Adalimumab

(HUMIRA®)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal (MTA)

Etanercept, abatacept, adalimumab and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35)

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abbvie

Appraisal technology: Adalimumab (HUMIRA®)

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DECLARATION

This submission does not omit any relevant evidence of which AbbVie is aware of and is not currently in the public domain, which could reasonably be considered to be related to the appraisal of adalimumab (HUMIRA®).

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FOREWARD

The aim of this multiple technology appraisal is to evaluate the clinical and cost-effectiveness of adalimumab, etanercept, abatacept, and tocilizumab within their licensed indications for the treatment of juvenile idiopathic arthritis (JIA).

NICE technology appraisal 35 recommends etanercept for the treatment of active polyarticular JIA (pJIA) in children aged 4 to 17 years whose condition has not responded adequately to methotrexate (MTX) or who have been unable to tolerate treatment with MTX. NICE has also recommended tocilizumab (technology appraisal guidance 238) for the treatment of children and young people with systemic JIA if their disease has not responded to NSAIDs, systemic corticosteroids and MTX.

In 2011, NICE posted the following statement on the use of adalimumab for patients with JIA following the scoping workshop and consultation with clinicians:

"*Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of adalimumab for the treatment of juvenile idiopathic arthritis is not appropriate.*

It is estimated that there are 9000 children age 4-17 with juvenile idiopathic arthritis. Of these, approximately 20% will have polyarticular type, and approximately 15% will have disease not adequately controlled by conventional DMARDs.

Etanercept is recommended as a treatment for juvenile idiopathic arthritis by NICE technology appraisal number 35 (static list) and would be the main comparator in an appraisal of adalimumab for this indication. Consultees at the scoping workshop indicated that the clinical effectiveness of adalimumab and etanercept is thought to be comparable in juvenile idiopathic arthritis, and both are available at the same price (approximately £360 per two weeks) to the NHS. Using adalimumab rather than etanercept, is in effect a substitution (similar product with similar cost and effect) with no major resource implications additional to those of etanercept.

Consultees indicated that adalimumab is currently being used without NICE guidance in children with juvenile idiopathic arthritis (age 13-17 years) and usage is expected to increase should the marketing authorisation be extended. The decision to use either etanercept or adalimumab is often based on parental choice, child preference and factors such as the frequency of the treatment.

Given the cost and benefit profile of adalimumab in comparison with etanercept and its existing usage on the NHS, it is not considered that a technology appraisal of adalimumab for juvenile idiopathic arthritis would provide value to the NHS."

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Executive Summary

Juvenile Idiopathic Arthritis (JIA):

JIA is the most common rheumatic disease of childhood and describes a group of conditions that involve joint inflammation which lasts for >6 weeks in people <16 years of age. JIA is an 'umbrella' term which covers a number of different sub-types including oligoarticular JIA, extended oligoarticular, poly-articular JIA (pJIA) (RF +ve or –ve), systemic onset JIA, psoriatic JIA, and enthesitis-related arthritis (ERA) that were proposed by the International League of Associations for Rheumatology (ILAR). JIA causes pain, swelling and limitation of movement and is characterised by relapsing and remitting episodes of inflammation of the synovial membrane of the joints (synovitis) which, unless treated, leads to damage and deformity of the affected joints and subsequent disability. In more severe cases, JIA can cause growth retardation, joint contractures, joint damage requiring joint replacements, and permanent disability. The disease is often associated with extra-articular manifestations (EAM) such as eye problems (uveitis), inflammatory bowel disease (IBD) and psoriasis.

Although there are similarities with adult forms of arthritis, JIA is not the same disease as rheumatoid arthritis or other forms of inflammatory arthritis, and should therefore be considered separately in both children and adults. One of the main differences between rheumatoid arthritis and JIA is the high proportion of EAMs – specifically, uveitis, in patients with JIA. The presence or absence of certain EAMs is an important component of JIA that affects the choice of treatment. Whilst the biologic treatments under review in this MTA have similar effects on the arthritic component of the disease, they have very different effects on the symptoms of uveitis, psoriasis or IBD related to JIA.

JIA can impair personal and social functioning and development. Children often miss out on schooling and other childhood activities, and as adults they may be limited in their ability to work. JIA may also have a considerable impact on the family of the child, including parents and carers who may need to miss work to take children to appointments. Central nervous system involvement is rare in JIA, but depressive and anxiety disorders are common and are attributed to social isolation, chronic pain, and deformity. Chronically ill young adults with a wide variety of disorders, when compared to their cohort in the general population, have lesser academic and employment achievement, less vocational education and less permanent employment, are more likely to be single and have delayed independence. It is therefore important that treatment of JIA, whilst controlling signs and symptoms of the disease, also focuses on improving social development of the child and adolescent with JIA.

The impact of JIA is not just limited to impairment of physical function associated with joint damage, but also extends to problems with growth as well – including asymmetric growth and low bone density. Before implementation of modern treatment paradigms, long term administration of systemic corticosteroids was often required for children and adolescents with JIA, but was a major cause of impaired growth. Thus, children and adolescents with these conditions are at high risk for growth failure, both from their underlying disease and from glucocorticoid therapy. Anti-TNFs have been shown to attenuate growth retardation in JIA patients, probably through a twofold mechanism of enabling steroids to be tapered or withdrawn and also by affecting the pro-inflammatory cytokine pathway related to JIA.

Aim of treatment:

Drug therapy in JIA patients aims to induce and maintain remission of both arthritic and non-arthritic symptoms, allowing a child to achieve normal growth, development, and achieve full participation in school, career, sport and all other aspects of a 'normal' life.

Adalimumab licence:

Adalimumab in combination with methotrexate is indicated for the treatment of active pJIA, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate (MTX) or when continued treatment with methotrexate is inappropriate. Additionally, adalimumab is indicated for the treatment of active ERA in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Clinical effectiveness of adalimumab – arthritic outcomes:

The adalimumab pJIA RCT trial programme was performed chronologically such that the first randomised controlled trial (RCT) – DE038, which evaluated adalimumab in pJIA patients aged 4-17, formed the basis of the original marketing authorisation (MA) granted by EMA in 2008. The original MA for adalimumab was for JIA patients aged 13-17, and was restricted to this age group initially because there was a lack of appropriate presentation to allow adequate dosing in children <13 years of age. In a type II variation approved by EMA in 2011, and based on data from DE038, it was agreed that dosing by body surface area from a paediatric single-use vial sufficed for children aged 4-12. The MA for pJIA was therefore amended at this point to include patients aged from 4-17. Subsequently, a trial in pJIA patients 2-4 years, M10-444, resulted in a licence extension to include this age group, which was approved by EMA in 2013. Additionally, a Type Ib variation removed the upper age bound of 17, thereby acknowledging that the disease persists into adulthood. Finally, in September 2014, EMA approved adalimumab for the treatment of ERA in patients 6 years of age and older, based on data from study M11-328.

- Results from the end of the open-label lead in phase (Week 16) in DE-038 showed that 94%, 91%, 71% and 28% patients in the adalimumab + MTX arm and 74%, 64%, 46%, and 26% patients in the adalimumab only arm were PedACR30, 50, 70 and 90 responders, respectively. At the end of the double blind phase (Week 48), statistically significantly more patients in the placebo arm experienced disease flare compared to either the adalimumab + MTX arm or the adalimumab only arm. Furthermore, greater proportions of adalimumab-treated patients achieved a PedACR30/50/70 response compared to placebo-treated patients at the end of the double-blind phase.

- Data from M10-240 in Japanese pJIA patients confirmed similar results to DE-038.

- In M10-444, the study in children aged 2-4, the primary outcome measures were safety indicators. Nevertheless, a PedACR30/50 response was achieved by at least 80% of patients from Week 12 through to Week 108. The percentage of patients with PediACR30 responses at weeks 12, 24, 60, and 96 were 94%, 90%, 90%, and 92%, respectively.

- Finally, in M11-328, the trial investigating adalimumab in ERA patients aged 6 and older showed statistically significant larger decrease in mean percent change from baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) was observed in patients in the adalimumab group (–62.6) compared with the placebo group (–11.6, $p = 0.039$).

- Safety data from across the RCTs show that adalimumab was generally well tolerated.

In addition to the RCT data, AbbVie has included data from a multicentre, non-interventional, observational, ongoing registry of patients diagnosed with moderately to severely active pJIA – STRIVE, which aims to evaluate the long-term safety and effectiveness of adalimumab in patients with moderately to severely active pJIA who are prescribed and treated with adalimumab in routine clinical practice.

Clinical effectiveness of adalimumab – non-arthritic outcomes:

Due to the ethical restraints in the design of paediatric trials there is a limit in the ability to collect data for certain outcomes and sub-groups. As result, the adalimumab JIA RCT programme did not collect data for non-arthritic outcomes in patients with JIA such as JIA-U and growth.

There is an increasing amount of evidence relating to the use of adalimumab and the other anti-TNFs in the treatment of childhood chronic uveitis. Results from a systematic review of the literature in JIA-U conducted between 2000 and October 2012, showed that although RCTs are needed, the available evidence suggests that infliximab and adalimumab provide proven similar benefits in the treatment of childhood autoimmune chronic uveitis and they are both superior to etanercept. An iterative review of the literature from October 2012 onwards revealed an additional n=260 JIA-U patients who received adalimumab in either case series or prospective open-label studies, all showing that adalimumab appears to be an effective and safe treatment for uveitis associated with JIA. Finally there is an ongoing RCT funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK, the Sycamore trial (ISRCTN 10065623), evaluating the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with MTX for the treatment of JIA-U.

Observational data indicate that anti-TNF treatment is associated with growth velocity improvements in JIA patients with marked growth retardation. A post hoc analysis of DE-038 examining the impact of adalimumab on growth showed that long-term adalimumab treatment was associated with improvement and maintenance of growth in children with JIA who were within the lowest height percentiles at baseline.

Challenges in conducting an economic evaluation of the biologics in JIA:

There are a number of challenges associated with conducting an economic evaluation of etanercept, abatacept, adalimumab and tocilizumab for treating JIA.

Firstly, AbbVie considers that there are difficulties in conducting an indirect comparison in this disease area. This is primarily because the ethical constraints applied to paediatric trial design mean that there are no true common comparator arms to generate the ‘reference’ treatment arm needed to calculate the relative effectiveness of the biologics under review. All the RCTs for the biologics in this MTA included an open-label lead in phase where all patients received open-label therapy. Patients with a PedACR30 response at the end of the open-label lead in phase were then randomised in a double-blind manner to receive placebo or continue biologic treatment until the end of the double-blind treatment period or until flare, whichever event occurred first. As a result, the length of the double-blind period has an impact on the probability of achieving the primary outcome measure (time to flare). Unfortunately, because shorter trial duration means that there is a smaller chance of reaching the time-dependent outcome (disease flare); shorter treatment duration may result in better outcomes. It is therefore plausible that any differences in efficacy between biologic agents generated from a network meta-analysis (NMA) do not reflect actual differences between treatments, but instead could be due to differences in the pharmacodynamics of the different drugs, patient characteristics and the time frame of assessment. A robust NMA in

JIA is also challenged by the considerable heterogeneity of trial subjects, small sample size of the RCTS, and differences in the calculation of PedACR responders across the RCTs.

Secondly, JIA is not exclusively a disease of childhood with 50% of JIA patients continuing to have intermittent or active disease into adulthood. Nor is JIA the same disease as rheumatoid arthritis or other forms of inflammatory arthritis. As such, assumptions regarding disease progression and outcomes for JIA, based on information for rheumatoid arthritis studies, should be done with caution. Additionally, as a disease that starts in childhood and continues into adulthood, many patients with JIA transition to adult rheumatology services at some point. This transitioning may pose difficulties for both the NHS not only in terms of the administrative burden and costs, but also to patients who may not receive the same services in adult rheumatology clinics as in paediatric rheumatology clinics.

Thirdly, as a result of joint contractures, joint disease requiring joint replacements and uveitis associated complications, the rate and cost of surgery and follow up care, including revision surgery and complications such as visual impairment and blindness, need to be incorporated into an economic evaluation. Another direct cost that factors in the economic evaluation is the acquisition costs of the different biologics, which will be dependent upon patient weight or body surface area (BSA). Data on the weight distribution of JIA patients in England and Wales are difficult to obtain and the information from the adalimumab RCTs may not be generalisable to the UK. Additionally, the weight and height of the JIA patients will increase with age, and as result so will the cost.

Whilst AbbVie recognises that NICE's reference case uses an NHS perspective to account for costs and benefits, it is important to note that societal costs in JIA may be considerable, from both a parent and patient perspective. For example, for a JIA patient the data indicate there may be potential loss of income as a result of not achieving education potential; in addition, not surprisingly due to the disabling nature of the disease if not treated appropriately, people with JIA over 16 may be eligible for Disability Living Allowance, Incapacity Benefit, and Income Support. These potential societal costs are further compounded by parental loss of productivity and income because of time taken from work to take care of an affected child. As a result, AbbVie considers that societal costs need to be considered as part of an overall value judgement when appraising the biologics in this MTA.

Finally, given the lack of directly collected health related quality of life (HRQoL) data from the RCTs to calculate utilities, and a lack of utility data in this disease area, any mapping algorithm to estimate utilities in JIA and the inability to capture all the HRQoL benefits in such mapping algorithms pose some difficulties. There are also challenges around the best methodology for extrapolating costs and benefits over a lifetime horizon for both biologics and conventional DMARDs. Challenges around estimating disease progression whilst on biologics vs. DMARDs, and extrapolation of any data to a lifetime horizon are more pronounced in JIA because there is a lack of a data to support some of the long-term assumptions.

Due to above mentioned factors and challenges; AbbVie has not conducted a cost-effectiveness analysis of etanercept, abatacept, adalimumab and tocilizumab for treating JIA.

Section 1: Background and Context

1.1 Juvenile idiopathic arthritis

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood and describes a group of conditions that involve joint inflammation which lasts for more than 6 weeks in people under 16 years of age. JIA causes pain, swelling and limitation of movement, which can change from day to day. It is characterised by relapsing and remitting episodes of inflammation of the synovial membrane of the joints (synovitis) which, unless treated, leads to damage and deformity of the affected joints and subsequent disability. When the condition becomes more active and the symptoms worsen, this is known as a 'flare'. In more severe cases, JIA can cause growth retardation, joint contractures, joint damage requiring joint replacements, and permanent disability, and the disease can be associated with eye problems (uveitis) and other extra-articular manifestations (EAMs) (such as inflammatory bowel disease (IBD) and psoriasis).

JIA can impair personal and social functioning and development. Children often miss out on schooling and other childhood activities, and as adults they may be limited in their ability to work. JIA may also have a considerable impact on the family of the child, including parents and carers who may need to miss work to take children to appointments.

JIA has an annual incidence of 1:10,000 children and an overall prevalence in childhood of 1:1000. The term Juvenile refers to the *age at onset* - historical data suggest that around half of children with JIA continue to have active arthritis as adults.[1]

The NHS interim clinical commissioning policy statement for biologic therapies for the treatment of JIA estimates that there are 12,000,000 children <18yrs in England and Wales.[2] At any one time there are >12,000 children with JIA, and it is estimated that half of these will go on to have arthritis in adulthood. Furthermore, it is estimated that 1 in 3 will not have arthritis in adulthood but will have sustained permanent damage to one or more joints affecting physical function and health-related quality of life into adulthood.[2]

JIA is not the same disease as rheumatoid arthritis or other forms of inflammatory arthritis and, although there are similarities with adult forms of arthritis, JIA should be considered separately in both children and adults. JIA is an 'umbrella' term which covers a number of different sub-types listed below that were proposed by the International League of Associations for Rheumatology (ILAR) in 1995 for the classification of JIA:

- Oligoarticular JIA - Oligoarthritis is the most common type of JIA, accounting for up to 50% of new diagnoses in Europe each year. It is diagnosed when four or fewer joints are affected in the first 6 months of disease.

- Extended Oligoarticular JIA - If oligoarthritis progresses and affects more than four joints during the first 6 months, it is called extended oligoarthritis.

- Poly-Articular JIA (RF –ve or RF +ve) - Polyarticular JIA is diagnosed when five or more joints are affected at presentation, and can be further divided into rheumatoid factor positive arthritis and rheumatoid factor negative disease.

- Systemic-Onset JIA - Systemic JIA accounts for 5-10% of new diagnoses and is diagnosed when arthritis is part of a general illness involving features such as fever, lymphadenopathy, hepatosplenomegaly and serositis.

- Psoriatic JIA - Psoriatic arthritis accounts for 2-15% of new diagnoses and is diagnosed when there is joint swelling associated with psoriasis, or a family history of psoriasis.

- Enthesitis-Related Arthritis (ERA) - ERA accounts for 2-10% of new diagnoses and is diagnosed in the presence of arthritis or inflammation of tendon attachments to the bones (entheses), in association with two or more other features of spondyloarthropathy.

In JIA, the term 'polyarthritis' can refer to either the ILAR subtype of JIA at diagnosis for classification purposes (i.e. referring to the ONSET of pJIA), or the number of joints affected at a specific time point (polyarticular COURSE JIA). Around 40% of people with JIA have polyarthritis, and polyarticular onset disease accounts for 25% of new diagnoses. For example, a patient may be diagnosed as having psoriatic arthritis according to the ILAR classification at diagnosis, but may go on to have ≥5 active joints two years later – which means they will also have polyarticular course JIA (see Figure 1).

Pharmacological treatment of JIA is dependent upon the number and type of joints involved, as well as the presence of any extra-articular manifestations. The most common extra-articular complication of JIA is inflammation of the eye (uveitis). Uveitis may predate the onset of arthritis and can be severe even if the degree of arthritis is of a milder course. Unless treated properly, uveitis can rapidly cause irreversible damage to the eye leading to permanent blindness (see Section 1.2.1).

1.2 EAMs of JIA – with specific focus on uveitis

As stated in Section 1.1, JIA is distinctly different from rheumatoid arthritis, and one of the main differences is the high proportion of extra-articular manifestations (EAMs) – specifically, uveitis, in patients with JIA. In fact the presence or absence of certain EAMs is an important component of JIA that affects the choice of treatment. Whilst the biologic treatments under review in this MTA have similar effects on the arthritic component of the disease, they have very different effects on the symptoms of uveitis, psoriasis or IBD related to JIA. For example, the interim commissioning policy statement from NHS England looking at anti-TNF agents for the treatment of refractory uveitis states that "*etanercept is known to cause uveitis and the onset of uveitis in a child on etanercept for the treatment of JIA is an indication to switch to an alternative agent*." Whereas, it states "*In addition to their effect on arthritis, adalimumab and infliximab are highly effective in the treatment of uveitis in JIA and clinically similar childhood uveitis not associated with JIA*."[3] The data for the differential effectiveness of the biologics in this review on EAMs is discussed in detail in Section 4. Whilst psoriasis and IBD are important EAMs associated with JIA, the most common and the most worrying EAM according to clinical experts in the UK is uveitis – discussed in detail in Section 1.2.1 below.

1.2.1 Association of childhood uveitis with JIA

An estimated 0.5% of childhood blindness in England and Wales is caused by uveitis. JIA-related uveitis (JIA-U) remains one of the main causes of visual impairment in children: 20-25% of all childhood uveitis is associated with JIA and 12-38% of patients with JIA will develop uveitis within 7 years following the onset of arthritis.[3] This represents approximately 100 new presentations per annum. JIA-U occurs predominantly in patients with early onset of arthritis, with a mean age in the onset of arthritis in children with JIA-U of between 3-5 years, most commonly in oligoarticular JIA. Uveitis may be a presenting feature of JIA in 3-7% of patients and, in 50%, develops simultaneously or within 6 months of the onset of arthritis. The incidence of bilateral eye disease in JIA is between 67-85%.

Asymptomatic chronic anterior uveitis (CAU) is associated with high levels of complications compared to acute anterior uveitis. JIA-U does not usually manifest with symptoms of red, painful eyes, and unless screening examinations are performed, the presentation of ocular disease is usually delayed until impaired vision due to complications of chronic intraocular inflammation (such as cataract and glaucoma) is obvious. At this stage, it is often not possible to restore normal vision despite treatment. Young children are most at risk of delayed presentation as they are unable to articulate low grade symptoms of photophobia and floaters. In such small children, because the symptoms of arthritis are usually more obvious than the symptoms of uveitis, there may be advanced ocular disease at the time of presentation with joint swelling or impaired mobility, such that in 30-50% of children with JIA associated uveitis structural complications are present at diagnosis and 50-75% of those with severe uveitis will develop visual impairment secondary to the ocular complications detailed above.

Because of the association with asymptomatic uveitis, children with JIA undergo regular screening eye examinations.[3] Before the advent of uveitis screening for patients with JIA, and modern forms of treatment, rates of blindness in childhood uveitis were up to 30%. Despite this, the risk of irreparable visual impairment remains high for such children.

Permanent visual impairment in children with uveitis is associated with, at first presentation: poor vision (<6/18); high inflammatory activity; uveitis onset before diagnosis of arthritis; <6 month interval between onset of arthritis and onset of uveitis; early onset of disease; long duration of uveitis; macular oedema; dense vitreous opacity; ocular hypotony (low intraocular pressure), and glaucoma. The presence of prolonged inflammation following diagnosis, even at a low level (>0.5+) is associated with an increased risk of vision.[3]

Children who present with JIA-U are treated with topical, or in rare cases periocular steroid injection, followed by systemic corticosteroids. However, the use of topical, periocular and systemic steroids is complicated by ocular side effects such as cataract and glaucoma, and systemic side effects such as growth retardation, weight gain, hypertension and diabetes.[3]

Children in whom disease remission is not induced by treatment with topical or systemic steroids, or who require prolonged treatment with high dose steroid in order to maintain remission, then proceed to treatment with a second line agent because of the concerns about the side effects of prolonged high dose steroid treatment. The standard second line agent, for both JIA-associated uveitis and uveitis, is MTX.[3]

Children in whom disease remission is not induced by treatment with a combination of steroids and MTX, or who are unable to tolerate these agents because of side effects, are then considered for treatment with other agents – including biologics such as anti-TNF therapy.[3]

1.3 Impact of JIA on growth, schooling and social development

1.3.1 Growth

Physical growth is a dynamic process that starts at conception and ends after full pubertal development. Chronic illness may lead to growth retardation, either because of the illness itself, or because of treatments required for it (e.g. steroids). Furthermore, short stature is commonly perceived to be associated with social and psychological disadvantage. Parents often attribute behavioural disorders, anxiety, depression, social and attentional problems to short stature, and are concerned that their children are subjected to height related stressors of being teased or infantilised.[4] However, it is difficult to determine if problems in

psychosocial functioning are due to the underlying illness, treatment, or the resultant effects such as impaired growth.

Long term administration of systemic corticosteroids (e.g. dexamethasone, prednisone) is a major cause of impaired growth but is often required for children and adolescents with a range of chronic inflammatory, autoimmune, and neoplastic diseases. Steroids are often used to treat IBD, systemic lupus erythematosus, and JIA. Children and adolescents with these conditions are at high risk for growth failure, both from their underlying disease and from glucocorticoid therapy.

In children with severe rheumatic disorders, treatment with glucocorticoids is frequently needed and is associated with growth retardation and osteopenia.[5] Growth hormone treatment may improve growth and lean body mass, but these benefits disappear when growth hormone therapy is stopped. Chronic inflammation and prednisone therapy may adversely affect growth, and final height may be closely dependent on both severity of growth retardation during the active phase of the disease and on linear growth after remission.[6] After remission of active disease and discontinuation of prednisone treatment, 70% of children will show catch-up growth, but 30% will still show persistent loss of height.[7]

Therefore, because patients with JIA experience onset of symptoms during childhood which continue in to adolescence, the impact of the inflammatory condition is not just limited to impairment of physical function associated with joint damage, but also extends to problems with growth as well – including asymmetric growth and low bone density. Anti-TNFs have been shown to attenuate growth retardation in JIA patients, probably through a twofold mechanism of enabling steroids to be tapered or withdrawn and also by affecting the pro-inflammatory cytokine pathway related to JIA. Data relating to the effects of anti-TNFs on growth are discussed in Section 4 – Clinical Interpretation.

1.3.2 Social development

Normative developmental tasks throughout childhood center on developing a sense of self and acquiring autonomy in all areas of life. However, chronically ill young adults with a wide variety of disorders, when compared to their cohort in the general population, have lesser academic and employment achievement, less vocational education and less permanent employment, are more likely to be single and have delayed independence.[8,9]

Central nervous system involvement is rare in JIA, but depressive and anxiety disorders are common and are attributed to social isolation, chronic pain, and deformity. In adults with long standing JIA, who on average had 28 years of illness, 31.6% were anxious, 5.2% were depressed, and 21.1% had previously suffered from depression.[10] Both physical and psychological factors influence pain, and psychological variables explain the majority of variance in depression and anxiety in adults with JIA.

It is important that treatment of JIA, whilst controlling signs and symptoms of the disease, also focuses on returning the sense of independence and 'normality' to children/adolescents who might otherwise feel isolated and unable to get involved in school activities e.g. sport/drama due to either the physical incapacity caused by JIA or time spent off school due to illness or hospital appointments.

1.4 Aim of treatment in JIA

The aim of drug therapy in JIA patients is to induce and maintain remission of symptoms, and thus allow a child to achieve normal growth, development, and allow full participation in school, career, sport and all other aspects of normal life.[2] The initial aim

is induction of complete disease remission using corticosteroids – either intravenously (IV) or intra-articular. Oral corticosteroids are avoided where possible to avoid side effects (can affect growth or increase risk of osteoporosis) but may be needed for short time periods.

In patients with mild disease limited to <5 joints it may be possible to induce remission which lasts for >6 months with intra-articular steroids, particularly if using long-acting corticosteroids. Patients with more severe disease may need IV steroids to induce remission, although intra-articular steroids are used in some patients as an alternative.[2]

The NHS interim commissioning policy in JIA states that to maintain remission, those patients whose arthritis affects a cumulative total of 5 or more joints, or severely affecting crucial joints such as the spine, ankles, hips, and wrists, should initially be treated with MTX. This accounts for around half of all children who develop JIA – i.e. around 6000 children in the UK at any one time. Whilst effective in reducing the amount and severity of arthritis, MTX only induces complete remission in 30-50% of patients. Those with JIA arthritis that remains active despite optimal dosing, or who are intolerant of MTX should then receive treatment with a biologic – the focus of this review.[2]

1.5 Licensed indication for adalimumab in JIA

Figure 1 below illustrates the different sub-types that fall under the umbrella term JIA. As discussed in Section 1.1, patients may be diagnosed under one of the four non-polyarticular sub-types at onset of symptoms (blue segments), but go on to develop 5 or more active joints >6 months since diagnosis and therefore have course pJIA – covered by the green segments in the Venn diagram in Figure 1.

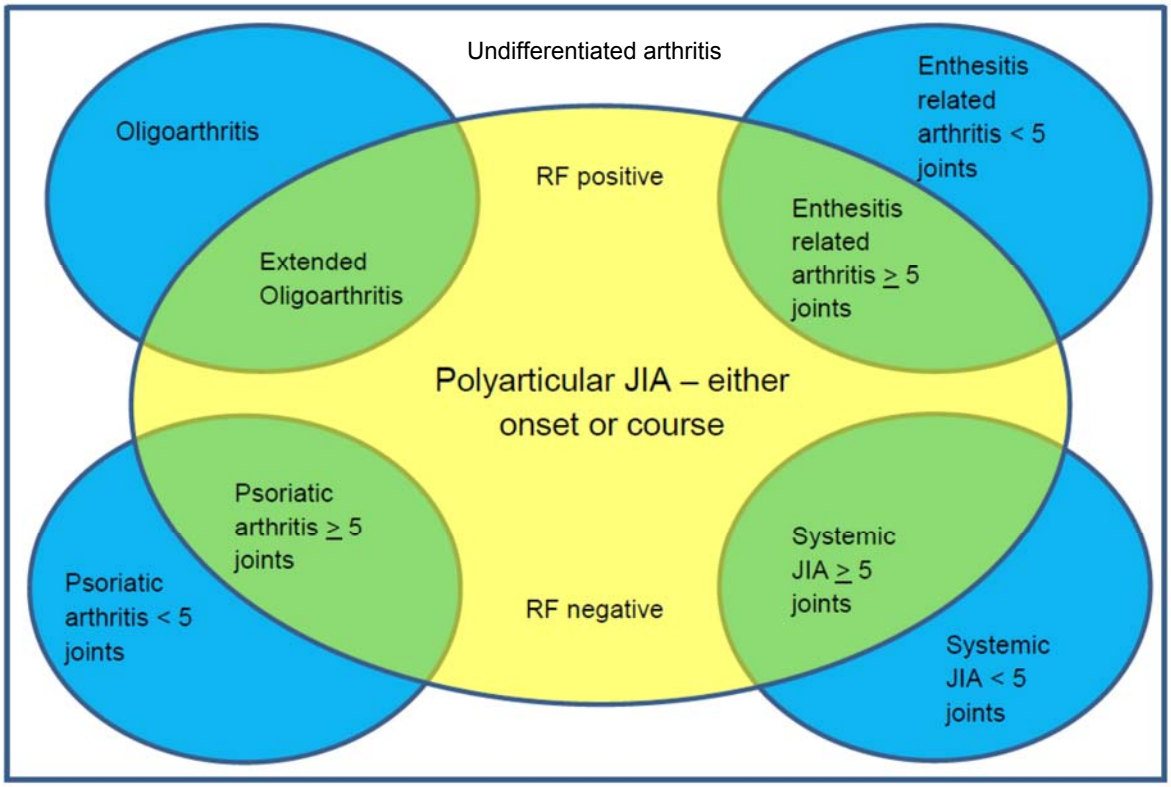

Figure 1: Classification of JIA based on the ILAR criteria

The EMA licence for adalimumab in JIA is as follows:

"Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years."

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

Based on the same Venn diagram used in Figure 1, the red and purple sections in Figure 2 below highlight which sub-types of JIA based on the ILAR classification criteria are covered by the adalimumab licence:

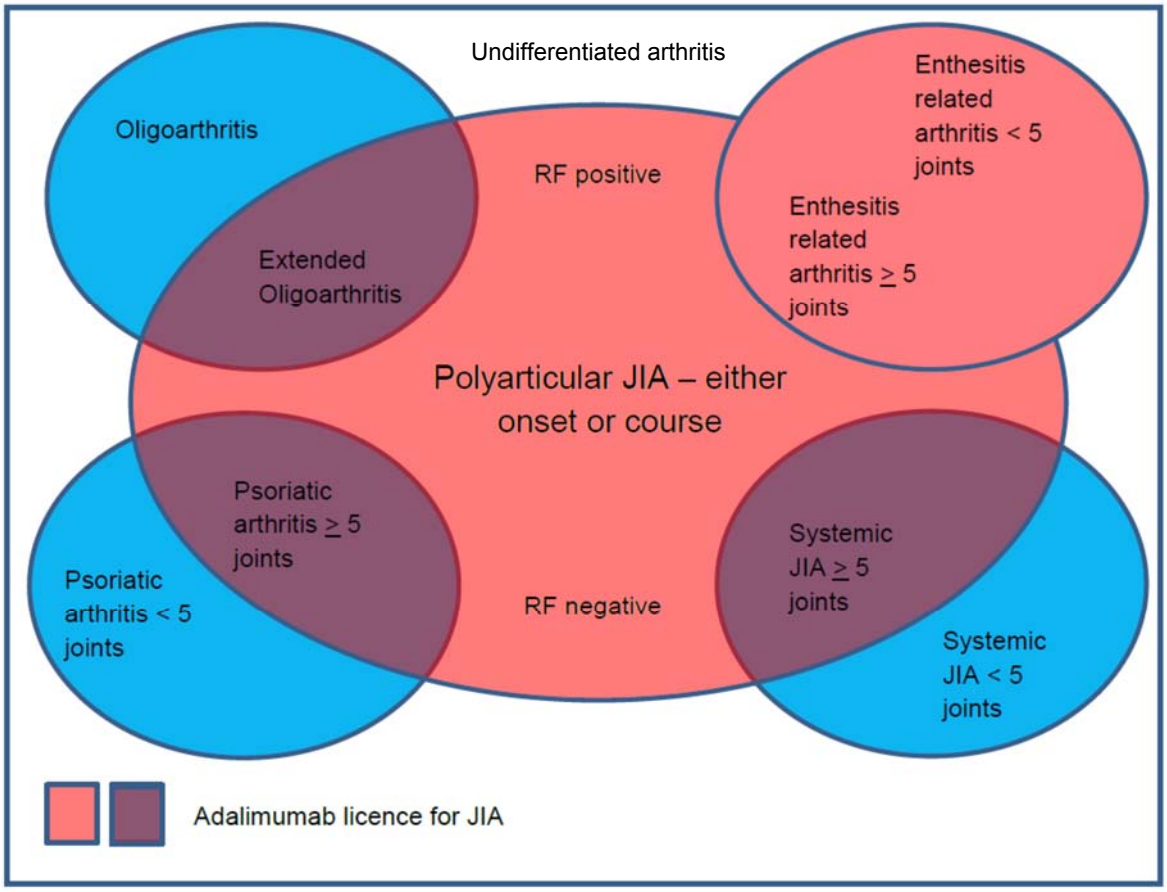

Figure 2: Sub-types of JIA covered by the licence for adalimumab

Section 2: Clinical Effectiveness

2.0 Overview of clinical evidence for adalimumab in pJIA

This section focuses specifically on the randomised controlled trials (RCTs) of adalimumab in patients with pJIA and ERA, and hopefully provides additional information for the AG, on top of that identified in the systematic literature review, that will help inform the economic model. AbbVie has not conducted a comprehensive systematic literature review, more an iterative literature review, but is confident that all RCTs of adalimumab in the treatment of JIA have been identified.

EMA guidelines for the development of medicinal products for the treatment of JIA indicate that extrapolation opportunities have to be performed to spare children from unnecessary trials where reasonably accurate information may be obtained by other means e.g. when a considerable amount of data have been collected in adults. But, extrapolation may result in a reduction in the amount of data required (size of trial, focus on subpopulations or certain ages only, exploratory/confirmatory design of the study) to ascertain efficacy.

Given the ethical constraints with regards to the design of RCTs in paediatric and adolescent populations, the adalimumab JIA clinical trial programme utilised a randomised placebo controlled withdrawal design, which limits the placebo controlled period and when used with early escape rules, such as return of symptoms (disease flare), the period of exposure with poor response that a patient would have to undergo remains short. Furthermore, to minimise exposure of children to ineffective treatments there is an open-label lead in phase such that any futility analysis is performed at the end of the lead-in open label phase of the randomised withdrawal trial, and if the pre-defined level of improvement is not met before randomisation the study should be discontinued.

The adalimumab pJIA RCT trial programme was performed chronologically such that the first RCT – DE038 (see Section 2.1), which evaluated adalimumab in pJIA patients aged 4-17, formed the basis of the original marketing authorisation (MA) granted by EMA in 2008. The original MA for adalimumab was for JIA patients aged 13-17, and was restricted to this age group initially because there was a lack of appropriate presentation to allow adequate dosing in children below 13 years of age. In a type II variation approved by EMA in 2011, and based on data from DE-038, it was agreed that dosing by BSA from a paediatric single-use vial sufficed for children aged 4-12. The MA for pJIA was therefore amended at this point to include patients aged from 4-17.

A subsequent trial in pJIA patients aged 2-4, M10-444 (see Section 2.2), resulted in a licence extension to include this age group, which was approved by EMA in 2013. In addition, a Type Ib variation was approved to remove the upper age bound of 17, thereby acknowledging that the disease persists into adulthood. In June 2012, AbbVie notified EMA of results from M10-240 (see Section 2.3), a study performed in Japanese paediatric subjects between the ages of 4 and 17 years with active pJIA. The open label study was designed to evaluate the efficacy and safety of subcutaneous (SC) adalimumab and to confirm the similarity between the data obtained from this study and those from study DE-038 conducted in Western subjects with JIA. It was concluded by EMA that the results of the study demonstrate that adalimumab treatment was generally safe and well tolerated, and that they do not influence the benefit risk ratio for adalimumab.

Finally, in September 2014, EMA approved adalimumab for the treatment of ERA in patients 6 years of age and older, based on data from study M11-328 (see Section 2.4).

In addition to the RCTs detailed in Sections 2.1-2.4, AbbVie has included data from an ongoing registry funded by AbbVie – STRIVE, which aims to evaluate the long-term safety and effectiveness of adalimumab in patients with moderately to severely active pJIA who are prescribed and treated with adalimumab in routine clinical practice. This is an ongoing, multicentre, non-interventional, observational registry of patients diagnosed with moderately to severely active pJIA that are prescribed and treated in a routine clinical setting with either adalimumab ± MTX or MTX alone.

AbbVie is aware that there are other registries, e.g. BCRD in the UK, the Dutch registry, and the BIKER registry in Germany which were set up primarily to evaluate the safety of the biologics in routine clinical practice, but which also have some efficacy outcomes. AbbVie expects that the AG will identify any relevant papers in their systematic literature review.

2.1 Study DE038 – pJIA aged 4-17[11,12]

2.1.1 Protocol identification: NCT00048542

The primary objectives of this study were to evaluate the long-term efficacy, safety, and pharmacokinetics of adalimumab treatment for up to 6 years in pJIA patients. The study included four phases, a stratified open label lead in (OL LI) phase, a double-blind (DB) withdrawal phase, and an open-label extension (OLE) phase. This design was chosen so that all patients who were enrolled in the trial received active treatment. This design was considered more ethical in a paediatric population and was agreed with the FDA.

2.1.2 Study design and methods

The study design and methods are presented in Figure 3 and Table 1.

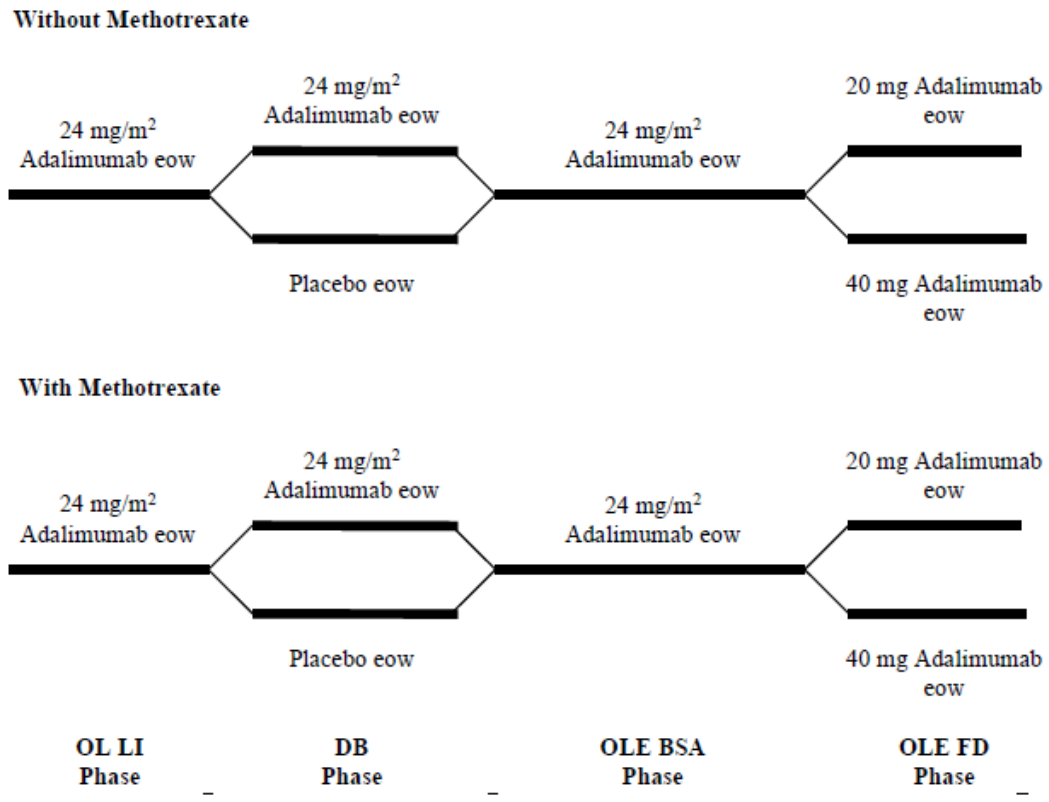

Figure 3: Study design schematic[13]

OL LI = open-label lead in (16 weeks); DB = double-blind (32 weeks); OLE BSA = open-label extension body surface area (136 weeks); OLE FD = open-label extension fixed dose (224 weeks). Total maximum duration = 408 weeks.

Table 1. DE038 study design and methods[11,12]

Item	DE038
Design	RCT; double-blind, stratified, placebo-controlled, multicenter, medication-withdrawal study with a 16-week OL LI phase, a 32-week DB withdrawal phase, and an OLE phase.
Number of participants	171
Countries and setting	United States, Belgium, Czech Republic, France, Germany, Italy, Slovakia, Spain; 31 sites.
Objectives	Primary objectives: Efficacy • To determine and compare disease flare in polyarticular-JIA patients treated with adalimumab ± MTX compared to placebo ± MTX treated patients. Safety • To contrast the safety profile of adalimumab with placebo in non-MTX-treated patients with pJIA. • To contrast the safety profile of adalimumab with placebo in concomitant MTX-treated patients with pJIA. • To evaluate the long-term safety profile of repeated SC administration of adalimumab in paediatric patients with JIA. Pharmacokinetic • To estimate adalimumab population pharmacokinetic parameters in paediatric patients (at least 4 years old) with pJIA. Secondary objectives: Efficacy • To determine and compare time to onset of flare in non-MTX/adalimumab-treated pJIA patients to non-MTX/placebo-treated pJIA patients. • To determine and compare disease flare in MTX/adalimumab-treated pJIA patients to MTX/placebo-treated pJIA patients. • To determine continued clinical benefit at the 30%, 50%, 70% and 90% improvement response in the Paediatric American College of Rheumatology (PedACR) scores after repeated SC administration of adalimumab. • To compare the efficacy of fixed dose (FD) adalimumab every other week (eow) based on body weight to variable eow dosing based on body surface-area (BSA) of patients rolled over into the OLE FD phase of the trial. Pharmacokinetic • To characterise adalimumab pharmacokinetics and identify important patient characteristics that will explain pharmacokinetic variability in paediatric patients with pJIA. • To compare adalimumab pharmacokinetics in children with JIA to adult RA patients. • To compare the pharmacokinetics of FD eow based on body weight to variable eow dosing based on BSA of patients rolled-over into the OLE FD phase of the trial whose pharmacokinetic samples were drawn.
Inclusion criteria	• 4 to 17 years of age • Diagnosis of pJIA according to the American College of Rheumatology (ACR) criteria (with any type of onset). If the disease was systemic onset, then the patients were to be free of any systemic JIA manifestations for at least 3 months before the time of qualification. • At the time of study screening, patients were to have had continuing active disease defined as 5 swollen joints and 3 joints with LOM. These joints were not mutually exclusive. • Patients were either naïve to MTX, inadequate responders to MTX, or intolerant of MTX. Intolerance to MTX was defined by the patient's physician. MTX administration was to have been maintained for a minimum of 3 months prior to Screening at a dose of at least 10 mg/m^2 BSA/week in all patients with a BSA ≤1 m^2 and at least 10 mg/week in those with a BSA > 1 m^2.

	• Duration of disease was not limited, but was to have been long enough for a patient to have been given an adequate trial of NSAIDs. • Patients were not to have received other DMARDs including penicillamine, hydroxychloroquine, sulfasalazine, oral or injectable gold, cyclosporine; or IV immunoglobulin (IV Ig); or cytotoxic agents, for at least 4 weeks prior to receiving the first dose of study drug. Patients currently on one or more of these DMARDs were to have demonstrated active disease (defined above) prior to a minimum 4 weeks (28 days) washout of all DMARDs. • Patients who were refractory to MTX after 3 months of treatment were to have demonstrated active disease (defined above) prior to enrollment in the OL LI phase. • Patients were not to have received an intra-articular glucocorticoid injection within 4 weeks (28 days) prior to enrollment into the study. • Patients were to have had good venous access and stable haematocrit ≥24%. • All sexually active study participants were required to use contraception, and serum pregnancy tests were performed before dosing and during the trial in all girls of reproductive potential. • Parent or legal guardian was to have voluntarily signed and dated an informed consent form. Paediatric patients were to be included in all discussions in order to obtain verbal or written assent. • Parent or legal guardian was to have been willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the patient's diary.
Exclusion criteria	The following criteria excluded patients from this study:- • Pregnant or nursing female • Functional class IV by ACR criteria • Clinically significant deviations in haematologic, hepatic, or renal indicators • Patients who had known positive human immunodeficiency virus (HIV) status. • Patients who had positive serology results for hepatitis B surface antigen or hepatitis C antibody. • Patients who had previous treatment with anti-TNF, anti-CD4, DAB-IL-2, IL1ra, or other investigative biological agent. • Patients who had been administered a live or attenuated vaccine within 3 months prior to study drug administration. • Patients who had joint surgery within 2 months prior to the Screening evaluation. • Ongoing chronic or active infection or had recently had a major infection requiring hospitalisation or IV antibiotics within 30 days or oral antibiotics within 14 days prior to the Screening evaluation.. • Patients who had intra-articular, intramuscular or IV administration of corticosteroids within 4 weeks prior to enrollment. • Patients who had treatment with any other investigational agent within 30 days or 5 half-lives of the agent, whichever was longer, prior to the Screening evaluation. • Patients who had a history of a central nervous system (CNS) neoplasm, active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease. • Patients who had poorly controlled diabetes. • Patients who had a history of active tuberculosis (TB) or listeria infection. • Patients who had a history of malignancy with the exception of successfully treated non-metastatic basal cell carcinoma of the skin. • Patients who had any concurrent medical condition that would, in the Investigator's opinion, compromise the patient's ability to tolerate study drug or would make the patient unable to cooperate with the protocol were excluded. • History of/or current psychiatric illness that would interfere with ability to comply with protocol requirements or give informed consent.

	• Recent history of alcohol or drug abuse within the past 6 months that would interfere with ability to comply with protocol requirements. • Inability to comply with the study requirements.

Outcomes (including definition and measurement details)	Primary effectiveness outcome:-
	• Percentage of patients not receiving MTX who had a disease flare during the DB phase of the study (weeks 16 to 48).
	• PedACR 30/50/70/90/100 defined as at least 30%, 50%, 70%, 90%, 100% improvement, respectively, from baseline in any 3 of the following 6 core criteria, and ≥ 30% worsening in not more than 1 of the criteria. The criteria are
	  o physician's global assessment of disease activity
	  o patient's or the parent's global assessment of overall well-being (both measured with the use of a 100-mm visual-analogue scale, in which 0 represented no disease activity or an assessment of "very well" for overall well-being, and 100 represented the most disease activity or an assessment of "very poor" for overall well-being)
	  o the number of joints with active arthritis (defined as joints with swelling not caused by deformity or joints, in the absence of swelling, with limitation of passive motion accompanied by pain, tenderness, or both),
	  o the number of joints with limitation of passive motion
	  o physical function (measured by the Disability Index of the Childhood Health Assessment Questionnaire)
	  o laboratory assessment of inflammation (C-reactive protein concentrations (CRP))
	
	Primary safety outcome:-
	• Adverse events (evaluated based on physical examinations, laboratory results, and vital signs).
	• Serious Adverse Effects (SAEs) (measured as adverse effects above). SAE classified as:-
	  o Death of patient
	  o Life-threatening
	  o Hospitalisation
	  o Prolongation of Hospitalisation
	  o Congenital Anomaly
	  o Persistent or Significant Disability/Incapacity
	  o Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome
	  o Spontaneous Abortion
	  o Elective Abortion
	
	All patients who discontinued study medication were followed for adverse events for 70 days after their last dose.

Stratification	Patients underwent stratification into two groups according to MTX use (with-MTX and without-MTX).
Patient enrolment	19 September 2002 to 13 January 2005
Intervention	<u>Phase 1: Open Label Lead-In (OL LI)</u> Comparison of SC injection of 24 mg adalimumab per square meter of BSA eow either with or without concomitant MTX treatment for a maximum of 16 weeks. Patients stratified into two arms based on current MTX use. Arms were:- • adalimumab with MTX • adalimumab without MTX <u>Phase 2: Double-blind (DB)</u> SC injection of 24 mg adalimumab or placebo BSA eow with or without concomitantly MTX for 32 weeks. Total body dose of adalimumab was not to exceed 40 mg. Arms were:-

	• adalimumab with MTX • Placebo with MTX • adalimumab without MTX • Placebo without MTX Phase 3: Open Label Extension Body Surface Area (OLE BSA) Comparison of SC injection of 24 mg adalimumab per square meter of BSA eow either with or without concomitant MTX treatment for a minimum of 44 weeks (up to a maximum of 136 weeks). Arms were:- • adalimumab with MTX • adalimumab without MTX Phase 4: Open Label Extension Fixed Dose Comparison of adalimumab administered SC eow either with or without concomitant MTX treatment for up to 224. Arms were:- • adalimumab with MTX • adalimumab without MTX
Comparator	For the Double-blind phase only Placebo with MTX Placebo without MTX
Concomitant medication	Stable doses of NSAIDs, low dose of stable corticosteroids (10 mg/day of prednisone or prednisone-equivalent medication), or both were permitted. Prednisone or prednisone-equivalent dose was to remain unchanged for at least 30 days prior to enrollment. NSAID medications were to remain unchanged for at least 14 days prior to enrollment. Pain medications were allowed except during the 12 hours before a joint assessment was performed DMARDs, other than MTX, were to be discontinued 4 weeks before receiving the first dose of adalimumab. For patients enrolled within the MTX stratum, the dose of MTX was to be stable for at least 3 months prior to the Screening visit. For patients enrolled in the non-MTX stratum, prior MTX use was to have been discontinued as least 2 weeks prior to the Baseline visit. Intra-articular and soft-tissue corticosteroid injections were not permitted for 4 weeks prior to enrollment. No corticosteroid injections were permitted during the OL LI phase. One intra-articular and/or soft-tissue corticosteroid injection was permitted after the patient was randomised into the DB phase. However, the joint that was injected was considered non-evaluable for 3 months.
Sequence generation	At week 16, patients with an PedACR 30 response underwent randomisation at a 1:1 ratio within their respective strata to receive SC injections of either adalimumab or placebo eow in a 32-week, double-blind treatment phase. Abbott generated the randomisation schedule that determined patient treatment using the interactive voice response system (IVRS). A separate randomisation scheme was generated for each stratum.
Allocation concealment	The investigators, study coordinators, assessors, patients, and parents were unaware of the treatment assignment during the double-blind phase of the study.
Participant and outcome assessor blinding	Yes
Outcome assessor blinding to interventions	The investigator, study coordinator, blinded assessor, and patient remained blinded to each patient's treatment throughout the course of the DB study, although some patients entered the OLE phase without breaking the blind. The blind could be broken if, in the opinion of the Investigator, it was in the patient's best interest for the Investigator to know the study drug assignment. Abbott was to be notified before breaking the blind unless identification of study drug was

	required for emergency therapeutic measures. Abbott was to be notified within 24 hours of the blind being broken and the date and reason that the blind was broken was to have been recorded on the appropriate CRF.
Statistical analyses	Continuous variables were compared by means of analysis of covariance. Categorical data, including those used for the primary end-point analysis, were analysed with either the Pearson chi-square test or Fisher's exact test, as appropriate. All comparisons were two-sided at an alpha level of 0.05. The efficacy and safety analyses were performed in an intent-to-treat (ITT) population. An ITT population was defined as all patients who received at least one dose of the study drug during the phase of the study for which the analysis was being conducted. The safety analyses included all patients who received the study drug during the designated study phase. Pre-specified analyses for the blinded phase and other analyses, such as that for PedACR100, for the extension phase were reported.
Power calculation	Based on 80% power, two-sided test, and an initial monotherapy responder rate of 70%, a minimum of 29 patients were needed per treatment group within the appropriate strata. However, in order to achieve a sample of 29 patients within each treatment group within each stratum, it was anticipated that about 42 patients may need to be enrolled initially for each treatment group within each stratum assuming that there was an initial 70% responder rate. Consequently, it was planned that 168 patients would be enrolled in the OL LI phase of the study. Sample size calculation was not applicable to the OLE phases of the study as these phases were introduced to follow the patients for a longer period of time.
Missing data	For the primary efficacy end point and for all secondary analyses of disease flare, missing values were treated as disease flares. For secondary analyses of PedACR 30, 50, 70, and 90 responses during the OL LI and DB phases, missing values were imputed as nonresponses. In addition, patients in whom a flare occurred according to the protocol definition during the double-blind phase were classified as having no response (PedACR <30) at week 48, regardless of their actual PedACR responses. PedACR response rates during the open-label extension phase were calculated by using the last observation carried forward (LOCF) for missing values.

ACR: American College of Rheumatology; BSA: Body surface area; eow: every other week; FD: fixed dose; IVRS: interactive voice response system; MTX: Methotrexate; NSAIDS: Non-steroidal anti-inflammatory drugs RCT: Randomised control trial

2.1.3 Baseline characteristics

The demographic and disease profile of the patients were consistent with a JIA population. All patients All patients enrolled in the study had chronic, very active, widespread joint inflammation at baseline. baseline. There were no statistically significant differences between groups in both demographic and demographic and disease baseline demographics. See Table 2 for baseline demographic and clinical characteristics for the OL LI phase, Table 3 for the DB phase,

Table 4 for the OLE BSA phase and Table 5 for the OLE FD phase.

Table 2: Baseline Demographic and Clinical Characteristics (OL LI phase)[11,12]

Characteristic	**Open-Label Lead-in Phase**	
	Methotrexate	**No Methotrexate**
	Adalimumab (N = 85)	**Adalimumab (N = 86)**
Age, years, mean ± SD	11.4 ± 3.3	11.1 ± 3.8
Age category, n(%)		
4-8 years	19 (22)	21 (24)
9-12 years	30 (35)	32 (37)
13-17 years	36 (42)	33 (38)

Female sex, n (%)	68 (80)	67 (78)
Race		
White, n(%)	81 (95)	76 (88)
Body weight, kg, mean ± SD	43.8 ± 18.3	40.9 ± 19.3
Negative for rheumatoid factor, n/total n (%)	64/83 (77)	67/85 (79)
Duration for juvenile rheumatoid arthritis, years, mean ± SD	4.0 ± 3.7	3.6 ± 4.0

* Plus-minus values are means ± SD.
† Race was determined by the patient or the parent
a. The P value is based on a one way ANOVA for continuous data and on Chi-square test or Fisher's exact test if 20% of cells have expected cell count < 5 for categorical data.
b. Statistically significant, ***p 0.001, **p 0.01, and *p 0.05.

Table 3: Baseline Demographic and Clinical Characteristics (DB phase)[11,12]

	Methotrexate			No Methotrexate		
	Placebo (N = 37)	**Adalimumab (N = 38)**	**p-value [a,b]**	**Placebo (N = 30)**	**Adalimumab (N = 30)**	**p-value [a,b]**
Age, years, mean ± SD	10.8 ± 3.4	11.7 ± 3.3	0.259	11.3 ± 3.8	11.1 ± 4.1	0.857
Age category, n (%)						
4-8 years	12 (32)	6 (16)	0.149	8 (29)	8 (27)	0.778
9-12 years	10 (27)	17 (45)		7 (25)	10 (33)	
13-17 years	15 (41)	15 (40)		13 (46)	12 (40)	
Female sex, n (%)	30 (81)	30 (79)	0.817	20 (71)	23 (77)	0.649
Race						
White, n(%)	36 (97)	36 (95)	0.394	27 (96)	28 (87)	0.566
Body weight, kg, mean ± SD	44.3 ± 18.9	42.1 ± 17.9	0.611	45.4 ± 24.4	41.3 ± 17.3	0.466
Negative for rheumatoid factor, n/total n (%)	30/36 (83)	27/37 (73)	0.285	21/27 (78)	24/30 (80)	0.837
Duration for juvenile rheumatoid arthritis, years, mean ± SD	4.0 ± 3.5	4.3 ± 4.1	0.779	2.9 ± 3.3	3.6 ± 4.0	0.444

* Plus-minus values are means ± SD.
† Race was determined by the patient or the parent
a. The P value is based on a one way ANOVA for continuous data and on Chi-square test or Fisher's exact test if 20% of cells have expected cell count < 5 for categorical data.
b. Statistically significant, ***P 0.001, **P 0.01, and *P 0.05.

Table 4: Demographic and clinical characteristics (OLE BSA phase)

Characteristic	Methotrexate			No Methotrexate		
	Adalimumab (Placebo during DB phase) N = 36	**Adalimumab 24 mg/m2 BSA eow N = 35**	**p-value [a,b]**	**Adalimumab (Placebo During DB Phase) N = 28**	**Adalimumab 24 mg/m2 BSA eow N = 29**	**p-value [a,b]**
Age, years, mean ± SD	10.9 ±3.37	11.7 ± 3.26	0.333	11.1 ± 3.53	11.4 ± 3.7	0.863
Age category, n(%)						
4-8 years	11 (30.6)	6 (17.1)	0.288	8 (28.6)	8 (27.6)	0.873
9-12 years	10 (27.8)	15 (42.9)		7 (25.0)	9 (31.0)	
13-17 years	15 (41.7)	14 (40.0)		13 (46.4)	12 9 (41.4)	
Female sex	29 (80.6)	27 (77.1)	0.725	20 (71.4)	22 (75.9)	0.704
Race, n(%)						
White	35 (97.2)	33 (97.1)	1.000	27 (96.4)	26 (92.9)	1.00
Body weight, kg, mean ± SD	44.0 ± 18.8	43.4 ± 18.04	0.896	45.4 ± 24.36	41.0 ± 17.47	0.437

Negative for rheumatoid factor, n/total n (%)	29/35 (82.9)	25/34 (73.5)	0.348	21/27 (77.8)	23/29 (79.3)	0.889
Duration for juvenile rheumatoid arthritis, years, mean ± SD	4.1 ± 3.55	3.9 ± 3.60	0.764	2.9 ± 3.26	3.8 ± 4.05	0.375

BSA = body surface area; DB = double-blind
a. The P value is based on a one way ANOVA for continuous data and on Chi-square test or Fisher's exact test if 20% of cells have expected cell count < 5 for categorical data.
b. Statistically significant, ***P 0.001, **P 0.01, and *P 0.05.

Table 5: Demographic and clinical characteristics (OLE FD phase)

Characteristic	Methotrexate			No Methotrexate		
	Same/ decreased dose N=28	**Increased dose N=31**	**p value** [a,b]	**Same/ decreased dose N=25**	**Increased dose N=22**	**p value** [a,b]
Age, years, mean ± SD	12.6 ±3.33	9.8 ± 2.86	0.001**	12.1 ± 4.28	9.8 ± 3.62	0.050*
Age category, n(%)						
4-8 years	4 914.3)	11 (35.5)		6 (24.0)	9 (40.9)	
9-12 years	5 (17.9)	15 (48.4)	<0.001***	4 (16.0)	8 (36.4)	0.034*
13-17 years	19 (67.9)	5 (16.1)		15 (60.0)	5 (22.7)	
Female sex	20 (71.4)	25 (80.6)	0.406	17 (68.0)	16 (72.7)	0.724
Race, n(%)						
White	26 (96.3)	30 (96.8)	1.000	22 (88.0)	21 (100.0)	0.239
Body weight, kg, mean ± SD	55.4 ± 18.14	32.0 ± 9.64	<0.001***	52.2 ± 24.39	32.6 ± 10.49	0.001**
Negative for rheumatoid factor, n/total n (%)	16/27 (59.3)	28/30 (93.3)	0.002**	15/25 (60.0)	22/22 (100.0)	<0.001***
Duration for juvenile rheumatoid arthritis, years, mean ± SD	3.4 ± 3.08	4.6 ± 3.58	0.191	2.7 ± 3.38	3.5 ± 3.69	0.486

a. The P value is based on a one way ANOVA for continuous data and on Chi-square test or Fisher's exact test if 20% of cells have expected cell count < 5 for categorical data.
b. Statistically significant, ***P 0.001, **P 0.01, and *P 0.05.

2.1.4 Results

The patient flow through the study phases can be seen in Figure 4 (OLE LI and DB phase), Figure 5 (OLE BSA phase) and a) % of patients enrolled within treatment group. b) % of total patients enrolled in that particular phase. c) % of patients within strata-treatment group.

Figure 6 (OLE FD phase).

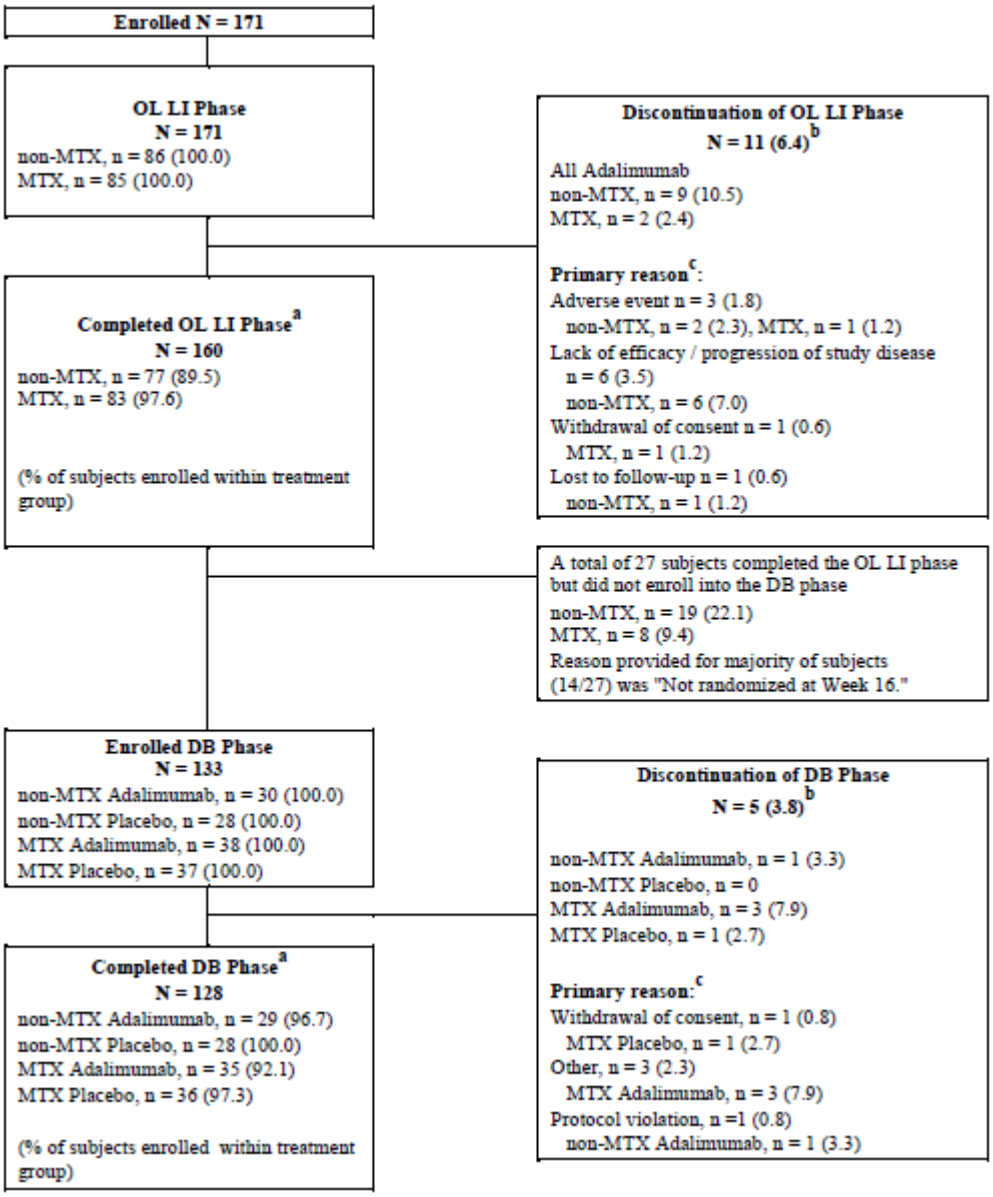

Figure 4: Study disposition (OL LI & DB phases)

a) % of patients enrolled within treatment group. b) % of total patients enrolled in that particular phase. c) % of patients within strata-treatment group.

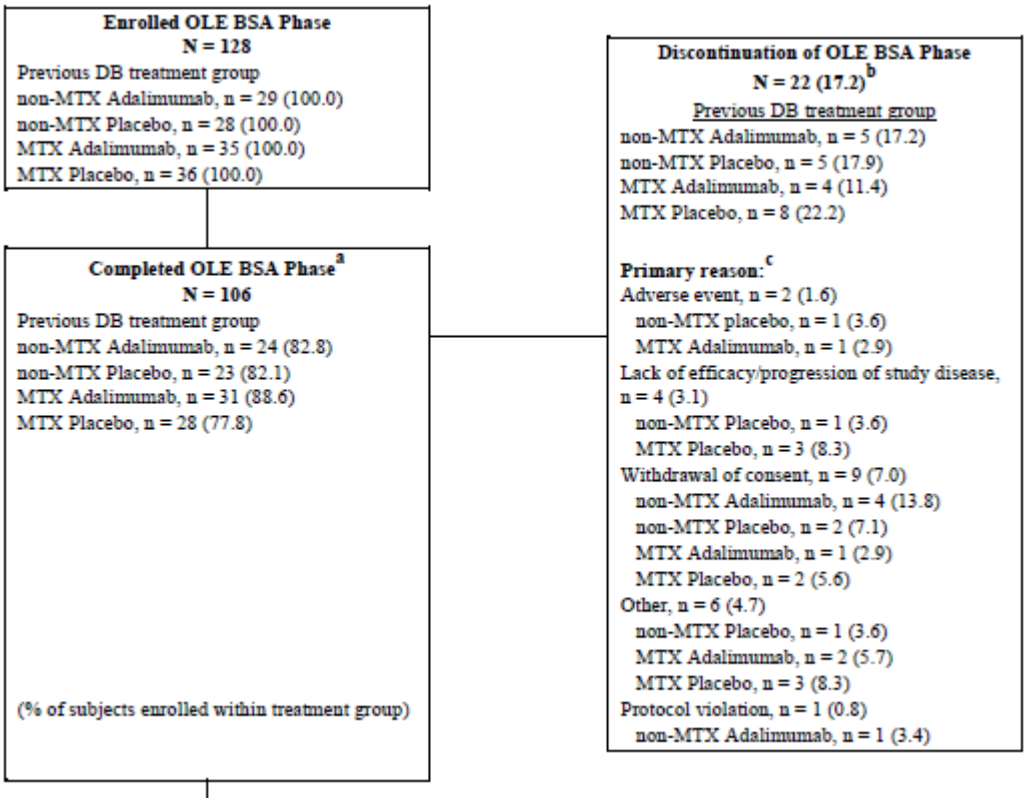

Figure 5: Study disposition (OLE BSA phase)
a) % of patients enrolled within treatment group. b) % of total patients enrolled in that particular phase. c) % of patients within strata-treatment group.

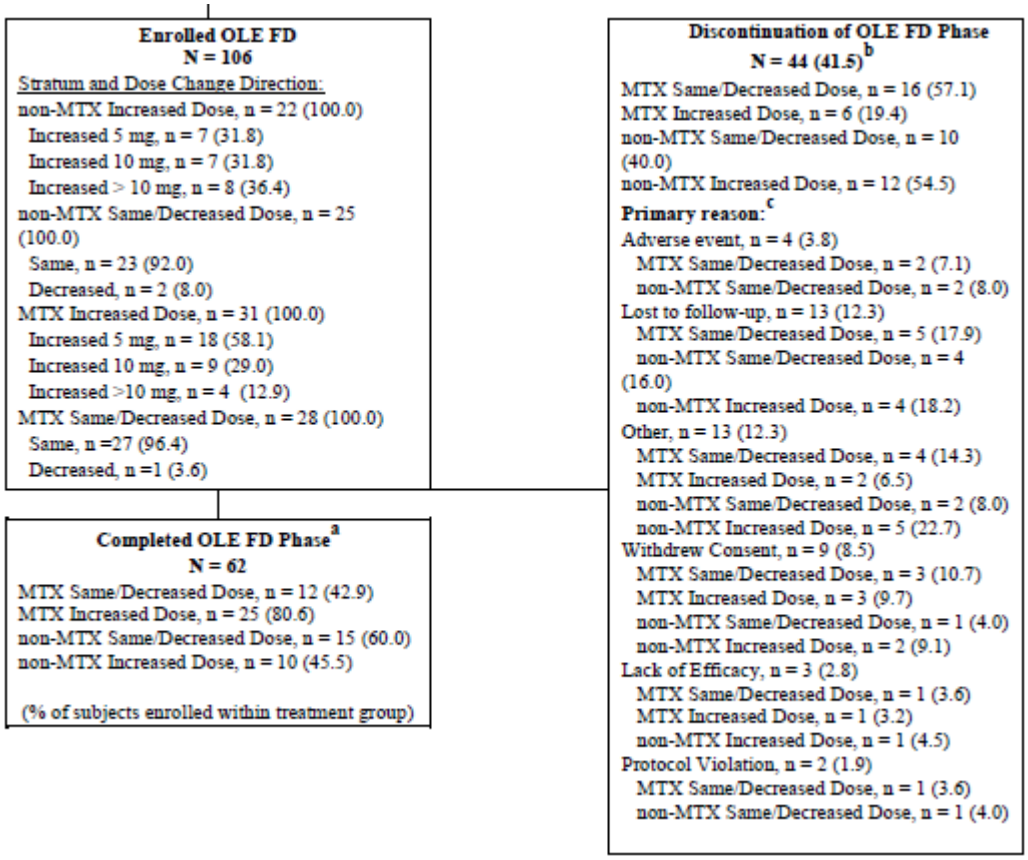

Figure 6: Study disposition (OLE FD phase)
a) % of patients enrolled within treatment group. b) % of total patients enrolled in that particular phase. c) % of patients within strata-treatment group.

2.1.4.1 OLE LI phase primary efficacy outcomes

A total of 144 (84.2%) patients were PedACR30 responders. At Week 16 there were 80 (94.1%) patients in the MTX stratum and 64 (74.4 %) patients in the non-MTX stratum who were PedACR30 responders. The patients improved according to all levels of PedACR response during the OL LI phase as seen in Figure 7.

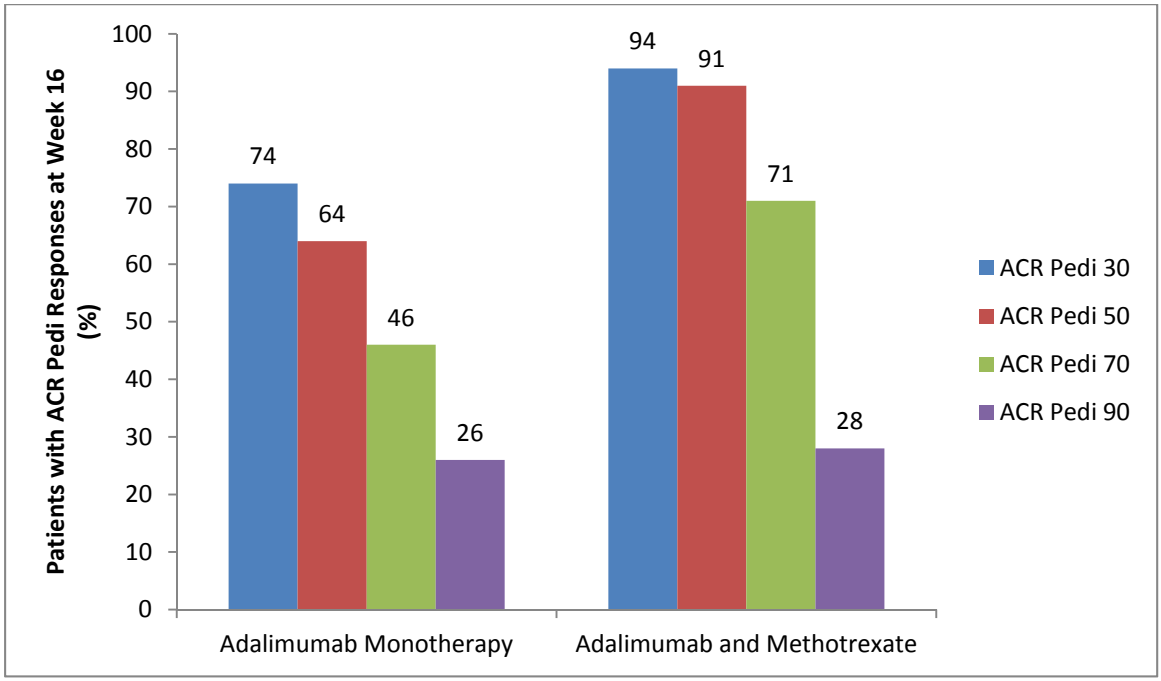

Figure 7: PedACR response levels among patients receiving adalimumab with or without concomitant MTX

2.1.4.2 DB phase primary efficacy outcomes

Patients who were PedACR30 responders at the end of the OL LI phase were eligible to continue to the continue to the DB phase. A statistically significantly lower proportion of adalimumab-treated patients patients demonstrated disease flare compared to placebo-treated patients in both the MTX and non-MTX and non-MTX strata (

Table 6). Furthermore, in both the non-MTX and MTX strata, adalimumab was superior to placebo in reducing the odds of a disease flare (odds ratio (OR) = 0.2; 95% CI: 0.1 to 0.6 in the non-MTX stratum and OR=0.3; 95% CI: 0.1 to 0.7 in the MTX stratum) after controlling for NSAID or corticosteroid use. Prior use of NSAIDs or corticosteroids did not seem to have an impact on disease flare. In the MTX stratum, adalimumab was superior to placebo for delayed the time to onset of disease flare (>32 weeks for the adalimumab arm; ~20 weeks for the placebo arm) (p=0.03).

At the end of the DB phase, statistically significantly greater proportions of adalimumab-treated patients achieved a PedACR30/50/70 response compared to placebo-treated Patients in the MTX stratum. This difference was not observed for PedACR 90 response. For the non-MTX stratum, the proportions of adalimumab patients achieving PedACR30/50/70/90 response were greater than the proportions of patients receiving placebo; however, the differences did not reach statistical significance (

Table 6).

Table 6: Primary efficacy outcomes (DB phase)

	Non- MTX			MTX		
	Placebo (N =28)	**Adalimumab 24 mg/m^2 BSA eow (N =30)**	**p Value**	**Placebo (N =37)**	**Adalimumab 24 mg/m^2 BSA eow (N =38)**	**p Value[a,b]**
Primary efficacy outcomes						
Disease flare[c], n(%)	20 (71.4)	13 (43.3)	0.031	24 (64.9%)	14 (36.8)	0.015
PedACR response						
PedACR30	9 (32.1)	17 (56.7)	0.061	14 (37.8)	24 (63.2)	0.028
PedACR50	9 (32.1)	16 (53.3)	0.103	14 (37.8)	24 963.2)	0.028
PedACR70	8 (28.6)	14 (46.7)	0.156	10 (27.0)	24 (63.2)	0.002
PedACR90	5 (17.9)	9 (30.0)	0.280	10 (27.0)	16 (42.1)	0.170

a. The p value is based on Chi-square test; b. The p value is based on Pearson's Chi-square test. If cell count was < 5, then Fisher's exact test was used. c. Missing values were treated as disease flare.

2.1.5 OLE BSA primary efficacy outcomes

All patients who completed 32 weeks of double-blind phase or experienced a flare during the double-bind phase were eligible to receive open-label adalimumab during the OLE BSA phase.

For patients in both the MTX and non-MTX strata, Figure 8, Figure 9, Figure 10, and Figure 11 show a similar increase or maintenance in the proportion of patients achieving a PedACR30/50/70/90 response at Week 8 (the first measurement time point) of OLE BSA compared to the last observed value of the DB phase. The proportion of patients previously receiving placebo in the DB phase achieving PedACR30 at week 8 of the OLE BSA phase was noticeably increased from 35.4% at the end of the DB phase to 100.0% of patients at week 8 of the OLI BSA phase. This robust response was maintained throughout the OLE BSA phase.

In those patients who received adalimumab during the DB phase, the proportion of patients achieving a PedACR30 response at the end of the DB phase (60.3% of patients had PedACR30 responses) also significantly increased by Week 8 of the OLE BSA phase (95.0% of patients had PedACR30 responses), and was similar in proportional change to the placebo group. As with the placebo group, the high percentage of adalimumab-treated PedACR30 responders by Week 8 of the OLE BSA phase was maintained throughout the OLE BSA period. In addition, PedACR50/70/90 responses were generally maintained throughout the OLE BSA phase. During the OLE phase, PedACR responses were sustained during 2 years of treatment. After 104 weeks of treatment, 40% of patients had an PedACR 100 response.

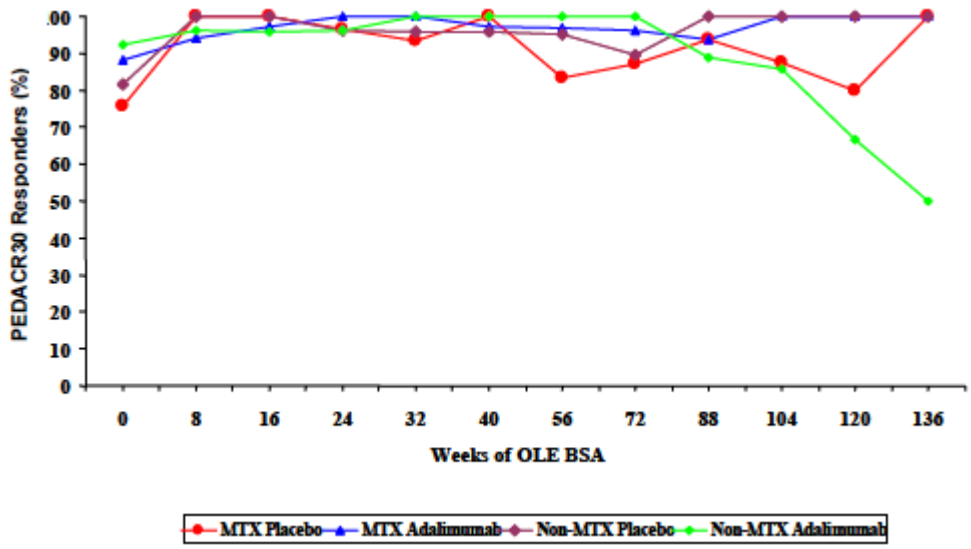

Figure 8: PedACR30 Response by Stratification and Treatment Group for the OLE BSA phase[13]

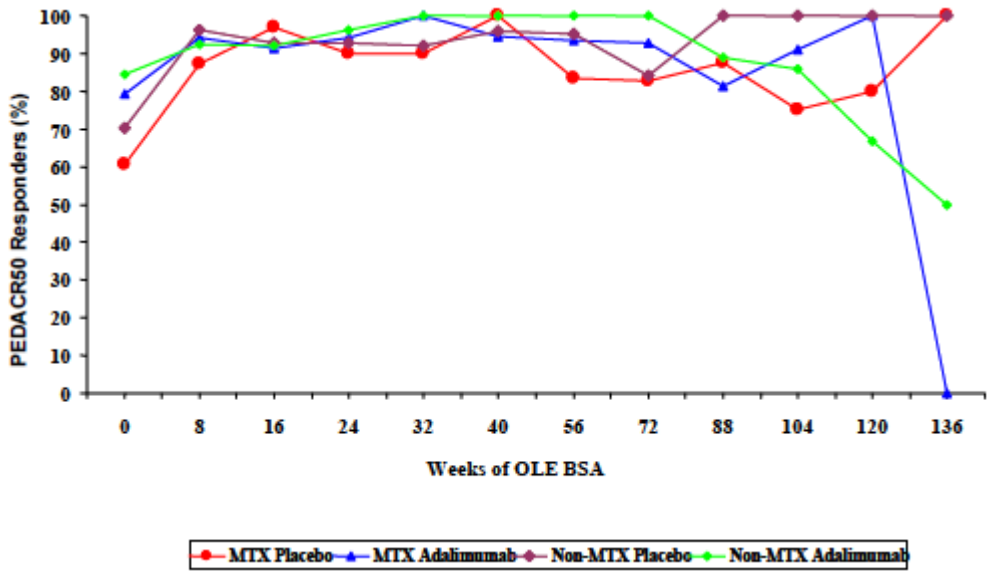

Figure 9: PedACR50 Response by Stratification and Treatment Group for the OLE BSA phase[13]

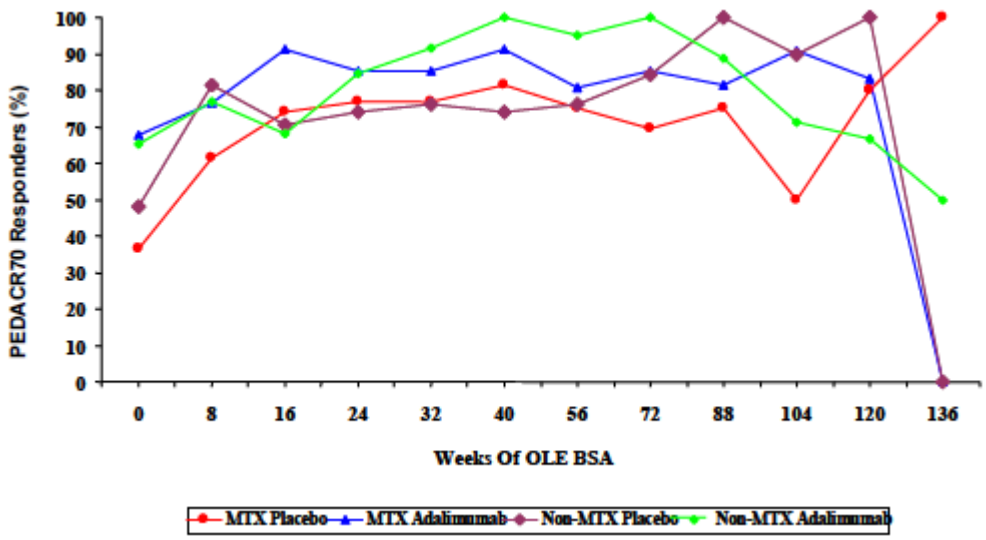

Figure 10: PedACR70 Response by Stratification and Treatment Group for the OLE BSA phase[13]

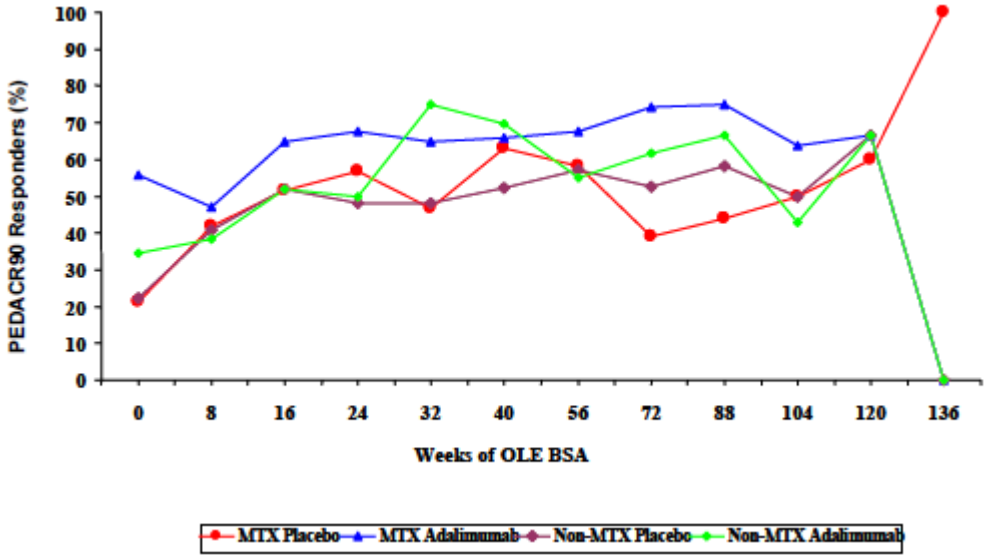

Figure 11: PedACR90 Response by Stratification and Treatment Group for the OLE BSA phase[13]

2.1.6 OLE FD primary efficacy outcomes

The maintenance of PedACR responses during the OLE FD phase, regardless of whether patients remained on the same dose/decreased dose or increased dose, compared to the dose received during the OLE BSA phase is shown in Figure 12, Figure 13, and Figure 14. Week 0 data represented the last observed PedACR response before first dose of FD adalimumab. Evaluation of PedACR30/50/70/90 response rates in the OLE FD phase indicates that the response rate observed in the OLE BSA phase 72 weeks before the start of the OLE FD phase was maintained through the duration of the OLE FD phase.

Patients generally had positive PedACR responses throughout the entire OLE FD phase, regardless of whether they remained on the same/decreased dose or increased dose compared to the dose received during the OLE BSA phase. However, a few significant response differences were found based on dose change from BSA dosing and age category. In the age category of 9-12 years, a greater proportion of patients with increased doses were PedACR70 (Week 32 and final visit) and PedACR90 (Week 48 and 96) responders compared to patients with the same/decreased doses at these time points. Also, in the age category of 13-17 years and in the non-MTX stratum, statistically significantly fewer patients with increased doses were PedACR90 responders at Week 144 than patients with the same/decreased doses.

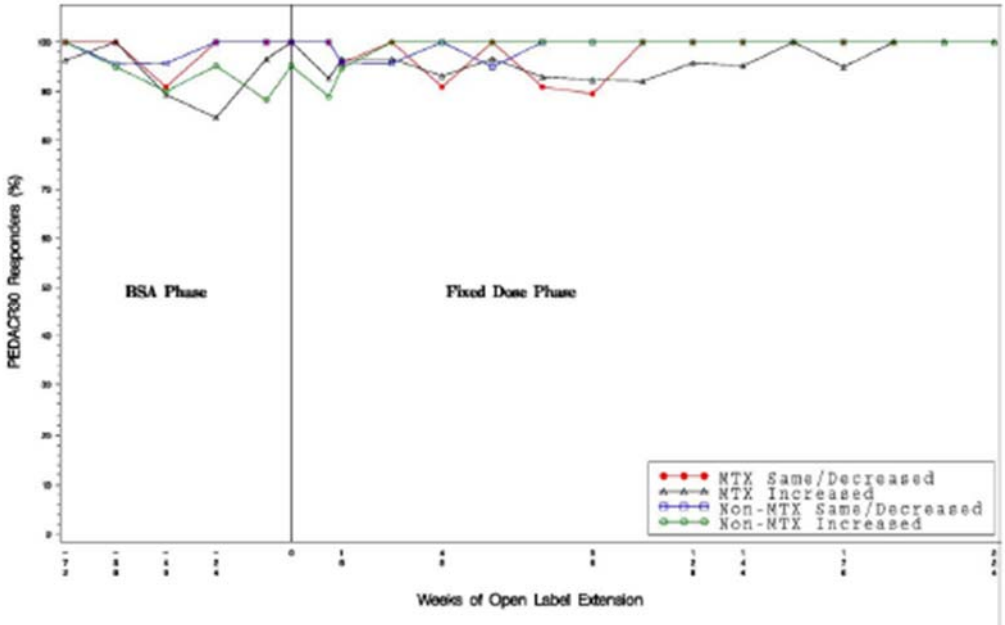

Figure 12: PedACR30 Responders for the OLE FD phase Population from Week -72 of the OLE BSA phase (in relation to OLE FD Baseline) through the OLE FD phase[13]

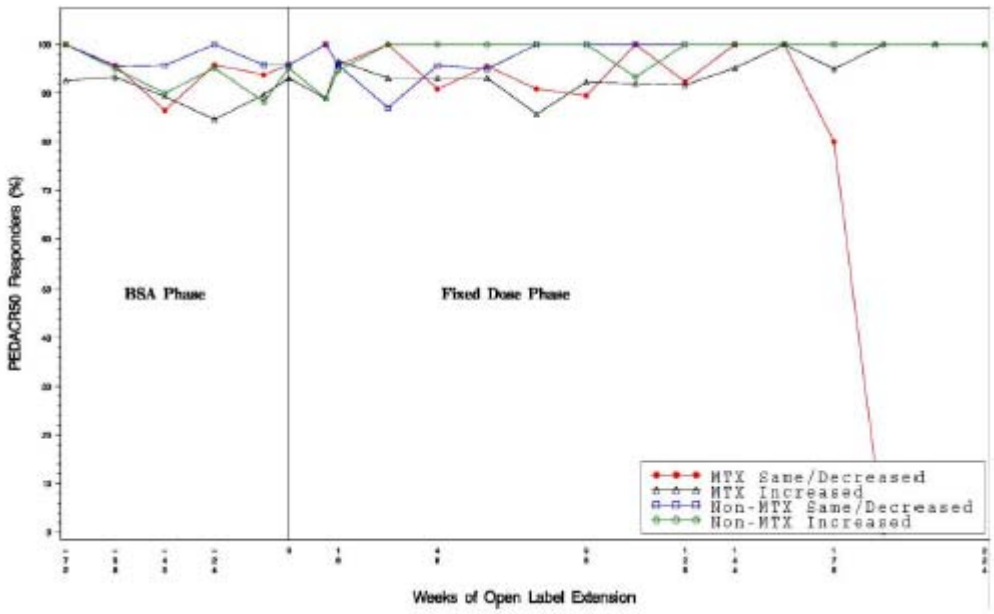

Figure 13: PedACR50 Responders for the OLE FD phase Population from Week -72 of the OLE BSA phase (in relation to OLE FD Baseline) through the OLE FD phase[13]

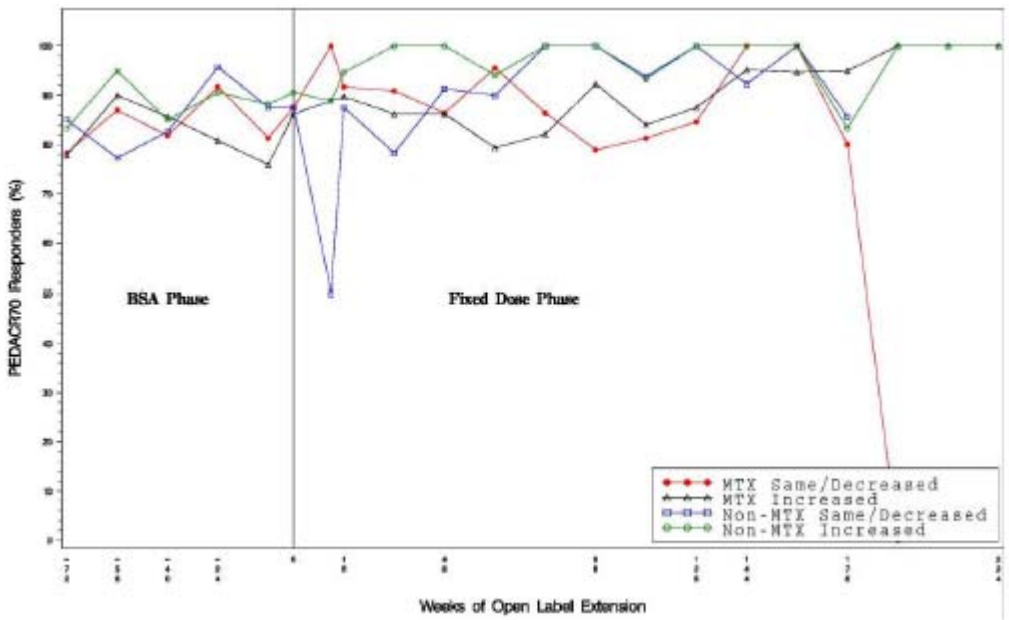

Figure 14: PedACR70 Responders for the OLE FD phase Population from Week -72 of the OLE BSA phase (in relation to OLE FD Baseline) through the OLE FD phase[13]

2.2 Study M10-444 – pJIA aged 2-4[14]

2.2.1 Protocol identification: NCT00775437

This was a phase 3b open-label (OL), single arm, multicentre study with a primary objective to evaluate the safety and efficacy of adalimumab in patients aged 2 to 4 years and patients older than 4 years weighing <15kg, with moderate to severe active pJIA or polyarticular course JIA. Very early onset of JIA is known but relatively rare; therefore, the study design was chosen to demonstrate safety in a very young patient population.

2.2.2 Study design and methods:

The study design and methods for M10-444 are presented in Figure 15 and

Table 7.

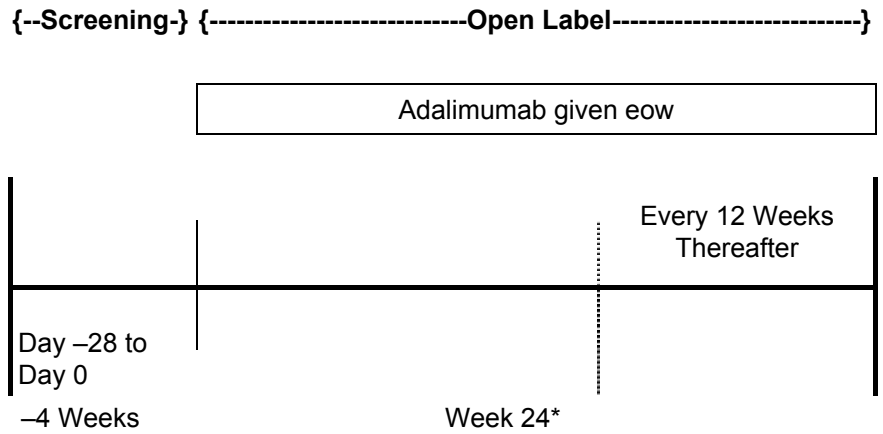

Figure 15: Study design schematic[15]

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

Table 7: Study design and methods of the M10-444 study

Item	M10-444
Design	International, multicentre, open-label
Number of participants	32
Countries and setting	US, Czech Republic, France and Germany; 14 sites
Study Objectives	Primary objectives • To evaluate the safety of adalimumab in patients aged 2 to 4 years and patients older than 4 years weighing <15kg, with moderate to severe active pJIA or polyarticular course JIA. • To collect pharmacokinetic data and evaluate the efficacy of adalimumab in these patients
Inclusion criteria	• Patients were aged 2 to <4 years at Screening or aged ≥4 years and weighing <15 kg. • Patient had a disease diagnosis of moderately to severely active polyarticular or polyarticular course JIA as defined per the ILAR criteria. • Patients had moderately to severely active disease with 5 active joints at the time of study entry. • In the EU, patients must have previously failed, had an insufficient response to, or been intolerant of at least one DMARD, consistent with the local prescribing information for adalimumab in older patients (defined as arthritis affecting ≥ 5 joints at the time of treatment initiation). • Patient judged by the investigator to be in generally good health on the basis of medical history, laboratory profile, and physical examination performed at Screening and confirmed at Baseline. This included, but was not limited to, a normal cardiopulmonary and normal neurological examination result. • Parent or legal guardian had to be able and willing to administer SC injections or have a qualified person available to administer SC injections. • Parent or legal guardian had to be willing to actively supervise storage and administration of adalimumab and had to ensure that the time of each dose was accurately recorded in the Patient's diary. • Patient must have had a negative purified protein derivative (PPD) test (or equivalent) at Screening. If Patient had a positive (≥ 5 mm induration) PPD test result, a chest x-ray (CXR, posterior-anterior [PA] and lateral [LAT] views) was to be performed. If patient had a positive test (or equivalent), had a past ulcerative reaction to PPD placement, and/or a CXR consistent with tuberculosis (TB) exposure, Patient was not to be enrolled into the study. • For patients in the EU, patient must have previously failed, had an insufficient response to, or been intolerant to ≥ 1 disease-modifying anti-rheumatic drug (DMARD). • A parent or guardian signed and dated an ICF.
Exclusion criteria	• Patient had prior exposure to natalizumab, efalizumab, or any other biologic therapy, such as abatacept, anakinra, tocilizumab, rituximab. Any previous use of anti-tumor necrosis factor (TNF) agents, including etanercept, infliximab, certolizumab pegol, golimumab, and adalimumab was also prohibited. • Infection(s) requiring treatment with IV anti-infectives within 30 days prior to the Baseline visit or oral anti-infectives within 14 days prior to the Baseline visit (added to global amendment only [excludes the Czech Republic]). • Patient had undergone joint surgery within the 2 months preceding the Screening visit (at joints to be assessed within the study). • Patient had a previous diagnosis of a condition that could cause arthritis other than pJIA.

	• Patient had a history of an allergic reaction or significant sensitivity to constituents of the adalimumab.
	• Patient had been treated with any investigational drug of chemical or biologic nature (e.g., anakinra or rituximab) within a minimum of 30 days or 5 half-lives (whichever was longer) of the drug prior to Baseline visit. If these biologics were approved, they would continue to be excluded.
	• Patient had a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, recent cerebrovascular accident (CVA), seizure disorder, and any other condition which, in the opinion of the investigator, would put the patient at risk by participation in the study.
	• Patient had a history of clinically significant haematologic (e.g., severe anaemia, leukopaenia, thrombocytopaenia, clotting) disorder, renal or liver disease (e.g., fibrosis, cirrhosis, hepatitis), or active gastroenteric ulcer.
	• Patient was considered by the investigator, for any reason, to be an unsuitable candidate for the study.
	• Patient had evidence of active TB infection.
	• Patient had history of moderate to severe congestive heart failure (CHF) (New York Heart Association class (NYHA) III or IV), recent CVA or thrombotic event, and any other condition which, in the opinion of the investigator, would have put the patient at risk by participation in the protocol.
	• Evidence of dysplasia or history of malignancy (including lymphoma or leukaemia).
	• History of demyelinating disease (including myletis) or neurologic symptoms, suggestive of central nervous system demyelinating disease.
	• History of invasive fungal infection (e.g., listeriosis, histoplasmosis), active viral disorders, or human immunodeficiency virus infection.
	• Positive hepatitis B test result.
	• Chronic recurring infections or active TB.
	• Screening laboratory and other analyses showed any of the following abnormal results:
	  o Electrocardiogram – with clinically significant abnormalities
	  o Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range
	  o Total bilirubin ≥ 3 mg/dL
	  o Serum creatinine > 1.6 mg/dL (convert to mmol/L)
	• Evidence of dysplasia or history of malignancy (including lymphoma or leukaemia) other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma.

Outcomes	<u>Primary outcomes (safety)</u>
	• Adverse effects
	  o Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not the event was considered causally related to the use of the product.
	• SAE
	  o Death
	  o Life-threatening
	  o Hospitalisation or prolongation of hospitalisation
	  o Congenital anomaly
	  o Persistent or significant disability/incapacity
	  o Important medical event requiring medical or surgical intervention to prevent serious outcome
	
	<u>Secondary outcomes</u>
	• PK data
	• Change from baseline in laboratory findings
	• Individual indicators of efficacy

	• PedACR 30/50/70/90 responses as defined as at least 30%, 50%, 70%, 90% improvement, respectively, in ≥ 3 of the 6 core set parameters with worsening of ≥ 30% in no more than 1 of the 6 core set parameters. Clinical assessments using:- • Physical function of the Disability Index of Childhood Health Assessment Questionnaire [DICHAQ] • Parent's Global Assessment (PGA) of Patient's overall disease activity (VAS) Efficacy assessment by physician global assessment using:- • PGA (VAS) • Joint pain and swelling • Number of active joints • Number of joints with LOM • CRP • Inactive disease – defined as:- o No active arthritis o No fever o No rash o No serositis o No splenomegaly o No generalised lymphadenopathy attributable to JIA o No active JIA-associated uveitis o Normal CRP level o PGA indicating clinical disease quiescence
Recruitment/selection of patients (method)	Recruited by physician
Patient enrolment dates	24 March 2009 to 21 March 2013
Intervention	Adalimumab was administered by SC injection eow in either:- • A 0.4-mL prefilled graduated syringe containing adalimumab 20 mg/0.4 mL for a final concentration of 50 mg/mL (US/Puerto Rico only) OR • A single-use 0.8-mL vial containing adalimumab 40 mg/0.8 mL for a final concentration of 50 mg/mL (EU only) 24 mg/m^2 body surface area up to a maximum 20 mg/dose
Comparator	N/A
Concomitant medication	The continuation of prior JIA treatments, such as MTX, stable doses of NSAIDs and/or low-dose corticosteroids (equal to prednisone <0.2 mg/kg/day) was permitted
Participant blinding	OL study – not blinded
Outcome assessor blinding to interventions	OL study – not blinded
Statistical analyses, e.g. ITT	The ITT/safety population included all patients who had received at least one dose of adalimumab. Safety data are summarised up to 120 weeks of treatment: AEs are reported as number and percentage of patients affected and as events per 100 patient-years (E/100 PYs). Efficacy data are presented based on observed values (weeks 12, 24, 60, and 96) and non-responder imputation (NRI) (weeks 12 and 24). Growth data was analyzed as observed.
Power calculation	The size of the study was determined based upon a commitment to the US FDA to provide safety and efficacy data for adalimumab when used in 2 to <4 year old patients with JIA, and, in accordance with the FDA, the proposed sample size for this study was approximately 30 patients
Missing data	Two patients withdrew prior to week 60, while one patient withdrew from the study at the week 60 visit. Three additional patients discontinued the study after week 60.

AEs: Adverse events; DMARD: Disease modifying anti rheumatic drug; FDA: Food and drug administration; ILAR: ITT: Intention-to-treat; TB: Tuberculosis; MTX: Methotrexate; NRI: Non-responder imputation; NSAID: Non-steroidal anti-inflammatory; TNF: Tumour necrosis factor

2.2.3 Baseline characteristics:

A full set of patient baseline characteristics is presented in Table 8 and baseline disease activity in

Baseline disease activity was consistent with moderately to severely active JIA.

Table 9.

Table 8: Baseline characteristics by patient enrolled in Study M10-444[16]

Characteristics	Adalimumab (N=32)
Sex, n (%)	
Female	28 (87.5)
Male	4 (12.5)
Race, n (%)	
White	25 (78.1)
Black	3 (9.4)
Asian	1 (3.1)
Other	3 (9.4)
Ethnicity, n (%)	
Hispanic or Latino	1 (3.1)
Non-Hispanic or Non-Latino	31 (96.9)
Country, n	
United States of America	15
France	4
Czech Republic	9
Germany	4
Age category, n (%)	
< 4 years	28 (87.5)
≥ 4 years	4 912.5)
Age, years	
Mean ± SD	0.723
Median (min – max)	3.15 (2.0 – 4.6)
Weight, kg	
Mean ± SD	13.4 ± 1.96
Median (min – max)	13.0 (10.4 – 18.9)
Height, cm	
Mean ± SD	92.8 ± 5.80
Median (min – max)	93.5 (83.0 – 102.0)
BMI (Kg/m^2)	
Mean ± SD	15.5 ± 1.25
Median (min – max)	15.4 (13.1 – 18.5)
BSA (Kg/m^2)	
Mean ± SD	0.6 ± 0.06
Median (min – max)	0.6 (0.5 – 0.7)

Baseline disease activity was consistent with moderately to severely active JIA.

Table 9: Baseline disease activity (ITT)

Baseline Characteristic	Adalimumab N = 32

TJC75	
Mean ± SD	3.8 ± 5.02
Median (min – max)	2.0 (0 – 19)
SJC66	
Mean ± SD	8.9 ± 7.37
Median (min – max)	7.0 (0 – 36)
LOM69	
Mean ± SD	8.6 ± 7.69
Median (min – max)	7.0 (0 – 32)
POM75	
Mean ± SD	5.3 ± 4.66
Median (min – max)	4.5 (0 – 19)
AJC73	
< 5, n (%)	3 (9.4)
≥ 5, n (%)	29 (90.6)
Mean ± SD	10.0 ± 7.47
Median (min – max)	7.0 (1 – 36)
Parents' assessment of pain (VAS, mm)	
Mean ± SD	46.1 ± 25.73
Median (min – max)	51.0 (0 – 83)
Parents' global assessment of disease activity (VAS, mm)	
Mean ± SD	47.6 ± 25.91
Median (min – max)	51.5 (0 – 90)
PGA (VAS, mm)	
Mean ± SD	55.3 ± 19.70
Median (min – max)	60.5 (9 – 84)
DICHAQ	
Mean ± SD	1.2 ± 0.66
Median (min – max)	1.3 (0 – 2.9)
CRP, mg/dL[a]	
Mean ± SD	1.6 ± 2.43
Median (min – max)	0.4 (0.4 – 12.8)
Normal (< 0.9 mg/dL), n (%)	19 (61.3)
Abnormal (≥ 0.9 mg/dL), n (%)	12 (38.7)
Missing, n	1
RF, IU/mL	
Mean ± SD	10.2 ± 1.24
Median (min – max)	10.0 (10.0 – 17.0)
Positive (≥ 12 IU/mL), n (%)	1 (3.1)
Negative (< 12 IU/mL), n (%)	31 (96.9)

2.2.4 Results

There were no primary efficacy variables for this study. The primary objective of this study was to evaluate the safety of adalimumab and this is presented in the Safety section of this submission.

2.2.4.1 PedACR response

A PedACR30/50 response was achieved by at least 80% of patients from Week 12 through Week 108 when the observed and LOCF data were analysed. The percentage of patients with PedACR30 responses at weeks 12, 24, 60, and 96 were 94%, 90%, 90%, and 92%, respectively as seen in **Error! Reference source not found.**. All three patients completing week 120 had a good and sustained response achieving PedACR90. PedACR response rates at weeks 12 and 24, using NRI method, were similar to rates in the observed case analysis shown in Figure 16.

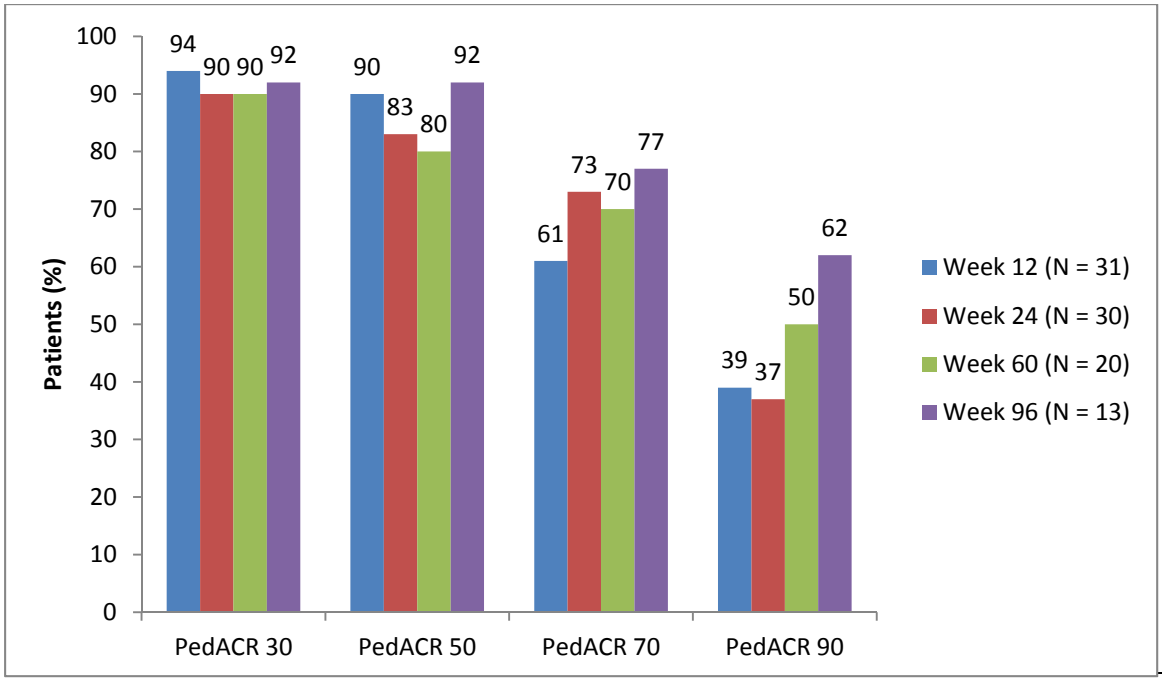

Figure 16. Percentage of patients achieving PedACR 30/50/70/90 responses at weeks 12, 24, 60, and 96 (observed analysis)

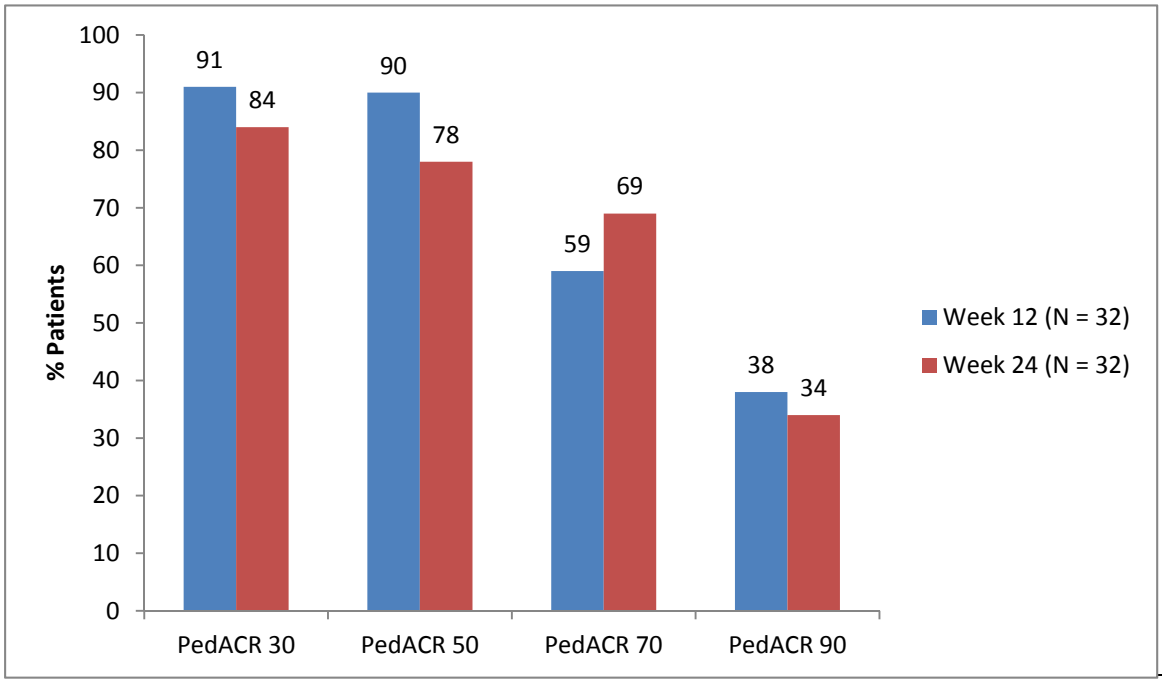

Figure 17. Percentage of patients achieving PedACR 30/50/70/90 responses at weeks 12 and 24 (NRI analysis)

2.2.4.2 Joint assessments

A decrease in mean change from baseline was observed for all joint assessments including TJC75 TJC75 (Table 10), SJC66 (

), POM75 (

Table 12), LOM69 (Table 13), and AJC73 (n are included in the analysis.

Table 14) indicating a decrease in disease activity. The greatest change occurred from Week 60 through to Week 84, however, the number of patients participating decreased to nearly 50% during this period. Adalimumab proved effective with sustained improvement of core JIA disease activity parameters for 96 weeks of therapy.

Table 10: TJC75 by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0	32	3.8		
Week 2	32	3.8	1.5	–2.3 ± 4.62
Week 4	32	3.8	1.0	–2.8 ± 4.48
Week 8	32	3.8	0.7	–3.1 ± 4.31
Week 12	31	3.8	1.1	–2.7 ± 5.09
Week 16	31	3.8	0.3	–3.5 ± 4.77
Week 20	29	4.0	0.1	–3.9 ± 5.09
Week 24	30	4.0	1.0	–3.0 ± 5.54
Week 36	28	4.2	1.3	–2.9 ± 5.65
Week 48	24	4.9	0.5	–4.4 ± 4.85
Week 60	20	4.9	0.4	–4.5 ± 5.85
Week 72	17	5.5	0.2	–5.3 ± 5.53
Week 84	17	5.5	0.7	–4.8 ± 5.20
Week 96	13	4.9	0.9	–4.0 ± 5.46
Week 108	9	3.9	2.8	–1.1 ± 4.73
Week 120	3	1.3	0.0	–1.3 ± 2.31

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 11: SJC66 by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline
				Mean ± SD
Week 0	32	8.9		
Week 2	32	8.9	4.4	–4.5 ± 6.46
Week 4	32	8.9	3.5	–5.3 ± 6.63
Week 8	32	8.9	2.8	–6.0 ± 5.32
Week 12	31	9.0	2.7	–6.2 ± 4.24
Week 16	31	9.0	2.9	–6.1 ± 6.59
Week 20	29	8.9	2.0	–6.9 ± 5.62
Week 24	30	9.1	2.8	–6.3 ± 5.83
Week 36	28	8.5	2.3	–6.2 ± 4.73
Week 48	24	8.8	2.1	–6.7 ± 5.34
Week 60	20	9.2	0.8	–8.4 ± 7.15
Week 72	17	10.1	1.2	–8.9 ± 6.06
Week 84	17	10.1	0.7	–9.4 ± 7.15
Week 96	13	9.8	1.3	–8.5 ± 6.89
Week 108	9	10.6	4.8	–5.8 ± 3.31
Week 120	3	7.3	0.0	–7.3 ± 2.08

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 12: POM75 by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0	32	5.3		
Week 2	32	5.3	1.9	–3.3 ± 4.50
Week 4	32	5.3	1.3	–4.0 ± 4.01
Week 8	32	5.3	0.6	–4.6 ± 5.17
Week 12	31	5.3	0.4	–4.9 ± 4.59
Week 16	31	5.3	0.5	–4.9 ± 4.60
Week 20	29	5.6	0.1	–5.4 ± 4.81
Week 24	30	5.5	1.3	–4.1 ± 7.32
Week 36	28	5.8	1.4	–4.3 ± 7.34
Week 48	24	6.2	0.5	–5.8 ± 4.42
Week 60	20	6.5	0.6	–5.9 ± 5.25
Week 72	17	6.6	0.2	–6.4 ± 5.41
Week 84	17	6.6	0.6	–6.1 ± 5.34
Week 96	13	6.0	0.3	–5.7 ± 5.12
Week 108	9	5.4	1.9	–3.6 ± 5.85
Week 120	3	5.3	0.0	–5.3 ± 1.53

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 13: LOM69 by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0	32	8.6		
Week 2	32	8.6	4.1	–4.5 ± 7.14
Week 4	32	8.6	3.1	–5.4 ± 6.48
Week 8	32	8.6	3.2	–5.3 ± 5.02
Week 12	31	8.8	3.1	–5.6 ± 4.80
Week 16	31	8.8	2.5	–6.3 ± 6.31
Week 20	29	8.9	2.0	–6.8 ± 6.63
Week 24	30	9.0	3.3	–5.6 ± 5.54
Week 36	28	8.4	3.3	–5.1 ± 5.29
Week 48	24	9.1	3.5	–5.5 ± 7.06
Week 60	20	9.5	4.0	–5.5 ± 8.31
Week 72	17	10.1	3.2	–6.9 ± 7.84
Week 84	17	10.1	1.8	–8.4 ± 6.90
Week 96	13	8.8	1.4	–7.5 ± 6.73
Week 108	9	9.3	4.1	–5.2 ± 3.96
Week 120	3	6.3	0.3	–6.0 ± 2.65

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 14: AJC73 by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0	32	10.0		
Week 2	32	10.0	5.0	–5.0 ± 6.58
Week 4	32	10.0	3.9	–6.1 ± 6.69
Week 8	32	10.0	3.0	–7.0 ± 5.24
Week 12	31	10.1	2.8	–7.3 ± 4.52
Week 16	31	10.1	3.0	–7.1 ± 5.87
Week 20	29	10.1	2.1	–8.0 ± 5.68
Week 24	30	10.2	3.0	–7.2 ± 5.60
Week 36	28	9.7	2.4	–7.3 ± 5.21
Week 48	24	10.2	2.2	–8.0 ± 5.50
Week 60	20	10.6	1.1	–9.5 ± 7.50
Week 72	17	11.4	1.2	–10.2 ± 6.64
Week 84	17	11.4	1.0	–10.4 ± 7.57
Week 96	13	10.3	1.4	–8.9 ± 7.04
Week 108	9	10.8	4.9	–5.9 ± 3.33
Week 120	3	7.3	0.0	–7.3 ± 2.08

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 postbaseline observation are included in the analysis.

2.2.4.3 Health and Quality of Life assessments

A decrease in mean change from Baseline was observed for the Parent's Global Assessment of patient's overall disease activity (e similar to the observed data.

Table 15), the Parent's Assessment of Pain (

Table 16), and the PGA of Disease Activity (Table 17) from Week 12 through Week 120, indicating an improvement in disease activity. These assessments use a VAS, which is scored on a scale from 0 mm (absence of symptoms) to 100 mm (maximum symptoms) for the parameters assessed. In the observed data set, the largest mean changes (range from –42.6 to –47.7 mm) occurred from Week 72 through Week 120; however, the number of assessments completed during those scheduled visits decreased to nearly 50% by Week 72. Results from analysis of the LOCF data were similar to the observed data.

Table 15: Parent's Global Assessment of Patient's Disease Activity by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0		47.6		
Week 12	31	48.9	20.9	–28.1 ± 29.91
Week 24	30	48.1	15.8	–32.2 ± 29.74
Week 36	27	48.5	13.4	–35.1 ± 27.42
Week 48	24	49.0	13.4	–35.6 ± 32.19
Week 60	21	47.0	12.4	–34.5 ± 33.31
Week 72	17	53.3	9.5	–43.8 ± 25.58
Week 84	17	53.3	10.7	–42.6 ± 28.62
Week 96	13	56.6	10.8	–45.8 ± 29.10
Week 108	9	59.3	19.4	–39.9 ± 37.54
Week 120	3	58.0	10.3	–47.7 ± 34.96

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 16: Parent's Assessment of Pain by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0		46.1		
Week 12	31	45.0	17.8	–27.2 ± 25.36
Week 24	30	44.2	14.7	–29.5 ± 28.28
Week 36	27	46.8	9.3	–37.5 ± 24.88
Week 48	24	47.0	8.7	–38.3 ± 27.33
Week 60	21	51.3	16.1	–35.2 ± 34.40
Week 72	17	55.6	6.5	–49.1 ± 22.22
Week 84	17	55.6	11.6	–43.9 ± 28.55
Week 96	13	53.6	8.5	–45.1 ± 26.45
Week 108	9	58.4	11.7	–46.8 ± 26.49
Week 120	3	53.3	3.3	–50.0 ± 18.52

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.
a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.
b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

Table 17: Physician's Global Assessment of Disease Activity by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0		55.3		
Week 12	31	54.5	13.1	–41.4 ± 21.20
Week 24	30	55.3	10.0	–45.3 ± 21.32
Week 36	28	53.0	10.0	–43.0 ± 23.90
Week 48	24	55.9	9.4	–46.5 ± 18.35
Week 60	21	56.1	13.4	–42.7 ± 28.17
Week 72	17	59.5	8.4	–51.1 ± 19.53
Week 84	17	59.5	9.0	–50.5 ± 16.77
Week 96	13	59.1	11.6	–47.5 ± 24.42
Week 108	9	61.7	13.3	–48.3 ± 28.24
Week 120	3	57.7	1.3	–56.3 ± 5.13

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.
a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.
b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

2.2.4.4 Physical function (DICHAQ)

DICHAQ is a patient reported outcome measure and the physical function portion of the questionnaire encompasses 8 categories, including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The questionnaire is scored on a scale of 0 (no disability) to 3 (complete disability).

A decrease in mean change from Baseline was observed for the DICHAQ from Week 12 through Week 120, indicating an improvement in disease activity (Table 18). In the observed data set, the largest mean change from Baseline (–0.9) occurred at Week 72 and Week 84; however, the number of assessments completed during those scheduled visits decreased to approximately 50% (Table 18). Results from analysis of the LOCF data were similar to the observed data.

Table 18: Disability Index of Child Health Assessment Questionnaire by Visit (Observed) (ITT)

Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Week 0		1.2		
Week 12	31	1.2	0.7	–0.5 ± 0.64
Week 24	30	1.2	0.7	–0.5 ± 0.69
Week 36	27	1.1	0.5	–0.6 ± 0.70
Week 48	24	1.1	0.4	–0.6 ± 0.68
Week 60	21	1.0	0.5	–0.6 ± 0.71
Week 72	16	1.2	0.3	–0.9 ± 0.64
Week 84	17	1.2	0.3	–0.9 ± 0.68
Week 96	13	1.1	0.3	–0.8 ± 0.56
Week 108	9	1.0	0.3	–0.8 ± 0.63
Week 120	3	1.0	0.2	–0.8 ± 1.09

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.

a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.

b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

2.2.4.5 Physical function (CHQ-PF50)

The CHQ-PF50 is a patient-reported outcome measure that includes 50 questions related to physical and mental health, social limitations, and impact on parents and family. Scores for each category were converted to a scale from 0 (implies higher disease activity) to 100 (implies lower disease activity).

At Week 12, mean change from Baseline increased for all categories and the greatest increase was observed for physical functioning, role/social limitations/emotional/behavioural, and role/social limitations – physical, and bodily pain/discomfort (Table 19). Other categories showed a slow, steady increase in mean from Baseline through Week 120. The categories that demonstrated the greatest increase overall were global health, physical functioning, role/social limitations – physical, bodily pain/discomfort, and parental impact – emotional (Table 19, split across the next few pages). Results for the observed and LOCF data were similar.

Table 19: Child's Health Questionnaire Parent Form by Visit (Observed) (ITT)

Category Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Global health				
Week 0		50.5		
Week 12	29	49.8	66.9	17.1 ± 29.48
Week 24	28	52.7	76.4	24.3 ± 25.77
Week 36	24	51.7	77.0	25.0 ± 27.27
Week 48	22	47.0	75.9	30.9 ±23.79
Week 60	19	50.3	66.8	21.8 ± 27.35
Week 72	17	47.1	78.5	31.5 ± 24.86
Week 84	17	47.1	73.2	26.2 ± 25.89
Week 96	11	45.9	78.6	32.7 ± 20.66
Week 108	8	37.5	74.4	36.9 ± 19.99
Week 120	3	40.0	85.0	45.0 ± 17.32

Table 19: Child's Health Questionnaire Parent Form by Visit (Observed) (ITT) - Continued

Physical functioning				
Week 0		50.9		
Week 12	31	50.9	81.5	30.6 ± 32.14
Week 24	30	52.1	83.7	31.6 ± 31.91
Week 36	27	52.3	88.7	36.4 ± 31.26
Week 48	23	56.5	88.6	31.5 ± 28.39
Week 60	21	54.8	83.9	29.0 ± 32.30
Week 72	16	52.5	93.1	40.6 ± 27.00
Week 84	17	51.4	91.4	40.0 ± 30.44
Week 96	13	55.6	90.0	34.3 ± 27.88
Week 108	9	54.9	92.0	37.0 ± 27.92
Week 120	3	44.4	98.1	53.7 ± 8.49
Role/social limitations/emotional/behavioural				
Week 0		75.2		
Week 12	23	73.4	94.7	20.8 ± 32.53
Week 24	22	74.9	93.5	17.7 ± 29.43
Week 36	20	76.7	92.8	17.2 ± 25.86
Week 48	18	78.4	95.0	16.0 ± 27.28
Week 60	16	77.8	96.9	20.8 ± 31.91
Week 72	13	72.2	99.3	26.5 ± 32.25
Week 84	13	72.6	94.4	20.5 ± 33.29
Week 96	9	69.1	100.0	30.9 ± 32.76
Week 108	7	71.4	95.8	23.8 ± 25.20
Week 120	2	66.7	100.0	33.3 ± 47.14
Role/social limitations – physical				
Week 0		61.3		
Week 12	21	57.6	88.5	28.6 ± 32.97
Week 24	20	59.1	94.2	31.7 ± 35.00
Week 36	18	60.0	91.7	30.6 ± 39.30
Week 48	17	60.8	90.0	27.5 ± 37.24
Week 60	15	62.2	95.6	34.4 ± 39.07
Week 72	12	59.0	95.8	36.1 ± 41.34
Week 84	12	58.3	92.7	34.7 ± 43.50
Week 96	8	54.2	97.2	41.7 ± 37.80
Week 108	6	41.7	91.7	47.2 ± 37.14
Week 120	1	33.3	100.0	66.7
Bodily pain/discomfort				
Week 0		40.0		
Week 12	30	40.7	76.5	35.0 ± 30.60
Week 24	29	41.4	78.0	36.2 ± 32.99
Week 36	26	40.4	80.0	38.8 ± 27.76
Week 48	23	42.2	80.4	41.7 ± 29.64
Week 60	20	39.5	74.8	39.0 ± 34.78
Week 72	17	36.5	84.7	48.2 ± 20.38
Week 84	17	36.5	77.6	41.2 ± 25.47
Week 96	13	40.8	83.1	42.3 ± 23.51
Week 108	9	38.9	80.0	41.1 ± 37.56
Week 120	3	50.0	100.0	50.0 ± 17.32

Table 19: Child's Health Questionnaire Parent Form by Visit (Observed) (ITT) - Continued

Category Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Behaviour				
Week 0		70.4		
Week 12	29	71.0	75.6	5.6 ± 15.78
Week 24	28	72.3	75.7	4.2 ± 13.58
Week 36	27	72.4	72.8	0.4 ± 16.87
Week 48	24	74.4	78.0	3.6 ± 17.04
Week 60	21	75.8	75.5	–0.3 ± 13.95
Week 72	17	74.0	74.1	0.1 ± 16.44
Week 84	17	74.0	75.4	1.5 ± 13.97
Week 96	13	69.5	76.6	7.1 ± 11.81
Week 108	9	71.1	80.0	8.9 ± 10.46
Week 120	3	63.3	57.2	–6.1 ± 31.28
Global behaviour item				
Week 0		68.8		
Week 12	19	72.3	75.4	4.5 ± 18.17
Week 24	19	68.8	76.7	10.8 ± 17.66
Week 36	18	68.3	79.0	9.2 ± 25.04
Week 48	16	75.0	76.3	4.1 ± 18.55
Week 60	13	83.1	76.2	–3.5 ± 20.35
Week 72	10	81.0	82.0	2.0 ± 15.31
Week 84	11	82.9	78.4	–5.0 ± 14.32
Week 96	9	77.2	79.2	0.0 ± 17.68
Week 108	6	81.7	80.0	–4.2 ± 10.21
Week 120	1	85.0	76.7	–25.0
Mental health				
Week 0		75.6		
Week 12	31	77.3	80.8	3.5 ± 11.12
Week 24	30	77.3	80.8	3.5 ± 10.76
Week 36	27	76.1	80.2	4.1 ± 14.01
Week 48	24	77.1	82.5	5.4 ± 11.88
Week 60	21	77.6	79.8	2.1 ± 14.02
Week 72	17	77.1	82.1	5.0 ±12.37
Week 84	17	77.1	79.7	2.6 ± 8.50
Week 96	13	81.2	85.4	4.2 ±11.88
Week 108	9	82.8	81.9	–0.8 ± 15.00
Week 120	3	83.3	80.0	–3.3 ± 20.21
Self esteem				
Week 0		73.4		
Week 12	23	74.0	86.5	10.6 ± 23.91
Week 24	22	74.3	87.2	10.5 ± 24.75
Week 36	19	74.9	92.0	16.8 ± 22.02
Week 48	16	77.8	92.9	15.2 ± 22.60
Week 60	14	81.1	91.6	10.2 ± 22.53
Week 72	13	83.5	81.7	–2.8 ± 31.78
Week 84	13	83.5	93.9	9.4 ± 18.52
Week 96	9	88.9	96.6	6.9 ± 19.87
Week 108	6	95.1	93.2	–4.2 ± 10.87
Week 120	1	91.7	93.1	4.2

Table 19: Child's Health Questionnaire Parent Form by Visit (Observed) (ITT) - Continued

Category Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
General health perceptions				
Week 0		43.0		
Week 12	26	43.3	44.8	0.7 ± 14.27
Week 24	25	44.1	49.3	3.8 ± 14.98
Week 36	22	41.6	50.6	6.2 ± 15.99
Week 48	19	41.8	51.2	7.2 ± 13.36
Week 60	18	43.1	45.7	0.7 ± 10.65
Week 72	15	43.2	52.8	9.1 ± 10.10
Week 84	15	43.2	51.4	7.2 ± 13.03
Week 96	11	40.2	52.0	10.9 ± 16.00
Week 108	7	41.4	52.9	9.0 ± 16.61
Week 120	3	46.9	51.7	4.7 ± 12.92
Change in health				
Week 0		2.8		
Week 12	30	2.8	4.2	1.4 ± 1.75
Week 24	29	2.9	4.6	1.7 ± 1.67
Week 36	25	2.9	4.6	1.7 ± 1.80
Week 48	22	2.8	4.5	1.7 ± 2.40
Week 60	20	3.0	4.2	1.3 ± 2.57
Week 72	16	2.8	4.4	1.6 ± 2.13
Week 84	16	2.8	4.1	1.3 ± 1.98
Week 96	12	3.0	4.5	1.5 ± 2.02
Week 108	8	3.0	4.0	0.9 ± 2.70
Week 120	3	1.3	3.7	2.3 ± 0.58
Parental impact – emotional				
Week 0		43.8		
Week 12	30	43.9	54.0	11.4 ± 26.12
Week 24	28	45.2	62.9	19.0 ± 28.59
Week 36	26	43.3	69.8	29.2 ± 33.10
Week 48	23	44.2	76.0	34.1 ± 33.98
Week 60	20	45.4	75.8	31.7 ± 32.40
Week 72	16	43.2	74.5	34.4 ± 36.37
Week 84	16	43.2	69.1	27.6 ± 41.69
Week 96	11	37.5	77.8	43.9 ± 40.15
Week 108	8	26.0	75.9	46.9 ± 40.81
Week 120	2	8.3	80.6	62.5 ± 41.25
Parental impact – time				
Week 0		69.2		
Week 12	30	68.9	74.4	4.6 ± 24.50
Week 24	28	69.0	80.8	13.5 ± 28.59
Week 36	26	69.7	90.9	21.8 ± 24.24
Week 48	23	72.0	90.7	18.4 ± 24.76
Week 60	20	73.3	85.7	13.3 ± 31.55
Week 72	16	71.5	94.1	22.2 ± 30.09
Week 84	16	71.5	89.5	17.4 ± 35.13
Week 96	12	66.7	88.0	20.4 ± 27.15
Week 108	8	65.3	82.7	15.3 ± 25.85
Week 120	2	44.4	100.0	55.6 ± 62.85

Table 19: Child's Health Questionnaire Parent Form by Visit (Observed) (ITT) - Continued

Category Visit	n[a] (N = 32)	Baseline[b] Mean	Visit Mean	Change from Baseline Mean ± SD
Family activities				
Week 0		70.6		
Week 12	30	70.1	79.0	8.3 ± 28.41
Week 24	28	70.1	87.1	17.6 ± 24.15
Week 36	26	70.2	90.6	20.0 ± 28.50
Week 48	23	70.7	88.0	16.8 ± 26.43
Week 60	20	71.7	86.1	14.8 ± 30.90
Week 72	16	71.1	89.0	17.2 ± 31.43
Week 84	16	71.1	90.0	18.2 ± 30.27
Week 96	12	67.4	87.8	19.4 ± 27.60
Week 108	8	60.9	83.8	20.8 ± 29.38
Week 120	2	27.1	97.2	68.8 ± 20.62
Family cohesion				
Week 0		76.8		
Week 12	30	76.5	78.4	2.5 ± 14.00
Week 24	28	77.9	82.2	4.3 ± 23.28
Week 36	26	74.0	79.8	5.6 ± 20.66
Week 48	23	76.1	79.0	3.7 ± 15.61
Week 60	20	76.0	81.7	4.8 ± 16.66
Week 72	16	73.4	80.9	7.2 ± 29.15
Week 84	16	73.4	82.1	8.4 ± 39.19
Week 96	12	67.1	85.8	18.8 ± 35.36
Week 108	8	64.4	83.9	19.4 ± 35.30
Week 120	2	85.0	66.7	–27.5 ± 38.89

N = number of patients in the ITT population; n = number of patients with a nonmissing value at each visit.
a. Number of patients with both Baseline and Visit means whose values were used to calculate mean change from Baseline.
b. Baseline is defined as the last nonmissing value prior to the first dose of study drug. Patients with nonmissing Baseline and at least 1 post-baseline observation are included in the analysis.

2.3 Study M10-240 – pJIA aged 4-17 in Japan[17]

2.3.1 Protocol identification: NCT00690573

The primary objective of this single-arm, OL study was to evaluate the efficacy, pharmacokinetics, and safety of adalimumab in patients aged 4 to 17 years with JIA in Japan.

2.3.2 Study design and methods

The study design and methods are described in Table 20. It should be noted that the due to the study design, direct comparisons between treatment groups are not possible; this was not a RCT and therefore is not a comparative study. Baseline characteristics of the enrolled participants were variable and therefore study populations are not directly comparable.

Table 20: Study M10-240 design and methods[17]

Item	M10-240
Design	Single-arm, open-label, multicenter study of adalimumab
Number of participants	25
Countries and settings	Japan, 14 sites
Objectives	The primary objective of this study was to evaluate the efficacy, pharmacokinetics, and safety of adalimumab therapy in paediatric patients with pJIA in Japan.
Inclusion criteria	• Paediatric patients aged 4 to 17 years • Diagnosis of pJIA by ACR criteria at screening

	• Active disease defined as five or more swollen joints (not due to deformity) and three or more joints with limitation of passive motion due to pain and/or pain by pressure (tenderness) • Patients could have systemic, polyarticular, or oligoiarticular JIA at disease onset but free of any systemic JIA manifestations for at least 12 weeks before screening. • Patients must have an inadequate clinical response (or intolerance) to NSAIDs or MTX (8–10 mg per 1 m^2 of body surface area per week for 12 weeks or more), or other conventional therapies for JIA such as corticosteroids. • Negative urine pregnancy test at screening and baseline for all post-pubertal females. • Use of use of adequate contraception during the study and for 150 days after last injection was required for all sexually active patients.
Exclusion criteria	• Patients with a history of or comorbid inflammatory joint disease other than JIA, including psoriatic arthritis, arthritis related to enthesopathy, and systematic lupus erythematosus. • Patients classified as functional class IV by ACR criteria, prior treatment with alkylating agents or biologic therapies for JIA, joint surgery within 8 weeks prior to screening, or articular corticosteroids or sodium hyaluronate within 28 days prior to baseline. • Significant cardiac disease • Abnormal laboratory values • Positive serology for anti-human immunodeficiency virus antibody, hepatitis B surface antigen, or hepatitis C antibody • History of a central nervous system (CNS) neoplasm • Active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease • Ongoing chronic or active infection or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 28 days or oral antibiotics within 14 days prior to screening; history of Listeria infection • Tuberculosis confirmed by chest X-ray or chest computed tomography at screening or confirmed history of tuberculosis • History of cancer, lymphoma, leukaemia, or lymphoproliferative disease other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localised carcinoma in situ of the cervix; and vaccination with a live vaccine within 12 weeks of study drug administration through 70 days of the last dose.

Outcomes (including definition and measurement details)	Clinical measures were assessed at weeks 2, 4, 8, 16, and 24 and every 12 weeks after Week 24.
	
	Primary effectiveness outcome
	• PedACR scores as assessed by:-
	  o Physician's Global Assessment of disease activity (PhGA)
	  o Patient's Global Assessment of well-being (PaGA)
	  o Active joint count in 73 joints (AJC73)
	  o Limitation of motion in 69 joints (LOM69)
	  o Childhood Health Assessment Questionnaire (CHAQ) to assess physical function
	  o CRP concentration.
	
	PedACR 30 response was defined as ≥30 % improvement in at least three of six JIA core criteria and ≥30 % worsening in not more than one of six JIA core criteria. PedACR 50/70/90 responses were defined similarly according to the respective level of response for at least three of the six JIA core

	criteria and ≥30 % worsening in not more than one of six JIA core criteria. Primary safety outcomes • Incidence of SAEs and AEs of interest assessed by: o Observational AEs Duration of exposure was calculated as the number of days between the first dose of study drug and the last dose plus 14 days.
Stratification	N/A
Patient enrolment	From May 2008 to August 2010
Intervention	Adalimumab After a 2- to 4-week screening period, patients received SC adalimumab injections eow. Patients weighing <30 kg received adalimumab 20 mg eow and patients weighing ≥30 kg received adalimumab 40 mg eow. Adalimumab dosage was re-evaluated based on actual body weight at week 16 and every 12 weeks after week 24 through week 60.
Comparator	N/A
Concomitant medication	With MTX: N=20 Without MTX: N=5 DMARDs other than MTX were to be discontinued at least 28 days before baseline. NSAIDs or low-dose corticosteroids (≤0.2 mg/kg of prednisone per day, up to a maximum of 10 mg/day, including SC or intramuscular injection) were permitted at stable doses.
Sequence generation	N/A
Allocation concealment	Based on pharmacokinetic simulations performed using body surface area-dependent dosing data from a Western (USA and Europe) clinical JIA study (NCT00048542) a fixed dose dosing regimen was established in which two different doses of adalimumab were administered based on body weight.
Participant and outcome assessor blinding	N/A
Outcome assessor blinding to interventions	N/A
Statistical analyses	Efficacy analyses were conducted on the full analysis set, which was defined as all patients who received at least one dose of study drug. The primary efficacy endpoint, PedACR 30 response rate at week 16, was analysed with non-responder imputation (NRI), whereby patients with missing data at week 16 or who failed to meet PedACR 30 response at week 16 were considered non-responders. Secondary endpoints, including longitudinal data for PedACR 30/50/70/90 response rates and the JIA core variables from week 16 through week 60, were analysed using observed cases. Serum adalimumab and AAA concentrations were summarised descriptively. The numbers and percentages of patients who experienced AEs with an onset on or after the first adalimumab injection up to 70 days (five half-lives) after the last injection were summarized for the safety analysis set, which was identical to the full analysis set

AAA: anti-adalimumab antibody; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-Reactive Protein; DMARDs: Disease modifying anti-rheumatic drugs; eow: Every other week; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; PhGA: Physician's Global Assessment of disease activity; PaGA: Patient's Global Assessment of well-being

2.3.3 Baseline Characteristics

Baseline demographic and clinical characteristics were similar between groups (Table 24). However, baseline anti-cyclic citrullinated peptide (anti-CCP) antibody concentrations were considerably greater in patients who were receiving MTX compared with those not receiving MTX. All patients had pJIA at disease onset, except for one patient (not receiving MTX) who had oligoarticular JIA at disease onset.

Table 21: Baseline Characteristics for study M10-240[17]

Demographics	Adalimumab with MTX (N=20)	Adalimumab without MTX (N=5)	All Patients (n = 25)
Age			
Mean (SD), years	13.2 (3.22)	12.6 (4.39)	13.0 (3.38)
4–12 years, n (%)	9 (45)	3 (60)	12 (48)
13–17 years, n (%)	11 (55)	2 (40)	13 (52)
Female, n (%)	15 (75)	5 (100)	20 (80)
Body weight			
Mean (SD), kg	40.5 (11.28)	35.3 (16.64)	39.5 (12.31)
≥30 kg, n (%)	14 (70)	3 (60)	17 (68)
Duration of JIA, mean (SD), years	4.8 (3.97)	4.2 (2.75)	4.7 (3.72)
RF positive, n (%)	14 (70)	3 (60)	17 (68)
Anti-CCP antibody, mean (SD), U/mL	105.5 (135.67)	8.5 (15.50)	86.1 (127.19)
LOM69, mean (SD)	8.6 (5.65)	5.8 (2.05)	8.0 (5.22)
AJC73, mean (SD)	12.0 (6.10)	13.6 (9.32)	12.3 (6.66)
CRP concentration			
Abnormal (>0.3 mg/dL), n (%)	11 (55)	3 (60)	14 (56)
Mean (SD), mg/dL	1.0 (1.32)	3.6 (3.86)	1.5 (2.22)
CHAQ (0–3), mean (SD)	0.8 (0.79)	0.7 (1.11)	0.8 (0.84)
PhGA (0–100 mm), mean (SD)	56.5 (18.49)	58.6 (25.83)	56.9 (19.56)
PaGA (0–100 mm), mean (SD)	44.6 (24.84)	48.6 (34.20)	45.4 (26.19)

AJC: active joint count; CCP: cyclic citrullinated peptide; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-reactive Protein; JIA: juvenile idiopathic arthritis; LOM: limitation of motion; MTX: methotrexate;, PaG: Patient's Global Assessment; PhGA: Physician's Global Assessment; RF: rheumatoid factor; SD: standard deviation

2.3.4 Results

Twenty-four patients completed 24 weeks of therapy, including the primary endpoint assessment at week 16, and 22 patients completed up to 60 weeks. Three patients discontinued the study due to lack of efficacy. All three were in the concomitant MTX group. The average duration of adalimumab treatment through week 60 was 393 days.

2.3.4.1 Primary efficacy outcome

Overall, a very high proportion of patients achieved PedACR 30 at week 16 and week 60 of adalimumab therapy (see **Error! Reference source not found.**)

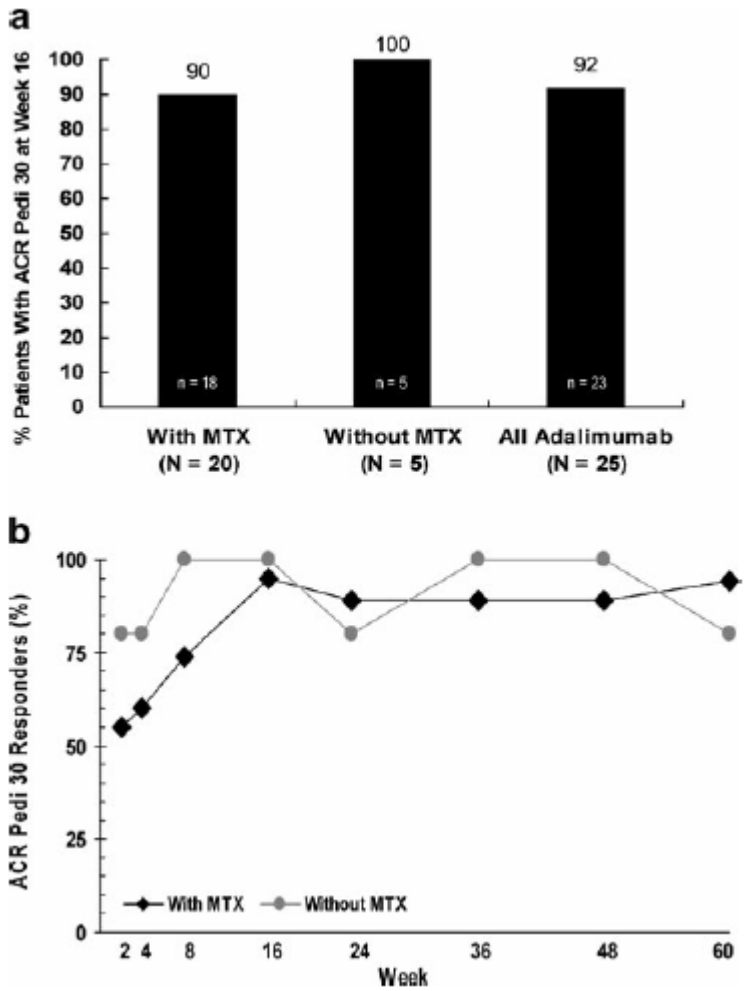

Figure 18: PedACR 30 response rates
a: PedACR 30 response rates at week 16 of adalimumab therapy (NRI).
b: PedACR 30 response rates over time with adalimumab therapy (as observed) (black diamond with MTX, grey circle without MTX)

PedACR 50/70 response rates at week 16 of adalimumab therapy were generally consistent with those at Week 60, with approximately 90 and 75% of patients achieving these levels of response. Overall, PedACR 90 response rates increased from ≤20 % at week 16 to 50 % at week 60. Overall, PedACR 90 response rates increased from ≤20 % at week 16 to 50 % at week 60.

Adalimumab therapy was associated with improvements in each of the six JIA core variables over time (Table 22). Mean decreases in disease activity generally started as early as week 2 (data not shown) and remained consistent with improvements observed through week 60.

Table 22: JIA core variables at Weeks 16 and 60 of adalimumab therapy, as observed[17]

	Adalimumab with MTX			Adalimumab without MTX		
	Mean baseline value	Mean visit value	Mean % Change	Mean baseline value	Mean visit value	Mean % Change
Week 6						
PhGA (mm)	55.8	20.6	−64.8	58.6	10.6	−83.8
PaGA (mm)	44.7	22.1	−50.5	48.6	15.4	−74.5
AJC73	11.0	3.8	−59.9	13.6	3.2	−80.3
LOM69	7.5	3.7	−38.3	5.8	1.6	−76.7
CHAQ	0.7	0.4	−32.8	0.7	0.4	−35.7

CRP (mg/dL)	0.9	0.3	−23.8	3.6	1.7	−65.1
Week 60						
PhGA (mm)	55.0	16.7	−74.0	58.6	12.8	−81.5
PaGA (mm)	42.9	16.6	−51.7	48.6	27.0	−48.6
AJC73	11.1	1.9	−81.5	13.6	3.0	−79.8
LOM69	7.6	1.5	−78.7	5.8	2.4	−72.2
CHAQ	0.7	0.2	−46.9	0.7	0.5	−41.0
CRP (mg/dL)	1.0	0.4	−46.6	3.6	1.4	−4.0

AJC: active joint count; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-reactive protein; LOM: limitation of motion; MTX: methotrexate; PaGA: Patient's Global Assessment; PhGA Physician's Global Assessment

2.4 Study M11-328 – ERA aged 6-17

2.4.1 Protocol identification: NCT01166282[18,19]

The primary objectives of this double-blind, placebo-controlled, OL rescue/extension study (Figure 19) were to evaluate the safety and efficacy of adalimumab given SC eow as compared with placebo in paediatric patients with ERA and the pharmacokinetics (PK) and immunogenicity of adalimumab following SC administration in the patient population.

2.4.2 Study design and methods

The study design and methods of this study are described in Table 23.

The study included a:

- screening period (30 days)
- DB placebo-controlled treatment period with an early escape option (12 weeks)
- OL adalimumab eow treatment period (maximum 144 weeks)
- follow-up phone call (70 days after last dose of adalimumab)

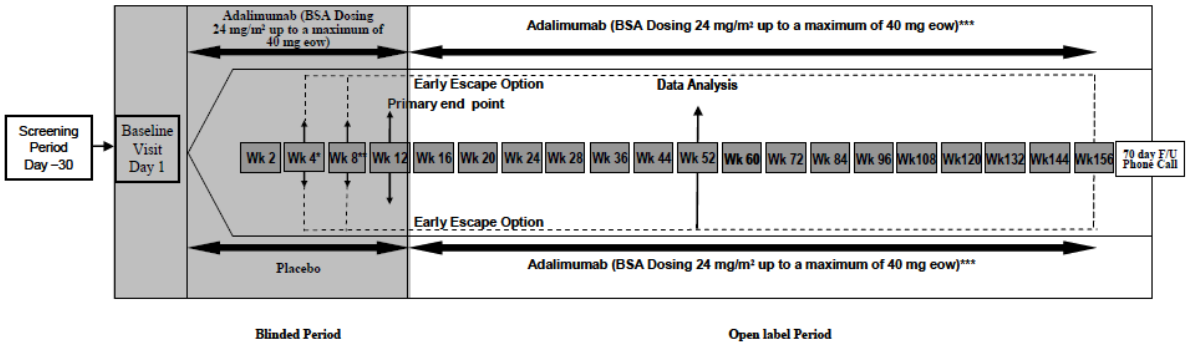

Figure 19: Study design schematics

* Patients fulfilling protocol defined criteria for worsening of ERA may early escape into OL period.
** Patients who have failed to demonstrate improvement in ERA may early escape into the OL period.
*** Each patient will receive a maximum of 144 weeks of OL ADA. The OL period continues until Week 156 or until a patient has completed 108 weeks of treatment (from Baseline) and adalimumab has received country and local (if applicable) regulatory approval for ERA, whichever occurs first.

Table 23: Study M11-328 design and methods

Item	Study M11-328
Design	RCT; double-blind, placebo-controlled, multiple-centre, multiple dose study with an OL rescue/extension period
Number of participants	46
Countries and	Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and

setting	Switzerland; 16 sites
Objectives	• Evaluate the efficacy and safety of adalimumab given SC eow compared to placebo in paediatric patients with ERA • To examine the pharmacokinetics and immunogenicity of adalimumab following SC administration in this patient population.
Inclusion criteria	• Patients (age ≥ 6 to < 18 years at Baseline) • A diagnosis of ERA as defined by the ILAR prior to patient's sixteenth birthday. • Diagnosis of ERA as defined by ILAR • Disease activity defined as at least 3 active joints and evidence of enthesitis in at least one location • Inadequate response or intolerance to at least one nonsteroidal anti-inflammatory drug and at least one disease modifying anti-rheumatic drug, either sulfasalazine or MTX. • Patient must have had an updated immunisation schedule according to the Canadian Immunization Guide in Canada, the Mexican Immunization Guide in Mexico, or the local European guideline. • If female, patients who were sexually active and were of childbearing potential were to practice an approved method of birth control throughout the study and for 150 days after last dose of study drug. • Signed inform consent from the parent or legal guardian. • Parent or legal guardian willing to actively supervise storage and administration of study drug and to ensure that the time of each dose was accurately recorded in the patient's diary. • Patient was judged to be in good health as determined by the PI on the basis of results of medical history, laboratory profile, physical examination, CXR (if indicated by TB screening test results), and 12-lead ECG performed during Screening. • Patient had a negative PPD test and/or QuantiFERON-TB Gold test. If the patient had a positive (≥ 5 mm induration) PPD test and/or QuantiFERON-TB Gold test at Screening, a CXR (post anterior and lateral view) was to be performed for evaluation of active TB disease. If the patient had evidence of a latent TB infection, the patient was to initiate and complete a minimum of 2 weeks of an ongoing course of anti-TB therapy or was to have documented completion of a full course of anti-TB therapy prior to Baseline. • Patient had to be able and willing to self-administer SC injections or had a qualified person available to administer SC injections.
Exclusion criteria	• Any ILAR JIA subtype other than ERA • Psoriasis or a history of psoriasis in the patient or first-degree relative • Presence of Immunoglobulin M (IgM) rheumatoid factor • Presence of systemic JIA • History of IBD, previous biologic therapy including anti-TNF therapy with a potential impact on paediatric ERA • Diagnosis of acute inflammatory joint disease not associated with ERA. • Known hypersensitivity to adalimumab or its excipients. • Patient had received intra-articular joint injections with corticosteroids within 28 days prior to Baseline. • Joint surgery within 2 months prior to Baseline. • If entering the study on concomitant MTX or SSZ at Screening/Baseline, patient was not on stable dose of MTX (≤ 15 mg/m^2 with a maximum dose of 25 mg/week) or SSZ (≤ 50 mg/m^2 with a maximum dose of 3 g/day) for 28 days prior to Baseline. • Patient was on concomitant DMARDs other than MTX or SSZ within 28 days prior to Baseline. • If entering the study on concomitant prednisone (and/or prednisone

	equivalents), patient was not on a stable dose (≤ 10 mg/day or 0.2 mg/km body weight, whichever was lower) for 14 days prior to Baseline.
	• If entering the study on NSAIDs and/or analgesics, patient was on opioid analgesics within 14 days prior to Baseline or patient was not on stable dose for 14 days prior to Baseline.
	• Patient who had been treated with any investigational drug of chemical or biologic nature within 30 days or 5 half-lives (whichever was longer) of the drug prior to Baseline.
	• Patient had an infection(s) requiring treatment with IV anti-infectives within 30 days prior to Baseline or oral anti-infectives within 14 days prior to Baseline
	• History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
	• History of moderate to severe CHF NYHA class III or IV), recent CVA and any other condition, which, in the opinion of the investigator, would have put the patient at risk by participation in the protocol.
	• Evidence of dysplasia or history of malignancy (including lymphoma and leukaemia) other than a successfully treated nonmetastatic cutaneous squamous cell or basal carcinoma or localized carcinoma in situ of the cervix.
	• History of clinically significant drug or alcohol abuse in the last 12 months.
	• History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
	• Positive pregnancy test at Screening or Baseline.
	• Female patient who was pregnant or breastfeeding or considering becoming pregnant during the study.
	• Patient was considered by the investigator, for any reason, to be an unsuitable candidate for the study.
	• Patient had received any live or live/attenuated vaccines within 90 days prior to Screening.
	• Patient with diagnosis and current symptoms of fibromyalgia.
	• Screening laboratory and other analyses that showed any of the following abnormal results:
	  o ECG with clinically significant abnormalities;
	  o AST or ALT > 1.75 × the upper limit of the reference range;
	  o Total bilirubin ≥ 3 mg/dL;
	  o Serum creatinine > 1.6 mg/dL (141.4 µmol/L);
	  o Clinically significant abnormal screening laboratory results as evaluated by the investigator.
	• Hepatitis B (HBV): hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the hepatitis B deoxyribonucleic acid polymerase chain reaction (HBV-DNA PCR) qualitative test for hepatitis B core antibody total (HBc Ab)/hepatitis B surface antibody (HBs Ab) positive patients.
	• Prior exposure to natalizumab (Tysabri®) or efalizumab (Raptiva®).
	• Chronic recurring infections or active TB.
	• Patients with an active systemic viral infection or any active viral infection that, according to the investigator's clinical assessment, made the patient an unsuitable candidate for the study.

Outcomes (including definition and measurement details)	Primary safety outcomes • Adverse effects o Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not the event was considered causally related to the use of the product. • SAEs

	o Death o Life-threatening o Hospitalisation or prolongation of hospitalisation o Congenital anomaly o Persistent or significant disability/incapacity o Important medical event requiring medical or surgical intervention to prevent serious outcome o Spontaneous abortion o Elective abortion Primary efficacy outcome • Percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness). Secondary efficacy outcomes • Number of sites of enthesitis • TJC for 72 joints • SJC for 68 joints • PedACR30 response • PedACR50 response Other efficacy variables • Number and percent change in active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) (component of PedACR30) (excludes Week 12 as that was the primary variable) • Number of sites of enthesitis (excluding Week 12) • SPARCC enthesitis index • MASES • TJC for 72 joints (excluding Week 12) • SJC for 68 joints (excluding Week 12) • Number of joints with LOM (component of PedACR30) • Number of digits with dactylitis • PedACR30/50/70 responses (excluding Week 12) • BASDAI • Inflammation (mean of questions 5 and 6 of the BASDAI) • BASDAI50 • PGA (component of PedACR30) • Patient's assessment of total back pain • Parent's assessment of patient's pain • hs-CRP (component of PedACR30) • Parent's global assessment of patient's overall well-being (component of PedACR30) • CHAQ (component of PedACR30) • Parent's assessment of patient's eye disease • Parent's assessment of patient's school attendance
Stratification	Randomisation was not stratified by site, because of the small expected number of patients per site, or by any other stratification factor
Patient enrolment	September 2010 to November 2012
Intervention	adalimumab (BSA dosing 24 mg/m2 up to a maximum of 40 mg) eow
Comparator	Biological: placebo for adalimumab – blinded; matching BSA dosing An early escape option at Weeks 4 and 8 was provided for patients who either experienced a worsening of disease or failed to improve. Worsening of disease at Week 4 is defined as increase in active joint count (AJC) ≥ 30% with a minimum of at least 2 additional active joints compared to Baseline. Failure to improve at Week 8 is defined as <30% improvement in AJC compared to

	Baseline
Concomitant medication	The influence of concomitant treatment with MTX was evaluated. However patients had to be on stable dose of MTX, SSZ, prednisone (or prednisone equivalents) to enter the study and not have been on any DMARDS other than MTX or SSZ within 28 days prior to Baseline.
Sequence generation	An IVRS/IWRS was used to determine the randomisation of patients. Eligible patients were randomised in a 2:1 fashion to adalimumab or placebo.
Allocation concealment	An IVRS supported by a contracted vendor generated the randomisation schedule and assigned participants to treatment groups.
Participant and outcome assessor blinding	All personnel with direct oversight of the conduct and management of the trial (with the exception of the AbbVie drug supply management team), the investigator, study site personnel, and the patient remained blinded to each patient's treatment throughout the blinded period of the study.
Outcome assessor blinding to interventions	The investigator, study site personnel, and the patient remained blinded to each patient's treatment throughout the blinded period of the study. The IVRS/IWRS was to provide access to blinded patient treatment information in the case of medical emergency.
Statistical analyses	The primary and secondary variables were to be analysed for the ITT population, defined as all randomised patients who received at least 1 dose of study drug. A Per Protocol (PP) Analysis of the primary and secondary variables was added by Amendment 1 to the Statistical Analysis Plan (dated 20 November 2012) in order to evaluate the impact of major protocol violations on the results of the study. The identification of major protocol deviations was done before unblinding. In the efficacy analyses, missing or incomplete data were handled using last LOCF as the primary method for continuous variables, non-responder imputation (NRI) as the primary method for dichotomous variables, and as observed cases and LOCF as sensitivity analyses. The primary efficacy variable was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness). The primary confirmatory analysis was done using an analysis of covariance (ANCOVA) model adjusting for the number of active joints at Baseline at alpha level of 0.05. For patients who did not have an active joint count at Week 12 or who had escaped early to OL treatment, their last available joint count from the DB period was used. For the comparison of secondary endpoints between the 2 treatment groups, Fisher's exact test was used for discrete variables, and 1-way ANOVA was used for continuous endpoints. Results in the OL period were reported stratified by the treatment the patient was randomised to in the DB period and overall.
Power calculation	Approximately 45 paediatric patients with ERA were planned to be enrolled. With a total sample size of 45 patients (2:1 randomisation: adalimumab 30 patients, placebo 15 patients) and an expected percent change of 70% for adalimumab versus 35% for placebo, assuming common standard deviation (SD) of 33%, the study provided 90% power to detect the treatment difference using a 2-sided 1-way ANOVA with type 1 error level alpha = 5%
Missing data	Missing data were imputed for efficacy variables only. Missing data could occur due to a missed visit, due to dropout from the study, or (for the DB period) due to early escape to the OL period. The following imputation approaches were used to impute missing data: • LOCF: Only post-Baseline values were considered to carry forward. Values from the DB period could be carried forward to the OL period when necessary for patients who entered the OL period. • NRI: Any missing binary responses at a given visit were imputed as nonresponders for that visit. This imputation approach ensured the most conservative estimate for a response.

	• As observed: No imputation of missing values, only available data are presented.

2.4.3 Baseline characteristics

A full set of baseline characteristics is presented in Table 24.The patient groups were considered well matched at baseline. No statistically significant differences were observed between treatment groups in baseline demographic and disease profiles (p>0.05).

Table 24: Baseline characteristics of Study M11-328 (18), values are mean and SD unless otherwise specified[18]

Demographics	Placebo (n = 15)	Adalimumab (n = 31)	Total (n = 46)
Sex (%)			
Female	6 (40.0)	9 (29.0)	15 (32.6)
Males	9 (60.0)	22 (71.0)	31 (67.4)
P value[a]	0.514		
Mean age ± SD (years)	11.9 ± 2.85	13.4 ± 2.86	12.9 ± 2.92
P value[a]	0.091		
Age Group (%)			
6 to <9 years	0	2 (6.5)	2 (4.3)
9 to <12 years	8 (53.3)	5 (16.1)	13 (28.3)
12 to <15 years	4 (26.7)	12 (38.7)	16 (34.48)
≥ 15 years	3 (20.0)	12 (38.7)	15 (32.6)
Race (%)			
White	10 (66.7)	25 (80.6)	35 (76.1)
Black	1 (6.7)	0	1 (2.2)
Asian	1 (6.7)	0	1 (2.2)
Other	3 (20.0)	6 (19.4)	9 (19.6)
P value[a]	0.462		
Mean body mass index (BMI) ± SD (kg/m^2)	19.7 ± 4.42	20.7 ± 4.33	20.4 ± 4.34
P value[a]	0.460		
Mean percentile on CDC growth chart ± SD	57.3 ± 36.51	54.4 ± 32.05	55.3 ± 33.18
P value[a]	0.787		

a. *P* value for difference between treatment groups from Fisher's exact test for categorical data and from 1-way ANOVA for continuous data
b. Non-white races were combined for analysis of race. NOTE: percent calculated on non-missing values

2.4.4 Results

2.4.4.1 Primary efficacy outcome

A statistically significant larger decrease in mean percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) was observed in patients in the adalimumab group (–62.6) compared with the placebo group (–11.6, p = 0.039). A sensitivity analysis using the observed case analysis method, which included only those patients with an active joint count at Week 12 (excludes early escapers), produced larger decreases in mean percent change from Baseline compared to the ITT (LOCF) analysis in both treatment groups (–32.1 with placebo versus –83.3 with adalimumab; p=0.02).

Numerically superior, but not statistically significant results, were demonstrated for the adalimumab group compared to the placebo group using the PP analysis set (LOCF), which excluded significant protocol violators. In this analysis, the placebo group response was higher compared to the primary analysis (ITT [LOCF]) (mean percent change from Baseline –30.2 versus –11.6, respectively), but the response in the adalimumab group was similar in both analyses (and –66.0 versus –62.6, respectively). Results are presented in

Table 25.

Table 25: Percent Change from Baseline at Week 12 in Number of Active Joints with Arthritis (ITT and PP)[18]

		Placebo		Adalimumab	Between Group Differences (95% CI)		
Week 12	**N**	**Mean % Change ± SD**	**N**	**Mean % Change ± SD**	**Difference**	**95% CI**	***P* Value[a]**
Primary analysis ITT (LOCF)	15	-11.6 ± 100.5	31	-62.6 ± 59.53	-51.17	-99.69, -2.66	0.039
Sensitivity analyses							
ITT (as observed)	12	-32.1 ± 100.72	27	-83.3 ± 24.85	-51.58	-93.60, -9.55	0.018
PP (LOCF)	14	-30.2 ± 72.38	27	-66.0 ± 57.29	-36.00	-78.31, 6.30	0.093

LOCF: Last observation carried forward; ITT: intention-to-treat

a. *P* value for difference between treatment groups from ANCOVA with treatment group and number of active joints at Baseline in the model.

Although not statistically significant (p>0.05), the majority of patients demonstrated numerical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), PedACR50 response. However, results for the 6th ranked secondary efficacy variable, PedACR70 response, reached statistical significance at Week 12 (p=0.03).

2.5 STRIVE registry[20]

2.5.1 Protocol identification: NCT00783510

This ongoing global registry study is evaluating the long-term safety and effectiveness of adalimumab in patients with moderate to severe pJIA. Patients will be followed in both the adalimumab and MTX arms for up to 10 years from the enrolment date into one of the treatment arms.

The primary efficacy objective was to determine and evaluate the clinical effectiveness and patient-reported outcomes associated with adalimumab (monotherapy and in combination with MTX) in patients diagnosed with moderately to severely active polyarticular or polyarticular-course JIA. The primary safety objective was to assess and evaluate the long-term safety profile of adalimumab (monotherapy and in combination with MTX) on observational and treatment-emergent (TE) SAEs, Adverse Events of Special Interest (AESI), and pregnancy in patients diagnosed with moderately to severely active polyarticular or polyarticular-course JIA.

These safety and effectiveness measures will be collected through year 5. Starting at Year 6, patients will be followed annually for SAEs, CHF, pregnancies and malignancies through Year 10. For JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry, emergent AESI, SAEs and pregnancy (at the age when a patient can become pregnant) will be collected for the up to 10 years.

2.5.2 Study design and methods

The study design and methods are described in Table 26.

Table 26: Study M10-240 design and methods

Item	STRIVE
Design	Observational; Long-term, Multi-centre, Longitudinal Post-Marketing, Observational Registry
Number of participants	842
Countries and setting	United States, Australia, Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Portugal, Puerto Rico, Slovakia, Spain, and Sweden; 93 sites

Objectives	Primary objectives
	• Efficacy
	  o Evaluate the clinical effectiveness of adalimumab with or without concomitant MTX.
	  o Evaluate the patient-reported outcomes of adalimumab with or without concomitant MTX.
	• Safety
	  o Evaluate the observational and TE AEs and SAEs associated with adalimumab treatment (± concomitant MTX).

Inclusion criteria	For a patient enrolling into the adalimumab arm; a paediatric patient diagnosed at any time with moderately to severely active polyarticular or polyarticular-course JIA (defined as arthritis affecting >= 5 joints at the time of diagnosis of polyarticular or polyarticular-course JIA) who has been prescribed adalimumab therapy according to the local approved adalimumab product labelling and meets one of the following criteria: • 4 to 17 years of age, 2 to <4 years of age in countries with available local approval at the time of consent • Newly initiated (either at the registry entry or within 24 months from registry entry) adalimumab therapy and continuous (≤70 consecutive days off drug) adalimumab therapy for those with previous adalimumab treatment, with documentation of adverse events (AEs) and dosing information • Prior participation in an AbbVie sponsored study with continuous adalimumab therapy and documentation of AEs and dosing information Patients who were treated in the MTX arm of this registry and prematurely discontinued from the MTX arm due to being a non-responder, or became intolerant of MTX treatment or are in need of combination treatment with adalimumab therapy were still eligible to enrol into the adalimumab treatment arm if all ongoing AEs/SAEs had been resolved, and they met inclusion criteria and could enrol within the registry enrolment period. In case of ongoing AEs/SAEs at the time of the treatment arm switch, the AbbVie Designated Physician was contacted to assess the eligibility of patient to roll into the adalimumab treatment arm.
Exclusion criteria	Patients were excluded from the adalimumab and MTX arms if: • The patient could not be prescribed and treated in accordance with the approved local adalimumab and/or with the local MTX product label. • The patient required on-going treatment with anakinra, abatacept, rituximab, etanercept, and infliximab, or any other approved biologic agents or investigational agents. • The patient had prior treatment with any investigational agent or anti-rheumatic biologic therapy such as, but not limited to, abatacept, etanercept, infliximab, rituximab, or tocilizumab
Outcomes	Incidence of SAEs and AEs of interest assessed by:

(including definition and measurement details)	• Observational AEs (recorded from the first day in the registry through last contact) Clinical and functional outcomes assessed by: • 27-Joint Juvenile Arthritis Disease Activity Score (JADAS27), based on CRP • JADAS27(CRP) is a sum of the following 4 scores: Physician's global assessment of disease severity (0–10 cm VAS), parent's global assessment of patient's overall well- being (0–10 cm VAS), active joint count for 27 joints, and normalized CRP Functional outcomes assessed by: • Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) Patient reported outcomes Physical function assessed by: • Disability Index of Childhood Health Assessment Questionnaire (CHAQ-DI), which ranges from 0 (no disability) to 3 (worst disability); the minimal clinically important difference (MCID) for improvement is -0.188[a] Health-related Quality-of-life assessed by: • Child Health Questionnaire-Parent Form (CHQ-PF50), with a scale of 0 (worst possible health state) to 100 (best possible health state)
Stratification	N/A
Patient enrolment	July 2008 to January 2014
Intervention	(1) MTX alone (2) adalimumab with MTX
Comparator	N/A
Concomitant medication	N/A
Sequence generation	N/A
Allocation concealment	N/A
Participant and outcome assessor blinding	N/A
Outcome assessor blinding to interventions	N/A
Statistical analyses	N/A
Power calculation	N/A
Missing data	N/A
a. Dempster H, et al. Arthritis Rheum. 2001;44(8):1768–74.	

2.5.3 Baseline characteristics

A full set of baseline characteristics is presented in Table 27. The majority of patients in both groups were female and white. The two groups were similar in gender, race, weight, height and thus BMI distributions. The MTX arm had a large proportion of patients less than 8 years of age, whilst the adalimumab ± MTX arm included a greater percentage of patients over 9 years of age, the larger proportion of this being between 13-17 years of age. Overall, both arms were well matched for baseline disease characteristics. Although the adalimumab ± MTX arm had a large proportion of patients who had experienced prior synthetic DMARDs and biologic DMARDs therapies.

Table 27: Baseline Demographic and Clinical Characteristics of Patients in STRIVE registry study

Characteristics	MTX alone (N=302)	ADA ± MTX (N=540)
Mean (SD), years	9.6 (4.1)	12.2 (4.0)
< 4 years, n (%)	20 (6.6)	2 (0.4)
4-8 years, n (%)	109 (36.1)	113 (20.9)
9-12 years, n (%)	88 (29.1)	116 (21.5)
13-17 years, n (%)	85 (28.1)	297 (55.0)
≥ 18 years, n (%)	0	12 (2.2)
Female, n (%)	230 (76.2)	375 (69.4)
White, n (%)	271 (91.2)	478 (91.2)
Weight (kg)	38.1 (18.9)[a]	47.6 (20.0)[b]
Height (cm)	137.3 (24.6)[c]	150.3 (21.4)[d]
BMI (kg/m^2)	18.9 (4.9)[c]	20.0 (5.0)[d]
Disease Characteristics		
Disease duration, mean (SD), years	1.3 (2.4)[e]	3.7 (3.9)[f]
CRP (mg/L)	14 (40)	14 (65)
ESR (mm/hr)	18.8 (19.3)	18.4 (19.6)
CHAQ-DI (0-3)	0.6 (0.6)	0.6 (0.6)
JADAS27 (CRP)	12.1 (8.1)	12.1 (8.6)
PhGA (0-10 cm VAS)	31.1 (22.6)	31.8 (24.3)
PaGA (0-10 cm VAS)	26.3 (23.9)	29.2 (26.6)
TJC75	4.0 (8.3)	4.3 (8.6)
SJC66	5.1 (6.3)	4.6 (6.5)
POM75	3.5 (7.1)	4.2 (7.2)
LOM69	4.2 (5.9)	4.6 (6.7)
AJC27	4.6 (5.1)	4.2 (5.1)
AJC71	5.8 (6.5)	5.4 (6.8)
Prior JIA Therapies		
Systemic NSAIDs, n (%)	235 (77.8)	353 (65.4)
Systemic Corticosteroids, n (%)	109 (36.1)	194 (35.9)
Synthetic DMARDs†, n(%)	39 (12.9)	434 (80.4)
Biologic DMARDs, n (%)	2 (0.7)*	154 (28.5)

Data are mean (SD) unless otherwise noted. [a]N = 300, [b]N = 506, [c]N = 299, [d]N = 504, [e]N = 301, [f]N = 535.
Percentages are based on patients with non-missing values. AJC, active joint count; CRP, C-reactive protein (<9 mg/L = normal); CHAQ-DI, Disability Index Childhood Health Assessment Questionnaire; DMARD, disease modifying anti rheumatic drug; JADAS, juvenile arthritis disease activity score; LOM, limitation of passive motion; NSAID, non-steroidal anti -inflammatory drug; PaGA, Parent's Global Assessment of Patient's Overall Well-Being; PhGA, Physician's Global Assessment of Disease Severity; POM, pain on passive motion; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale of 0–100 mm. †Synthetic DMARDs include azathioprine, chloroquine, gold hydroxychloroquine, leflunomide, mesalazine, MTX, mycophenolic acid, sulfasalazine, and tetracycline.*Both of the patients in the MTX arm were considered as protocol deviations.
For JIA effectiveness measures, for non-rollover patients, baseline is the last non-missing observation on or before the registry enrollment date. For rollover patients, the baseline measurement from the previous study will be used, if the measure was collected.
If the measure was not collected in the previous study, baseline will be the last non-missing observation on or before the registry enrollment date.

2.5.4 Results

2.5.4.1 Clinical effectiveness

An improvement from baseline in mean JADAS27 (CRP) was observed at months 1, 3, 6 and 12 in the MTX arm (9.4, 6.1, 5.1, 4.4 respectively) as well as the adalimumab ± MTX arm (7.4, 5.5, 4.4 and 4.5 respectively) (Figure 20). Minimal disease activity (defined as JADAS27 ≤3.87) was achieved by a high proportion of patients in the MTX arm (78.8%) and in the adalimumab ± MTX arm (63.2%) when assessed at 24 months. Remission, defined as JADAS27 ≤1[21], was achieved by 51.3% in the MTX arm and 38.6% in the adalimumab ± MTX arm.

Improvements in functional outcomes were observed in both arms as the percentages of those patients achieving low impairment of function, defined as CHAQ-DI <0.13[22], improved

to 63.6% in the MTX arm and 52.1% in the adalimumab ± MTX arm at 24 months. This reflects the fact that adalimumab was administered as a second-line treatment. The percentages of patients achieving normal function, defined as CHAQ-DI = 0[22], reached 55.2% in the MTX arm and 46.3% in the adalimumab ± MTX arm at 24 months (Figure 21).

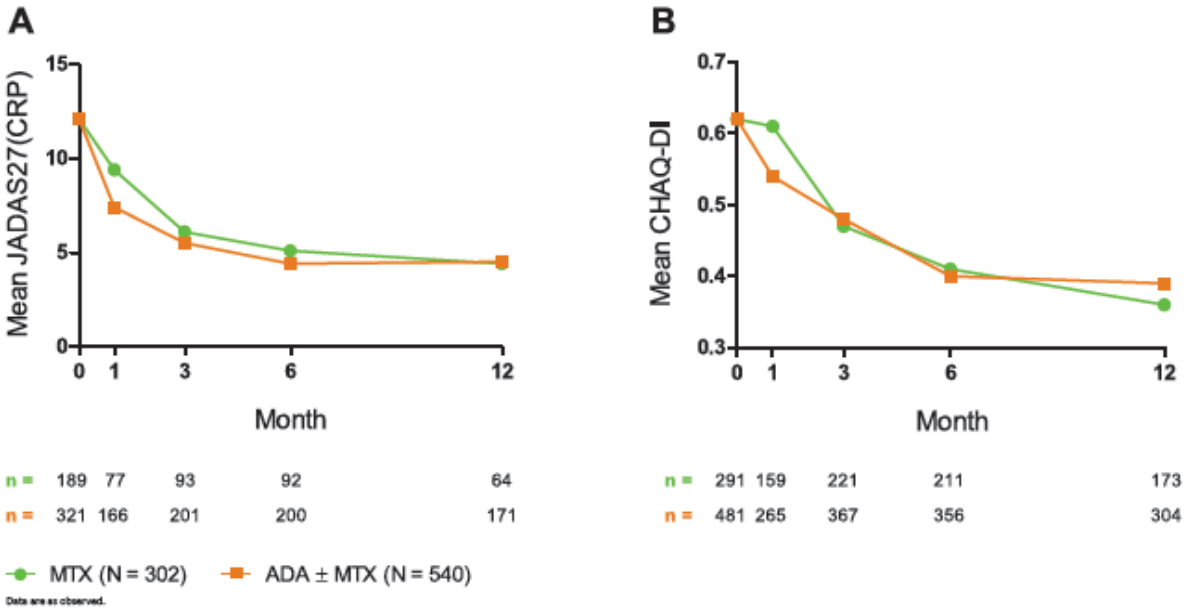

Figure 20: Mean JADAS27 (CRP) and CHAQD1 over time[23]

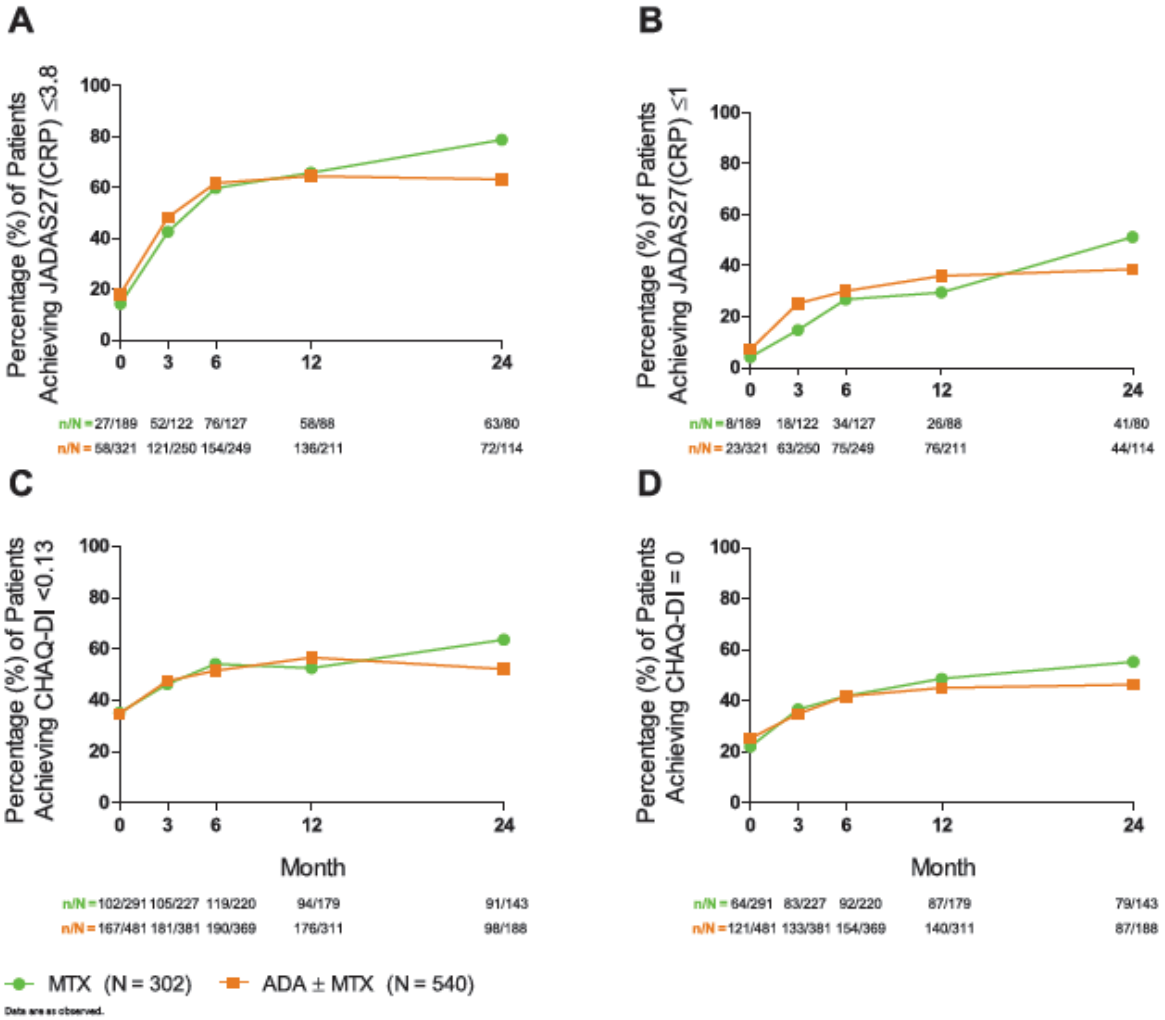

Figure 21: Percentage of patients achieving A) minimal disease activity, B) remission, C) low impairment of function, D) normal function Error! Bookmark not defined.

2.5.4.2 Patient-reported outcomes[24]

Physical function, as measured by the CHAQ-DI, improved from baseline from a mean of 0.62 in the MTX treatment arm to 0.61, 0.47, 0.41 and 0.36 at months 1, 3, 6 and 12 respectively (see Figure 22). A similar trend was observed in the adalimumab ± MTX arm with a change from 0.62 at baseline to 0.54, 0.48, 0.40, and 0.39 at months 1, 3, 6 and 12 respectively.

For patients who provided data at both baseline and 12 months, an improvement in physical function was observed with a mean change in CHAQ-DI of -0.24 for the MTX arm and -0.22 for the adalimumab ± MTX arm. The scores of the individual health concepts in the CHQ-PF50 increased for both treatment arms for those patients with data at both baseline and 12 months (Table 28). The exception to this was the Family Cohesion item which showed minimal changes over time points. The Global Health and Global Behaviour domains also showed modest changes over time. Mean scores for Physical Functioning were also substantially increased from 74.2 to 86.1 in the MTX treatment arm and 71.7 to 81.8 in the adalimumab ± MTX treatment arm from baseline to 12 months. A substantial increase in mean score on Parental Emotional Impact was observed in both the MTX arm (from 58.4 to 73.0) and the adalimumab ± MTX arm (from 57.6 to 68.8) from baseline to 12 months.

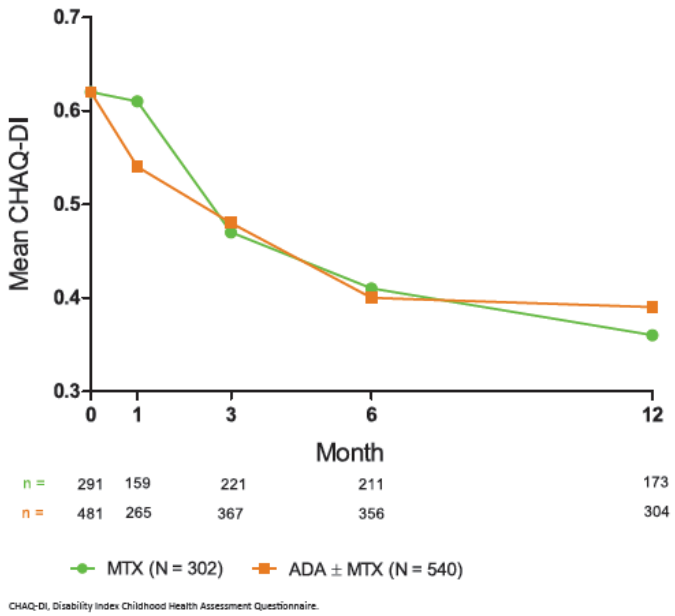

Figure 22: Mean CHAQ-DI over time

Table 28: Summary of the Child Heath Questionnaire Parent Form (CHQ-PF50)

	Baseline		Month 12	
	MTX	**Adalimumab ± MTX**	**MTX**	**Adalimumab ± MTX**
Global Health	72.7 (22.9)158	63.1 (25.7)282	80.8 (17.6)158	73.5 (21.4)282
Physical Functioning	74.2 (27.9)171	71.7 (28.4)297	86.1 (21.1)171	81.8 (25.9)297
Role/Social Limitations – Emotional/Behavioural	86.2 (25.7)170	80.3 (27.9)296	92.3 (17.7)170	89.8 (20.1)296
Role/Social Limitations – Physical	80.8 (29.0)170	75.2 (30.8)295	90.7 (20.6)170	86.9 (25.9)295
Bodily Pain/Discomfort	56.5 (26.6)171	53.4 (28.6)296	75.1 (24.2)171	70.2 (27.0)296
Behaviour	75.6 (16.4)170	77.1 (16.0)296	80.5 (14.7)170	80.4 (17.2)296
Global Behaviour	80.3 (19.1)140	80.2 (18.4)263	81.9 (18.8)140	80.9 (19.7)263
Mental Health	75.1 (16.4)171	75.3 (17.6)295	79.6 (15.1)171	78.8 (16.6)295
Self Esteem	80.4 (19.6)169	76.3 (20.2)294	84.7 (17.2)169	79.5 (20.8)294
General Health Perceptions	59.3 (19.0)171	52.5 (17.2)294	61.2 (17.7)171	55.5 (18.1)294
Change in Health	2.9 (1.4)166	3.2 (1.4)280	4.3 (0.9)166	4.2 (1.0)280
Parental Impact – Emotional	58.4 (26.0)169	57.6 (27.1)295	73.0 (21.5)169	68.8 (25.6)295
Parental Impact – Time	78.8 (24.0)169	77.3 (27.0)293	87.1 (19.9)169	83.7 (22.1)293
Family Activities	78.9 (21.0)169	78.6 (21.7)295	86.8 (16.4)169	85.0 (18.9)295
Family Cohesion	80.1 (20.2)169	77.1 (20.0)291	79.5 (21.3)169	77.4 (22.1)291

Section 3: Safety

3.0 Overview of safety evidence for adalimumab in JIA

This section focuses specifically on safety data reported in the trials discussed in Section 2.

3.1 Study DE038 – pJIA aged 4-17[11,12]

The study design and methodology details of the DE038 study have been described in Section **Error! Reference source not found.** of this document.

TE AEs are defined as those events beginning on or after administration of study drug or pre-existing conditions that worsened on or after study drug administration. For patients who discontinued from the study, an AE was considered a TE AE if it occurred up to 70 days after the last dose of study drug. The safety analysis included all patients who received at least one dose of study drug in either the OL LI, DB, OLE BSA, or OLE FD phases.

3.1.1 OLE LI phase

A similar proportion of patients in each stratum reported any AEs (74 [87.1%] in the MTX stratum and 71 [82.6%] in the non-MTX stratum). With the exception of the number of patients reporting AEs leading to discontinuation of study drug, which was slightly higher in the non-MTX stratum than the MTX stratum (8.1% versus 2.4%), the distribution of all other AEs was similar between the two treatment groups. No deaths, malignancies, or opportunistic infections including TB were reported. See **Error! Reference source not found.** for AEs and SAEs the OL LI phase.

3.1.2 DB phase

The percentage of patients with any AE was higher (88.2%) in the adalimumab group than the placebo group (73.8%). Six patients reported SAEs, five in the MTX stratum (two placebo-treated patients and three adalimumab-treated patients) and one in the non-MTX stratum treated with adalimumab. Five patients reported immunologic reactions, all of whom received adalimumab treatment (two [5.3%] in the MTX stratum and three [10.0%]) in the non-MTX stratum. In both MTX strata, infections and AEs at least possibly related to study drug were reported by similar proportions of patients in each treatment group (>32% of patients per group), although the proportion of placebo-treated patients in the non-MTX stratum who reported these AEs was smaller than in the other treatment groups. The proportion of patients presenting with infections, AEs at least possibly related to study drug, and injection site reactions was greater in the adalimumab group than the placebo group. There were no deaths, opportunistic infections including TB, malignancies, or AEs leading to study drug discontinuation reported during the DB phase. See Table 29 for AEs and SAEs in the DB phase.

Table 29. Summary of Adverse Events per Patient-Year of Exposure[11]

Variable	Methotrexate				No Methotrexate			
	Open-Label Lead-in Phase	Double-Blind Phase		Open-Label Extension Phase	Open-Label Lead-in Phase	Double-Blind Phase		Open-Label Extension Phase
	adalimumab (N = 85; 27.3 patient-years)	placebo (N = 37; 15.0 patient-years)	adalimumab (N = 38; 18.3 patient-years)	adalimumab (N = 71; 127.4 patient years)	adalimumab (N = 86; 29.3 patient-years)	placebo (N = 28; 10.6 patient-years)	adalimumab (N = 30; 14.4 patient-years)	adalimumab (N = 57;102.6 patient-years)
	No. of events (no. of events per patient-year)							
Any AE	422 (15.5)	155 (10.3)	234 (12.8)	694 (5.4)	447 (15.3)	153 (14.4)	171 (11.9)	581 (5.7)
Most frequently reported AEs								
Related to injection-site reaction	142 (5.2)	57 (3.8)	73 (4.0)	224 (1.8)	166 (5.7)	20 (1.9)	1 (4.9)	149 (1.4)
Contusion	14 (0.5)	7 (0.5)	12 (0.7)	4 (<0.1)	7 (0.2)	5 (0.5)	2 (0.1)	7 (0.1)
Nasopharyngitis	6 (0.2)	6 (0.4)	5 (0.3)	9 (0.1)	2 (0.1)	6 (0.6)	0	7 (0.1)
Upper respiratory tract infection	9 (0.3)	5 (0.3)	6 (0.3)	32 (0.2)	11 (0.4)	4 (0.4)	6 (0.4)	42 (0.4)
Viral infection	9 (0.3)	3 (0.2)	7 (0.4)	26 (0.2)	8 (0.3)	1 (0.1)	8 (0.6)	9 (0.1)
Vomiting	4 (0.2)	2 (0.1)	4 (0.2)	5 (<0.1)	2 (0.1)	2 (0.2)	6 (0.4)	4 (<0.1)
Excoriation	5 (0.2)	1 (0.1)	10 (0.6)	12 (0.1)	5 (0.2)	0	0	8 (0.1)
SAE, possibly related to study drug*								
Total	3 (0.1)	1 (0.1)	0	7 (0.1)	4 (0.1)	0	0	2 (<0.1)
Abdominal pain	0	0	0	1 (<0.1)	0	0	0	0
Bronchopneumonia	0	0	0	0	0	0	0	1 (<0.1)
Gastroduodenitis	0	1 (0.1)	0	0	0	0	0	0
Haematochezia	0	0	0	1 (<0.1)	0	0	0	0
Herpes simplex infection	0	0	0	0	(1 <0.1)	0	0	0
Herpes zoster infection	0	0	0	1 (<0.1)	0	0	0	1 (<0.1)
Hydrocephalus	0	0	0	1 (<0.1)†	2 (0.1)	0	0	0
Juvenile rheumatoid arthritis disease flare	1 (<0.1)	0	0	1 (<0.1)	0	0	0	0
Leukopaenia	1 (<0.1)	0	0	0	0	0	0	0
Neutropaenia	1 (<0.1)	0	0	0	1 (<0.1)	0	0	0
Pharyngitis	0	0	0	1 (<0.1)	0	0	0	0

Pneumonia	0	0	0	0	7	0	0	0
Viral Infection	0	0	0	1 (<0.1)†	1 (<0.1)	0	0	0
Adverse events leading to discontinuation of drug								
Total	5 (0.2)	0	0	2 (<0.1)	7 (0.2)	0	0	2 (<0.1)
Arthralgia	0	0	0	0	1 (<0.1)	0	0	0
Dizziness	0	0	0	0	1 (<0.1)	0	0	0
Hydrocephalus	0	0	0	1 (<0.1)†	0	0	0	0
Juvenile rheumatoid arthritis	1 (<0.1)	0	0	0	4 (0.1)	0	0	2 (<0.1)
ALT elevation	1 (<0.1)	0	0	0	0	0	0	0
AST elevation	1 (<0.1)‡	0	0	0	0	0	0	0
Leukopaenia	1 (<0.1)	0	0	0	0	0	0	0
Neutropenia	1 (<0.1)‡	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	1 (<0.1)	0	0	0
Viral infection	0	0	0	1 (<0.1)†	0	0	0	0

*SAE were death or any event that was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent another serious outcome. In addition to the SAE listed, the following SAE also occurred (in 1 patient each, except where noted) but were not considered to be possibly related to the study drug: abdominal pain, abortion, adenoidal and tonsillar hypertrophy (2 patients), arthritis (2 patients), appendicitis (2 patients), diabetic ketoacidosis, femur fracture, unspecified injury, malabsorption, joint contracture, joint dislocation, juvenile rheumatoid arthritis disease flare (12 patients), osteoarthritis, speech disorder, retinal detachment, urinary tract infection, and vomiting.

† The patient entered the study with a ventricular peritoneal shunt in place because of preexisting hydrocephalus and had concurrent viral infection and shunt malfunction.

‡ Values returned to normal within weeks after discontinuation of study drug.

3.1.3 OL BSE phase

An overview of TE AEs for the OLE BSA phase is presented in Table 29. All Patients received adalimumab treatment in this phase but are referred to in the table by the study drug they received during the DB phase, either placebo or adalimumab.

The number (%) of patients with any AE was similar (58 [90.6%]) in the adalimumab group versus the placebo (61 [95.3%]). Similarly, the number (%) of patients experiencing specific AEs was comparable for the patients previously treated with placebo compared to adalimumab. The incidence rate of infections reported for the adalimumab-treated patients in the MTX stratum was greater compared to adalimumab-treated patients in the non-MTX stratum (29 [82.9%] versus 20 [69.0%], respectively). In this case, the concomitant use of MTX with adalimumab resulted in a higher frequency of infectious AEs compared to adalimumab treatment without concomitant MTX. In addition, the concomitant use of MTX resulted in a greater proportion of patients with hepatic-related AEs compared to non-MTX patients, regardless of treatment group. In the MTX stratum, a greater proportion of patients with hepatic-related AEs was also reported in the group previously receiving adalimumab (5 [14.3%]) than in the group previously receiving placebo (2 [5.6%]). However the sample sizes are prohibitively small for purposes of providing accurate statistical analysis.

There were no deaths, opportunistic infections, TB, malignancies, lymphomas, non-melanoma skin cancer, (CHF, CNS demyelinating disease, lupus-like syndromes, or serious blood dyscrasias (as determined by the Investigator) reported in the OLE BSA phase of this study.

3.1.4 OL FD phase

An overview of TE AEs for the OLE FD phase by dose change from the OLE BSA phase is presented in Table 30 and Table 31. Overall, the number (%) of patients with any AE was similar in the same/decreased adalimumab dose group (48 [90.6%]) and the increased adalimumab dose group (50 [94.3%]). Although MTX treatment appeared to have little influence on overall AE incidence across strata, in rare cases this concomitant treatment has resulted in LFT increases. In addition, the incidence rate of infectious AEs was approximately 20% higher in patients in the MTX stratum than in patients in the non-MTX stratum; however, cases of serious infections were rarely reported in both strata (1 patient in each). Overall, few severe or serious AEs, or AEs leading to study drug discontinuation, were reported during the OLE FD phase. A greater proportion of patients in the MTX stratum than the non-MTX stratum had infectious AEs at all dose increase levels, and the greatest proportion of injection site reaction-related AEs was reported in the > 10 mg increased dose group in the non-MTX stratum. Across strata, the greatest proportion of injection site reaction-related AEs was also reported in the > 10 mg increased dose group.

Table 30: Overview of TE AEs (ITT Population, OLE FD Phase)

Adalimumab Dose Change	**MTX**		**Non-MTX**		**Overall**	
	Same/ decreased	**Increased**	**Same/ decreased**	**Increased**	**Same/ decreased**	**Increased**
	N=28	**N=31**	**N=25**	**N=22**	**N=53**	**N=53**
Adverse Event	**N (%)**					
Any AE	27 (96.4)	30 (96.8)	21 (84.0)	20 (90.9)	48 (90.6)	50 (94.3)
At least possibly related to drug	12 (42.9)	14 (45.2)	11 (44.0)	12 (54.5)	23 (43.4)	26 (49.1)
SAE	5 (17.9)	4 (12.9)	4 (16.0)	3 (13.6)	9 (17.0)	7 (13.2)
SAE	5 (17.9)	2 (6.5)	4 (16.0)	6 (27.3)	9 (17.0)	8 (15.1)
Leading to discontinuation of	2 (7.1)	0	2 (8.0)	1 (4.5)	4 (7.5)	1 (1.9)

study drug						
At least possibly related to drug SAE	0	0	1 (4.0)	0	1 (1.9)	0
Infections	20 (71.4)	28 (90.3)	14 (56.0)	14 (63.6)	34 (64.2)	42 (79.2)
Serious infections	1 (3.6)	0	0	1 (4.5)	1 (1.9)	1 (1.9)
Malignancies	0	0	0	0	0	0
Lymphomas	0	0	0	0	0	0
Non-melanoma skin cancer	0	0	0	0	0	0
Injection site reactions	3 (10.7)	4 (12.9)	1 (4.0)	5 (22.7)	4 (7.5)	9 (17.0)
Opportunistic infections (excluding TB)	0	0	0	0	0	0
CHF failure related	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0
Hepatic-related adverse event	2 (7.1)	2 (6.5)	0	0	2 (3.8)	2 (3.8)
Immunologic reaction related	0	1 (3.2)	0	1 (4.5)	0	2 (3.8)
Lupus-like syndrome	0	0	0	0	0	0
Haematologic related	0	0	0	0	0	0
Serious blood dyscrasias	0	0	0	0	0	0
Non-serious blood dyscrasias	1 (3.6)	0	0	0	1 (1.9)	0
Fatal AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

3.2 Study M10-444 – pJIA aged 2-4[14]

The study design and methodology details of the M10-444 study have been described in Section 2.2 of this document.

A total of 29 patients (90.6%) reported at least one AE as shown in Table 31. The most frequently reported AEs (occurring in 10% of patients) were nasopharyngitis (n=8, 25%), pyrexia (n=7, 22%), bronchitis, cough, rhinorrhoea, and upper respiratory infection (n=6 each, 19%), otitis media, worsening of rheumatoid arthritis (JIA), and vomiting (n=5 each, 16%), and diarrhoea, gastroenteritis, rash, and rhinitis (n=4 each, 13%), regardless of investigator's assessment for any relationship to study drug. Two patients discontinued the study due to an AE (worsening of JIA and loss of efficacy with JIA flare). While a majority of patients had non-serious events, 5 patients were reported to have one SAE each, which included dental caries, gastroenteritis rotavirus, worsening of JIA, type 1 diabetes mellitus, and varicella; these were considered to be "not related" or "probably not related" to adalimumab by the investigators. All SAEs were considered to be mild or moderate with the exception of diabetes mellitus (new onset, type 1), which was considered to be severe. No deaths occurred during this study.

Table 31: Overview of AE in the M10-444 study[14]

	N = 32; n(%)	PYs=45.1; E(E/100 PYs)
Any AE	29 (90.6)	217 (481)
At least "possibly drug related" per the investigator	11 (34.4)	22 (48.8)
Severe AE	6 (18.8)	6 (13.3)
SAE[a]	5 (15.6)	5 (11.1)
AE leading to discontinuation of study drug[b]	2 (6.3)	2 (4.4)
Infectious AE[c]	25 (78.1)	93 (206)

Serious infectious AE[d]	3 (9.4)	3 (6.7)
Injection site-related AE	4 (12.5)	6 (13.3)

E number of events, *PYs* patient-years. [a]Serious AEs included dental caries, gastroenteritis rotavirus, worsening of JIA, type 1 diabetes mellitus, and varicella. [b]AEs leading to discontinuation of study drug were worsening of JIA and JIA flare. [c]No opportunistic infections or cases of TB were reported. [d]Three patients had infections that were categorised as serious (one case each of dental caries, rotavirus gastroenteritis, and varicella virus)

Five patients (15.6%) reported an SAE during the study Table 32. The SAEs that were reported were dental caries, gastroenteritis rotavirus, juvenile arthritis, type 1 diabetes mellitus, and varicella. These SAEs were considered by the investigator to be not related or probably not related to study drug.

Table 32: TE SAEs by MedDRA PT (ITT)

MedDRA PT	**Number (%) of Patients Adalimumab N = 32**
Any SAE	5 (15.6)
Dental caries	1 (3.1)
Gastroenteritis rotavirus	1 (3.1)
Juvenile arthritis	1 (3.1)
Type 1 diabetes mellitus	1 (3.1)
Varicella	1 (3.1)

Note: A TEAE is any AE with onset on or after first dose of study drug and up to 70 days after last day of study drug.

A total of four patients (one patient reported two events) reported TE injection site reaction-related events. These events were considered by the investigator to be mild in severity and probably related to study drug. The events resolved and the patients continued in the study.

Two patients (6.3%) reported an allergic reaction. Both were considered to be mild in severity and only one was considered to be possibly related to study drug. Two patients report a TE haematological disorder. Both were considered to be not related to study drug. One event was considered to be severe but assessed to be resolved after further tests. The majority of patients reported TEAEs that were considered by the investigator to be not related or probably not related to study drug.

A total of 11 patients (34.4%) had events that were considered by the investigator to be at least “possibly related” to study drug. Five patients had ≥1 events that were considered by the investigator to be “possibly related” to study drug (pyrexia, bronchitis, ear infection, laryngitis, otitis media, pharyngitis, pharyngitis streptococcal, pneumonia, viral pharyngitis, upper respiratory tract congestion, and rash). Six patients reported events that were considered by the investigator to be “probably related” to study drug (injection site reaction, injection site pain, injection site pruritus, injection site rash, injection site swelling, cystitis, and juvenile arthritis). Rash was the most frequently reported TEAE that was considered by the investigator to be at least possibly related to study drug (2 patients).

The majority of patients experienced TEAEs that were considered by the investigator to be mild to moderate in severity. A total of six patients (18.8%) experienced severe TEAEs and include uveitis, otitis media, platelet count decreased*, Type 1 diabetes mellitus, arthritis, and juvenile arthritis. The patient that experienced a juvenile arthritis flare was discontinued from study drug; the investigator considered the event to be probably related to study drug.

* A repeat platelet count was performed by a local hospital laboratory and the results were within normal range.

The other severe events were considered by the investigator to be not or probably not related to study drug.

A total of 26 (81.3%) patients completed the study and six patients (18.8%) withdrew from the study (Table 33). Two patients discontinued because of an AE.

Table 33: Study withdrawals

	n (%) N = 32
Discontinuations (all reasons)	6 (18.8)
AEs	2 (6.3)
Withdrew consent	3 (9.4)
Lost to follow-up	1 (3.1)
Other*	2 (6.3)

* loss of efficacy

3.3 Study M10-240 – pJIA aged 4-17 in Japan[17]

The study design and methodology details of the M10-240 study have been described in Section 2.2 of this document. Through to Week 60, all patients had experienced at least one AE (an overview is given in Table 34). Six patients (30%), all with concurrent MTX, experienced nine serious AEs as follows: JIA, pyrexia, and arthralgia; pneumonia; hepatitis B infection; pharyngitis; dehydration, pharyngeal pain, and pyrexia. Consistent with study exclusion criteria, the patient with hepatitis B infection had been negative for hepatitis B antigen and antibodies against HBs and HBc at the start of the trial; no risk factors for transmission (i.e., travel to endemic areas, injection drug use, or other exposure) were reported, and the patient discontinued the study because of this event. Of the six patients with serious AEs, four occurred in AAA-negative patients and two occurred in AAA-positive patients (one with serious AE of JIA; one with serious AEs of dehydration, pharyngeal pain, and pneumonia).

Infections occurred in 80% of patients receiving MTX and 100% of patients not receiving MTX. Three patients (15%) in the MTX group developed serious infectious AEs (acute pharyngitis, pneumonia, and hepatitis B infection). Six patients (24%), with or without MTX, had an injection-site reaction and three (12%) had a hepatic event. No deaths, malignancies, opportunistic infections, CHF, demyelinating disease, allergic reactions, lupus-like syndrome, or blood dyscrasias were reported in any patient through to Week 60 of the study.

Table 34: Overview of AE in the M10-240 study[17]

Adverse event	Adalimumab with MTX (N=20) N (%)	Adalimumab without MTX (N=5) n (%)	All Adalimumab (N=25) N (%)
Any AE	20 (100)	5 (100)	25 (100)
Any severe AE	0	0	0
Any AE leading to discontinuation of study drug	1 (5)	0	1 (4)
Any serious AE	6 (30)	0	6 (24)
Any infectious AE	16 (80)	5 (100)	21 (84)
Any serious infectious AE	3 (15)	0	3 (12)
Injection-site reaction	6 (30)	0	6 (24)
Hepatic-related AE	2 (10)	1 (20)	3 (12)

AE: adverse event; MTX: methotrexate

3.4 Study M11-328 – ERA aged 6-17[18]

The study design and methodology details of the M11-328 study have been described in Section 2.4 of this document. The overview of TEAEs[1] during the DB period and at any time after the first injection of adalimumab is presented in Table 35. Mean duration of treatment with adalimumab was 78.5 days during the DB period and 338.2 days for patients who received adalimumab at any time during the study.

No deaths or fatal AEs occurred through Week 52 of the study. During the DB period, most patients (63.0%) reported ≥ 1 TEAE; of these, a greater percentage of patients who received adalimumab reported at least 1 AE (67.7%) compared with patients who received placebo (53.3%). The proportions of patients who reported at least one AE that was considered related to study drug by the Investigator were similar between groups.

All AEs were considered mild or moderate in severity by the investigator and most patients (n=16) reported AEs that were considered by the investigator to be not related to study drug.

Table 35: Overview of Patients with TEAEs (Safety Analysis Set and Any Adalimumab Set) Error! Bookmark not defined.

Patients with:	DB Period, n (%)			
	Placebo N = 15	Adalimumab N = 31	Total N = 46	Any Adalimumab[a] n(%) N = 46
Any AE	8 (53.3)	21 (67.7)	29 (63.0)	43 (93.5)
Any AE at least possibly drug related[b]	4 (26.7)	9 (29.0)	13 (28.3)	22 (47.8)
Any severe AE	0	0	0	3 (6.5)
Any serious AE	0	1 (3.2)	1 (2.2)	5 (10.9)
Any AE leading to discontinuation of study drug	0	0	0	3 (6.5)
Death[c] or any fatal AE	0	0	0	0

[a]TEAs are counted from first dose of adalimumab onward. [b]As assessed by the investigator. [c]Includes non-TE

3.5 STRIVE registry

The study design and methodology details of the STRIVE study have been described in Section 2.5 of this document.

Safety data will be collected annually for SAEs, CHF, pregnancies and malignancies. For patients aged 2 to 4 years, in countries where approved at the time of consent to the registry, TE AEs of special interest, SAEs, and pregnancy (at an age when the patient can become pregnant) will be collected for up to 10 years. Observational AEs were recorded from the first day in the registry through last contact, irrespective of treatment duration.

The mean duration of drug exposure was 643 days for the MTX arm and 653 days for the adalimumab ± MTX arm. The total exposure was 590.8 PYs for the MTX arm, and 1161.8 PYs for the adalimumab ± MTX arm. Overall, 50.7% of patients in the MTX arm and 24.4% of patients in the adalimumab ± MTX arm discontinued the registry drug.

Of those who discontinued, 5.6% of the MTX and 6.5% of the adalimumab ± MTX arm experienced serious AEs[2]. However, of these SAEs, no deaths, malignancies, tuberculosis (active or latent), or opportunistic infections, including oral candidiasis, were reported.

[1] All AEs discussed in this report are TEAEs unless otherwise noted.

[2] SAEs include death and events that are life-threatening (i.e, result in immediate fatality without medical intervention), hospitalisation, prolongation of hospitalisation, persistent or significant disability, or any important medical event requiring medical or surgical intervention to prevent serious outcome.

SAEs were observed in 8 patients (2.6%) in the MTX arm and 13 patients (2.4%) in the adalimumab ± MTX arm.

Where a serious infectious AEs was observed, incidence of all types of AE was less than 1 patient per arm (≤0.3%), except for pyelonephritis in the adalimumab ± MTX arm (n=2; 0.4%).

See Table 36 for observed adverse effects and Table 37 for observed serious infections.

Table 36: Overview of observational AEs

	MTX		adalimumab ± MTX	
	N = 302	**PYs = 863.9**	**N = 640**	**PYs = 1226.8**
	n(%)	**E (E/100PYs)**	**n(%)**	**E (E/100PYs)**
Any AE‡	136 (44.7)	40.6 (36.5, 45.1)	169 (31.3)	36.4 (33.1, 40.0)
At least 'possibly drug related' per the investigator	68 (22.5)	14.0 (11.6, 16.7)	80 (14.8)	12.0 (10.1, 14.1)
Severe AE	11 (3.6)	1.7 (1.0, 2.9)	19 (3.5)	2.5 (1.7, 3.6)
SAE†	17 (5.6)	3.0 (2.0, 4.4)	35 (6.5)	4.6 (3.5, 6.9)
AE leading to discontinuation of study drug or study	20 (6.6)	3.0 (2.0, 4.4)	27 (5.0)	3.2 (2.3, 4.4)
Infectious AE	75 (24.8)	15.4 (12.9, 18.3)	93 (17.2)	12.1 (10.3, 14.3)
Serious infectious AE	8 (2.6)	1.3 (0.6, 2.3)	13 (2.4)	1.2 (0.7, 2.0)
Injection site-related AE	6 (2.0)*	0.9 (0.4, 1.8)	24 (4.4)	2.4 (1.6, 3.4)

CI: confidence interval; E: events; PYs: patient years, *3 patients experienced injection site-related AEs with adalimumab injections. †SAEs include death and events that are life-threatening (i.e. result in immediate fatality without medical interventions), hospitalisation, prolongations of hospitalisation, persistent or significant disability, or any important medical event requiring medical or surgical intervention to prevent serious outcomes. ‡ refers to number of patients with any AE

Table 37: Overview of observed serious infections

	MTX		adalimumab ± MTX	
	N = 302	**PYs = 863.9**	**N = 640**	**PYs = 1226.8**
	n(%)	**E (E/100PYs)**	**n(%)**	**E (E/100PYs)**
Abdominal abscess	0	0	1 (0.2)	1 (0.1)
Acute tonsillitis	0	0	1 (0.2)	1 (0.1)
Appendicitis	1 (0.3)	1 (0.1)	1 (0.2)	1 (0.1)
Cellulitis	0	0	1 (0.2)	1 (0.1)
Gastroenteritis	0	0	1 (0.2)	1 (0.1)
Infectious mononucleosis	0	0	1 (0.2)	1 (0.1)
Meningitis Viral	0	0	1 (0.2)	1 (0.1)
Pneumonia	0	0	1 (0.2)	1 (0.1)
Pyelonephritis	1 (0.3)	1 (0.1)	2 (0.4)	2 (0.2)
Respiratory tract infection	1 (0.3)	1 (0.1)	0	0
Scarlet fever	0	0	1 (0.2)	1 (0.1)
Septic shock	1 (0.3)	1 (0.1)	0	0
Staphylococcal infection	1 (0.3)	1 (0.1)	0	0
Subcutaneous abscess	0	0	1 (0.2)	1 (0.1)
Tonsillitis	1 (0.3)	3 (0.3)	1 (0.2)	1 (0.1)
Urinary tract infection	1 (0.3)	1 (0.1)	1 (0.2)	1 (0.1)
Varicella	1 (0.3)	1 (0.1)	1 (0.2)	1 (0.1)
Viral infection	1 (0.3)	1 (0.1)	0	0

Section 4: Clinical interpretation of the evidence

As discussed in Section 2, because of the ethical restraints in the design of paediatric trials there is a limit in the ability to collect data for certain outcomes and sub-groups (i.e. a powering issue). As result, the adalimumab JIA RCT programme did not collect data for non-arthritic outcomes in patients with JIA. Therefore, this section focuses on outcome data collected from other sources not relating to the arthritic component of JIA – for example data around the effectiveness of adalimumab as a treatment for uveitis; as well as including data looking at the effect of anti-TNFs on other outcomes such as growth.

In addition, issues concerning the interpretation of the clinical evidence are also discussed here, with particular reference to the difficulties of conducting an indirect comparison in this disease area.

4.1 Evidence for the effectiveness of adalimumab in JIA associated uveitis (JIA-U)

There is an increasing amount of evidence relating to the use of adalimumab and the other anti-TNFs in the treatment of childhood chronic uveitis – predominantly derived from case studies and open-label prospective trials.

Indeed, a systematic literature review conducted between 2000 and October 2012 identified a number of studies looking at the effectiveness of anti-TNFs in childhood chronic uveitis, the majority of which were conducted in patients with JIA associated uveitis (JIA-U).[25] The authors identified 989 articles, of which 148 were potentially eligible. In total, 22 retrospective chart reviews and 1 randomised clinical trial were deemed eligible, comprising 229 children (adalimumab: n = 31, etanercept: n = 54, and infliximab: n = 144). On pooled analysis of observational studies, the proportion of responding children was 87% (95% confidence interval [95% CI] 75-98%) for adalimumab, 72% (95% CI 64-79%) for infliximab, and 33% (95% CI 19-47%) for ETA. There was no difference in the proportion of responders between adalimumab and infliximab (χ^2 = 3.06, p = 0.08), although both showed superior efficacy compared with etanercept (adalimumab versus etanercept: χ^2 = 20.9, P < 0.001 and infliximab versus etanercept: χ^2 = 20.9, P < 0.001). The authors concluded that although RCTs are needed, the available evidence suggests that infliximab and adalimumab provide proven similar benefits in the treatment of childhood autoimmune chronic uveitis and they are both superior to etanercept.[25]

Since the systematic literature review performed by Simonini et al.,[25] there have been a few more published studies investigating the safety and efficacy of adalimumab in the treatment of refractory uveitis associated with JIA (JIA-U):

- García-De-Vicuña[26]

This multicentre, prospective case series study assessed the efficacy and safety of adalimumab in patients with JIA and associated refractory uveitis. Thirty-nine patients (mean [SD] age of 11.5 [7.9] years) with JIA-associated uveitis who were either not responsive to standard immunosuppressive therapy or intolerant to it were enrolled. Patients aged 13–17 years were treated with 40 mg of adalimumab eow for 6 months and those aged 4–12 years received 24 mg/m^2 body surface.

Inflammation of the anterior chamber (2.02 [1.16] versus 0.42 [0.62]) and of the posterior segment (2.38 [2.97] versus 0.35 [0.71] decreased significantly between baseline and the final visit (P < 0.001). The mean (SD) macular thickness at baseline was 304.54 (125.03) μ and at the end of follow-up was 230.87 (31.12) μ (P < 0.014). Baseline immunosuppression load was 8.10 (3.99) as compared with 5.08 (3.76) at the final visit (P < 0.001). The mean

dose of corticosteroids also decreased from 0.25 (0.43) to 0 (0.02) mg (P < 0.001). No significant side effects requiring discontinuation of therapy were observed.

The authors concluded that adalimumab seems to be an effective and safe treatment for JIA-associated refractory uveitis and may reduce steroid requirement.

- Diaz-Llopis M et al.[27]

This prospective case series evaluated adalimumab therapy in patients with refractory uveitis, the majority of which were in JIA patients. A total of 131 patients with refractory uveitis and intolerance or failure to respond to prednisone and at least 1 other systemic immunosuppressive drug participated. Patients received a 40 mg adalimumab SC injection eow for 6 months. Associated immunosuppressants were tapered after administering 3 adalimumab injections (week 6). Degree of anterior and posterior chamber inflammation (Standardization of Uveitis Nomenclature Working Group criteria), immunosuppression load (as defined by Nussenblatt et al), visual acuity (logarithm of the minimal angle of resolution [logMAR]), and macular thickness (optical coherence tomography) were measured.

There were 61 men and 70 women (mean age, 27.3 years). The most common causes were JIA in 39 patients, pars planitis in 16 patients, and Behçet's disease in 13 patients. Twenty-seven patients had uveitis of idiopathic origin. Inflammation in the anterior chamber was present in 82% of patients and in the vitreous cavity in 59% of patients. Anterior chamber inflammation and vitreous inflammation decreased significantly (p < 0.001) from a mean of 1.51 and 1.03 at baseline to 0.25 and 0.14, respectively, at 6 months. Macular thickness was 296 (102) μ at baseline versus 240 (36) μ at the 6-month visit (p < 0.001). Visual acuity improved by -0.3 logMAR in 32 of 150 eyes (21.3%) and worsened by +0.3 logMAR (-15 letters) in 5 eyes (3.3%). The dose of corticosteroids also decreased from 0.74 (3.50) to 0.20 (0.57) mg/kg/day (P < 0.001). Cystoid macular edema, which was present in 40 eyes at baseline, showed complete resolution in 28 eyes at 6 months. The mean suppression load decreased significantly (8.81 [5.05] vs 5.40 [4.43]; P < 0.001). Six months after the initiation of the study, 111 patients (85%) were able to reduce at least 50% of their baseline immunosuppression load. Only 9 patients (6.9%) had severe relapses during the 6 months of follow-up.

The authors concluded that adalimumab seems to be well tolerated and helpful in decreasing inflammatory activity in refractory uveitis and may reduce steroid requirement.

- Magli et al.[28]

This prospective, interventional case series aimed to assess the long-term outcomes and complications of patients with uveitis from JIA treated with adalimumab. All patients who underwent treatment with adalimumab for JIA and anterior uveitis were prospectively included in the study. The anterior chamber inflammation was evaluated according to the Standardization of Uveitis Nomenclature criteria. Twenty-one patients (16 females, five males, 38 eyes) were included in the study. Mean age of patients at referral was 11.1± 3.8 (5–17) years. Before initiation of treatment, mean duration of arthritis was 7.0±5.5 (median, 6) months, mean duration of uveitis was 7.0±4.4 (median, 7) months. Oligoarticular arthritis was present in 15 cases (71 %), polyarticular arthritis in six cases (28 %).

After a mean follow-up of 18.2 ± 7.7 (9–41) months, resolution of anterior chamber inflammation was obtained in 29/38 eyes (76 %). The anterior uveitis flare rate during the 12 months prior to enrolment was 1.6 ± 0.4/year, and was reduced during adalimumab treatment to 0.7±0.3/year (p<0.001). A significant decrease of the number of relapses/month was present after onset of treatment with adalimumab (0.18 ± 0.2 before versus 0.02 ± 0.1

after treatment onset, p<0.001). No significant correlation was found between relapse number and age, sex, type of JIA and doses of previous steroid treatment (p>0.05).

The authors concluded that adalimumab was shown to be effective and relatively safe for treatment of JIA-associated uveitis.

- Zannin et al.[29]

Zannin et al evaluated the safety and efficacy of adalimumab and infliximab for the treatment of juvenile idiopathic arthritis-related anterior uveitis (JIA-AU) based on data from the National Italian Registry (NIR). At baseline, all patients were refractory to standard immunosuppressive treatment and/or were corticosteroid-dependent. Data recorded every 3 months included uveitis course, number/type of ocular complications, drug-related AE, treatment change or withdrawal, and laboratory measures. Data of patients treated for at least 1 year were retrieved from the NIR and analysed using descriptive statistics. Treatment efficacy was based on change in uveitis course and in number of ocular complications.

Up to December 2009, data for 108 patients with JIA-AU treated with anti-tumor necrosis factor-α agents were recorded in the NIR and data from 91, with at least 12 months' follow-up, were included in the study. Forty-eight patients were treated with infliximab, 43 with adalimumab. Forty-seven patients (55.3%) achieved remission of AU, 28 (32.9%) had recurrent AU, and 10 (11.8%) maintained a chronic course. A higher remission rate was observed with adalimumab (67.4% vs 42.8% with IFX; p = 0.025). Ocular complications decreased from 0.47 to 0.32 per subject. Five patients experienced resolution of structural complications. No patient reported serious AE; 8 (8.8%) experienced 11 minor AE (9 with infliximab, 2 with adalimumab).

The authors concluded that infliximab and adalimumab appear to be effective and safe for treatment of refractory JIA-related uveitis, with a better performance of adalimumab in the medium-term period.

- Simonini et al.[30]

Simonini et al. compared the efficacy of adalimumab when used as first anti-TNFalpha therapy versus adalimumab used after the failure of a previous anti-TNFalpha (infliximab) in an open-label, comparative, multi-centre, cohort study of childhood chronic uveitis. Twenty-six patients (14 F, 12 M; median age: 8.6 years) with refractory, non-infectious active uveitis were enrolled. Due to the refractory course of uveitis to previous DMARD treatment, Group 1 received adalimumab (24 mg/m^2, every 2 weeks), as first anti-TNFalpha choice; Group 2 received Adalimumab, as second anti-TNFalpha drug, due to the loss of efficacy of Infliximab, administered after a period of at least 1 year. Both groups received Adalimumab for at least 1 year of treatment. Primary outcome was, once remission was achieved, the time to a first relapse.

Fourteen children (10 with JIA, three with idiopathic uveitis, one with Behcet's disease) were recruited in Group 1; 12 children (7 with JIA, 3 with idiopathic uveitis, 1 with early-onset sarcoidosis, one with Behcet's disease) were recruited in Group 2. Group 2 showed a lower probability to steroid discontinuation during the first 12 months of treatment (Mantel-Cox chi24.12, p<0.04). In long-term follow-up, Group 1 had higher probability of uveitis remission during the time of treatment on adalimumab (median ±SE: 18 +/-1.1 vs 4 ±0.6 months, CI 95%: 15.6-27.5 vs 2.7-5.2, Mantel-Cox chi^{2}10.12, p<0.002). The authors concluded that even if limited to a relatively small group, the study suggests a better efficacy of adalimumab when used as first anti-TNF alpha treatment in childhood chronic uveitis.

- The Sycamore RCT[31]

Finally, a RCT is currently under way in the UK examining the efficacy of adalimumab in JIA-U and uveitis. The Sycamore trial (ISRCTN 10065623) is an RCT evaluating the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with MTX for the treatment of JIA-U. The trial is funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK. To date, 88/114 patients aged between 2 and 18 years have been randomised, and recruitment has been extended to December 2016. All participants will be treated for 18 months, with follow up of 3 years from randomisation. All participants will receive a stable dose of MTX and, in addition, either adalimumab or placebo by SC injection every 2 weeks.

The data above show that adalimumab is effective in the treatment of JIA-U, and the benfits of adalimumab on JIA-U should be considered in this appraisal.

As an aside, the efficacy and safety of adalimumab is also being investigated in the multicentre, double-blind, placebo-controlled VISUAL trials in adult patients with uveitis.[32]

4.2 Evidence for the effectiveness of anti-TNFs on growth

As discussed in Section 1.3, the combination of chronic inflammation and steroid therapy can cause marked growth retardation in JIA. Observational reports suggest that anti-TNF treatment is associated with growth velocity improvement in these patients:[33, 34, 35, 36, 37]

- A registry analysis of 594 patients with polyarticular (~90% patients) or systemic JIA showed statistically significant increases in mean height percentile with etanercept at year 3 (4.8 percentile points), and with etanercept plus MTX years 1, 2, and 3 (2.4, 3.3, and 5.6 percentile points, respectively).[33]

- Another study reported growth outcomes of 71 patients with polyarticular course JIA two years prior to, and after, anti-TNF treatment. For the 53 patients with delayed growth before anti-TNF treatment, the growth velocity, measured as the change in height standard deviation score, accelerated +0.45 (95% CI, 0.33 to 0.56) ($p<0.001$) during anti-TNF treatment. In the patients with normal or accelerated growth before anti-TNF ($n = 18$), the change in growth velocity was +0.05 (0.07 to 0.16) ($p = 0.39$). At two years on anti-TNF treatment, the growth velocity between these two groups was similar.[34]

- These results are supported by small case series showing statistically significant improvement in growth velocity vs baseline after etanercept initiation.[35, 36, 37] In the Vojvodich study, the statistical significance was restricted to the pre-pubertal cohort. Schmeling *et al* compared the linear growth change in the etanercept group to patients with recent onset active JIA commencing MTX, and reported statistical significance in the anti-TNF group only.[37]

These statistically significant results contrast with a retrospective analysis in 100 JIA children on biologic therapy for a median of 2.92 years (range: 0.59 to 10.17 yrs). In this study, statistical significance was not reached for change in median height. However, multivariate analysis demonstrated that patients treated with > 1 biologic agent and those with systemic JIA had significantly lower changes in height SDS on biologic treatment than other patients ($p = 0.01$ and $p = 0.04$, respectively), suggesting the lack of statistical significance in this study may be attributable to the large number of patients with systemic-onset JIA (n=29%) and refractory disease.[38]

The effect of adalimumab on growth in patients aged 4–17 with polyarticular course JIA was examined in a post hoc analysis of DE-038 - a phase 3 randomised, withdrawal, double-blind study. In the patients in the lowest quartiles for height at baseline (<5th and 5th–24th

percentile groups), there was a larger change in mean height percentile through 250 weeks of adalimumab treatment (10.5, 13.5, 5.4, 4.0% change for <5th, 5th–24th, 25th–49th, and ≥50th percentile, respectively) (see Table 38). Long-term adalimumab treatment was associated with improvement and maintenance of growth in children with JIA who were within the lowest height percentiles at baseline.[39]

Table 38: Distribution of height and weight by CDC percentile and final visit from DE-038

N(%)	CDC Percentile <5%	CDC Percentile ≥5%-<25%	CDC Percentile ≥25%-<50%	CDC Percentile ≥50%
Height, n=171				
Baseline	28 (16.4)	35 (20.5)	42 (24.6)	66 (38.6)
Final visit	20 (11.7)	39 (22.8)	32 (18.7)	80 (46.8)
Weight, n=171				
Baseline	22 (12.9)	39 (22.8)	36 (21.1)	74 (43.3)
Final visit	15 (8.8)	35 (20.5)	35 (20.5)	86 (50.3)

Therefore, whilst not extensive, the data indicate that anti-TNFs have a positive impact on growth retardation. Given the complexities involved in generating utility data from the RCTs i.e. potentially using a mapping algorithm to link function (CHAQ) to utility (see Section 5), AbbVie understands that it is unlikely that these benefits will be captured in the economic modelling. It is therefore important that the benefits of adalimumab on growth and uveitis are considered in addition to the cost/QALY gained.

4.3 Differences in the trial designs for the biologics under review and the potential impact this has on estimates of relative effectiveness

In order to calculate the relative effectiveness of the biologics under review as per the protocol for this technology appraisal, evidence synthesis in the form of a network me-analysis (NMA) or pairwise comparison using a common comparator will need to be performed. AbbVie has some concerns, discussed in Sections 4.3.1 - 4.3.3 below, with the validity of this methodology in this disease area.

4.3.1 Issues with the comparability of the different trials specifically around the length of the double-blind withdrawal period

In order to obtain estimates of relative effectiveness of one agent vs. another for the biologics in this MTA, efficacy data from the trials will need to be compared. The most commonly used approach for a NMA and the approach NICE prefers is the treatment-effect model, modelling the relative effect of each intervention within each study. It has the advantage of preserving the randomisation within each study, which ensures that the difference observed between arms only reflects the difference between treatments and not differences in patient characteristics. For this reason, treatment-effect models are generally less prone to bias due to model misspecification and variability in prognostic factors than other types of models. However, a treatment-effect model requires that the included studies are designed with a comparator arm or 'reference' treatment arm; and the most common of these comparator arm forms the reference treatment in a network allowing pairwise comparisons of all treatments of interest within the network.

The problem with performing an NMA in JIA is that the ethical constraints applied to trial design mean that there are no true common comparator arms to generate the 'reference' treatment arm. All the RCTs for the biologics in this MTA included an open-label lead in

phase where all patients received open-label therapy. Patients with a PedACR30 response at the end of the open-label lead in phase were then randomised in a double-blind manner to receive placebo or continue biologic treatment until the end of the double-blind treatment period or until flare, whichever event occurred first.

As a result, the length of the double-blind period has an impact on the probability of achieving the primary outcome measure (time to flare). Unfortunately, because shorter trial duration means that there is a smaller chance of reaching the time-dependent outcome (disease flare); shorter treatment duration may result in better outcomes. Table 39 below shows the different treatment phases for the RCTs of the biologics under review. As can be seen from the table, the double-blind treatment withdrawal phase for adalimumab was twice as long as the etanercept study, with the double-blind phase for abatacept and tocilizumab halfway between that of etanercept and adalimumab.

Table 39: Comparison of treatment periods in the RCTs of the biologics under review

Drug	Length of open-label phase	Length of double-blind phase
Adalimumab	12 weeks	32 weeks
Etanercept	12 weeks	16 weeks
Abatacept	16 weeks	24 weeks
Tocilizumab	16 weeks	24 weeks

Furthermore, the double-blind withdrawal phase was conducted in an enriched population i.e. only in patients who had a PedACR30 response at the end of the open-label lead in phase. The proportion of responders carried through to the double-blind phase differs across the studies, for example the percentage of PedACR30 responders at the end of the open-label lead in period ranges from circa 60% up to 90% across the different trials. This introduces an element of bias when calculating the relative effectiveness of the agents at the end of the double-blind period.

Rather than the primary outcome measure of time to flare, the Assessment Group may choose to use PedACR30/50/70 response to calculate the relative effectiveness of the different biologics under review (in a similar manner to the adult RA models which utilise % ACR response). However, again this is problematical because of the open-label lead in phase in the JIA RCTs. For example, at the end of the lead in phase, only patients with a PedACR30 response were randomised in to the double-blind withdrawal period to continue active treatment or receive placebo, meaning that the PedACR30 response rate at the start of the double-blind period for both the placebo and active arms was 100%. The percentage of PedACR30 responders at the end of the double-blind phase in the 'placebo' arms will then obviously be affected by the length of the treatment period and the half-lives of the drugs. Otten *et al.* describe similar problems with performing an indirect comparison of biological agents in JIA in their systematic review.[40]

Finally, calibration of the 'placebo' arms to establish a reference arm for the calculations of relative effectiveness will be difficult because the placebo arms aren't representative of a true placebo response and are confounded by the length of the double-blind phase and the half-lives of the drugs. This means that it is highly plausible that any differences in efficacy between biologic agents generated from an NMA do not reflect actual differences between treatments, but instead could be due to differences in the pharmacodynamics of the different drugs, patient characteristics and the time frame of assessment.

An additional point to note, which is discussed further in Section 4.3.3, is that in the pivotal adalimumab pJIA trial, a patient who had a flare according to the protocol definition was classified as having no response from that point forward, regardless of the PedACR response at that time. This means that in both the adalimumab and 'placebo' arms, the

proportion of PedACR responders is likely to be an underestimation, furthermore this is more likely to affect the adalimumab arms which will have a negative effect in any calculations of relative effectiveness.

4.3.2 Heterogeneity of the trial subjects according to the ILAR classification criteria and small sample sizes

In addition to the issues discussed in Section 4.3.1 around the design of the biologic JIA trials and the impact this has on a potential NMA; performing an indirect comparison for the biologic agents is further complicated by the heterogenic nature of JIA as a disease. As discussed in Section 1.1 and 1.5, the ILAR classification categorises JIA into 7 subtypes by presentation at onset of disease. This MTA review excludes systemic JIA, unless the patient has ≥ 5 or more joints involved in which case they would be included as having course pJIA, however it does include oligoarthritis (extended), psoriatic arthritis, polyarthritis RF +ve, polyarthritis RF –ve, and ERA.

Firstly, outcome measures such as PedACR response are not appropriate for some sub-types of JIA like ERA as there are a reduced number of joints involved, and involved joints may include the spine, which is not assessed in the same way. Outcome measures like BASDAI would be more appropriate – although this hasn't been validated in children. In which case, pooling trial data from a pJIA and an ERA trial to determine the overall effectiveness of an agent wouldn't be appropriate. Furthermore, not all the biologic agents under review have a licence for the ERA sub-type of JIA.

Secondly, even if we focus specifically on trials of pJIA and exclude trials investigating biologics for ERA or psoriatic arthritis, the trial populations for pJIA comprise a mixture of onset and course polyarthritis with a variety of JIA onset types – in the adalimumab trial DE-038, the most frequent type of onset was RF –ve or +ve polyarthritis and extended oligoarthritis. It is unclear whether the different sub-types have an effect on treatment response; however it is worth noting that the proportions of the different sub-types of JIA vary quite substantially across the trials.

Finally, as discussed in Section 2.0, the ethical constraints associated with paediatric trial design mean that children will not be subjected to unnecessary treatment, particularly if there is a placebo element to the trial designs. Therefore, the sample size across the biologic JIA clinical trials is relatively small and the number of trials per agent required to demonstrate safety and efficacy are limited. As a consequence of this, and in addition to the substantial clinical heterogeneity, there may be issues of convergence with any models used to conduct the evidence synthesis.

4.3.3 Underestimation of the percentage of PediACR responders in the adalimumab pJIA trials

In the adalimumab pJIA clinical trial programme, a disease flare was defined as either ≥30% worsening in at least three of the six JIA core set criteria and also a minimum of two active joints or ≥30% improvement in not more than one of the six JIA core set criteria. If a patient experienced a disease flare at any timepoint during the trial (clinic visits were performed every 4 weeks), they were considered a non-responder from that point onwards for any of the PedACR outcome measures. PedACR30, 50, 70 and 90 responses are defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis, with worsening of 30% or more in no more than one criterion.

It is therefore possible that at one of the visits, e.g. the week 20 visit, a patient may have had a ≥30% improvement in only one of the six JIA core set criteria and would therefore qualify as having experienced disease flare. However, at subsequent visits the same patient may go on to fulfil the criteria for a PedACR30/50/70/90 response. Based on the trial protocol, regardless of the fact that this patient could be a PedACR90 at the end of the double-blind period, i.e. at week 48, this patient would be considered an PedACR non-responder.

As far as AbbVie can judge from the publications of the other biologic's clinical trials, no other RCT has this caveat in the trial design. As a result of the fact that only the adalimumab trial has this definition of an PedACR response, the calculation of relative effectiveness of the biologics in this MTA review will be biased if it is based on the percentage of ACR 30/50/70/90 responders, as it is highly likely that the PedACR data pertaining to adalimumab at the end of the double-blind period will be underestimated. There is a danger of comparing 'apples and pears', because the definitions of response differ.

4.4 Intolerance to MTX

MTX is the first-choice DMARD for the treatment of JIA. However, there is marked variability in clinical response and tolerability to the drug. In a randomised trial, MTX failed to achieve a basic clinical response (PedACR30) in 28-40% polyarticular course JIA patients, and failed to achieve more stringent measures of response (PedACR70 and complete disease control) in 50-88%, even at intermediate/high dose (15-30mg/m^2).[41,42]

SAEs including hepatotoxicity and bone marrow suppression are uncommon and generally transient with MTX cessation. However, symptoms associated with MTX intolerance include abdominal pain, oral pain, and behavioural symptoms (e.g. restlessness, crying, irritability, and refusal of MTX) and may affect 50% of the JIA patients prescribed MTX even at a relatively low median dose of 10.9 mg/m^2.[43] Gastrointestinal effects, including nausea, abdominal pain, vomiting, or diarrhoea, are more common than previously thought, and have been reported in up to 73% adolescents with JIA.[43,44] Adolescents in this study were estimated to have over 6 fold higher odds of nausea compared with adults (OR 6.31, p=0.0002).

Clinically, these symptoms may result in MTX dose reduction or poor adherence leading to inefficacy and the requirement for treatment escalation. There is therefore a need to provide additional efficacious treatment options for patients with JIA.

Section 5: Cost-effectiveness

Due to numerous factors discussed in Section 4.3 and challenges outline in Section 5.8 – 5.10 below, AbbVie has not been able to conduct a robust cost-effective analysis. Instead, we present the key factors that need to be considered in an economic evaluation of etanercept, abatacept, adalimumab and tocilizumab for treating JIA.

5.1 Natural history of disease

JIA is not exclusively a disease of childhood and as such does not always remit. Indeed, outcomes studies performed after 2000 show that JIA frequently continues into adulthood. Ongoing or intermittent disease activity into adulthood has been found in more than half of cases and despite most remissions occurring in the first 5 years after disease onset, 40% to 60% of patients still have active JIA after >10 years of disease duration.[45,46] As noted in Section 2, the upper age limit for JIA has been removed from the SPC in recognition of this fact.

As mentioned in Section 1.1, JIA is not the same disease as rheumatoid arthritis or other forms of inflammatory arthritis and, although there are similarities with adult forms of arthritis, JIA should be considered a separate disease to rheumatoid arthritis in both children and adults. For example, in contrast to rheumatoid arthritis, rheumatoid factor (autoantibodies), can be detected only rarely in patients with JIA. The long term outcome of JIA varies depending on the disease classification; course and health status in the child.[45,46]

As such, assumptions regarding disease progression and outcomes for JIA, based on information for rheumatoid arthritis studies, should be done with caution.

5.2 Transition services

As a disease that starts in childhood and continues into adulthood, many patients with JIA transition to adult rheumatology services at some point. This transitioning may present difficulties for both the NHS and patients. There are many differences between adult and paediatric care. Young people need to be aware of these differences and to be equipped with knowledge and skills to allow them to interact effectively with their new adult health care providers. Conversely, adult providers need to be aware of the dramatic change that these young people experience at this time.

Several audits have been conducted looking at transition from paediatric to adult services in JIA. The first audit found that despite their imminent transfer to adult care, ongoing transitional issues were identified in the cohort of 17 old patients. For example, 55.8% were still seeing the rheumatologists with their parent, 20% were not self-medicating, 68.5% had not had intra-articular injections under local anaesthetic and 14% had received no careers counselling. This age group also had significant disease-related issues; 54.6% had moderate to severe functional disability, 67.5% were still on disease-modifying anti-rheumatic drugs and, as a group, they had significantly.[47]

A second audit looking at patients with JIA transferred to adult centred rheumatology care was conducted in 10 UK paediatric rheumatology centres before and 12-24 months after the implementation of a structured coordinated programme of transitional care.[48] This showed that a large multidisciplinary team approach was taken, mainly on an outpatient basis, with transfer of large number of documentation relating to notes, tests results and outcomes measures. Although the median age at transfer was 18 years (ranging from 12-49 years), preparation for transition started at a median age of 16 years. The authors noted that the administrative burden of this transfer had not been adequately recognised up to the time

they conducted the audit. Additionally, the authors noted that difference between paediatric and adult services may come as a shock to patients and influence their attendance at adult clinics, for example; consultation times were twice as long in the paediatric setting as in the adult setting and pain management for joint injections as adults did not include general anaesthesia as it did in paediatric services. The authors considered that this may ultimately impact on the patients' disease control and had planned a follow up study on the outcomes of the transitional care programme in terms of patients' QoL, satisfaction and knowledge. As of time of writing this submission, no further publication could be obtained on the results from that follow up study.

More recently, an audit of paediatric rheumatology services from 2007-2012 at a single UK hospital showed that of the 152 patients (of which 69% had JIA and 59% were on a DMARD/biologic during transfer), 35 were transferred to adult rheumatologists, 90 patients were discharged to primary care and 11 were lost to follow up. The authors concluded that although there had been an improvement in the transfer since their previous audit in 2007, there continued to be variation within their paediatric rheumatology services, despite having an established transitional care programme. They recommend further attention to the administrative workload of transition and consistency of practice to ensure equity and quality of care within centres.[49]

The administrative and human resource burden on the NHS of transitioning patients from paediatric to adult services is clearly substantial, and whilst AbbVie recognises that the costs will apply to all patients in the economic model and so should cancel out when relative effectiveness is assessed, the cost and administrative burden should be noted in the economic evaluation. Similarly, the impact this transition has on the patients may affect maintenance of, and adherence to, effective treatment and as a result impact their QoL and disease control.

5.3 Surgery for JIA complications

As discussed in Section 1.1, JIA can cause growth retardation, joint contractures, joint disease requiring joint replacements and permanent disability, and may be associated with other inflammatory co-morbidities such as uveitis, IBD and psoriasis.

As a result, the rate and cost of surgery and follow up care, including revision surgery and complications of JIA, need to be considered as these could be significant. An overview of types of surgery and follow up care for patients with JIA are provided below.

Surgery for JIA may be required for severe disease causing joint damage and for complications relating to uveitis. The types of joint related surgery include, but are not limited to, soft tissue release of contractures, resurfacing or athroplasty of affected joints, orthognathic surgery and costochondral graft reconstruction for temporomandibular joint involvement. Surgery for uveitis for complications of uncontrolled ocular inflammation or its treatment with corticosteroids include vitrectomy, intraocular pressure lowering surgery such as trabeculectomy for secondary uveitic glaucoma and cataract surgery.

Joint surgery in children and adolescents pose inherent challenges such as the choice of implant for an often atypical anatomical morphology, fixation of the prosthesis to an immature growing skeleton and the bearing surface employed. As result, custom devices may be required as patients with JIA cannot be treated with standard devices.[50,51] Revision surgery for joints may be particularly difficult because of the risk of the presence of chronic disability, joint contractures, osseous abnormalities and bone loss[52]. Cataract surgery in children is also complicated because of anatomical and functional characteristics such as small globe size, increased tissue reactivity, lower scleral rigidity, changing axial length and the risk of amblyopia.[53]

The cost of such surgeries and prosthesis need to be incorporated into the economics evaluation, however, this poses difficulties due to the range of products available, for example, the average list price cost for five manufacturers of adult total hip replacements ranges from £1,557 to £3,869, depending on the type of prosthesis.[54]

Joint surgeries are not only associated with increased mortality risk, but may also result in complications such as persistent pain, periprosthetic infection, intraoperative bone fractures, mechanical failure and nerve injury that require further medical management.[52,55,56,57] Complications related to ocular surgery may include fibrin formation resulting in synechiea formation (an eye condition where the iris adheres either to the cornea or lens), pupillary membrane formation, hypotony, secondary cataract formation, inflammation and glaucoma, all of which require further management.[58,59]

After joint surgery, patients need to undergo rehabilitation to restore and increase the range of motion and strength in the joints, which will ultimately improve their functional status. Follow up visits will also be required for patients who undergo ocular surgery.

Surgery rates vary, with the literature reporting rates of 7- 28% for joint surgery and 9-65% for ocular surgery. Revision joint surgery to remove old implants and replace them with new components later in life may also be required in some patients, these rates range from 9-25% of surgeries, or 21-41% of patients. Some evidence exists to suggest that surgery rates may be related to time since disease onset or diagnosis and immunomodulatory drug treatment history. These results are limited by the retrospective or observational nature of the studies as well as small sample sizes and data obtained from single centres. A summary of results from the literature are provided below:

In an observational study, 7% of 58 JIA patients with mean age of 23.5 years and mean disease duration of 13.1 years had previous hand or feet surgery[60]. In the Dutch Arthritis and Biologicals in Children register, 14% of 43 JIA patients with a median age of 22 receiving etanercept for a median of 8.5 years, had a history of joint surgery.[61] Similarly, a single centre chart review in Brazil found that 16% of 94 JIA patients with mean disease duration of 14.7 year underwent surgery – the majority of these were arthroplasties and ophthalmic surgery[62].

In a retrospective observational study of 144 adult JIA patients with a median age of 25.5 years and median disease duration of 19 years attending a teaching hospital clinic in the UK the authors report that 28% had received joint surgery and 41% had required revision surgery.[57] Revision surgery was also required in 21% of 24 patients on the joint registry at the Mayo clinic who had elbow replacements between 1983 and 2005,[63] whilst Heyse et al. report a revision rate of 9% out of 349 total knee athroplasties performed between the years 1979 and 2011.[50] This was higher in the study by Daurka: 25% of 52 uncemented total hip replacements required revision over a 10 year follow-up period in 35 children with JIA.[51]

Glaucoma filtering surgery was performed in 9% of 104 patients diagnosed with JIA between 1989 and 1996 in a single centre in Finland, and the majority still required ongoing glaucoma medication after surgery.[64] In a Canadian cohort of 142 children with a diagnosis of JIA and uveitis, 15% underwent ocular surgery, the majority of which were for cataract extraction and glaucoma.[65] Katargina *et al*. reported that whilst remission of uveitis was achieved in six out of 10 patients aged 4-12 years who were treated with abatacept; four underwent uncomplicated glaucoma or cataract surgery[66]. Data in 53 children with JIA-associated uveitis, identified in a database search of a single centre in the Netherlands from 1990 to 2006 found that 51% had undergone cataract extraction.[53] In a separate study, Heinz *et al*.[67] report on average, 55 patients with JIA and a follow-up period longer than one year required

1.3 surgical procedures for uveitis complications in two German tertiary referral uveitis centres.

The risk of surgery for cataract surgery appear to increase over the patient's lifetime as shown in a review of 65 paediatric patients with JIA associated uveitis, examined between 1981 and 2008 in a single centre in the Netherlands.[68] The study found that in the first year of follow up, 7% of patients' eyes required cataract surgery. The cumulative incidence increased to 13% at 3 years of follow up, 35% at 5 years and 65% at 10 years. For glaucoma surgery, the corresponding figures were 0%, 8%, 35% and 35%.

Data from a cohort database in Japan[69] found that the percentage of 114 JIA patients requiring orthopaedic surgery decreased from 54% before the 1970s to only 10% in the 2000s. At the same time, the induction ratio of biological DMARDs has increased for patients with more recent disease onset, with a shorter period from disease onset to induction (16.7% in the 1970s, with 27.3 ± 2.1 years to induction vs. 80.0% in the 2000s, with 5.6 ± 2.3 years to induction). Similarly, Mertelman-Voss *et al.* found that the rate of arthroplasty for JIA decreased by nearly 50% (0.22 per 100,000 versus 0.13 per 100,000, $p<0.001$) during the period 1991 to 2005 in a US administrative discharge database[70]. As this finding is consistent with the increased use of immunomodulatory agents among children in recent decades, the authors suggest that DMARDs and biologic agents may have successfully prevented end-stage joint damage and the need for athroplasty if initiated soon after disease onset. Similarly, in the study by Sijssen *et al*.,[53] children treated with MTX had a significantly longer interval between uveitis onset and first cataract extraction than children not treated with MTX (HR 0.29; 95% CI 0.10 to 0.87).

5.4 Cost of visual impairment and blindness

As discussed in Section 1.2.1, a proportion of JIA patients will have JIA associated uveitis. Early onset blindness adversely affects psychomotor, social and emotional development as well as survival rates in children.[71] As such, vision impairment or blindness will have a lifetime impact on children and affect their opportunities for education, employment and earning potential. Given the fact that such a large proportion of children with JIA have associated uveitis, AbbVie considers that the cost of visual impairment needs to be factored into the economic model.

An iterative literature review of the cost of blindness in children found no information relevant to the UK, as such a review of NICE technology appraisals from 2010 was conducted to determine costs associated with visual impairment and/or blindness. The review found a wide range of costs associated with blindness in the economic evaluations: £585[72] to £17,300[73] per year, with most appraisals using an annual cost of approximately £6,000. [74,75,76,77] Unfortunately, these results are limited by the varied definitions of blindness used in the appraisals, a lack of appraisals in children, and use of the same methodology - that of Meads and Hyde[78] - in every appraisal, with costs updated to the respective year of the appraisal.

To support the cost calculations for visual impairment or blindness in this appraisal, the outcomes considered by Meads and Hyde are listed below:

- Blind registration
- Low vision aids
- Low vision rehabilitation
- Housing benefit and council tax benefit
- Social security
- Tax allowance

- Depression
- Community care
- Residential care

Whilst all of these would not be applicable to this appraisal, practical support from local social services would be required for parents of children with visual impairment or blindness. Such support from social care services would be required to help assess care and support needs as well as special education needs, and assist parents teaching their children to live more independently.

5.5 Cost of drugs and weight distribution of children starting biologic in UK cohort

Drug acquisition costs in the economic model will be dependent upon patient weight or body surface area as this is how the biologics under review are dosed.

Although the cost of one adalimumab injection is fixed, the cost of treatment for the other biologics may vary depending on available presentations and vial sharing practices within the NHS. AbbVie considers the weight distribution of JIA patients in England and Wales to be an important consideration in the economic model. Although information on the weight of patients included in the AbbVie studies are available and are summarised in Section 2, Tables 2-5, 8, 24, 27 and 30, it may not be generalisable to the UK as none of the studies were conducted in the UK. A similar issue may exist with the studies of the other biologics under review.

An additional an important consideration the AG needs to factor in to the economic model is that the weight of the children and adolescents will not remain constant. The weight and height of the JIA patients will increase as they grow older, and as such, the cost will increase up to a point where the full adult dose is used and at this point the drug acquisition cost will stabilise (for adalimumab this is approximately aged 12-13).

In the absence of data on the weight distribution for JIA patients in the UK, AbbVie is unable to suggest drug acquisition costs for the other biologics in this MTA. However, it is likely that weight distribution data for a decent sized cohort of JIA patients in the UK initiating a biologic should be available from the BSPAR-ETN and BCRD registries, which the AG should be able to use in their model.

5.6 Societal costs

In addition to the direct cost of visual impairment and blindness, cost of rehabilitation services, equipment and support from family for functional impairment may be substantial and should also be borne in mind. In a recent review of burden of illness, indirect costs associated with JIA have been estimated to be up to 86% of total cost, consisting mainly of loss of income from parents.[79]

This is not unexpected as JIA related functional impairment outlined in Section 1.1 may require children to be dependent on family members for many of their activities of daily living. Such support includes help with e.g. getting dressed and transportation and obtaining assistive devices such as pencil grip to help with writing at school, or adapted workstations that can assist with integration at school.

Other societal costs include parental loss of productivity and income because of time taken from work to take care of an affected child. A recent study by Rasu *et al.*[80] found that parents having a child with JIA were 2.78 times more likely to report work-time loss than those having no children with JIA. They also had a mean number of reported missed work-time

hours of 281.81 hours in a 9 year period compared to 183.36 hours for parents without children with JIA.

Not surprisingly due to the disabling nature of the disease if not treated appropriately, people with JIA over 16 may be eligible for Disability Living Allowance, Incapacity Benefit, and Income Support. Other types of monetary support include Disabled Person's Tax Credit for disabled people who are unable to go out to work at least 16 hours a week; housing benefit, council tax benefit, Social Fund for people on low income; Direct Payment Schemes via Social Services and Independent Living Funds for personal assistance and Carer's Allowance for carers. Young people with arthritis may be eligible for an Individual Education Plan in schools which will set their goals for the school year as well as any special support they may need to achieve them. This will require the support from a teacher who is a special educational needs co-ordinator.[81]

The costs of these however, are not covered by the NHS and thus would not be incorporated into an economic model, despite the economic impact it may have on society. AbbVie considers that these factors need to be considered as part of an overall value judgement when appraising the biologics in this MTA.

5.7 Model structure

AbbVie notes that in previous health technology appraisals in the UK it was not possible to model the cost-effectiveness of biologics due to the difficulties of comparing the treatments against each other or due to lack of empirical information that precluded the construction of a model with high validity. Instead, a cost-minimisation analysis was done in one appraisal, and the other appraisal based the cost-effectiveness analysis on an adult rheumatoid arthritis model.[82,83]

This cost-utility analysis had as its main assumption that the measures of clinical response used in children and adults were comparable (i.e. JRA 30 can be equated to ACR20), that the CHAQ is equivalent to the adult HAQ version and that the HAQ relationship to utility and mortality also applied in children. However, the AG felt that these assumptions had no evidence base and as result, they could themselves not provide a model with greater validity.

As will be argued in the sections hereafter, these assumptions continue to pose challenges.

5.8 Challenges with utility estimation

5.8.1 Mapping algorithms of utility in JIA

Unfortunately, none of clinical trials of the biologics under review in this MTA collected health related quality of life (HRQoL) data sufficient to calculate utility values necessary for a cost utility analysis. Therefore, in the absence of a preference based HRQoL measure, the consensus from NICE's technical support documents (TSD 10) is to use a mapping algorithm enabling data from the trials e.g. clinical outcome data to be used to estimate EQ-5D utility scores. This isn't uncommon, and indeed for the majority of the technology appraisals conducted in adults with rheumatoid arthritis, utility values have been estimated using mapping algorithms linking HAQ to EQ-5D.

Normally, mapping involves three stages. Firstly a separate 'estimation' dataset is required that contains the data that are being mapped from, the 'source', and the 'target' preference-based measure. Secondly regression methods are used to 'map' this data onto either the index score or the classification system of the target measure. Thirdly the regression results

are applied to the trial(s) or observational study dataset to estimate utility scores for the target measure at either the mean or observational level.[84]

The protocol developed by the Assessment Group suggests two studies as possible sources for the estimation of utilities.[85,86] However, AbbVie is unclear how Khan *et al.* would be used to inform estimates of utility; e.g. Khan *et al.* map EQ-5D utility scores from the PedsQL generic core scales, but PedsQL was not collected in the JIA biologics RCTs, so it is unclear how any EQ-5D utility estimates mapped from this measure would be applied in this appraisal.

Prince *et al.* collected HUI-3 (utilities can be derived directly from this) as well as the JIA core set of variables used to calculate PedACR response rates, one of which is the CHAQ total score – so it would theoretically be possible to estimate utilities from the biologic RCTs based on a regression of CHAQ onto HUI-3. However, there are a number of limitations with doing this. Firstly, the study by Prince *et al.* is only in n=49 patients, an extraordinarily small sample size to fit an equation predicting utility values from a CHAQ score with any confidence. Secondly, following experience with adult rheumatoid arthritis mapping algorithms, typically the total HAQ score (in this case it would be the total CHAQ score) is insufficient to generate a good model fit for predicting utilities. Mapping algorithms in adult RA with a good model fit required the answers of up to 11 individual questions of the HAQ, and sometimes combine a separate pain and a fatigue element. Finally in order to generate any regression equation, the AG would need the individual CHAQ and HUI-3 data from each of the 49 individual JIA patients reported in the paper, not the mean and SEM values for the cohort (as is reported), which hopefully the authors can provide to the AG.

AbbVie conducted an iterative literature review for utilities in JIA and found similar data sources to the AG. In addition, AbbVie reviewed the mapping algorithms adopted for previous NICE appraisals of tocilizumab in sJIA and etanercept for pJIA. However, both these appraisals used mapping formulae derived from an adult RA population, which imply the following assumptions: that CHAQ of child is equal to the HAQ score of adult (which AbbVie contends is flawed, see Section 5.5) and that adult EQ-5D is equal to the HRQoL of a child. The manufacturers of the biologics both acknowledge that the above assumptions have no evidence basis and the rationale for this mapping methodology was solely due to lack of other available data.

In addition, AbbVie looked into the possibility of using any unpublished data from the UK registries to derive utilities for this appraisal. However, in communication with the principal investigator for the registries we received the following response, " *there are limited tools in paediatrics which can be used to measure QALY's and even less on mapping of other outcomes to these tools, such as has been done for the EQ-5D and HAQ in RA. Unfortunately, though, I think you have been provided with inaccurate information about CAPS and the registers. CAPS does not currently capture a health utility measure. Both BSPAR-ETN and BCRD studies have just received ethical approval for inclusion of the Child Health Utility (CHU)-9D (which has been mapped to QALY's in some age groups), but the total number of forms received so far is sparse. Also, we currently don't collect the full CHAQ (only the total score), which is also required for mapping, if I understand it correctly. Although we are now capturing all aspects required for future mapping, we are just not in a position to do this at this time. As far as I know, the EQ-5D has not been validated for use in children and would not be the best tool anyway in this situation*."[87]

Therefore, in the absence of any other data AbbVie considers that the AG's approach of using HUI-3 mapped to CHAQ might be the only reasonable option for this appraisal, but as discussed it has some limitations. Absence of robust utility data was one of the main reasons AbbVie did not conduct an economic evaluation.

5.8.2 Inability to capture all the HRQoL benefits if a mapping algorithm used

A further challenge in this appraisal will be the ability to capture all the changes in HRQoL if a mapping algorithm derived from a purely functional outcome measure is used (i.e. DI-CHAQ is a patient reported questionnaire to describe functional disability). Whilst HUI-3 would capture changes in HRQoL if it was employed directly; when it is fitted to CHAQ data, any changes in utility in the economic model will be driven by changes in CHAQ total score derived from the RCTs. Therefore any improvements in HRQoL that could be attributed to an improvement in say visual impairment or in reducing a flare of inflammatory bowel would not be captured. For example, hypothetically a pJIA patient with a baseline CHAQ total score of 1.7 and co-morbid uveitis might achieve a CHAQ score of 1.0 following 6 months treatment with a biologic. Using the mapping algorithm to derive changes in utility linked to changes in CHAQ, this would result in a utility improvement of 0.13 (driven by the -0.7 improvement in CHAQ). However, what if this patient also had complete remission of active uveitis following 6 months treatment of a biologic? All the HRQoL benefits associated with uveitis remission e.g. improved visual acuity and reduction in pain would not be captured.

The only way to account for this would be to assess the original estimation sample for co-morbid uveitis and examine HUI-3 changes by both CHAQ and uveitis to potentially infer the separate effects of each outcome on HRQoL. However, looking at the dataset this doesn't look like it would be possible.

AbbVie understands that there are limited options to derive utilities in this disease area; however it is important for the AG and the Appraisal Committee to consider the additional benefits some of the biologics have on HRQoL that won't be captured if HUI-3 is mapped solely to changes in CHAQ.

5.9 Challenges with disease progression, extrapolation and time horizon

Historically in adult RA, there has been a great deal of discussion around the best methodology for extrapolating costs and benefits over a lifetime horizon for both biologics and conventional DMARDs (e.g. MTX). At least in RA, there are some long-term data for up to 15 years of treatment with a biologic, which is unfortunately not the case in JIA. Challenges around estimating disease progression whilst on biologics vs. DMARDs, and extrapolation of any data to a lifetime horizon are more pronounced in JIA because there is a lack of a data to support some of the long-term assumptions.

5.9.1 Time horizon

At the scoping workshop for this appraisal, there was some discussion around the most appropriate time horizon that should be adopted e.g. model up to the age of 17 or to model a lifetime horizon. As previously mentioned, JIA continues into adulthood for a large proportion of patients and as such, continued functional impairment still occurs in those adults who have active, uncontrolled JIA – this must be captured in the economic model as any joint damage that occurs will be associated with a commensurate (discounted) cost and decrease in HRQoL. Furthermore, it is also important to consider adult patients who no longer have active disease, but who sustained irreversible functional impairments as children - the impact of which continues to affect their adult life.

Additionally, as discussed in Section 5.2, the administrative burden (and thus cost to the NHS) associated with rheumatology services when patients transition as paediatric patients to adult patients, may be substantial and also may impact on the patients' disease control and QoL at the point of transition or beyond that.

Other long term outcomes for JIA may include surgery, including revision surgery, later in life to improve functional impairment that occurred during childhood or adolescence.

As such, the time horizon in the economic model should be sufficiently long to capture these costs and outcomes.

5.9.2 Disease progression and extrapolation

In the adult RA economic models, in its most simplistic form disease progression beyond the trial durations is modelled by applying differential rates for HAQ progression dependent on treatment. For example, for biologics it has been accepted that the HAQ progression rate is zero, for DMARDs an annual deterioration rate of 0.045 has been applied, and for palliation i.e. when there are no more treatment options, an annual rate of 0.06 has been used.

AbbVie considers that the disease progression and extrapolation from RA economic models would not be applicable in JIA for a number of reasons, but predominantly because onset of JIA symptoms occurs during the growth period. The functional impairment sustained as a result of uncontrolled disease as a child during growth is likely to be much worse than irreversible damage sustained as an adult due to uncontrolled RA. Complications of affected joints in JIA include asymmetric growth and a reduction in growth velocity and bone density. Therefore, applying a linear HAQ deterioration rate to model disease progression wouldn't necessarily capture the potentially exponential effect active disease has during growth and the subsequent continuing functional deterioration as a result.

In a similar vein, if the assumptions around long-term costs used in the adult RA models are applied here, then long-term costs would be estimated by applying a cost per total CHAQ score. There is limited data available in the literature to estimate the cost for each of the permutations of CHAQ score, and if adult costs were applied AbbVie considers this would underestimate the actual cost of disease. This is because there appears to be a greater incidence of surgical complications and revisions for JIA than for adult RA (see Section 5.3). Furthermore, there is also the cost of the extra-articular manifestations associated with JIA that are not as common in adult RA. For example, Section 5.3 highlights some of the surgical costs potentially incurred for patients with concomitant uveitis that is an important consideration in JIA that would not be captured if the RA cost per HAQ score was applied to JIA.

Therefore, and as noted in Section 5.1, applying assumptions used in the adult RA economic models to JIA should be done with caution, even in the absence of other data to inform the model. Further, if adult assumptions are used, the Appraisal Committee need to be mindful that it is likely that some of the costs and potential effects will be underestimated for JIA.

5.10 Challenge of implementing efficacy estimates in to model given issues with NMA discussed in Section 4.3

Section 4.3 describes a number of issues with the RCTs of the biologics under review in this appraisal – including trial design, heterogeneity and sample size – that makes a robust indirect comparison in this area very challenging. This has obvious implications for the robustness of any economic model estimating the relative cost-effectiveness of the biologics vs. conventional treatment or incrementally vs. each other.

AbbVie is unclear at this stage how the AG is going to incorporate the efficacy estimates generated from an indirect comparison in to their de novo economic model. However, in most of the adult RA models, ACR response rates from the RCTs were synthesised from a NMA of the trials and then applied to HAQ scores. These HAQ scores then generated EQ-

5D derived utilities via different mapping algorithms, the goodness-of-fit of which have evolved over time.

The concern with this appraisal is that if the 'placebo' arms of the RCTs for the biologics are treated like true placebo arms and form the reference treatment in an indirect comparison, as well informing the estimate for standard of care, the analysis will be fundamentally flawed for all the reasons outlined in Section 4.3. The effectiveness of standard of care will be impacted by the fact that not only had all patients received active drug, but in order to enter the double-blind phase they also had to be responders. As a result, the PedACR response rates will depend on the duration of the withdrawal phase and not on response rates that would one would expect to observe in a true DMARD failure population.

Furthermore, if the synthesised percentage PedACR response data are subsequently linked to CHAQ scores, and then to utilities via mapping to HUI-3 as discussed in Section 5.8, then the level of uncertainty in the estimates of effectiveness will increase, potentially resulting in this appraisal becoming untenable due to huge uncertainty in the data.

Section 6: NHS Resource Implications

JIA can result in a wide range of complications for people with the disease, their carers, the NHS and society in general. The economic impact of this disease includes:

- Direct costs to the NHS and associated healthcare support services
- Indirect costs to the economy, including the effects of early mortality, lost productivity of parents as well as that of the patients later in life, and monetary support from the UK government for living with a disability or being unable to work
- The personal impact of JIA and subsequent complications for people with JIA and their families.

A 2014 systematic review of burden of illness of JIA, amongst others, found that the study perspective, sample size, mean age and data reference year varied significantly in the eight studies identified, making it difficult to compare evidence across the studies and over time. Nonetheless, the annual cost per patient were reported to be as high as €30,000/patient (2010 cost year). Direct costs included the cost of medication (up to 54%), inpatient stay (up to 40%), outpatient care, equipment, devices and aids (up to 3%) whilst indirect costs were attributed to loss of income for parents (up to 86% of direct cost). Patients not in remission had the highest cost, more than seven times those in remission. Treatment costs for patients with entheitsis-related, systemic onset, extended oligoarticular and pJIA (RF+) were almost double that for all JIA patients. The authors point out that the introduction of new pharmaceutical therapies such as biologics significantly affected both direct and indirect treatment costs: whilst the direct treatment costs increased, indirect cost reduced due to lower productivity losses accruing to parents for escorting their child to treatment.[79]

Thus, although only direct costs are considered in this application, it should be borne in mind that indirect costs are not insubstantial and carries a burden on society.

Implications to the NHS relating to direct costs are discussed below.

6.1 Anticipated direct cost associated with drug treatment

The cost associated with each intervention needs to take into account a number of factors. These include: drug acquisition cost; average weight of JIA patients for those interventions that are weight based and administration costs associated with infusions.

Drug acquisition costs will depend on the loading and maintenance dose and patient weight or body surface area. AbbVie consider the weight distribution of JIA patients in England and Wales to be an important consideration in the likely budget impact which results from using anti-TNF in eligible patients. In the absence of data on the height and weight for JIA patients, AbbVie is unable to calculate drug acquisition costs, but outline the other cost considerations below.

Adalimumab is supplied in a pre-filled, pen or syringe, which, with support and training, can be administered at home as a SC injection. This administration method is associated with lower NHS service requirements and cost when compared to drugs which are administered intravenously in specialist settings. Adalimumab is delivered to the patient's home, with training and support provided for administering the drug, using a homecare delivery service provided by the manufacturer at no additional cost to the NHS. Homecare delivery services such as this also means adalimumab is exempt from VAT.

Some people may need to attend community or hospital facilities for the infusion of IV drugs. Depending on the facilities used, the cost for infusion services are £99 for a rheumatoid

outpatient follow up attendance[88] or £453 for combined rheumatoid day case / ordinary elective spell[89]. Attendance at these facilities or clinics may impact on the need for specialists' nurses in rheumatology and multidisciplinary rehabilitation and physiotherapy resources.

6.2 Budget Impact model

No formal budget impact has been calculated for the use of adalimumab in JIA patients in England and Wales as AbbVie believe there is considerable uncertainty in the likely number of patients who may be eligible and receive adalimumab for their condition in clinical practice.

Additionally, the definition, and therefore the numbers of patients with polyarticular disease depends on whether it is polyarticular *onset* (the disease classification according to the ILAR criteria based on arthritis presentation and evolution over the first 6 months from diagnosis) or polyarticular *course* disease (5 or more affected joints whatever the JIA classification) that is referred to. While the prevalence of polyarticular onset JIA according to the ILAR criteria is ~25%, the prevalence of polyarticular course JIA is higher. Calculations for the number of patients eligible for biologic treatments should therefore take into consideration these definitions. In the previous NICE appraisal of etanercept, the percentage of patients with polyarthritis was estimated to be approximately 40%, which was a mixture of polyarticular onset and course disease.

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