • Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis, and tuberculosis (TB);<br>• Reactivation of hepatitis B;<br>• Pancreatitis;<br>• Lymphoma;<br>• Hepatosplenic T-cell lymphoma (HSTCL);<br>• Leukaemia;<br>• Non-melanoma skin cancer (NMSC);<br>• Melanoma;<br>• Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin);<br>• Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis [ON]);<br>• Immune reactions (including lupus-like reactions and allergic reactions);<br>• Sarcoidosis;<br>• Congestive heart failure (CHF);<br>• Myocardial infarction (MI);<br>• Cerebrovascular Accident (CVA);<br>• Interstitial lung disease (ILD);<br>• Pulmonary embolism;<br>• Cutaneous vasculitis;<br>• Stevens-Johnson syndrome (SJS);<br>• Erythema multiforme (EM);<br>• Worsening and new onset of Psoriasis (Ps);<br>• Haematologic disorders;<br>• Intestinal perforation;<br>• Intestinal stricture in Crohn's disease (CD);<br>• Liver failure and Other Liver Events; |
| Important potential risks | • Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma);<br>• Vasculitis (non-cutaneous);<br>• Progressive multifocal leukoencephalopathy (PML);<br>• Reversible posterior leukoencephalopathy syndrome (RPLS);<br>• Amyotrophic lateral sclerosis (ALS);<br>• Adenocarcinoma of colon in ulcerative colitis (UC) patients;<br>• Infections in infants exposed to adalimumab in utero;<br>• Medication errors with paediatric vial; and<br>• Off-label use. |
| Missing information | • Subjects with immune-compromised conditions either due |

| | |
|---|---|
| | to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications.<br>• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD.<br>• Pregnant and lactating women;<br>• Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and juvenile idiopathic arthritis (JIA).<br>• Long-term safety information in the treatment of adults with HS.<br>• Long-term safety information in the treatment of adults and children with uveitis. |

## *Pharmacovigilance plan*

| Actions | Milestone / Exposure | Milestones/ Calendar Time | Study Status |
|---|---|---|---|
| **Ongoing Pharmacovigilance Actions** | | | |
| Annual interim data from Registry for pedCD patients (Study P11-292) | -- | Reporting August through 2023 | Ongoing |
| Registry for pedCD patients (Study P11-292) | 10 years | TBD | Ongoing |
| Annual interim data from Registry for Ps patients (Study P10-023) | -- | Reporting February through 2022 | Ongoing |
| Registry for Ps patients (Study P10-023) | 10 years | Final Report February 2023 | Ongoing |
| Evaluation of treatment interruptions with the Ps registry (Study P10-023) | 10 years | February 2023 | Ongoing |
| Annual interim data from Registry for pJIA patients (Study P10-262) **STRIVE** | -- | Reporting August through 2023 | Ongoing |
| Registry for pJIA patients (Study P10-262) **STRIVE** | 10 years | Final Report Including safety subgroup analyses for pedUV patients December 2024 | Ongoing |
| Evaluation of treatment interruptions with the pJIA registry (Study P10-262) **STRIVE** | 10 years | December 2024 | Ongoing |
| Support Rheumatoid Arthritis National Registry in Germany (RABBIT) until the end of 2017 | NA | Reporting February through 2017 (Biennially) | Ongoing |
| | NA | Final summary report 3Q 2018 | Ongoing |

| Actions | Milestone / Exposure | Milestones/ Calendar Time | Study Status |
|---|---|---|---|
| Support Rheumatoid Arthritis National Registry in United Kingdom (BSRBR) until April 2017 | NA | Final summary report 4Q 2017 | Ongoing |
| Support Rheumatoid Arthritis National Registry in Sweden (ARTIS) until the end of 2015 | NA | Final summary report 4Q 2016 | Ongoing |
| Long-term HS data (Study M12-555) | -- | 1Q 2017 | Ongoing |
| Long-term uveitis data (Study M11-327) | -- | 4Q 2018 | Ongoing |
| Annual Interim data from Registry for UC (Study P11-282) | -- | Reporting August through 2019 | Ongoing |
| Biannual Interim data from Registry for UC (Study P11-282) | -- | Reporting August from 2019 through 2023 | Ongoing |
| Registry for UC patients (Study P11-282) | 10 years | TBD | Ongoing |

## *Risk minimisation measures*

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important Identified Risk** | | |
| Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of serious infections associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| Lymphoma | Labelling as detailed in SmPC | To educate prescribers and patients about the risk of lymphoma associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| HSTCL | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of HSTCL associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| Leukaemia | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of leukaemia associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| NMSC | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of NMSC associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| Melanoma | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of melanoma associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| Merkel cell carcinoma (Neuroendocrine carcinoma of the skin) | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of MCC associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Demyelinating disorders | Labelling as detailed in SmPC. | To educate prescribers and patients about 1) the risk of demyelinating disorders associated with the use of Humira, and 2) the underlying risk of demyelinating disorders associated with uveitis, particularly intermediate uveitis:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| CHF | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of CHF associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |
| **Important Potential Risks** | | |
| Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma) | Labelling as detailed in SmPC. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert/Information Card<br>• HCP Educational Material. |

The rest of safety concerns not listed above only have routine risk minimisation measures.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. Changes to SmPC sections 4.1 and 4.2 are shown below (new text is shown in **bold)**:

- SmPC section 4.1

**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.**

- SmPC section 4.2

***Paediatric Uveitis***

**In paediatric uveitis, there is no experience in the treatment with Humira without**

**concomitant treatment with methotrexate.**

***Paediatric uveitis patients < 30 kg:***

**The recommended dose of Humira is 20 mg every other week in combination with methotrexate.**

**When Humira therapy is initiated, a loading dose of 40 mg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).**

***Paediatric uveitis patients ≥ 30 kg:***

**The recommended dose of Humira is 40 mg every other week in combination with methotrexate.**

**When Humira therapy is initiated, a loading dose of 80 mg may be administered one week prior to the start of maintenance therapy.**

**There is no relevant use of Humira in children aged less than 2 years in this indication.**

**It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).**

For Humira 40 mg/0.8 ml solution for injection for paediatric use, SmPC section 4.2 was furthermore updated to advise ophthalmologists to consult with an appropriate specialist before initiation of treatment with Humira. In addition, section 5.1 was updated to incorporate the data from adult uveitis studies. This information had already been reflected in the product information of other Humira presentations at the time of approval of the adult uveitis indication.

Finally, the package leaflet was updated to provide details of how patients can access the information in alternative formats such as Braille, audio, cd-rom or large print.

## 2.7.1. User consultation

No additional consultation with target patient groups on the package leaflet has been conducted in support of this application. However, the changes to the package leaflet are minimal and do not require user consultation.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

In this application, an extension of the indication for Humira to "the treatment of chronic non-infectious uveitis in paediatric 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" was sought. During the course of the procedure, the MAH agreed to limit the indication to paediatric chronic non-infectious anterior uveitis.

Non-infectious uveitis is a rare condition involving intraocular inflammation, vision impairment and pain. It is highly heterogeneous in terms of anatomical location, clinical presentation and aetiology. Non-infectious anterior uveitis is the most common type of paediatric uveitis with juvenile idiopathic arthritis associated anterior uveitis (JIAU) being the leading cause. The onset of the disease is commonly at the age of 2-4 years. While anterior uveitis would be expected to have a similar clinical course and responsiveness to treatment irrespective of the underlying aetiology, this is less clear for other forms affecting the intermediate or posterior segment.

### 3.1.2. Available therapies and unmet medical need

In non-infectious uveitis, the treatment goal is to rapidly control acute inflammation, limit recurrences, reduce both dose and duration of CS and minimise permanent damage. Delays in diagnosis and limited options for management together with the prolonged duration and increased risks of complications make paediatric uveitis a major cause of significant ocular morbidity and patients are at risk of severe vision loss or blindness. CS form the mainstay of treatment early in the course of non-infectious uveitis. Topical CS are usually effective for early control of milder anterior uveitis, but in patients who require prolonged therapy non-biologic IMMs, such as MTX, are the standard of care for paediatric patients. Clinical guidelines recommend adalimumab for the treatment of severe refractory anterior uveitis in paediatric patients. In clinical practice, anti-TNF compounds are also used for various other forms of paediatric uveitis that are otherwise difficult to manage. Prolonged use of local CS is associated with a high risk of ocular complications in children including progressive cataracts, increased IOP and steroid-induced glaucoma. IMMs such as MTX or ciclosporin are also poorly tolerated in a subset of children.

Thus, there is a need for additional effective and safe treatment options for paediatric patients with uveitis, in particular in those who are refractory to or do not tolerate CS and/or non-biologic IMMs.

### 3.1.3. Main clinical studies

SYCAMORE was a randomised, parallel, double-masked, placebo-controlled, multicentre Phase 3 trial in patients with active uveitis in association with JIA refractory to MTX monotherapy. Patients received either adalimumab (20 mg for participants weighing <30 kg or 40 mg for participants weighing ≥ 30 kg) or placebo in addition to MTX for up to 18 months with an additional 6-month, off-treatment follow-up period. Overall 90 patients (60 adalimumab, 30 placebo) were recruited aged 2 to less than

18 years. The primary endpoint was time to treatment failure defined as a composite of anterior segment inflammation, use of concomitant medication and suspension of study treatment.

## 3.2. Favourable effects

In the SYCAMORE study, treatment of paediatric patients with active JIAU with Humira, in combination with MTX, resulted in a statistically compelling delay in the median time to treatment failure compared to MTX plus placebo. In the placebo group, the median time to treatment failure was 24 weeks, while in the adalimumab group less than 50% of subjects experienced treatment failure during the 18 month treatment period and thus time to treatment failure could not be estimated (HR=0.25; 95% CI: 0.12, 0.49; p<0.0001). Post-hoc analyses by subgroups with a lower as well as higher degree of inflammation defined by the level of AC cells and AC flare at baseline also showed a statistically significant treatment effect in favour of adalimumab irrespective of disease activity.

Secondary efficacy outcomes supported the outcome of the primary endpoint. Less patients receiving Humira experienced treatment failure compared to placebo (60% versus 26.7%, RR 0.44, p=0.002). Likewise, more patients in the adalimumab arm compared to placebo were able to reduce the use of CS during the course of the study (before treatment failure or the 18 months treatment visit) with 48.9% versus 16.7% of the patients with ≥ 2 drops/day of topical CS at baseline being able to limit the use to <2 drops/day (p=0.049) and 46.9% versus 16% of patients being able to cease CS use completely (p=0.018). In addition, more patients on Humira than on placebo achieved disease control (zero AC cells with topical CS allowed) or remission (zero AC cells without topical CS), e.g. at month 6, 23.3% of the patients on adalimumab were in disease remission but none of the patients in the placebo group (RR = 14.74, 95% CI: 0.91, 238.95, p=0.004).

## 3.3. Uncertainties and limitations about favourable effects

In SYCAMORE, there was no relevant difference in visual acuity (BCVA) between treatment arms. However, baseline BCVA was not or only mildly impaired in the study population (logMAR range: -0.23 to 0.56) and hence no significant improvement was to be expected. It was reassuring that BCVA remained on average stable throughout the study period and that no reduction in visual acuity in any of the treatment arms occurred. Disease progression to permanent loss of vision and blindness is a risk in particular in patients with low-grade chronic intraocular inflammation. Based on the patient characteristics, SYCAMORE likely captured such patients with low-grade inflammation. Elevated AC flare has shown to be predictive of complications and vision loss in children with chronic anterior uveitis and additional analyses of the effect on AC flare showed a greater reduction with adalimumab (e.g. from 0.83 at baseline to 0.21 at 3 month [best case]) compared to placebo (e.g. from 0.73 at baseline to 0.63 at 3 month [best case]). While these data were reassuring, many years of observation and a large sample size would be needed to verify a beneficial effect of Humira on the long-term risk of sight-threatening complications.

The MAH applied for a broad indication of chronic non-infectious uveitis in paediatric patients from 2 years of age irrespective of anatomical location of the inflammation or aetiology. The CHMP agreed that the data from SYCAMORE in paediatric patients with JIAU were representative for other forms of paediatric anterior uveitis due to similar clinical expression and responsiveness to treatment. However, there was insufficient support to extrapolate efficacy to uveitides affecting the posterior segment. Furthermore, uncertainties remained in relation to several underlying systemic conditions. Although acknowledged that it would be difficult to comprehensively study all different forms and underlying causes of paediatric uveitis, the CHMP encouraged the MAH to continue gathering data in at least some additional aetiologies that involves also the intermediate and posterior segment of the eye. At the time

of this report, nevertheless, the available data only supported an indication of paediatric chronic non-infectious anterior uveitis.

Furthermore, in SYCAMORE, adalimumab was only used in combination with MTX. Therefore, and given that population PK analyses suggested that plasma concentrations of adalimumab were lower when administered in children without MTX, and as MTX was likely to reduce the risk of antibody development with a subsequent risk for a reduced effect, the CHMP was of the view that the available data were insufficient to support Humira monotherapy. At the same time, there was insufficient support for the safe and effective use of Humira in combination with other (non-biological) IMMs. Overall, the available data supported the use of adalimumab in combination with MTX in patients who are otherwise intolerant to conventional therapy, or in whom conventional therapy is inappropriate was considered adequate and in line with current clinical practice.

Other uncertainties arose in relation to ethnicity and use of systemic CS. Information on ethnicity was not collected in SYCAMORE, but according to the investigator, the majority of patients were Caucasian. Given that previously neither data from adult uveitis studies, nor population PK analyses in other indications had shown any impact of race on adalimumab PK or PD, an ethnicity related sensitivity was considered unlikely. With regards to systemic CS use, there were too few subjects on systemic CS to allow any conclusion on a steroid-sparing effect.

Finally, data for the full follow-up period were not available at the time of this report and the CHMP recommended the submission as soon as available to complete the picture with regards to long-term management (up to 2 years in total) of patients.

## *3.4. Unfavourable effects*

In SYCAMORE, the most frequently reported AEs in the adalimumab (+MTX) group were infections and infestations (76.7%) and general disorders including administration site conditions (50%). The most frequently reported AEs that occurred in more than 10% of patients and 1.5 times more often with adalimumab compared to placebo were diarrhoea (13.3%), injection site reaction (11.7%), lower respiratory tract infection (13.3%), tonsillitis (20%), viral infection (21.7%), arthralgia (20%), cough (36.7%) and oropharyngeal pain (26.7%).

With regards to infections, the reporting rate for adalimumab adjusted by treatment duration (236.4 E/100PY) was higher in SYCAMORE compared to previous studies in paediatric patients (JIA, Ps and CD). Similarly, more serious infections (13.3%, 17.1 E/100PY) were reported in JIAU patients. This inconsistency was considered likely due to the characteristics of the SYCAMORE trial e.g. increased reporting in an investigator initiated trial, methotrexate treatment, and the small sample size, and did not raise further concerns. Nevertheless, a follow-up is expected in future PSURs.

Overall the safety data from JIAU patients in SYCAMORE as well as paediatric uveitis patients in the JIA registry STRIVE were consistent with the known safety profile as observed in other paediatric indications as well as in adult uveitis patients. This includes previously recognised safety issues such as malignancies, demyelinating disorders and sarcoidosis, although not reported in paediatric uveitis patients. Malignancies may have been too rare to be detected in the limited safety database. As for demyelinating events, an increased reporting rate has previously been observed with adalimumab in adult uveitis studies and resulted in additional safety warnings and precautions in the SmPC, given that demyelinating events are an important identified risk of Humira and since an association between demyelinating disorders and uveitis has been reported in the scientific literature. Sarcoidosis was also reported in adult patients with uveitis. It is a rare systemic conditions associated with non-infectious

uveitis (including anterior uveitis) and TNF-alpha antagonists have been reported to trigger this disorder.

## 3.5. Uncertainties and limitations about unfavourable effects

The available data for the evaluation of the safety of Humira in the treatment of paediatric uveitis was limited to 90 JIAU patients in SYCAMORE, amongst whom 60 patients were exposed to adalimumab + MTX for up to 18 months, and 42 JIA patients with uveitis in STRIVE who were exposed to adalimumab for up to 1457 days (208 weeks). The limited size of the safety database precludes the detection of rare events and realistic frequency estimations. However, given the rarity of the disease, the small sample size was considered by the CHMP acceptable. Furthermore, as of 31 December 2015, a total of 577 paediatric patients have been studied in clinical trials for JIA, CD, and Ps and the cumulative post-marketing experience amounted to more than 80,000 PY. These data were considered supportive. Overall, the safety profile of Humira was regarded reasonable well established in paediatric patients (in addition to being very similar to that in adults).

No clinical data were available to support the use of a loading dose in children younger than 6 years of age. However, according to population PK model simulation, in presence of MTX, adalimumab serum concentrations immediately after administration of a loading dose appear not to exceed steady-state concentrations. Furthermore, no correlation between the occurrence of AEs and systemic exposure was identified based on data form the already approved paediatric indications. Therefore, the option of a loading dose in patients with paediatric uveitis down to the age of 2 years was considered acceptable.

Furthermore, given that in SYCAMORE no other disease-modifying IMMs than MTX were allowed, the CHMP was of the view that there were insufficient data to support the combination of adalimumab with other IMMs for the treatment of paediatric uveitis.

Given the limitations of the data and in light of the fact that only a narrow indication of paediatric chronic non-infectious anterior uveitis was eventually pursued, the MAH was encouraged to explore the use of adalimumab further e.g. in a post-approval open-label study including the collection of additional safety with a loading dose in the lower paediatric age range. Furthermore, paediatric patients will be followed in future PSUR.

## 3.6. Effects Table

**Table 11 - Effects Table for Humira in the Treatment of paediatric chronic non-infectious anterior uveitis**

| Effect | Short Description | Unit | Adalimumab | Placebo | Uncertainties/ Strength of evidence |
|---|---|---|---|---|---|
| **Favourable Effects*** | | | | | |
| Prevention of treatment failures | Time to treatment failure after Month 3 (1) | Weeks (median) | NE (>18 months) | 24.1 | Statistically compelling ($p<0.0001$) and clinically convincing primary outcome (time to treatment failure, HR 0.25). |
| | Treatment failure rate(1) | n/N (%) | 16/60 (26.7) | 18/30 (60) | |

| Effect | Short Description | Unit | Adalimumab | Placebo | Uncertainties/ Strength of evidence |
|---|---|---|---|---|---|
| Steroid sparing effect | Reduction in CS use<br><br>to <2 drops/day [2]<br><br>to 0 drops/day [3] | n/N (%) | <br><br>22/45 (48.9)<br><br>23/49 (46.9) | <br><br>3/18 (13.3)<br><br>4/25 (16.0) | Statistically significant to compelling (p=0.0013 – 0.0002) and clinically convincing outcomes (HR 0.31-0.32). |
| | Disease control (remission) defined as zero AC cells without CS use<br><br>for 3 months<br><br>for 6 months | N (%) | <br><br>15 (25.0)<br><br>14 (23.3) | <br><br>2 (6.7)<br><br>0 | |
| **Unfavourable Effects**** | | | | | |
| Infections and infestations | Incidence rate<br>• All infections | % (E/100PY) | 76.7 (236.4) | 40.0 (164.4) | Incidence rate in STRIVE (E/100 PY): All infections: 11.1; serious infections: 1.5.<br><br>No cases of opportunistic infections or active tuberculosis have been observed.<br><br>Incidence rate in other paediatric indications:<br>- All infections: 81.8%/ 150.7 E/100 PY (JIA), 75.5%/132.2 E/100 PY (CD), and 73.9%/ 168.7 E/100 PY (Ps),<br>- serious infections: 7.7%/2.7 E/100 PY (JIA), 0.9%/ 0.8 E/100 PY (Ps), 13%/6.6 E/100 PY (CD). |
| | • Serious infections | | 13.3 (17.1) | 0 (0) | |
| Malignancies | Incidence rate | % | 0 | 0 | Incidence rate in STRIVE (%; E/100 PY): 0; 0 |
| Demyelinating disorders | | | 0 | 0 | Incidence rate in STRIVE (%; E/100 PY): 0; 0<br><br>Incidence rate in adult uveitis (studies M10-877 and M10-88): 0.6 vs.0 E/100 PY for adalimumab vs. placebo |
| Sarcoidosis | | | 0 | 0 | Incidence rate in STRIVE (%; E/100 PY): 0; 0<br><br>Incidence rate in adult uveitis (studies M10-877 and M10-88): 4.8 vs.3.3 E/100 PY for adalimumab vs. placebo |

Abbreviations: AC= anterior chamber; E=events, CS=corticosteroids; HR=hazard ratio; NE=not estimable; PY=Patient Year

* Results refer to the main study SYCAMORE.

** Rates refer to the observations in the main study SYCAMORE unless stated otherwise. The limited size of the safety database precludes the detection of rare events and realistic frequency estimations.

(1) Proportion of patients with treatment failure, which was defined as one or more of the following: (i) anterior segment inflammation after ≥ 3 months of therapy: Increased AC cell score, sustained non-improvement, no or partial improvement with ocular co-morbidities, or worsening of ocular co-morbidities; (ii) use of concomitant medication; (iii) suspension of study treatment for >4 weeks.

(2) For subjects at >2 drops/day topical CS at baseline.

(3) For subjects at any dose of topical CS at baseline.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

There is an unmet medical need in the treatment of paediatric patients with chronic uveitis that are refractory or do not tolerate to CS and/or non-biologic IMMs. In the SYCAMORE study, adalimumab in combination with MTX has demonstrated a clear benefit over placebo (+MTX) in patients with JIAU in preventing treatment failure with a hazard ratio of 0.25 for time to failure ($p<0.0001$). Compared to placebo, the risk of having a treatment failure was significantly reduced by 56% in patients receiving adalimumab ($p=0.002$). Furthermore, a steroid sparing effect with regards to topical CS has been convincingly demonstrated with a higher proportion of subjects in the adalimumab group compared to placebo being able to discontinue CS use (47% versus 16%, $p=0.018$). More patients achieved disease remissions (no AC cells without CS treatment) under adalimumab (23.3%) compared to placebo (0) by month 6 ($p=0.0004$). Altogether, these data support a clinically relevant benefit with Humira in combination with MTX in the treatment of paediatric patients with chronic JIAU refractory to topical CS and MTX monotherapy.

The study subjects with JIAU were furthermore considered sufficiently representative for patients with other forms of paediatric anterior uveitis irrespective of the presence or absence of associated systemic (arthritic) conditions. However, the available data were considered insufficient to support a broad indication for refractory paediatric uveitis including other anatomical locations as well as multiple diverse aetiologies. This was in view of the limitedness of the data and uncertainties to what extent the clinical course, disease severity and treatment response are similar in adult uveitides involving the intermediate and posterior segment and the paediatric population.

The most notable safety findings in SYCAMORE were related to infections which occurred in 76.7% of the patients treated with adalimumab + MTX including serious infections reported by 13.3% of the patients. Overall, the safety profile was in line with the one previously observed in other paediatric indications and adult uveitis patients and there were no new or unexpected AEs observed. Safety data from children with JIA (but also other paediatric indications) were considered supportive and complemented the limited safety data in paediatric uveitis patients in particular below the age of 6 years. Other relevant important identified risks with the use of Humira include malignancies, demyelinating events and sarcoidosis, although not reported in the small number of paediatric uveitis patients in SYCAMORE.

### 3.7.2. Balance of benefits and risks

The clinical benefits of Humira in preventing treatment failures and reducing the need for CS use in paediatric uveitis patients were of clear clinical relevance. In a patient population at risk of severe vision loss, these benefits outweighed the risks of infections observed in 76.7% of the patients treated with adalimumab during the 18 month study period. Considering all favourable and unfavourable effects, the benefit-risk balance of Humira 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 is considered positive.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

### *3.8. Conclusions*

The overall benefit-risk balance of Humira is positive.

## 4. Recommendations

### *Outcome*

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

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of Indication to include a new indication for Humira 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; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet was updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement an alternative format statement for blind/partially sighted patients in the Package Leaflet. Furthermore, the MAH has made some editorial changes to the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP) (latest version 13.0).

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0200/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

### *Scope*

Extension of Indication to include a new indication for Humira 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; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet was updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement an alternative format statement for blind/partially sighted patients in the Package Leaflet. Furthermore, the MAH has made some editorial changes to the Package Leaflet.

## *Summary*

Please refer to the published Assessment Report Humira H-481-II-163.