NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal (MTA)

Etanercept (Enbrel®) for treating juvenile idiopathic arthritis (including review of TA35)

Company evidence submission

Submitted by Pfizer Ltd.

17 March 2015

Contents

1 Executive summary ... 7
1.1 Statement of decision problem ... 12
2 The technology ... 15
2.1 Description of the technology being appraised ... 15
2.2 Marketing authorisation/CE marking and health technology assessment ... 17
2.3 Administration and costs of the technology ... 19
2.4 Changes in service provision and management ... 22
2.5 Innovation ... 23
2.5.1 Innovation: impact on the management of JIA ... 23
2.5.2 Benefits unlikely to be included in the QALY calculation ... 24
3 Health condition and position of the technology in the treatment pathway ... 26
3.1 Definition and classification of JIA ... 27
3.2 Epidemiology ... 27
3.3 Aetiology and risk factors ... 27
3.4 Diagnosis ... 28
3.5 Assessment of response to therapy ... 28
3.6 Symptoms and burden ... 29
3.7 Treatment guidelines/guidance for juvenile idiopathic arthritis ... 30
3.7.1 NICE Technology appraisals ... 31
3.7.2 Other guidance or guidelines ... 32
3.8 Treatment pathway for juvenile idiopathic arthritis ... 34
3.8.1 Treatment pathway for juvenile idiopathic arthritis in adult rheumatology care 34
3.9 Equality issues ... 35
4 Clinical effectiveness ... 36
4.1 Identification and selection of relevant studies ... 36
4.2 Identification of studies ... 36
4.2.1 Study selection and data extraction ... 38
4.2.2 PRISMA diagram, clinical effectiveness ... 41
4.3 List of relevant interventional studies ... 42
4.4 Summary of methodology of the relevant interventional trials ... 45
4.5 Statistical analysis and definition of study groups in the relevant interventional trials 49
4.6 Participant flow in the relevant interventional trials ... 51
4.6.1 Baseline demographic and disease characteristics of interventional studies .. 53
4.7 Quality assessment of the interventional trials ... 61
4.8 Clinical effectiveness results of the interventional trials ... 65
4.8.1 JIA ACR response ... 66
4.8.2 ACR core assessment set outcomes ... 72
4.8.3 Disease inactivity and remission ... 76
4.8.4 Pain assessment ... 78
4.8.5 JADAS/DAS score ... 78
4.8.6 Other efficacy outcomes ... 78
4.9 Subgroup analysis ... 79
4.10 Meta-analysis ... 79

4.11 Indirect and mixed treatment comparisons ... 79
4.12 Evidence from observational studies ... 80
4.12.1 List of relevant observational studies ... 80
4.12.2 Inclusion and exclusion criteria for the relevant observational studies ... 84
4.12.3 Baseline characteristics in the relevant observational studies ... 88
4.12.4 Quality assessment of the relevant observational studies ... 101
4.12.5 Clinical effectiveness results of the observational studies ... 101
4.12.6 Health-related quality of life ... 129
4.13 Adverse reactions ... 133
4.13.1 Interventional studies ... 134
4.13.2 Observational studies ... 139
4.14 Interpretation of clinical effectiveness and safety evidence ... 151
4.15 Ongoing studies ... 152
5 Cost effectiveness ... 154
6 Assessment of factors relevant to the NHS and other parties ... 157
6.1 Cost analysis ... 157
7 Reference List ... 159
8 Appendices ... 179

Tables and figures

Table 1 The decision problem ... 13
Table 2 Description of the technology ... 16
Table 3 Costs of the technology being appraised ... 21
Table 4 Long-term outcomes in JIA ... 30
Table 5 Biological agents licensed for the treatment of JIA ... 33
Table 6 Eligibility criteria used in the search strategy for the clinical effectiveness evidence ... 40
Table 7 List of relevant interventional studies (randomised and non-randomised) ... 44
Table 8 Summary of methodology of RCT and non-randomised interventional trials ... 46
Table 9 Statistical analysis and definition of study groups in the RCTs ... 50
Table 10: Summary of the participant flow in the relevant interventional studies ... 52
Table 11 Baseline demographic, disease and concomitant treatment characteristics of interventional studies ... 55
Table 12 Baseline disease severity of participants in the studies across treatment groups (clinical measures) ... 59
Table 13 Quality assessment results for the interventional trials with randomised phases ... 62
Table 14 Newcastle-Ottawa quality assessment (non-randomised interventional studies; * indicates good quality) ... 63
Table 15 JIA ACR response in the interventional studies ... 69
Table 16 Outcomes for individual components of the ACR core assessment set ... 73
Table 17 Inactive disease and remission outcomes, interventional studies ... 77
Table 18 List of the relevant observational studies ... 81

Table 19 Inclusion and exclusion criteria and permitted concomitant medications, observational studies 84
Table 20 Baseline characteristics of participants in the studies 89
Table 21 Baseline disease activity, observational studies 96
Table 22 JIA ACR response, relevant observational studies 103
Table 23 Outcomes for ACR core set components, observational studies 111
Table 24 Inactive disease and remission outcomes, observational studies 121
Table 25 Studies included in the HRQoL review, and data extracted 132
Table 26 Discontinuations and patient-years of etanercept use (safety analyses), interventional studies 135
Table 27 Adverse events, interventional studies 137
Table 28 Discontinuations and total patient-years of etanercept use (safety analyses), observational studies 140
Table 29 Summary of adverse events, observational studies 145
Table 30 Limitations with the models in TA35 & TA238 (NICE 2002, NICE 2006) . 155
Table 31 Cost analysis 158

List of figures

Figure 1 PRISMA diagram for the electronic database for clinical effectiveness 42
Figure 2 Functional assessment and HRQoL, Robinson 2003 131

List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ANCOVA	Analysis of covariance
bDMARD	Biological disease-modifying anti-rheumatic drug
BSPAR	British Society for Paediatric and Adolescent Rheumatology
BSR	British Society for Rheumatology
CAHP	Childhood Arthritis Health Profile
CHQ	Child Health Questionnaire
CHAQ	Childhood Health Assessment Questionnaire
CHAQ-DI	Childhood Health Assessment Questionnaire Disability Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CSR	Clinical study report
DMARD	Disease-modifying anti-rheumatic drug
EMA	European Medicines Agency
eoJIA	Extended oligoarthritis JIA
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League Against Rheumatism
HR	Hazard ratio
HRQoL	Health-related quality of life
HUI	Health utilities Index
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IV	Intravenous
JAQQ	Juvenile Arthritis Quality of Life Questionnaire
JADAS	Juvenile arthritis disease activity score
JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
LOM	Limitation of motion
Mo	Months
MPR	Medication Possession Ratio
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PAS	Patient access scheme
PedsQL	Pediatric Quality of Life
PGA	Physician global assessment
PRD	Pediatric rheumatic disease
PReS	European Pediatric Rheumatology Congress
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-
PRQL	Paediatric Rheumatology Quality of Life Scale
PsA	Psoriatic arthritis

Pts	Patients
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RF	Rheumatoid factor
SAE	Serious adverse event
SmPC	Summary of product characteristics
TA	Technology appraisal
TACQOL	TNO AZL Children's quality of life
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
VAS	Visual Analogue Scale
Wk.	Week
Y	Years

1 Executive summary

Juvenile idiopathic arthritis (JIA) is a heterogeneous disease associated with inflammation, pain, stiffness and swelling of the affected joints; symptoms often lead to morbidity and loss of quality of life.

JIA includes a heterogeneous group of inflammatory arthritis conditions persisting for at least 6 weeks and diagnosed in persons <16 years old [1] JIA is characterised by inflammation, pain, stiffness, swelling of the affected joints and impaired growth. Several subtypes of JIA have been defined, classified according to the number of affected joints or other associated characteristics.[2] The pathogenesis of JIA remains unclear. However, symptoms typically begin in childhood and persist into adulthood. JIA is associated with painful and debilitating symptoms which may lead to a substantial impact on child's physical and educational functioning and psychological wellbeing, and on the health related quality of life of patients and their carers.[3] JIA may result in a considerable economic burden on patients, carers, employers and the healthcare system.

A wide range of estimates of incidence and prevalence for JIA are reported in the literature.[4] In England and Wales, at least 12,000 persons aged <18 years are thought to have JIA at any one time (approximately 1 in 1,000 children).[5] It is estimated that of these, half will continue to have the disease in adulthood [6], which can result in a significant humanistic and economic burden.[7] The standard classification for JIA is the International League of Associations for Rheumatology (ILAR) system which replaced the earlier systems used by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR); under these systems the disease was known as Juvenile Rheumatoid Arthritis and Juvenile Chronic Arthritis, respectively.

The main aim of treatment is to achieve complete remission of disease.[1] A step-wise approach to treatment is often recommended, [BSPAR, 2015] [5], starting with non-steroidal anti-inflammatory drugs (NSAIDS) and pulsed or intra-articular steroids. If NSAIDs are not adequate, a disease-modifying anti-rheumatic drug (DMARD), commonly methotrexate, is used. If response to methotrexate is not

adequate, or it is not tolerated, biological DMARDs (bDMARDs) such as etanercept may be used.

Etanercept is an innovative therapy that has become the established treatment for JIA and is the only bDMARD licenced for all JIA subtypes included in the final scope

The advent of biological therapies, of which etanercept was the first to be licensed in JIA, has been described as a ‘major new era in the medical management of JIA’ and a ‘paradigm shift’ [8] in the pharmacotherapy of JIA. Etanercept now has more than 15 years of clinical use following the initial Marketing Authorisation on 03 February 2000 for the treatment of active polyarticular-course JIA. It was first recommended by NICE in March 2002 and is the only biologic currently recommended for children aged 4 to 17 years who have active polyarticular JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.[9]

Since then, the therapeutic indication for etanercept has expanded and now also includes extended oligoarthritis (from the age of 2 years), psoriatic arthritis (from the age of 12 years) and enthesitis-related arthritis (from the age of 12 years) as supported by the pivotal CLIPPER study [10] [11]. Also, the lower age range for treating polyarticular disease has been reduced from 4 years to 2 years and the marketing authorisation no longer specifies an upper age limit of 17. The license was granted on the basis of a range of studies including, a pivotal open-label, double-blind two-part study [12], two open label single arm studies [13] including a safety extension study [14], and a 3-year registry study.[15]

Etanercept is the only recombinant, fully human soluble TNF receptor fusion protein available on the market.[11] Other biological agents with different mechanisms of action (abatacept, adalimumab, and tocilizumab) have also been licensed for the treatment of polyarticular JIA. Many factors will influence selection of treatments, however unlike monoclonal antibodies (e.g. adalimumab) , etanercept is not associated with the production of neutralising anti-drug antibodies or the potential consequences of this such as diminishing drug levels and reduced response to treatment (see section 2.5.1 for further details).[16]

Etanercept has demonstrated sustained ACR response in the treatment of JIA and across the subtypes included in the final scope

Etanercept was recommended by NICE for polyarticular JIA in 2002 on the basis of data available from the pivotal licensing study by Lovell et al. In the initial open-label phase 74% of etanercept patients had ACR 30 responses. In the subsequent double-blind phase, significantly more patients who received placebo (81%) than patients who received etanercept (28%) had disease flare (p=0.003). Response was maintained in 83% of patients evaluable at 8 years (last observation carried forward).

A broad range of evidence is now available from registries that support the consistency and duration of ACR response observed in the pivotal study (see section 4.2 and 4.11).

- The largest registry to report efficacy results was the German BIKER registry which analysed 863 JIA patients: 81.9% had achieved ACR30 at 6 months, 55.2% had achieved ACR 70 and 31.3% had achieved ACR 90.[17]

- Kearsley-Fleet 2014 reported data on 407 patients from the UK: at 12 months, response rates were 75%, 70%, 59%, and 41% for ACR 30, 50, 70 and 90 respectively.

- Sustained efficacy was reported by Halbig 2009 in the largest cohort that reported results at 24 months: of 114 patients, 96.5%, 93.8% and 90.3% achieved an ACR score of 30, 50 or 70 respectively.

- The BSPAR registry from the UK showed that in a cohort of JIA patients treated with etanercept and followed for a median of 2 years (maximum 5 years), the majority (69%) remain on the drug.[18]

Etanercept has also shown efficacy across JIA subtypes. In the CLIPPER study [13] ACR 30 was achieved by 89.7% of subjects with extended oligoarticular JIA, 83.3% with enthesitis-related JIA and 93.1% with psoriatic JIA at week 12. This was maintained in 99.1% of patients still on-study at 96 weeks [19]. Etanercept can therefore be considered efficacious in all patients included within the scope of the appraisal.

Patients treated with etanercept achieve important long-term outcomes such as remission and improved growth

Achieving inactive disease and subsequently remission are important long-term goals of treatment that are frequently achieved in registries recording practice with etanercept. Furthermore, improving growth and avoiding joint damage are both important factors in supporting patient's emotional and physical wellbeing.

- In an observational study of 173 patients, 50.3% achieved inactive disease after a median of 0.6 years of therapy. At last follow-up,49.1% still had inactive disease and 40.5% were in clinical remission on medication.[20]
- Of 787 patients from the German etanercept registry, 47.6% met the criteria for inactive disease (Wallace criteria) and 26.6% achieved remission on medication at last observation.[21]
- In the CLIPPER study, the percentages of subjects with extended oligoarticular JIA, ERA, and PsA who had inactive disease status at week 12 were 12.1%, 16.7%, and 6.9%, respectively. By week 96 week this was 34% across the entire cohort.
- Data from the Italian registry showed that during the first year of treatment with etanercept, patients with JIA showed a reduction in radiographic progression.[22]
- Etanercept treatment has been shown to improve growth over the first two years of treatment.[23] It has also demonstrated significant increases in mean height from baseline compared to patients treated with MTX.[24]

Etanercept has a well-defined long-term safety and tolerability profile

The safety and tolerability profile of etanercept has been examined in a clinical trial programme and reinforced by numerous observational and registry studies.

[redacted]

- Long-term, continuous treatment with etanercept was well tolerated for up to 10 years, and no significant increase in adverse events over time was observed.[14]

Treatment with etanercept improves HRQoL in a patient population with painful and debilitating symptoms

Due to factors such as impaired physical function JIA can have consequences for psychological wellbeing and HRQoL. Treatment with etanercept has been shown in three studies to significantly improve HRQoL from baseline in several generic instruments. Rapid improvements (over 3 months) have been observed in the Child Health Questionnaire (CHQ), the Health Utility Index 3 (HUI3) and PedsQL.[26-28] Follow-up from these studies indicates that improvements can be maintained long term (maximum follow-up 27 months). Pfizer note that the QALY does not capture the full impact of JIA, such as educational attainment and care-giver burden, which are also important factors to consider.

Etanercept is clinically effective and represents value for money to the NHS

Pfizer is confident that the efficacy of etanercept observed in the pivotal Lovell study has been validated by the numerous published registry studies. In the absence of head-to-head trials comparing etanercept to other biologics we considered undertaking an indirect comparison to other bDMARDS. However, it was not considered feasible due to substantial differences in respective marketing authorisations as well as heterogeneity in study design and patients recruited. Furthermore, this conclusion has been supported by independent research.[29;30] For these reasons we have limited the submission to direct clinical evidence for etanercept.

A similar feasibility assessment was undertaken regarding development of a cost effectiveness model. Pfizer note that previous technology appraisals (TA35 and TA238) have challenged data limitations and approaches to conducting cost-effectiveness analyses of JIA and systemic JIA, respectively. Following a targeted literature review it was identified that limitations remain with data for key model attributes such as utilities and natural history data required to model a life-time time horizon, as per the NICE Reference Case. For these reasons any cost-effectiveness

evidence submitted would continue to be associated with considerable and unresolvable uncertainty. Therefore, Pfizer have not submitted a cost-effectiveness model for this appraisal. We have undertaken a simple cost analysis which showed that for most ages, etanercept is the biologic treatment with the lowest acquisition cost compared to list prices for tocilizumab and adalimumab for the indication of polyarticular JIA. In selecting treatments for the management of JIA the NHS should also consider the cost of drug administration. Etanercept is administered subcutaneously, which can be undertaken by the patient or a carer at home. This offers flexibility to patients and their families and has no cost impact for the NHS.

Conclusions

In conclusion, we believe that, the clinical evidence base demonstrates that etanercept provides rapid and sustained improvements in disease activity, function and health-related quality of life in patients with polyarticular JIA and across JIA subtypes. Furthermore, it has a well-defined safety and tolerability profile, which is confirmed through over 15 years use in the real-world setting.

Finally, we believe that etanercept is cost saving compared to other biologic treatments with similar marketing authorisations, offers value to patients and the NHS and therefore should continue to be recommended by NICE as an effective treatment for JIA with the recommendation extended to include eoJIA, ERA and PsA subtypes.

1.1 Statement of decision problem

The decision problem for this appraisal in line with the NICE final scope is presented in Table 1 below. Where differences between the final scope and the decision problem of the submission are evidenced, justifications and/or rationales have been provided.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with the following forms of juvenile idiopathic arthritis: polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course), enthesitis related arthritis, and psoriatic arthritis	As scope	Not applicable
Intervention	Etanercept, abatacept, adalimumab and tocilizumab within their licensed indications	Etanercept within its licensed indication	Substantial differences in the respective marketing authorisations of the biologics may lead to inappropriate comparisons outside of license. Therefore, only evidence on etanercept (in line with its MA) as an intervention is considered for this appraisal
Comparator (s)	Disease modifying anti-rheumatic drugs (DMARDs) (such as methotrexate), if DMARDs can be tolerated; Best supportive care, if DMARDs are not tolerated; Etanercept, abatacept, adalimumab and tocilizumab should be compared with each other within their licensed indications where appropriate.	Evidence is presented from all etanercept studies identified regardless of comparator	Differences in study populations (e.g. patient characteristics, age, disease sub-group and treatment history), trial design, evolution of licences, and the scarcity of trials, limit comparability. Therefore, meta-analyses, mixed treatment comparisons /indirect comparisons were not appropriate and feasible to conduct.
Outcomes	The outcome measures to be considered include: disease activity; disease flares; physical function; joint damage; pain; corticosteroid reducing regimens; extra-articular manifestations (such as uveitis); body weight and height; mortality; adverse effects of treatment; health-related	As scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	quality of life.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY and that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account	A cost-effectiveness analysis is not presented. Nevertheless, where cost analysis based on distribution of patient weights is deemed feasible, this will be presented. Also, where available, HRQoL data will be presented	Cost-utility analyses will be associated with considerable uncertainty due to data limitations. Previous technology appraisals (TA35 and TA238) have also challenged data limitations and approaches to conducting cost-effectiveness analyses of JIA and systemic JIA, respectively. Valid utility estimates in young children are difficult to obtain and were not identified for a prior cost-effectiveness publication. [3] The authors also concluded that due to study heterogeneity cost-effectiveness of biological DMARDs should not be compared.
Subgroups to be considered	Where the evidence allows, subgroups by type of JIA will be considered: oligoarthritis, polyarthritis (rheumatoid factor positive, rheumatoid factor negative, and extended oligoarthritis), enthesitis-related arthritis and psoriatic arthritis, patients with JIA and extra-articular manifestations, such as uveitis.	As scope	Not applicable
Special considerations including issues related to equity or equality		None	Not applicable

2 The technology

2.1 Description of the technology being appraised

The brand name, UK approved name, therapeutic class and mechanism of action is presented in Table 2 below.

Table 2 Description of the technology

Brand name	Enbrel®
UK approved name	Etanercept
Therapeutic class	Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01
Mechanism of action	TNF is elevated in both the serum and the synovial fluid of children with JIA. Serum levels of soluble TNF receptor are elevated in patients with JIA (all subtypes), and the level is correlated with disease activity.[31] The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNF receptors, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.[32] Unlike monoclonal antibodies (e.g. adalimumab), etanercept is not associated with the production of neutralising anti-drug antibodies or the potential consequences of this such as diminishing drug levels and reduced response to treatment [16]. Antibodies have been detected in some patients but are non-neutralising and generally transient.[11] There appears to be no correlation between antibody development and clinical response or adverse events.[11] Many factors impact the efficacy and safety of biologics or how an individual patient responds to these treatments. The immunogenicity of a therapeutic agent is one of these factors and it should not be considered in isolation when evaluating the overall efficacy and safety of a drug. The occurrence of anti-drug antibodies is also influenced by several factors including the co-treatment with immunosuppressive drugs such as MTX. Anti-drug antibodies can be neutralising or non-neutralising and both may impact the bioavailability and safety of the drug. Neutralising antibodies bind to the binding site of the therapeutic protein and neutralise it, whereas non neutralising antibodies bind to the therapeutic protein but do not neutralise it. As immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.
Enbrel® brand of etanercept	The data in this document relates to Enbrel® (etanercept). Any etanercept biosimilars may or may not be licenced for the indication under review and care should be taken to ensure that clinicians are aware of all molecules included in the recommendation (including their brand name). In line with MHRA guidance for biologics (including biosimilars) we request that NICE also includes a reminder to clinicians to prescribe biologic medicines by brand name.

2.2 Marketing authorisation/CE marking and health technology assessment

UK approved name and brand name	Approved name: etanercept Brand name: Enbrel®
Marketing authorisation/CE mark status	Date of first authorisation: 03 February 2000 Authorisation for the updated licensed indication (2-3 years of age) was received on: 24 August 2011 Authorisation for the updated licensed indication (3 subtypes of JIA) was received on: 31 July 2012
Indications and any restriction(s) as described in the summary of product characteristics	Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. Enbrel has not been studied in children less than 2 years of age Contraindications to etanercept are as follows: Hypersensitivity to the active substance or to any of the excipients listed in the SPC; sepsis or risk of sepsis; treatment with etanercept should not be initiated in patients with active infections, including chronic or localised infections.[11]
Method of administration and dosage	Enbrel is administered by subcutaneous injection. The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly.[11]

Etanercept received UK Marketing Authorisation in JIA on 3rd February 2000, for the treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 4-17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. In July 2012 this was broadened to the current licensed indication:

- Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
- Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
- Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Etanercept has already undergone health technology assessment, with positive recommendations and/or advice, by NICE, the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG).

- Etanercept (Enbrel®) is recommended for children aged 4 to 17 years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate (NICE TA35, March 2002).[9]
- Etanercept (Enbrel®) is accepted for restricted use within Scotland for the treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate (SMC 782, 06 April 2012).[33]
- Etanercept (Enbrel®) is recommended as an option for use within NHS Wales for the treatment of: polyarthritis (rheumatoid factor positive or negative) in children aged 2 to < 4 years and extended oligoarthritis in children and adolescents ≥ 2 years who have had an inadequate response to, or who have

proved intolerant of, methotrexate; psoriatic arthritis in adolescents ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate; enthesitis-related arthritis in adolescents ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy AWMSG 1437 November 2013).[34]

2.3 Administration and costs of the technology

Etanercept is available in three different strengths of 10, 25 and 50 mg and is administered by subcutaneous injection.[35] Whilst these formulations are the most likely to be used due to weight based dosing, the prefilled syringe (25mg) and MyClic (50 mg) device can also be used for JIA patients of appropriate weight as these may be more convenient for some patients. Etanercept powder for solution must be reconstituted in 1 ml of solvent before use. Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA and psoriatic arthritis. Patients treated with etanercept should be given the Patient Alert Card. Further details on the special precautions for disposal and other handling as well as storage requirements are presented in the Enbrel SmPC.[11] It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating etanercept therapy. Etanercept should always be used in line with its SmPC.

- Etanercept has an advantage over intravenously administered treatment options in that it is administered via subcutaneous injection; it can be self-administered or administered by a parent or carer, giving patients more control over their therapy and enabling them to be treated at home.

- Etanercept is available as an auto-injection pen as well as a prefilled syringe. In a study of 104 adult patients receiving etanercept for a variety of conditions, 93% found the pen easier to use than the syringe and 94% chose the pen as their preferred injection system.[36] Pain at the injection site was significantly reduced and the percentage of patients self-administering etanercept rose from 66% to 94%. The availability of a more preferred means of administration may improve treatment adherence; however, the pen is not suitable for use by those children on doses below 50mg.

- Etanercept should be routinely stored in a refrigerator (2°C – 8°C). However, for a single period of up to four weeks, it may be stored at up to 25° C (if unused, it should be discarded after this time). This offers greater flexibility for patients and carers than other biologic DMARDS, which can only be stored in a refrigerator at 2°C – 8°C.

Table 3 Costs of the technology being appraised

		Source
Pharmaceutical formulation	Pre-filled pen (50 mg), prefilled syringe (25 mg and 50 mg), or powder and solvent for solution for injection (10 mg or 25 mg vial)	[11;35]
Acquisition cost (excluding VAT) *	List prices: 10 mg vial (with solvent) = £35.75 25 mg vial (with solvent) = £89.38 25 mg prefilled syringe = £89.38 50 mg prefilled pen or prefilled syringe = £178.75	
Method of administration	Subcutaneous injection	
Doses	0.4 mg/kg body weight (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses; or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly.	[11;35]
Dosing frequency	See above	
Average length of a course of treatment	Treatment is generally continuous but some patients may have a trial of discontinuation after long-term disease remission. As per SmPC, discontinuation of treatment should be considered in patients who show no response after 4 months	[11;35]
Average cost of a course of treatment	A year's treatment would be £1,859 to £9,295 (based on weight). See table 30.	
Anticipated average interval between courses of treatments	Not applicable	
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	None specified	[11;35]
Anticipated care setting	Etanercept is prescribed in secondary care and is normally administered at home	
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

Etanercept is an established treatment for JIA in UK clinical practice [37] and is recommended by NICE for use in children aged 4- to 17-years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.[9] However, the licensed therapeutic indication for etanercept was extended in July 2012 and is now broader than that covered by TA35 and has no upper age limit (i.e. etanercept can be used beyond age 17).[10] There have been no updates to the NICE guidance since that time.

The licence extension in the therapeutic indications allows for use of etanercept in these additional groups of patients (i.e. eligible patients with eoJIA ERA and PsA, and those aged >17 years) in England and Wales. Extending treatment to these patients is anticipated to be the only change to the treatment pathway and service provision.

Adherence and patient convenience/acceptability

Adherence to the prescribed dose of medication is an important factor in ensuring optimal disease outcomes. A targeted literature review using search terminology designed to retrieve treatment adherence studies found a number of studies in adult RA but only one in JIA (studies of 'treatment persistence' were not counted as they measure length of time on treatment rather than adherence).This study [38] measured adherence using the medication possession ratio (MPR; defined as number of days medication dispensed divided by number of days child would have been expected to take the medication based on the prescription duration), analysing records for 1964 children in US pharmacy database. Adherence to injectable anti-TNF agents was found to be greater than adherence to either oral or subcutaneous methotrexate.

Additional tests or investigations associated with the technology

There are no further additional tests, investigations or administration requirements above and beyond routine clinical practice for the use of etanercept. Etanercept should always be used in line with its SmPC.

2.5 Innovation

Etanercept may be considered an innovative technology with the potential to make substantial impact on health-related benefits that are unlikely to be included in the QALY calculation, such as productivity/educational participation and caregiver burden. A summary of etanercept-related innovation concepts is given below.

2.5.1 Innovation: impact on the management of JIA

Etanercept created a 'step change' in the management of JIA

The advent of biological therapies, of which etanercept was the first to be launched in JIA, resulted in a ‘major new era in the medical management of JIA’ and a ‘paradigm shift’ [8] or ‘dramatic change’ [39] in the pharmacotherapy of JIA. It was 8-years between when etanercept was first licenced for JIA and when the next bDMARD, adalimumab, received a licence. Etanercept therefore provided JIA patients with a real step-change in the management of the disease. Etanercept now has over 15 years of treatment experience, including information from multiple registries investigating long-term effectiveness and safety.

Etanercept is the only fully human soluble TNF receptor human protein available on the market. The other biological agents since licensed for the treatment of children with JIA are adalimumab (an anti-TNF monoclonal antibody), abatacept (a selective co-simulation modulator with IV administration in JIA indications) and tocilizumab (an anti-IL6 receptor monoclonal antibody with IV administration in JIA indications); licensing details are shown in Table 5.

Unlike monoclonal antibodies (e.g. adalimumab), etanercept is not associated with the production of neutralising anti-drug antibodies or the potential consequences of this such as diminishing drug levels and reduced response to treatment.[16] Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept, but these antibodies have all been non-neutralising and are generally transient. [11] There appears to be no correlation between etanercept antibody development and clinical response or adverse events. [11] Many factors impact the efficacy and safety of biologics or how an individual patient responds to

these treatments. The immunogenicity of a therapeutic agent is one of these factors and it should not be considered in isolation when evaluating the overall efficacy and safety of a drug. The occurrence of anti-drug antibodies is also influenced by several factors including the co-treatment with immunosuppressive drugs such as MTX. Anti-drug antibodies can be neutralising or non-neutralising and both may impact the bioavailability and safety of the drug. Neutralising antibodies bind to the binding site of the therapeutic protein and neutralise it, whereas non-neutralising antibodies bind to the therapeutic protein but do not neutralise it. As immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

2.5.2 Benefits unlikely to be included in the QALY calculation

The QALY calculation is unlikely to capture caregiver burden or wider societal benefits such as impacts on educational attainment. If not adequately managed, JIA can be a painful and disabling condition that impacts on many aspects of a child's life: physical functioning, psycho-social wellbeing (e.g. through disability-related stigma, reduced ability to participate in normal social activities, health-related anxiety) and educational functioning. [3] This impact can carry through to the caregivers (usually parents) in terms of the potential impact on quality of life and workforce participation of meeting the child's extra physical and mobility needs and the time needed to attend medical appointments. The benefits of treatments that have a beneficial effect on these domains are unlikely to be fully captured by the QALY calculation. A targeted literature review was used to identify articles relating to the wider benefits of etanercept in JIA, beyond clinical efficacy and gains in HRQoL. However, few studies were found; most research in this field relates to adult patients with RA.

Productivity and educational participation

Although JIA can have a major impact on patients' ability to perform usual daily activities and is likely to affect educational participation and future employment for a significant proportion of patients if not well managed, few studies were identified that addressed these issues. In a study of young adults with JIA in the UK, Hanson et al found widespread difficulties with education (e.g. missing school, inability to complete qualifications) and employment.[40] Van Royen-Kerkhof et al. noted that

‘children with effectively treated PRD [paediatric rheumatic disease] will experience less disease damage, and are able to participate normally in educational programmes. Eventually they will be able to participate in the labour market, and [will be] less dependent on healthcare support’.[41] Anink et al analysed long-term functional outcomes in 43 JIA patients in the Dutch ABC registry who had started etanercept a median of 8.5 years earlier and had a median age at the time of analysis of 22 years (40% were still using etanercept, 40% were using another biologic and 20% were off treatment). They found that the unemployment rate (12%) was comparable to the general population and that educational attainment was higher than for the general population.[42]

Caregiver burden

No studies directly analysing caregiver burden in JIA were found. Prince et al. analysed the costs of etanercept treatment in JIA in a group of 49 patients from the Dutch ABC registry.[27] Direct medical costs were collected for 1 year before and 27 months after the start of etanercept treatment. They found that the number of outpatient visits to rheumatologists and other specialists was ‘distinctly lower’ (data not reported) during etanercept treatment and that there was a substantial decrease in hospitalisation costs over time. A reduction in outpatient visits and hospitalisations will reduce the burden on the caregiver likely to be associated with travel and lost working time related to such visits.

3 Health condition and position of the technology in the treatment pathway

- Juvenile idiopathic arthritis (JIA) is a heterogeneous disease associated with inflammation, pain, stiffness and swelling of the affected joints; symptoms often leading to morbidity and loss of quality of life.
- Standard treatment for JIA includes use of DMARDs, such as MTX, alongside intra-articular and systemic corticosteroids and NSAIDs. Other treatments such as etanercept may also be used.
- The advent of biological therapies, of which etanercept was the first to be licensed in JIA, has been described as a 'major new era in the medical management of JIA' and a 'paradigm shift' [8] in the pharmacotherapy of JIA.
- Etanercept is the only bDMARD currently recommend by NICE for children aged 4 to 17 years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.
- Etanercept has been recognised as effective and value for money by other HTA bodies in the UK. It has been approved for use by the Scottish Medicines Consortium (SMC), and the All Wales Medicines Strategy Group (AWMSG).
- The licensed therapeutic indication for etanercept was extended in July 2012 and is now broader than that covered by TA35, and the upper age limit has been removed.
- Etanercept is the only bDMARD licensed for all JIA subtypes (eoJIA, ERA and PsA) included in the NICE final scope.
- Etanercept is an effective treatment associated with rapid and sustained improvements in disease activity, function and health related quality of life in patients with JIA. There is currently variation across the UK in the management of adult patients with JIA. Guidance from the Royal College of Paediatrics and Child Health (RCPCH) and Royal College of Nursing (RCN) emphasises the need for

transitional care into adulthood. Etanercept may be used in adult rheumatology care in those patients with active JIA in adulthood.

3.1 Definition and classification of JIA

The term juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis with onset before the age of 16 years and symptoms that persist for more than 6 weeks, and for which the cause is unknown.[43] The pathogenesis of JIA remains unclear. The onset of symptoms typically begins in childhood and progresses into adulthood.[1] The prognosis of JIA varies with subtype, however, the more severe types of JIA are associated with severe morbidity that persists into adulthood.[44] JIA is now classified according to the Revised ILAR Criteria (published in 2004) [2] which define seven subtypes: systemic arthritis, oligoarthritis (subcategories persistent and extended [eoJIA]), polyarthritis (rheumatoid factor [RF] positive), polyarthritis (RF negative), psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis. The original ILAR classification was published in 1998.[45] Previously, the ACR (1977) classification was used in North America and the EULAR (1978) classification in Europe. The pivotal study of etanercept was designed before the adoption of the Revised ILAR criteria and used the ACR 1997 classification. The CLIPPER study (Horneff 2014) was designed to assess the safety and efficacy of etanercept in JIA subtypes as classified using the ILAR criteria.

3.2 Epidemiology

Reports of JIA incidence and prevalence rates vary, ranging between 1.63 and 23 per 100,000 and from 3.8 to 400 per 100,000, respectively [46]. The annual incidence of JIA in the UK is approximately 0.1 per 1000 children (1000 new cases each year). A recent Interim Clinical Commissioning Policy Statement from NHS England suggests there are over 12,000 children with JIA in England and Wales at any one time.[5]

3.3 Aetiology and risk factors

The aetiology of JIA is not fully understood; both genetic and environmental factors are thought to play a role.[47] These may include immune system dysregulation,

psychological stress, trauma, hormonal abnormalities and infections. Concordance rates of 25-40% have been reported in monozygotic twins and the prevalence rate of JIA in the siblings of an affected person is 15- to 30-fold higher than in the general population.[6]

3.4 Diagnosis

Diagnosis of JIA is based on history and physical examination to exclude joint pains with a discernible cause. Joints should be assessed for pain or tenderness, swelling, limited movement, decreased strength or muscle atrophy, and bony deformity.[48] Laboratory tests include complete blood count, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), autoimmune markers (rheumatoid factor, HLA antigens for HLA B27), and imaging.

3.5 Assessment of response to therapy

The British Paediatric Rheumatology group (BPRG) guideline recommends a systematic pathway for initiation of biologics in children with arthritis [9]. This follows a stepped approach including core dataset for assessment, failure of standard therapy and eligibility criteria for etanercept as discussed below.

Failure of standard therapy: patients must have had adequate therapeutic trials of methotrexate (defined as below):

- treatment of at least 3 months at a dosage of parenteral methotrexate of 20 mg/m^2 weekly (unless significant toxicity limited the dose tolerated);
- ≥5 active joints and ≥3 joints with loss of motion plus pain/tenderness;
- the disease is only controlled by high doses of corticosteroids (> 0.25 mg/kg daily) with unacceptable side effects and have had active disease (as defined above in the last 6-months) before treatment with biologics is initiated.

Core data set for assessment: The core set data for assessment includes number of active joints, number of joints with loss of range of movement, physician's global assessment of disease activity, parent or patient's global assessment of wellbeing, Child Health Assessment Questionnaire (CHAQ), and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).

Eligibility criteria for biologic therapies such as etanercept: The eligibility criteria for treatment with biologics includes a diagnosis of any JIA subtype (polyarticular, extended oligo-articular, psoriatic, enthesitis-related or systemic) and features including five or more swollen joints and three or more joints with limitation of motion and pain, tenderness or both.

3.6 Symptoms and burden

JIA is characterised by an inflammatory process that results in painful, swollen joints. Joints are typically stiff after inactivity, including in the mornings. Systemic onset JIA (which is outside the scope of this MTA) requires the presence of fever along with either rash or other specified conditions, but other JIA subtypes may also have manifestations outside of the joints, most commonly uveitis and/or growth retardation.

Severity and disease course are variable, but for severely affected children the condition can involve significant pain and disability and can seriously affect health-related quality of life, daily activities, educational participation and emotional well-being.[7] In some children, if not adequately managed, JIA can lead to long-term damage to joints and connective tissue, resulting in growth retardation and/or long-term disability or functional limitation.[49] However, long-term outcomes have generally improved since the introduction of biological therapies. Information on long-term outcomes for the different subtypes was collated by Shepherd et al. for the Technology Assessment Report Protocol commissioned on behalf of NICE for this appraisal, and is reproduced in Table 4 below.[1] NHS England estimates that at least one-third of children with JIA will continue to experience active disease and require care into adulthood.[50]

Table 4 Long-term outcomes in JIA

Persistent oligoarthritis • Often mild and may resolve with little or no lasting damage to joints, has the best outlook of all the types of JIA. • Approximately half of children will have symptoms for at least 10 years, a third or more of children will have arthritis continuing into adulthood. • Chronic anterior uveitis may cause blindness if not detected and treated early enough.
Extended oligoarthritis • Causes damage to joints so early treatment to minimise this is needed.
Polyarthritis • Approximately half of children will have symptoms for at least 10 years and at least one third of children will have arthritis continuing into adulthood (most likely with the RF positive type, which is more aggressive and can require more aggressive treatment). • Joints may become damaged if inflammation is not controlled, leading to potential need for joint replacement.
Enthesitis-related JIA • May evolve to ankylosing spondylitis in the adult years and may require long term disease modifying or biologic agents.
Psoriatic arthritis Although there is not much long term data, disease course may be similar to chronic arthritis (either oligoarthritis or polyarthritis) and is likely to continue into adulthood.
Systemic-onset JIA • A third of children will have one or two episodes that settle with treatment, a third will have relapses and need intermittent treatment, a third require ongoing treatment into adulthood and are at risk of joint damage.
Undifferentiated arthritis Although there is not much long term data clinical advisors indicate that the long-term outcome is likely to depend on the predominant features of the arthritis and whether persistent oligoarthritis or polyarticular course arthritis.

Source: Shepherd 2014. [1]

3.7 Treatment guidelines/guidance for juvenile idiopathic arthritis

Guidelines and guidance for the treatment and management of JIA have been issued by NICE and professional organisations such as the British Society for Paediatric and Adolescent Rheumatology (BSPAR). In the UK, etanercept is the only biologic currently recommended by NICE for use in active polyarticular arthritis. Other biologic agents (abatacept, adalimumab and tocilizumab) have been licensed for the treatment of polyarticular juvenile idiopathic arthritis since TA35 was published. The majority of the guidelines and guidance are drafted in line with the NICE TA35.

3.7.1 NICE Technology appraisals

Etanercept (TA35)

NICE TA35 recommends etanercept as treatment option in children 4 to 7 years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.[9]

- Etanercept should only be initiated in a child with JIA in the following circumstances:
    - In the last 6 months, the child has five or more swollen joints and three or more joints with limitation of motion and pain, tenderness or both
    - The child has not responded following adequate treatment with methotrexate for at least 3 months
    - The child does not have a clinical condition that would constitute a contraindication to prescription of etanercept.

- Treatment with etanercept is withdrawn if the child experiences an unacceptable adverse event or if the child does not respond during the 6 months following the initiation of treatment or does not continue to respond after the initial 6-month trial.

3.7.2 Other guidance or guidelines

British Society for Paediatric and Adolescent Rheumatology (BSPAR)

The BSPAR guidance [37] stipulates the following:

- Referral to paediatric rheumatology multidisciplinary team should be made for patients with incident or suspected JIA
- Access to treatment should be prompt, monitoring should be undertaken in accordance with BSPAR and NICE guidelines and trained staff should be available to give advice, administer or train the patient or carer

Position of etanercept in the treatment pathway

The aim of treatment is to achieve complete absence of disease, controlling inflammation and joint pain and improving HRQoL.[1] In the UK, etanercept remains the most commonly prescribed biologic in JIA, although alternative biologics may be used primarily due to the heterogeneous nature of the disease.[51] Furthermore, in clinical practice, the choice of biologic treatment may be dependent on the burden of co-morbidity in JIA patients starting new therapies because of the increased risk of certain adverse events.[52] Etanercept is the only agent to be licensed specifically for the treatment of psoriatic JIA, extended oligoarticular JIA, and enthesitis-related JIA.[11] Recently, adalimumab has been licensed in enthesitis-related JIA, and tocilizumab is also licensed for the extended oligoarticular subtype.

A summary of the biological agents licensed for JIA in line with the NICE scope is presented in are shown in Table 5 below.

Table 5 Biological agents licensed for the treatment of JIA

Biological agent	Licensed patient population and formulation
Abatacept [53]	In combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor. Only IV formulation licensed in paediatric patients.
Adalimumab [54]	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). Can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate; 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. Administered by subcutaneous injection
Etanercept [11]	Polyarticular course JIA and extended oligoarthritis after inadequate response/intolerance to methotrexate, from age 2; psoriatic arthritis after inadequate response/intolerance to methotrexate, from age 12; enthesitis-related JIA after inadequate response/intolerance to conventional therapy from age 12. Administered by subcutaneous injection.
Tocilizumab [55]	In combination with methotrexate is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Also licensed for systemic JIA. Only IV formulation licensed in paediatric patients.

Etanercept is already established in the treatment pathway in England and Wales as a second-line therapy for JIA (following inadequate response or intolerance to methotrexate, or to NSAIDs in the case of enthesitis-related arthritis). It is currently the only biological agent recommended by NICE in children aged 4 to 17 years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.[9] However, the licensed therapeutic indication for etanercept was extended in July 2012 and is now broader than that covered by TA35, and the upper age limit has been removed.[10] The licensed therapeutic indications for etanercept in JIA are now as follows:

- Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

- Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
- Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

The new licensed therapeutic indication for etanercept allows for treatment of patients with JIA including eoJIA, ERA and PsA and, those aged >17 years in England and Wales. Extending treatment to these patient populations is anticipated to be the only change to the treatment pathway and service provision.

3.8 Treatment pathway for juvenile idiopathic arthritis

In UK clinical practice, treatment for JIA often follows a stepped approach, starting with non-steroidal anti-inflammatory drugs (NSAIDS) and pulsed or intra-articular steroids.[1] If NSAIDs are not adequate, a disease-modifying anti-rheumatic drug (DMARD), commonly methotrexate, is used. If response to methotrexate (or NSAIDs in the case of ERA) is not adequate, or it is not tolerated, biological DMARDs such as etanercept may be used. Currently, the choice of first biologic may be inconsistent due to the lack of standardised national guidance.[56]

NHS England in collaboration with BSPAR has issued a treatment pathway for consultation, for use pending updated guidance from NICE. However, the guidance does not differentiate anti-TNF agents according to their licences and by JIA subtypes.

3.8.1 Treatment pathway for juvenile idiopathic arthritis in adult rheumatology care

JIA symptoms may continue into adulthood but the provision of care for patients transitioning to adult services is variable within UK clinical practice. [1]

Guidance from the Royal College of Nursing (RCN) stipulates that data from the BSRBR-BNDR biologics register is fundamental in assessing the use of biologics as well as monitoring the transition of care of young people with JIA in to adult

services.[57] Furthermore, the Royal College of Paediatrics and Child Health (RCPCH) [58] emphasises the need for transitional care to be provided by specialised paediatric rheumatology teams involving adult rheumatology teams and local hospitals under a shared care arrangement in line with patients' needs.

3.9 Equality issues

No equality issues are expected in this appraisal. Of note, in UK clinical practice, the provision of care for patients transitioning to adult services is variable and therefore, relevant guidelines/guidance is warranted.

4 Clinical effectiveness

The clinical effectiveness of etanercept within its licensed indication in JIA is presented here based on a review of evidence from both interventional and observational/registry studies.

- It was first recommended by NICE in March 2002.[9] Since then, the therapeutic indication for etanercept has expanded and now also includes extended oligoarthritis (from the age of 2 years), psoriatic arthritis (from the age of 12 years) and enthesitis-related arthritis (from the age of 12 years) as supported by the pivotal CLIPPER study [10] [11].
- The lower age range for treating polyarticular disease has also been reduced from 4-years to 2-years and the marketing authorisation no longer specifies an upper age limit of 17.
- The license was granted on the basis of a range of studies including, a pivotal open-label, double-blind two-part study [12], two open-label single-arm studies [13] including a safety extension study [14] and a 3-year registry study.[15]
- Across all the studies, etanercept demonstrated significant clinical improvements from baseline in disease activity, functional capability and patient-/parent-reported well-being.

4.1 Identification and selection of relevant studies

4.2 Identification of studies

Three systematic reviews were carried out to identify the relevant evidence from the literature on the efficacy and safety of etanercept in a population with JIA (polyarthritis (including eoJIA), enthesitis and psoriatic arthritis) who have not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate:

- Interventional (both randomised and non-randomised) and observational evidence on the clinical effectiveness (both efficacy and safety) of etanercept in children and adolescents with JIA.
- Interventional and observational evidence on etanercept-associated innovation, caregiver burden and treatment adherence (see Appendix 1 for eligibility criteria).
- Interventional and observational evidence on HRQoL associated with etanercept in children and adolescents with JIA (see Appendix 1 for eligibility criteria).

The search strategies of the respective systematic reviews are provided in Appendix 1.

The systematic review process adhered to the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting checklist to ensure transparency and a reproducible method of conducting and reporting data from systematic reviews.[59] Flow charts of the study selection process are documented in Section 4.1.3 (clinical effectiveness) and Appendix 1 (HRQoL).

The electronic databases were searched from inception to 26 January 2015. Electronic database searches were limited to peer-reviewed publications available in English. Furthermore, only studies on human subjects were eligible for inclusion.

The following electronic databases were searched:

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;

– Cochrane Database of Systematic Reviews (CDSR)

- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment Database (HTA)
- NHS Economic Evaluation Database (NHS EED)
- PubMed (for E-publications ahead of print)

To retrieve further studies not identified through the electronic database search, reference lists of included articles were scanned, and searches for grey literature as well as completed and on-going trials, were also carried out.

Furthermore, the following key conference proceedings covering the last 3-years (2012 to February 2015) were searched:

- European League Against Rheumatism (EULAR)
- British Society for Rheumatology (BSR)
- American College of Rheumatology (ACR)
- European Pediatric Rheumatology (PReS) Congress

The 2012 EULAR and PReS congresses were conducted as a joint conference. Proceedings from all the conferences, except ACR 2014, were available to search through EMBASE; search strategies are shown in Appendix 1. ACR 2014 was hand-searched via the conference website.

4.2.1 Study selection and data extraction

The eligibility criteria for the clinical systematic review are shown in Table 6; those for the HRQoL and innovation reviews are outlined in Appendix 1. In all cases, inclusion was restricted to studies that used the licensed dose of etanercept for JIA (0.4 mg/kg twice weekly, maximum dose 25 mg; or 0.8 mg/kg once weekly, maximum dose 50 mg). The outcomes extracted are also described in the Appendix and were in line with the NICE scope. The screening process (titles ± abstracts and full paper stages of the three SRs) for both RCT and non-RCT evidence involved two reviewers working independently. Any disagreements were resolved through the involvement of a third reviewer or through team discussion until a consensus was

reached. The identified studies were initially assessed based on titles ± abstracts. Thereafter, full papers of the eligible studies were obtained and assessed further for inclusion/exclusion. The reasons for exclusion are documented in Appendix 2.

A summary of the eligibility criteria for the systematic reviews is presented below.

Table 6 Eligibility criteria used in the search strategy for the clinical effectiveness evidence

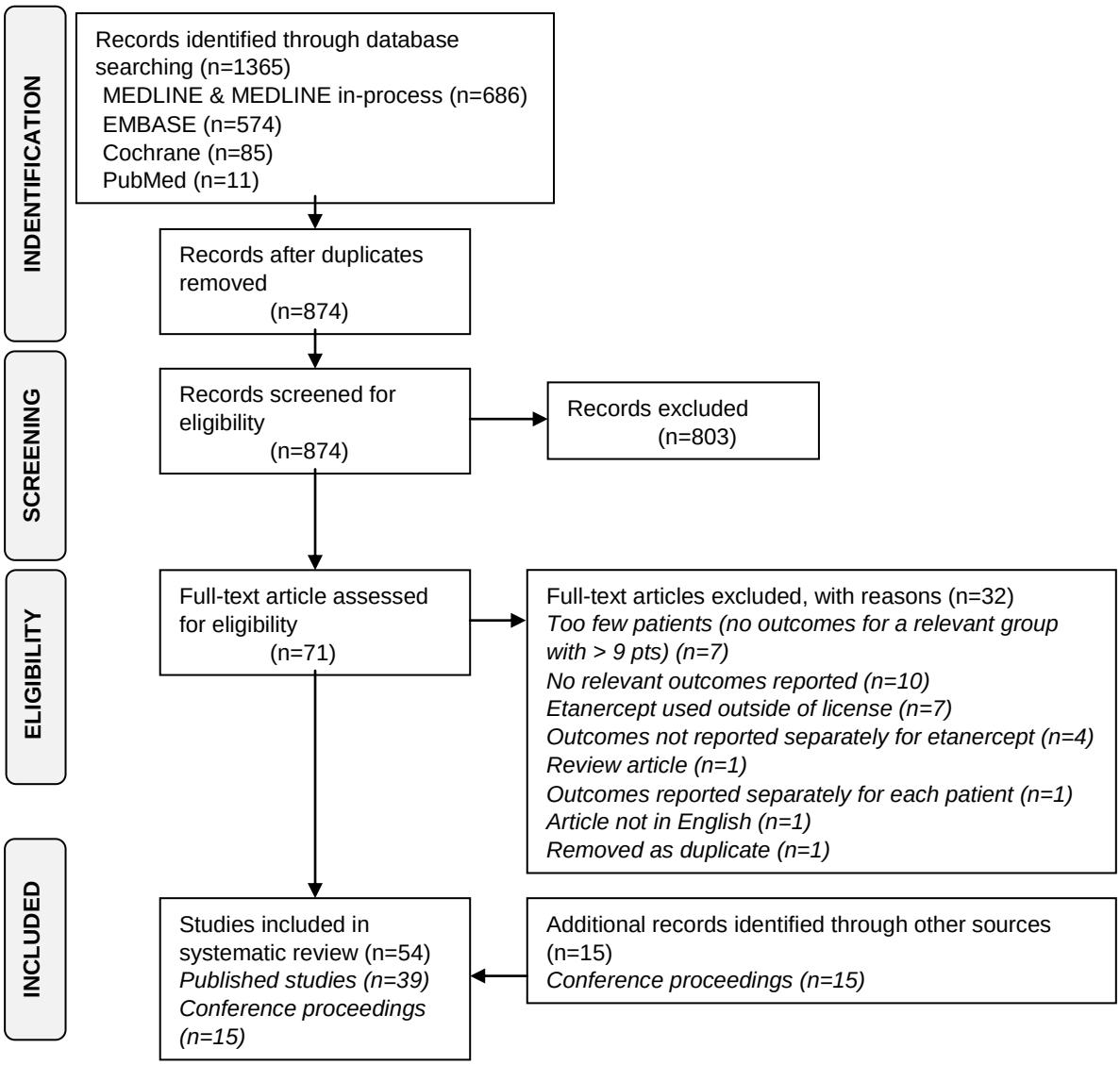
Domain	Description
Population	People with the following forms of JIA: • polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course) • enthesitis-related arthritis • psoriatic arthritis
Interventions	The following intervention within its licensed indication for JIA: etanercept
Comparators	• In interventional studies, any comparator as long as it is compared with etanercept within its licensed indication for JIA • In registries, only data relating to etanercept were extracted
Outcomes	The outcomes measures to be considered include: • Disease activity • Disease flares • Physical function • Joint damage • Extra-articular manifestations • Pain • Corticosteroid reducing regimes • Body weight and height • Adverse effects of treatment
Study design	All study designs with the exception of case reports. Data were only extracted from studies that reported outcomes for at least 10 patients in at least one relevant study group.

4.2.2 PRISMA diagram, clinical effectiveness

4.2.2.1 Clinical effectiveness evidence

The electronic database search identified 1365 articles, of which 874 were screened (after de-duplication). In total, 803 publications were excluded on the basis of title ± abstract. On reapplication of the inclusion/exclusion criteria to the remaining 71 full-text papers, a further 32 were excluded. Therefore, 39 publications met the inclusion criteria and were included in the systematic review for clinical effectiveness. In addition 15 conference abstracts were found eligible for inclusion and included in the review. In addition, unpublished information and/or data (Pfizer data on file) from five studies have been presented, two of which have been classified as on-going studies. The PRISMA diagram for the clinical effectiveness systematic review evidence is shown in Figure 1.

Figure 1 PRISMA diagram for the electronic database for clinical effectiveness



4.3 List of relevant interventional studies

The efficacy and safety of etanercept has been studied in both randomised and non-randomised interventional studies as well as observational studies. The evidence from observational studies, including registry/real-world data analyses, is presented in Section 4.11.

Eleven publications relating to five primary studies and three extension studies, all using the licensed doses of etanercept, were identified (Table 7). Due to the multiple time points reported in the long-term extension studies, the decision was made to extract data based on only the following time points; primary end point, 12 months,

and longest follow-up. Lovell 2006 was an interim publication of the Lovell 2000 study that did not meet any of these criteria, so data were not extracted. Three of the studies were used to inform the etanercept marketing authorisation in JIA; Lovell 2000 (original authorisation), Lovell 2008 (long term efficacy and safety) and Horneff 2014 (expanded authorisation in 2012, including JIA subtypes).

Table 7 List of relevant interventional studies (randomised and non-randomised)

Study ID	Intervention	Comparator	Study design	Location
Lovell 2000 NEJM† [60]	Etanercept	None (open-label phase) Placebo (Double blind phase)	2 part multicentre study: open-label, single arm phase, followed by randomised, double-blind, placebo-controlled phase	USA
Mori 2005 Mod Rheumatol [61]	Etanercept or control (control medication NR)	None	Open-label, prospective, single arm, multicentre	Japan
Horneff 2009 Rheumatol [62]	Etanercept	None	Open label, single arm, multicentre	Germany
Horneff 2014 Ann Rheum Dis*† [13]	Etanercept	None	Open label, single, arm, prospective, multicentre, phase 3b. Divided in to 2 parts. This paper reports Part 1, 12-wk primary analysis	Global
Zeng 2014 Ann Rheum Dis (EULAR conf. abstract) [63]	Etanercept	Unclear	Randomised controlled trial	China
Extension studies				
Lovell 2003 Arth Rheum [64]	Etanercept	None	Open label, single arm, multicentre, extension study of Lovell 2000	USA
Lovell 2006 Arth Rheum [65]	Etanercept	None	Open label, single arm, multicentre, extension study of Lovell 2000 (Data not extracted)	USA
Lovell 2008 Arth Rheum† [14]	Etanercept	None	Open label, single arm, multicentre, extension study of Lovell 2000	USA
Mori 2011 Mod Rheumatol [66]	Etanercept	Reduced dose etanercept	Open-label, single arm, multicentre (originally reported, in less detail, in Mori 2005), followed by double-blind, randomised, dose-down extension study	Japan
Mori 2012 Mod Rheumatol [67]	Etanercept	None	Open-label, multicentre study, extension of Mori 2011[includes 3 trials; Mori 2005, dose-down and lower-dose studies)	Japan
Constantin 2013* ACR/ARHP (conf. abstract) [19]	Etanercept	None	Open label, multicentre, phase 3b: Part 2: long-term safety and efficacy. Extension of Horneff 2014	Global

* Horneff 2014 reports outcomes separately for the following JIA subtypes in addition to polyarticular: extended oligoarthritis, enthesitis-related arthritis and psoriatic arthritis. All other studies report pooled results for a mix of subtypes (see Table 11).
† studies informing the etanercept marketing authorisation
NR: not reported; USA: United States of America

4.4 Summary of methodology of the relevant interventional trials

All included studies except for CLIPPER (Horneff 2014/Constantin 2013) included patients with active polyarticular JIA who had inadequate response or intolerance to methotrexate, in line with the etanercept license in JIA. The CLIPPER studies (Horneff 2014 and Constantin 2013) were in patients with the JIA subtypes ERA, eoJIA and PsA; the inclusion criteria extended below the threshold number of active joints for polyarticular disease, and prior MTX was not required for ERA patients (these patients had to have inadequate response to NSAIDs). Study populations are detailed in Table 8. CLIPPER studies stratified results by JIA subtype; all the other studies reported pooled results for the whole study populations.

The etanercept licensed dose of 0.4 mg/kg (up to a maximum of 25 mg per dose) twice weekly or 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly was used in all the included studies. Mori 2011 and Mori 2012 included a reduced dose arm but data for the reduced dose were not extracted as this dose is not licensed.

A major difference between study inclusion criteria was whether or not concomitant DMARDs (methotrexate and others) were allowed. Concomitant DMARDs and steroid injections were disallowed in the primary studies (Lovell 2000, Mori 2005) and extension studies (Mori 2011 and Mori 2012). However, concomitant DMARDs were allowed in Horneff 2009, and a maximum of 1 was allowed in Horneff 2014. For the rest of the studies, concomitant DMARDs and/or steroid treatments could be used.

Only Lovell 2000 and Mori 2011 (dose-down extension study) had randomised phases, both preceded by an open label single arm phase. In addition, a small RCT was identified from a conference abstract (Zeng 2014). All the other studies were single arm.

A summary of the methodology of RCT and non-randomised interventional trials is presented in Table 8 below.

Table 8 Summary of methodology of RCT and non-randomised interventional trials

Study ID	Population	Inclusion criteria	Exclusion criteria	Trial drugs	Concomitant DMARDs and other medications allowed	Primary outcome measure	Study duration
Lovell 2000 NEJM; open label phase	Patients 4-17 yrs. with active polyarticular JIA (≥5 swollen joints, ≥3 joints with LOM and pain/tenderness)	Active disease despite treatment with NSAIDs and MTX (≥10 mg/m^2 body surface area per week)	The patients had normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal-function tests. Pregnant and lactating patients were excluded, and girls with childbearing potential were required to use contraception throughout the study. Patients with major concurrent medical conditions were also ineligible	Etanercept 0.4 mg/kg twice weekly (max 25 mg/dose)	MTX discontinued 14 d prior to ETN initiation; other DMARDs discontinued 28 days prior. Steroid injections not allowed during or 1 month prior. Stable dose NSAIDs and low dose corticosteroids permitted (≤0.2 mg/kg/day prednisolone - max 10 mg/day). Pain medication (≥ 12 h before joint assessment)	Definition of improvemen t in open label phase was % achieving JIA ACR 30 (modified ACR)	7 months (3 months for open label phase and 4 months in the Double blind-phase)
Lovell 2000 NEJM; double-blind phase	Patients from open label phase who met improvement definition	-	As open label phase	Etanercept 0.4 mg/kg twice weekly (max 25 mg/dose), or placebo	As open label phase	No. of pts with disease flare	4 Months for Double blind phase)
Mori 2005 Mod Rheumatol	Japanese patients 4-17 yrs. with active polyarticular JIA	Refractory or intolerant to MTX	Functional ACR Class IV; specified liver or renal dysfunction; +ve HIV or hepatitis B or C test; anti-ds DNA antibody +ve. DMARDs, intravenous immunoglobulin, or cytotoxic agents or steroid injection ≤28 days before baseline; MTX ≤14 days prior to baseline. Anti-TNF, anti-CD4 , diphtheria IL2 fusion protein treatment; current steroid use > prednisolone equivalent of 0.2mg/kg per day (max10mg/day)	Etanercept 0.4 mg/kg twice weekly (max 25 mg)	No DMARDs allowed No corticosteroid injections. Pain meds not allowed within 12 h of assessment	Improvement of the score for JIA activity (core-set score) of at least 30%	3 mo
Horneff 2009 Rheumatol	Patients 4-17 yrs. with JIA polyarticular course with active polyarticular disease (≥5 active joints)	Active disease despite ttmt with NSAIDs and MTX (≥10 mg/m^2 BSA/wk) ≥3 mo	Systemic onset JIA; major concurrent medical conditions; abnormal lab values indicating increased risk IA corticosteroid injections were not permitted within 4 weeks prior to study entry and during the trial.	Etanercept 0.8 mg/kg once weekly (max 50 mg/wk)	Concomitant treatments had to be kept stable at least 3 months before and throughout the study Prednisone, up to 10 mg or 0.2 mg/kg, whichever less, to be stable during 4 wk before and throughout study	PedACR30/ 50/70	12 wk
Horneff 2014 Ann Rheum Dis	eoJIA: 2-17 y; ERA 12-17 yrs.; PsA 12-17 yrs. with ≥2 active joints (swollen or LOM) + pain or tenderness	Intolerance or unsatisfactory response to ≥ 3-mo course of ≥1 DMARD or, only for ERA, unsatisfactory response to ≥ 1-month course of ≥1	Other rheumatic diseases; pustular or erythrodermic psoriasis. Active or history of TB or evidence of latent TB, active uveitis within 6 mo, any medically important infection within 1 mo. Any prior biologics. Any live vaccine within 2 mo. Prohibited during specified washout periods: immunosuppressive drugs (other than	Etanercept 0.8 mg/kg once weekly (max 50 mg/wk)	Only 1 DMARD (MTX, SSZ, chloroquine or hydroxychloroquine), 1 oral corticosteroid ≤0.2 mg/kg/day or 10 mg/day (whichever was less), and 1 NSAID were allowed, with no dose changes throughout the study	% achieving JIA ACR 30 at wk 12	12 wk

Study ID	Population	Inclusion criteria	Exclusion criteria	Trial drugs	Concomitant DMARDs and other medications allowed	Primary outcome measure	Study duration
		NSAID	glucocorticosteroids or allowed medication), leflunomide within 6 mo, investigational non-biologic drugs within 3 mo, non-biologic DMARDs (other than MTX, SSZ, hydroxychloroquine, or chloroquine), combinations of non-biologic DMARDs, ultraviolet A/B, or psoralen plus UVA within 4 wk				
Zeng 2014 Ann Rheum Dis [abstract data only]	Chinese patients with oligoarticular polyarticular and SO-JIA	NR	NR	Etanercept 0.8 mg/kg once weekly or control (control medication NR)	Slow-acting antirheumatic, nonsteroidal drugs or adrenocortical hormone were applied in these cases as basic drugs	clinical remission rate	6 mo
Extension studies							
Lovell 2003 Arth Rheum	As Lovell 2000	As Lovell 2000	Significant concurrent medical conditions. MTX not permitted in 1st y	Etanercept 0.4 mg/kg twice weekly (max 25 mg/dose)	Low dose NSAIDs/corticosteroids (≤0.2 mg/kg/day prednisolone - max 10 mg/day). Pain medication (up to 12-18 h before joint assessment)		(interim analysis of Lovell 2008; patients had received at least 2 years of treatment time)
Lovell 2008 Arth Rheum	As Lovell 2000	As Lovell 2000	As Lovell 2000 and 2003	Etanercept 0.4 mg/kg twice weekly (max 25 mg/wk) or 0.8 mg/kg (max 50mg/wk)	DMARDs allowed After 1 y of the OLE, JRA medications permitted. MTX could be added at a dose of 10–20 mg/m^2/wk		8 y
Mori 2011 Mod Rheumatol; double blind phase; 0.4mg/kg arm	Japanese patients 4-17 yrs. with active JIA (≥5 swollen joints and ≥3 joints with LOM accompanied by pain or tenderness)	Etanercept-naïve. Unable to tolerate/ inadequate response to MTX. Must have received NSAIDs	DMARDs, immunosuppressants, IV immunoglobulins, cytotoxics or injected corticosteroids within 28 d before baseline	Etanercept 0.4 mg/kg or 0.2 mg/kg twice weekly	No DMARDs allowed	PedACR30/ 50/70	12 weeks
Mori 2012 Mod Rheumatol	Japanese patients C completing ≥48 wk of the open label study	-	NR	Etanercept 0.4 mg/kg or 0.2 mg/kg twice weekly	No DMARDs allowed	PedACR30/ 50/70	12 wk

Study ID	Population	Inclusion criteria	Exclusion criteria	Trial drugs	Concomitant DMARDs and other medications allowed	Primary outcome measure	Study duration
Constantin 2013 ACR/ARHP [extension study of Horneff 2014; CLIPPER Part 2]	Subjects with eoJIA (2–17 years old), ERA (12–17 years old), or PsA (12–17 years old)	As Horneff 2014	As Horneff 2014	Etanercept 0.8 mg/kg weekly (max 25 mg)	As Horneff 2014	As Horneff 2014	96 wk

ACR: American College of Rheumatology; DMARDs: disease-modifying anti-rheumatic drugs; ETN: etanercept; IV: intravenous; JRA: juvenile rheumatoid arthritis; LOM: limitation of motion; MTX: methotrexate; NR: not reported; NSAID: non-steroidal anti-inflammatory drugs; OLE: open-label extension; TB: tuberculosis

4.5 Statistical analysis and definition of study groups in the relevant interventional trials

Only three RCTs were identified, one of which had data available in abstract format only. A summary of the statistical analysis and definition of study groups for the RCTs are reported in Table 9.

Table 9 Statistical analysis and definition of study groups in the RCTs

Study	Hypothesis objective	Statistical analysis	Sample size and power	Data management, patient withdrawals
Primary studies				
Lovell 2000	Part 1 (Open label study) – assess safety and population PK of TNFR:Fc in paediatric patients with active polyarticular course JRA and patient response to TNFR:Fc at Day 90. Primary outcome: disease response. Part 2 (double-blind portion), determine the efficacy of TNFR:Fc by evaluating the number of patients with disease flare after randomization of responders at Day 90 to treatment with placebo or continued TNFR:Fc. Primary outcome: Disease flare.	Part 1: [redacted] Part 2: Baseline and demographic characteristics were compared between treatment groups using the Wilcoxon rank-sum test and the likelihood ratio Chi-square test. The percentages of patients with a response to therapy who had disease flare while receiving placebo or etanercept in the double-blind study were compared by Mantel–Haenszel methods. * tests were two-sided, with a significance level of 0.05.	[redacted] .	Part 1: Five patients prematurely discontinued the study during the first 90 days and did not continue to Part 2. All patients receiving at least one dose of the study drug were evaluated for the primary efficacy outcome. Part 2: Patients who withdrew early without disease flare were counted in the analysis with those who continued to have a response. In all summaries of measures of disease activity, a last-observation-carried-forward approach was used for missing data or visits and for patients who withdrew early.
Zeng 2014 (EULAR abstract data only)	NR	NR	NR	NR
Extension studies				
Mori 2011 (Dose-down extension study)	Efficacy and safety of etanercept (0.2 mg/kg (up to a maximum of 12.5 mg) †† vs. 0.4 mg/kg (up to a maximum of 25 mg) twice weekly).	Primary efficacy analysis was performed on the full analysis set (FAS) consisting of all the subjects who had received at least one dose of the investigated drug, and ACR Pedi core set data at baseline and at one subsequent visit at least.	FAS (Full Analysis Set) were used as the primary efficacy analysis.	The last-observation-carried-forward (LOCF) imputation approach was used to replace the missing data. Secondary endpoint results were reported as observed data.

Study	Hypothesis objective	Statistical analysis	Sample size and power	Data management, patient withdrawals
		Summary statistics of trough drug concentration on each assessment day were calculated.		
Mori 2012 (Dose-down extension study)	Evaluate the long-term safety and efficacy of etanercept in Japanese children with JIA.	Summary statistics such as mean, median, standard deviation, and confidence intervals were used to analyse both safety and efficacy results. Analysis of safety data was based on the safety population, defined as all patients who had received etanercept, even if only one dose was administered.	FAS (Full Analysis Set) were used as the primary efficacy analysis.	

†† unlicensed dose, data not extracted but included for completeness

4.6 Participant flow in the relevant interventional trials

Due to the heterogeneity in the reporting of the participant flow parameters across the relevant studies, consistently reported parameters were tabulated (Table 10). In most studies the number of patients included in efficacy and safety analyses were consistent with the number of patients enrolled. This shows low rates of discontinuation and loss to follow-up. The most commonly reported reasons across the studies for treatment discontinuation were patient refusal and adverse events. No deaths were reported during treatment across all the included interventional studies.

Table 10: Summary of the participant flow in the relevant interventional studies

Study	Number recruited and/or randomised	Number of efficacy evaluated population	Number of safety evaluated population	Number of patients completing the study	Overall discontinuations n(%)
Lovell 2000 NEJM	Open label phase: n=69	69	69	64	5 (7.2)
	Double blind phase: n=51	26 (19 etanercept and 7 placebo)	26 (19 etanercept and 7 placebo)	26 (19 etanercept and 7 placebo group)	Etanercept: 6(12%) placebo group: 7(14%)
Mori 2005 Mod Rheumatol	22	22	22	22	0
Horneff 2009 Rheumatol	20	20	20	20	0
Horneff 2014 Ann Rheum Dis[CLIPPER Part 1]	127	122	122	120	7 (5.5)
Zeng 2014 Ann Rheum Dis [Abstract data only]	124	124	124	NR	Unclear
Extension studies					
Lovell 2003 Arth Rheum	58	48	48	48	10 (17)
Lovell 2008 Arth Rheum at 8 years	69	Unclear	Unclear	26	43 (62)
Mori 2011 Mod Rheumatol (Dose -down extension study Etanercept 0.4 mg/kg vs. 0.2mg/kg)	12	12	12	10	2 (9)
Mori 2012 Mod Rheumatol [results based on patients enrolled in at least one of 3 short-term studies using etanercept])	32	32	32	18	14 (44)
Constantin 2013 ACR/ARHP[Long term extension of Horneff 2014 CLIPPER Part 2;	127	Unclear	Unclear	124	3 (2.3)

4.6.1 Baseline demographic and disease characteristics of interventional studies

The main differences between the study populations of the included studies were the proportion of patients with systemic JIA, and the use of concomitant DMARDs. Systemic JIA is outside the scope of this MTA and therefore, where outcomes for patients with JIA were reported separately, these data were not extracted. Where reporting was not stratified by subtype, the results of some studies include data from systemic JIA patients. Note etanercept is not licensed for the treatment of systemic JIA.

Baseline demographics

Mean age for overall study populations ranged from 10.5 (Lovell 2000) to 13.7 years (Mori 2012). Ethnicity was not generally reported. Where reported, 56-88% of patients were of white ethnicity, with Hispanic the second most frequently reported category. The Mori trials were in Japanese patients and the Zeng trial was in Chinese patients; this may limit generalisability to the UK JIA patient population.

Baseline height, weight and BMI were reported infrequently across the included studies. No study reported specifically on the proportion of patients with prior biological use, but patients previously treated with biologics were excluded from the Horneff 2009 and Horneff 2014 studies.

Disease subtype

Only one primary study, Horneff 2014 (the CLIPPER Part 1 study) and its associated extension study (Constantin 2013; CLIPPER Part 2), reported outcomes separately by JIA subtype (eoJIA, ERA and PsA). This study formed part of the evidence base supporting the licence extension across the JIA subtypes in 2012.

Concomitant treatment

Data are available for etanercept both as a monotherapy and in combination with DMARDs. In the pivotal study (Lovell 2002), concomitant DMARDs were not allowed in the initial phases (methotrexate could be added after 1 year in the long-term extension study). The Japanese studies (Mori 2005, 2011, 2012) also disallowed

concomitant DMARDs. In the other studies, high proportions of patients (79-90%) were on other DMARDs in addition to etanercept. Methotrexate was the most commonly used additional DMARD. All studies where the information was reported allowed corticosteroid use, although this was restricted to a low dose in some studies and some studies disallowed intra-articular steroids (Table 8). The proportion of patients using concomitant steroids at baseline, where reported, ranged from 12.6% in Horneff 2014 to 20% in Horneff 2009.

Baseline demographic characteristics, disease subtype and concomitant medication use are summarised in Table 11.

Table 11 Baseline demographic, disease and concomitant treatment characteristics of interventional studies

Study ID, arm and disease subgroup*	Age, yrs. mean (SD)	% female	JIA duration-yrs., mean (SD)	JIA subtype at inclusion, n (%)	Concomitant medication use at baseline, n (%)
Lovell 2000 NEJM Open label phase	10.5	62	5.9	Pauciarticular: 7 (10) Polyarticular: 40 (58) Systemic: 22 (32)	At washout) Corticosteroids: 25 (36)
Double-blind phase: etanercept	8.9	76	5.3	Pauciarticular: 2 (8) Polyarticular: 14 (56) Systemic: 9 (36)	At washout Corticosteroids: 6 (24)
Double-blind phase: placebo	12.2	58	6.4	Pauciarticular: 1 (4) Polyarticular: 17 (65) Systemic: 8 (31)	At washout Corticosteroids: 13 (50)
Mori 2005 Mod Rheumatol **[only Japanese patients included]**	11.4 (3.7)	81	4.72	EoJIA: 2 (9.1) Polyarticular RF+ve: 11 (50) Polyarticular RF-ve:8 (36.4) Systemic: 1 (4.5)	DMARDs not allowed
Horneff 2009 Rheumatol	12.9 (3.9)	80	4.1 (4.2)	Polyarticular (RF-): 12 (60) Polyarticular (RF+): 4 (20) EoJIA: 2 (10) ERA: 1 (5) Unclassified: 1 (5)	Prednisone: 4 (20) MTX: 12 (60) Other DMARDs: 4 (20)
Horneff 2014 Ann Rheum Dis [CLIPPER Part 1] All patients	11.7 (4.5)	56.7	26.8 (26.4) months	eoJIA: 60 ERA: 38 PsA: 29	Any DMARD: 109 (85.8) Oral corticosteroid: 16 (12.6)
eoJIA	8.6 (4.6)	68.3	31.6 (31.7) months	N/A	Any DMARD: 54 (90.0) Oral corticosteroid: 7 (11.7)
ERA	14.5 (1.6)	21.1	23.0 (19.8) months	N/A	Any DMARD: 32 (84.2) Oral corticosteroid: 8 (21.1)
PsA	14.5 (2)	79.3	21.8 (20.2) months	N/A	Any DMARD: 23 (79.3) Oral corticosteroid: 1 (3.5)
Zeng 2014 Ann Rheum Dis **[Abstract data; only Chinese patients included)**	NR	NR	NR	Oligoarticular: 17 (27.42) Polyarticular: 15 (24.19) Systemic: 30 (48.38)	NR
Extension studies					
Lovell 2003 Arth Rheum [Interim results of the Lovell 2008 long-term extension study]	10	67	5.9	Pauciarticular: 5 (9) Polyarticular: 34 (59) Systemic: 19 (33)	Corticosteroids: 22 (38)

Study ID, arm and disease subgroup*	Age, yrs. mean (SD)	% female	JIA duration-yrs., mean (SD)	JIA subtype at inclusion, n (%)	Concomitant medication use at baseline, n (%)
Lovell 2008 Arth Rheum **[Extension study of the Lovell 2000]**	10.8 (3.9)	81	6.4 (3.4)	Pauciarticular: 2 (8) Polyarticular: 19 (73) Systemic: 5 (19)	Patients were not receiving DMARDs at baseline of the OLE trial. At 8 years after initiation of the RCT, 31 of the 58 patients (53%) had received 1 or more DMARDs over the course of the OLE. MTX was the most common DMARD used, with 22 of the 58 patients (38%) having Received MTX at some point during the OLE.
Mori 2011 Mod Rheumatol (Down-dose extension study) [Japanese patients only; Double blind phase, etanercept 0.4 mg/kg arm]	13.5	100	6.68	Polyarticular: 5 (83.3) Pauciarticular: 1 (16.7) Systemic: 0 (0)	NR; DMARDs not allowed.
Mori 2012 Mod Rheumatol (patients recruited from Mori 2005; Mori 2011 (dose-down extension and double blind study and, lower dose open label study)	13.7	87.5	6.08	Polyarticular: 28 (87.5) Pauciarticular: 3 (9.4) Systemic: 1 (3.1)	Corticosteroids: 26 (81.3).
Constantin 2013 ACR/ARHP [Abstract data only; Extension study of Horneff 2014 CLIPPER Part 2)	11.7 (4.5)	56.7	26.8 (26.4) months	eoJIA: 60 (47.2) ERA: 38 (29.9) PsA: 29 (22.8)	Concomitant therapy with only 1 of the following was permitted: methotrexate, hydroxychloroquine, Chloroquine, or sulfasalazine.

* Except where otherwise stated, all studies report a single arm of etanercept-treated patients, with no separate baseline reporting by disease subgroup

Baseline disease activity

Baseline disease activity was measured in all studies using the JIA ACR (also known as PedACR) core assessment set (physician global assessment disease activity, parent global assessment wellbeing, number of active joints, number of joints with limitation of motion, CHAQ score, and ESR or CRP); some studies also reported a VAS rating for pain. Baseline severity is summarised in Table 12. Note that for all scales, including wellbeing, a higher score indicates worse severity. In most studies patient-reported ratings were given by either the patient or parent, depending on child's age.

- In the pivotal study (Lovell 2000), physician's global assessment (PGA) of disease activity was 7 on a 0 to 10 scale. Baseline disease activity in the other studies was somewhat lower, ranging from 1 (0-10 scale) in Mori 2012 to 42 (0-100 scale) in Horneff 2009 and 5 (0-10 scale) in Horneff 2014. Lovell 2000 and extension, and Mori 2005, reported median scores; all other studies reported means.

- Patients in Lovell 2000 had many more active joints at baseline (median 28) than any other study; in contrast, Horneff 2014 reported a mean of 6.7 active joints at baseline.

- CHAQ scores were also higher in Lovell 2000 and Mori 2005, indicating greater disability at baseline.

- Patients/parents in Horneff 2014 reported greater pain (mean 5.1 on 0-10 VAS) than those in Lovell (median 3.6). Patient/parent global assessment of wellbeing was 5 in both studies.

- JADAS score was not reported. Mori 2011 reported DAS28 (mean DAS28 score 5.62 at baseline; DAS score is not validated for children). Mori 2005 reported a DAS efficacy score but not baseline data.

- The ACR core assessment set also records a laboratory measure of inflammation. Some studies report erythrocyte sedimentation rate, some report C-reactive protein, and some report both; some report mean values and some

report median. Cross-trial comparisons may not be valid because of differences in laboratory techniques.

Table 12 Baseline disease severity of participants in the studies across treatment groups (clinical measures)

Study ID, arm and disease subgroup	PGA disease activity[a]		PGA wellbeing[b]		No. active joints		No. joints with LOM		CHAQ score		VAS pain	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Lovell 2000 NEJM Open label phase	NR	7*	NR	5 *	NR	28	NR	23	NR	1.4	NR	3.6*
Double-blind phase: etanercept	NR	7*	NR	5*	NR	32	NR	24	NR	1.6	NR	3.5*
Double-blind phase: placebo	NR	6*	NR	5*	NR	27	NR	23	NR	1.3	NR	3.5*
Mori 2005 Mod Rheumatol	NR	5.6*	NR	6*	NR	13	NR	10	NR	2.4	NR	6*
Horneff 2009 Rheumatol	42 (20.6)**	NR	41.3 (23.5)**	NR	17.0 (8.0)	NR	9.3 (8.9)	NR	0.5 (0.5)	NR	NR	NR
Horneff 2014 Ann Rheum Dis [CLIPPER Part 1] All patients	5.0* (1.8)	NR	5.0* (2.3)	NR	6.7 (4.6)	NR	5.7 (4.2)	NR	0.8 (0.6)	NR	5.1* (2.5)	NR
eoJIA	5.0* (1.8)	NR	4.8* (2.4)	NR	7.6 (5.1)	NR	6.3 (4.4)	NR	0.9 (0.7)	NR	4.8* (2.6)	NR
ERA	5.4* (1.9)	NR	5.4* (2.30	NR	5.2 (3.6)	NR	4.8 (4.0)	NR	0.7 (0.5)	NR	5.8* (25)	NR
PsA	4.7* (1.4)	NR	4.6* (2.2)	NR	7.0 (4.3)	NR	5.6 (4.1)	NR	0.7 (0.6)	NR	4.6* (2.3)	NR
Zeng 2014 Ann Rheum Dis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Extension studies												
Lovell 2003 Arth Rheum	NR	7*	NR	5*	NR	29	NR	24	NR	1.4	3.6*	NR
Lovell 2008 Arth Rheum	6.4* (0.3)	6.5*	4.8* (0.3)	5.0*	30.1 (1.9)	28.5	27.5 (2.0)	23.5	1.5 (0.1)	1.4	NR	NR
Mori 2011 Mod Rheumatol (Down-dose extension study) Double blind phase, etanercept 0.4 mg/kg arm	NR	NR	NR	NR	1.5	NR	0	NR	0.35	NA	NR	NA

Study ID, arm and disease subgroup	PGA disease activity[a]		PGA wellbeing[b]		No. active joints		No. joints with LOM		CHAQ score		VAS pain	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Mori 2012 Mod Rheumatol [patients recruited from Mori 2005; Mori 2011 (dose-down double blind and lower dose open label study)	1.03*	NR	2.4*	NR	3.0	NR	0.9	NR	0.492	NR	NR	NR
Constantin 2013 ACR/ARHP [CLIPPER Part 2; Extension study of Horneff 2014]	As Horneff, CLIPPER Part 1	NA	As Horneff, CLIPPER Part 1	NA	As Horneff, CLIPPER Part 1	NA	As Horneff, CLIPPER Part 1	NA	As Horneff, CLIPPER Part 1	NA	R	NA

[a] PGA, physician global assessment; [b], PGA parent or patient global assessment; CHAQ, childhood health assessment questionnaire, 0-3 scale, 0=no disability, 3=very severe disability; LOM, limitation of motion; VAS, visual analogue scale
* Visual analogue scale 0-10; ** visual analogue scale 0-100

4.7 Quality assessment of the interventional trials

Two studies, Lovell 2000 and Mori 2011 (dose-down extension Japanese study) had randomised double-blind phases and the rest were open-label, single-arm studies. Quality assessment for the interventional trials with randomised phases is shown in Table 13. Quality assessment was only carried out on the double-blind phases of these studies. Lovell 2000, the etanercept pivotal study, was of high quality and satisfied ethical and methodological considerations, with an initial open-label phase followed by a double-blind phase. Of note, Lovell 2000 was described as a high quality trial in NICE TA35.[9]

The quality of the non-randomised interventional studies was assessed using the Newcastle-Ottawa scale [68] (Table 14). In this assessment system, a star (*) indicates good quality for that parameter. Overall, the studies consistently fulfilled the criteria for patient selection, comparability and outcome measures, and can thus be considered representative of the JIA cohort seen in clinical practice.

Only full papers were assessed for quality: Zeng was reported as a conference abstract only and therefore insufficient information was available for a credible quality assessment to be carried out.

Table 13 Quality assessment results for the interventional trials with randomised phases

Trial number (acronym)	Lovell 2000 NEJM (pivotal study)	Mori 2011 Mod Rheumatol (dose-down extension study, etanercept 0.4 mg/kg arm)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

Table 14 Newcastle-Ottawa quality assessment (non-randomised interventional studies; * indicates good quality)

		Selection		Comparability	Outcome		
Study ID	**Study design**	**Representativeness of the exposed cohort**	**Ascertainment of exposure**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**
Mori 2005 Mod Rheumatol	Open-label, prospective, single arm, multicentre	Representative - Inclusion criteria matches that of other trials. No major exclusions*	Trial setting*	Single arm	Investigator assessment	Yes*	No pts lost to follow up*
Horneff 2009 Rheumatol	Open label, single arm, multicentre	Representative - Inclusion criteria matches that of other trials. No major exclusions except major concurrent medical conditions*	Trial setting*	Single arm	Investigator assessment	Yes*	No pts lost to follow up. Unlikely to introduce bias. *
Horneff 2014 Ann Rheum Dis	Open label, single, arm, prospective, multicentre, phase 3b. Divided in to 2 parts	Representative -. Inclusion criteria match that of other trials. No major exclusions except other rheumatic diseases*	Trial setting*	Single arm	Investigator assessment	Yes*	No pts lost to follow up. Unlikely to introduce bias. *
Lovell 2003 Arth Rheum	Open label, single arm, multicentre, extension study of Lovell 2000	Approx. 1/3 systemic- Inclusion criteria matches that of other trials. No major exclusions except major concurrent medical conditions - somewhat representative*	Trial setting*	Single arm	Investigator assessment	Yes*	1 pt. lost to follow-up. Unlikely to introduce bias*
Lovell 2008 Arth Rheum	Open label, single arm, multicentre, extension study of Lovell 2000	Approx. 1/3 systemic- Inclusion criteria matches that of other trials. No major exclusions except major concurrent medical conditions - somewhat representative*	Trial setting*	Single arm	Investigator assessment	Yes*	3 pts discontinued due to parental refusal, protocol issues or loss to follow-up. Unlikely to introduce bias*

		Selection		Comparability	Outcome		
Study ID	**Study design**	**Representativeness of the exposed cohort**	**Ascertainment of exposure**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**
Mori 2012 Mod Rheumatol [Japanese patients recruited from Mori 2005; Mori 2011 (dose-down double blind and lower dose open label study)	Open-label, multicentre study, extension of Mori 2011	Representative - Inclusion criteria matches that of other trials. No major exclusions unless safety problems in short-term study*	Trial setting*	Single arm	Investigator assessment	Yes*	No loss to follow-up. Unlikely to introduce bias*

4.8 Clinical effectiveness results of the interventional trials

Summary of efficacy, interventional studies

Etanercept demonstrates sustained ACR response on the treatment of JIA and across the subtypes

- Efficacy of etanercept at 3 months using JIA ACR response criteria has been demonstrated in a range of studies, including as monotherapy (no concomitant DMARDs) and combination therapy (i.e. concomitant methotrexate or other DMARDs were permitted), and in three JIA subtypes in addition to polyarticular JIA.
- In the pivotal study (Lovell 2000), 74% of patients in the open label phase achieved ACRPedi 30 (the definition of response) at 3 months with etanercept monotherapy and entered the double blind study phase (n=51).
- In the 4-month double-blind phase, 28% of patients receiving etanercept and 81% receiving placebo (p=0.003) withdrew due to disease flare (the primary end point).
- At the end of the study 80% of patients receiving etanercept achieved ACR Pedi 30, compared with 35% in the placebo arm (all of whom had previously received open label etanercept) (p<0.01).
- The majority of patients obtained greater degrees of improvement in ACR Pedi response from baseline with etanercept compared to placebo: at the end of the study (7 months) ACR Pedi 50 was achieved by 72% vs 23% and ACR Pedi 70 by 44% vs 19%.

Open label treatment extension

- JIA ACR 70 response of higher was achieved by 100% of patients with 8 years follow up (11/11) and 61% LOCF (28/46) (Lovell 2008).
- At 8 years, rates of JIA ACR 30, 50, 70, 90 and 100 were 83%, 77%, 61%, 41%

and 18% respectively (LOCF).

Etanercept is clinically effective in all the JIA subtypes studied

- The CLIPPER study was a phase IIIb open-label interventional study designed to assess the safety and efficacy of etanercept in JIA subtypes as classified using the ILAR criteria.
- In part 1 of the CLIPPER study [13] ACR 30 was achieved by 89.7% of subjects with extended oligoarticular JIA, 83.3% with enthesitis-related JIA, 93.1% with psoriatic JIA at week 12. Overall ACR50, 70 and 90 were achieved by 81.1%, 61.5% and 29.8%. Inactive disease was achieved by 12.1% at week 12.
- In part 2 of CLIPPER (Constantin 2013) at 96 weeks, 99.1% achieved ACR 30, 98.1% achieved ACR 50 and 65.4 achieved ACR 90 (observed case data). Inactive disease was achieved by 34.0%.

4.8.1 JIA ACR response

All the interventional studies (except Mori 2012) reported information on the number or percentage of patients achieving at least one of the JIA ACR response criteria (also known as ACRPedi) [69]: JIA ACR 30/50/70/90 indicates at least a 30/50/70/90 per cent improvement from baseline based on the six ‘core set’ assessments (physician global assessment disease activity, parent global assessment wellbeing, number of active joints, number of joints with limitation of motion, CHAQ score, and ESR or CRP). JIA ACR 30 is generally considered the minimum satisfactory level of response. JIA ACR response in the included studies is summarised in Table 15.

Achievement of JIA ACR 30 was the definition of response in the pivotal trial of etanercept (Lovell 2000). This was a modified definition in which ‘joints with limitation of motion’ (LOM) was modified to ‘joints with LOM and with pain, tenderness or both’; this was to eliminate counting joints with contractures that might not have improved during the short course of treatment (Lovell 2000). In the primary interventional study leading to the license amendment of etanercept for the eoJIA, ERA and PsA subtypes (Horneff 2014), JIA ACR 30 was the primary end point.

In the pivotal study (Lovell 2000), 74% of patients in the open label phase achieved JIA ACR 30 at 3 months. After a further 4 months, 80% of patients receiving etanercept in the double-blind phase achieved JIA ACR 30, compared with 35% in the placebo arm (all of whom had previously received open label etanercept). The percentage of patients achieving JIA ACR 30 at 3 months was 95% in Horneff 2009, 90.9% in Mori 2005 and 2011, and 88.6% in Horneff 2014. The percentage was lower (67%) in the Mori 2011 double-blind phase but only six patients were evaluated. JIA ACR 30 was frequently maintained in long-term follow-up studies: in Lovell 2003, 69% of 43 evaluated patients had JIA ACR 30 at 24 months, and 83% of 48 patients had JIA ACR 30 at 8 years (last observation carried forward in the 8 year analysis) in Lovell 2008.

The majority of patients obtain degrees of improvement with etanercept greater than JIA ACR 30, both at 3 months and in the long term. In the double-blind phase of the pivotal study (Lovell 2000), 72% of patients who received etanercept and 23% of patients receiving placebo met the definition of JIA ACR 50 at 7 months. Furthermore, the definition of JIA ACR 70 was met by 44% and 19% of patients receiving etanercept and placebo, respectively. After 8 years (Lovell 2008), the definitions of JIA ACR 50, 70 and 90 were met by 77%, 61% and 41% of patients (n = 46 to 48), respectively (LOCF; 16 patients completed year 8).

Outcomes by JIA subtype

The CLIPPER study (Horneff 2014, Constantin 2013) included only patients with extended oligoarticular (n=60), enthesitis-related (n=38) and psoriatic (n=29) JIA. In the overall study population, JIA ACR 50, 70, 90 and inactive disease were achieved in 81.1%, 61.5%, 29.8% and 12.1%, respectively at 12 weeks. At 96 weeks, 99.1%, 98.1% and 65.4% of those patients still receiving treatment had met the definition for JIA ACR 50, 70, 90 respectively.

Patients were also using varying regimens of other DMARDs and corticosteroids, which was noted as a limitation of the study (Horneff 2014), but these were already present at baseline and doses had to be stable throughout the study.

Improvements were also reported in subtype-specific outcome measures (not tabulated): in ERA there was a >50% improvement from baseline in tender entheseal

score at 12 weeks; in PsA there was a 48.2% improvement in body surface area of psoriasis and a 39.6% improvement in physician global assessment of psoriasis.

Table 15 JIA ACR response in the interventional studies

Study ID, design and time point	JIA subtype*	No. on arm at time point	No. in ACR evaluation population†	JIA ACR 30		JIA ACR 50		JIA ACR 70		JIA ACR 90	
				n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Lovell 2000 NEJM Open-label phase 3 mo	All	69	69	51	74 (NR)	44	64 (NR)	25	36 (NR)	NR	NR
Double-blind phase, etanercept 4 mo (7 mo from baseline)	All	25	25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Double-blind phase, placebo 4 mo (7 mo from baseline)	All	26	26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Mori 2005 Mod Rheumatol 12 wk	All	22	22	20	90.9 (70.8 to 98.9)	20	90.9 (70.8 to 98.9)	[redacted]	[redacted]	NR	NR
Horneff 2009 Rheumatol 12 wk	All	20	20	19	95	15	75	15	75	NR	NR
Horneff 2014 Ann Rheum Dis [CLIPPER Part 1] 12 wk	All	127	variable	[redacted]	88.6 (81.6-93.6)	[redacted]	81.1 (73.1-87.7)	[redacted]	61.5 (52.2-70.1)	[redacted]	29.8 (21.8-38.7)
12 wk	eoJIA	60	variable	[redacted]	89.7 (78.8-96.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 wk	ERA	38	variable	[redacted]	83.3 (67.2-93.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 wk	PsA	29	variable	[redacted]	93.1 (77.2-99.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zeng 2014 Ann Rheum Dis [Abstract data only] 6 mo	All	32	NR	NR	NR	NR	80	NR	>50	NR	NR
	Polyarticular	17	Unclear	NR	NR	NR	NR	NR	NR	NR	NR
	Oligoarticular	15	Unclear	NR	NR	NR	NR	NR	NR	NR	NR

Study ID, design and time point	JIA subtype*	No. on arm at time point	No. in ACR evaluation population†	JIA ACR 30		JIA ACR 50		JIA ACR 70		JIA ACR 90	
				n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Extension studies											
Lovell 2003 Arth Rheum											
12 mo	All	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
24 mo	All	51 (mITT)	43	35	69	34	67	29	57	NR	NR
24 mo	Pauciarticular	4 (mITT)	NR	3	75	3	75	2	50	NR	NR
24 mo	Polyarticular	30 (mITT)	NR	22	73	22	73	19	63	NR	NR
Lovell 2008 Arth Rheum 8 y	All	58 (but 26 were present in trial at year 8)	46-48 pts, LOCF; core set components reported for 16 pts who completed year 8	40/ 48	83	36 / 47	77	28/ 46	61	19/ 46	41
Mori 2011 Mod Rheumatol Open label phase 12 wk (Dose-down Double-blind phase, etanercept 0.4 mg/kg 12 wk	All	6	6	4	66.7	4	66.7	3	50	NR	NR
Mori 2012 Mod Rheumatol Etanercept 0.4 arm 192 weeks	All	19	NR	NR	NR	NR	NR	NR	NR	NR	NR
Constantin 2013 ACR/ARHP 96 wk	All	127	Unclear	Unclear	99.1 (94.9, 100)	125	98.1 (93.5, 99.8)	121	Unclear	121	65.4 (55.6, 74.4)
[CLIPPER Part 2; Extension study of	eoJIA	60	Unclear	53	Unclear	53	Unclear	55	Unclear	55	Unclear

Study ID, design and time point	JIA subtype*	No. on arm at time point	No. in ACR evaluation population†	JIA ACR 30		JIA ACR 50		JIA ACR 70		JIA ACR 90	
				n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Horneff 2014;abstract data]	ERA	38	Unclear	30	Unclear	30	Unclear	35	Unclear	35	Unclear
	PsA	29	Unclear	27	Unclear	27	Unclear	25	Unclear	28	Unclear

* if reporting stratified; 'all' indicates all patients reported; † number of patients on which the response rate is based

4.8.2 ACR core assessment set outcomes

Most studies reported percentage change from baseline in the individual components of the JIA ACR core assessment set. For all measures, a negative change denotes improvement; in the textual description of improvements, the negative has been removed.

- At 3 months, improvement in physician global assessment of disease activity ranged from 60% (Lovell 2000) to 93.6% (Mori 2011, dose-down extension study). Where longer follow-up was reported, improvement was durable; Lovell 2003 reported a 70% improvement at 24 months.

- Parent global assessment of child's overall wellbeing was consistently improved; improvement and ranged from 47% (ERA and PsA arms, Horneff 2014) to 72% (Horneff 2009) at 12 weeks.

- There were also consistently large reductions in the number of active joints. In the pivotal study (Lovell 2000) the median number fell from 28 at baseline to 13 at 3 months, 2.5 at 12 months, 3 at 24 months, and 1 in patients still on study at 8 years (Lovell 2008).

- Children's functional status, as measured by CHAQ score, was consistently improved. Improvement at 12 weeks was 37% in Lovell 2000 and ranged from 10% to 53.6% in other studies. At 24 months, the improvement was 58% in the Lovell 2003 study, and Mori 2012 reported an 84.6% improvement at 4 years.

- In the studies reporting on the JIA subtypes eoJIA, ERA and PsA (CLIPPER part 1 [Horneff 2014] and CLIPPER Part 2 [Constantin 2013]), no apparent differences in the percentage improvements in physician global assessment across the subtypes were noted. Improvements were broadly similar to those seen in the wider study populations.

Table 16 Outcomes for individual components of the ACR core assessment set

Study ID, arm, time point, no. on arm at time point	Physician global assessment disease activity (VAS)			Parent global assessment wellbeing (VAS)			No. of active joints			No. of joints with LOM			CHAQ score			ESR (mm/h)	CRP mg/L
	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change		
Lovell 2000 NEJM Open-label phase 3 mo (n=69)	NR	2	-60.0	NR	2	-50.0	NR	13	-56	NR	15	-37	NR	0.9	-37	Median 20	Median 0.8 mg/dL
Dbl-blind phase, ETN 4 mo (7 mo from baseline) (n=25)	NR	2	NR	NR	3	NR	NR	7	NR	NR	9	NR	NR	0.8	NR	Median 18	Median 0.4 mg/dL
Dbl-blind phase, placebo 4 mo (7 mo from baseline) (n=26)	NR	5	NR	NR	5	NR	NR	13	NR	NR	22	NR	NR	1.2	NR	Median 30	Median 3.0 mg/dL
Mori 2005 Mod Rheumatol 12 wk (n=22)	NR	0.6	-88.8	NR	3	-56.3	NR	2	-87.5	NR	1.5	-10.3	NR	1.5	-10.3	Median 15	Median 0.17
Horneff 2009 Rheumatol 12 wk (n=20)	11.1**	NR	-74	11.6** (7.9)	NR	-72	2.9 (3.6)	NR	-83	3.0 (3.9)	NR	NR	0.26 (0.46)	NR	-48	Mean (SD):6.9 (3.9)	Mean (SD)1.6 (2.9)
Horneff 2014 Ann Rheum Dis All pts, 12 wk (n=123)	-3.5 (NR)	NR	-70.6	-2.7 (NR)	NR	-50.2	NR	-5.1 (NR)	-73.0	-4.1 (NR)	NR	-66.9	-0.5 (NR)	NR	-53.6	NR	% change -22.1
EoJIA 12 wk (n=58)	-3.5 (NR)	NR	-73.2	-2.8 (NR)	NR	-53.1	NR	-5.5 (NR)	-69.8	-4.5 (NR)	NR	-64.1	-0.5 (NR)	NR	-52.2	NR	-18.9
ERA 12 wk (n=36)	-3.9 (NR)	NR	-70.9	-2.8 (NR)	NR	-47.6	NR	-4.3 (NR)	-77.7	-3.4 (NR)	NR	-67.4	-0.5 (NR)	NR	-57.8	NR	-36.8
PsA 12 wk (n=29)	-3.0 (NR)	NR	-65.0	-2.2 (NR)	NR	-47.7	NR	-5.2 (NR)	-73.8	-4.3 (NR)	NR	-71.7	-0.4 (NR)	NR	-51.3	NR	-11

Study ID, arm, time point, no. on arm at time point	Physician global assessment disease activity (VAS)			Parent global assessment wellbeing (VAS)			No. of active joints			No. of joints with LOM			CHAQ score				
	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Zeng 2014 Ann Rheum Dis [Abstract data only] 6 mo (n=32)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Extension studies																	
Lovell 2003 Arth Rheum 12 mo (n=NR)	NR	2.0*	NR	NR	2.0*	NR	NR	2.5	NR	NR	12.5	NR	NR	0.5	NR	Median 15.5	Median 0.4 mg/dL
24 mo (all pts) (n=51	NR	2.0*	-70	NR	1.0*	-67.0	NR	3.0	-88.0	NR	12	-43	NR	0.4	-58	NR	Median 0.1 mg/dL; -90% change
Lovell 2008 Arth Rheum 8 y (n=26, 16 completed 8 y)	1.6* (0.3)	1.0*	NR	2.0*(0.6)	1.0	NR	2.2 (0.9)	1.0	NR	11.8 (4.4)	6.0	NR	0.6 (0.2)	0.3	NR	NR	Mean 1.1 (SD 0.5); median 0.2
Mori 2011 Mod Rheumatol [Dose-Down extension study) Dbl-blind phase, ETN 0.4 mg/kg, 12 wk (n=6)	0.52*	NR	-93.6	2.5*	NR	-44.9	3.7	NR	-91.9	3.5	NR	-92.4	0.729	NR	-56	NR	0.025 mg/dL
Mori 2012 Mod Rheumatol Etanercept 0.4 or 0.2 mg/kg/wk 4 y (n=19)	0.57	NR	-90.7	1.8*	NR	-54.1	1.4	NR	-95.1	0.1	NR	99.1	0.217	NR	-84.6	NR	0.02
Constantin 2013 ACR/ARHP [CLIPPER 2, abstract data only] [Extension study of	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study ID, arm, time point, no. on arm at time point	Physician global assessment disease activity (VAS)			Parent global assessment wellbeing (VAS)			No. of active joints			No. of joints with LOM			CHAQ score				
	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Horneff 2014, CLIPPER Part 1] 96 wk (n=127)																	

(VAS, *1-10 scale, **1-100 scale); % change denotes % change from baseline

4.8.3 Disease inactivity and remission

Inactive disease or clinical remission were not specified as outcomes in the pivotal study but are now seen as feasible goals of treatment. The most common definitions used are 100% improvement in ACR Pedi, or the Wallace 2004 criteria (or the amended 2011 Wallace criteria); the Wallace criteria give definitions for inactive disease and for clinical remission (defined as inactive disease for at least 6 months). In those interventional studies that record it at this time point, 6.9% to 20% of etanercept-treated patients have achieved inactive disease by 12 weeks (Table 17). In the CLIPPER studies, the proportion with inactive disease across the JIA subtypes rose over time, from 12.1% at 12 weeks (Horneff 2014) to 34.0% at 96 weeks (Constantin 2013). The other study to report long-term follow-up was Lovell 2008, in which 8 of 45 patients still in follow-up met ACR Pedi 100 criteria at 8 years.

Table 17 Inactive disease and remission outcomes, interventional studies

Study ID, arm and time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
Lovell 2000 NEJM Open-label phase 3 mo	All	69	NR	NR	NR
Double-blind phase, etanercept 4 mo (7 mo from baseline)	All	25	NR	NR	NR
Double-blind phase, placebo 4 mo (7 mo from baseline)	All	26	NR	NR	NR
Mori 2005 Mod Rheumatol 12 wk	All	22	NR	NR	NR
Horneff 2009 Rheumatol 12 wk	All	20	Inactive disease	Wallace 2004 [70]	5
Horneff 2014 Ann Rheum Dis [CLIPPER Part 1] 12 wk	All	127	Inactive disease	Wallace 2011 [71]	12.1% (95% CI 6.9-19.2%)
12 wk	eoJIA	60	“	“	11.9% (4.9-22.9%)
12 wk	ERA	38	“	“	16.7% (6.4-32.8%)
12 wk	PsA	29	“	“	6.9% (0.8-22.8%)
Zeng 2014 Ann Rheum Dis 6 mo	All	32	NR	NR	NR
Lovell 2003 Arth Rheum 12 mo, 24 mo	All	NR	NR	NR	NR
Lovell 2008 Arth Rheum 8 y	All	26	ACR Pedi 100	ACR Pedi 100	18% (8 of 45)
Mori 2011 Mod Rheumatol Double-blind phase, etanercept 4 mg/kg 12 wk	All	6	NR	NR	NR
Mori 2012 Mod Rheumatol Etanercept 0.4 arm mg/kg/wk 4 y	All	19	NR	NR	NR
Constantin 2013 ACR/ARHP [CLIPPER Part 2; abstract data only] 96 wk	All	127	Inactive disease	Wallace 2011 [71]	34.0% (25.0-43.8%)
96 wk	eoJIA	60	“	“	Unclear
96 wk	ERA	38	“	“	Unclear
96 wk	PsA	29	“	“	Unclear

4.8.4 Pain assessment

Lovell 2000 and 2008, Mori 2005 and Horneff 2014 reported an assessment of pain by parent or child using a VAS (not tabulated). Lovell 2000 reported a 63% reduction in pain at 3 months and Mori 2005 reported a 66.7% reduction. Horneff 2014 reported a 51.9% improvement at the same time point for the overall study population; improvement was somewhat greater for eoJIA (58.9%) than for ERA (44.9%) or PsA (46.6%). In the longer term, Lovell 2003 reported a 75% improvement at 24 months. Lovell 2008 reported that in 16 patients completing year 8 of follow-up, median pain score was 0.6, compared with 3.6 at baseline.

4.8.5 JADAS/DAS score

Most studies did not report JADAS or DAS scores (scores not tabulated). Mori 2012 reported DAS outcome as a graph only: visual inspection shows a fall in mean DAS28 score from approximately 5.8 at baseline to approximately 2.2 at 96 weeks, a level which was maintained at 192 weeks. Mori 2011 reported DAS28 scores of 2.64 and 3.15 at the end of the open label and double-blind phases respectively, compared with 5.62 at baseline. Mori 2005 classed DAS28 response (by EULAR criteria) as ‘good’ in 8 patients, ‘moderate’ in 12 patients and ‘poor’ in 0 patients.

4.8.6 Other efficacy outcomes

Other efficacy outcomes within the scope of the review were reported infrequently in the interventional studies.

Disease flare: number of patients with disease flare was the primary efficacy end point in the double-blind phase of the pivotal study (Lovell 2000). The definition of flare was based on defined changes in the core set of response variables from the beginning of the double-blind study. In the etanercept arm, 7 patients (28%) experienced flare, compared with 21 (81%) in the placebo arm (p=0.003). Median time to disease flare with placebo was 28 days, compared with over 116 days (duration of study was 4 months) in the etanercept arm. After 8 years of the open label extension study, which consisted of patients in response at baseline, 6% of patients had experienced disease flare (Lovell 2008). No other study reported on disease flare.

Corticosteroid reduction: the only report of this was in Lovell 2003 at 24 months, when 26 of 32 pts (81%) receiving steroids had reduced their dose to <5 mg/day.

No outcomes relating to joint damage or children's growth were reported in the primary publications of the included studies. [redacted]

4.9 Subgroup analysis

Where relevant, pre-planned analyses specified by the studies, such as JIA categorisations (Horneff 2014 and Constantin 2013), have been presented.

4.10 Meta-analysis

A meta-analysis was deemed neither feasible nor appropriate to conduct due to the differences in study designs, inclusion and exclusion of study participants, variations in study outcomes and differences in outcome measures across the bDMARD studies.

4.11 Indirect and mixed treatment comparisons

In the absence of head-to-head trials comparing etanercept to other biologics we considered undertaking an indirect treatment comparison. However, we did not consider it feasible due to substantial differences in respective marketing authorisations across biologic treatments, scarcity of studies as well as substantial heterogeneity. Examples of heterogeneity include; differences in the classification of JIA, differences in treatment duration and study designs and type and nature of concomitant treatments used. Furthermore, our concerns regarding the robustness of an indirect comparison is consistent with the conclusions reached within independent published research, which found that no definite conclusions could be drawn about the comparative effectiveness of indirectly compared biological agents (Otten 2013 and Ungar, 2013). For this reason, we have decided within our submission only to present the evidence base for etanercept from the robust interventional and observational data for this MTA.

4.12 Evidence from observational studies

Observational/registry studies were included in the evidence base to support the long-term clinical effectiveness of etanercept in the JIA population. For example, Giannini 2009 formed part of the evidence base for informing the marketing authorisation as well as the extension of the etanercept therapeutic indications in 2012.The study was conducted to determine the long-term safety of etanercept administered with or without MTX compared with MTX alone in paediatric subjects with polyarticular JIA. Subjects were allowed to use other concomitant DMARDs. Per the protocol, subjects in the MTX only arm who discontinued from MTX treatment and switched to etanercept treatment or added etanercept to existing MTX within 30-months of enrolment were allowed to re-enrol in the etanercept only or etanercept + MTX arm of the registry. The observational studies cover a range of geographical regions including, but not limited to, UK, USA, Germany, France, Italy, Finland, The Netherlands, Switzerland and Poland. The results from observational studies may be generalisable to JIA populations across a range of clinical practice settings.

4.12.1 List of relevant observational studies

All observational studies identified in the review (see Figure 1) are presented. Forty-one publications, including relevant conference abstracts, were identified, and data were also extracted from two unpublished studies. Each publication reported a separate analysis, although data from the large registries were analysed in multiple publications. Data were extracted for etanercept only, and studies that evaluated only a non-licensed dose were excluded. In studies where the dose was not specified or not reported, it was assumed that etanercept was being used at its licensed dose, and as such these studies were included. Note that some studies included a minority of systemic JIA and persistent oligoarticular JIA for which etanercept is not licensed.

The number of patients analysed ranged from 13 (Opoka-Winiarska 2014) to 1925 (Horneff 2014, BIKER registry).

A summary of the included observational/registry studies is presented in Table 18 below

Table 18 List of the relevant observational studies

Study ID	Study design	Intervention	Number of patients	Duration of treatment*	Location
Horneff 2014 ACR [72]	Prospective, registry (BIKER)	Etanercept	1925	NR	Germany
Windschall 2015 Clin Rheumatol [73]	Prospective, registry (BIKER registry)	Etanercept	1678	≥3mo	Germany, Austria
Horneff 2012 EULAR [74]	Registry (BIKER)	Etanercept	1470	NR	Germany
Geikowski 2014 J Rhematol [17]	Registry (BIKER registry), retrospective	Etanercept	863	6 mo	Germany, Austria
Papsdorf 2011 Rheumatology [21]	Long-term, multicentre, prospective, open label observational study	Etanercept	787	NR	Germany
Davies 2013 ACR/ARHP [75]	Cohort study (BSPAR)	Etanercept	677	NR	UK
Horneff 2009 Ann Rheum Dis [76]	Prospective, observational, registry (German ETN Registry)	Etanercept alone Etanercept + methotrexate	604	12 mo	Germany
Giannini 2009† Arth Rheum [15]	Open-label, non-randomised, multicentre, phase IV, registry	Etanercept alone, 0.8 mg/kg once weekly (max 50mg) or 0.4 mg/kg twice weekly (max 25 mg) MTX alone, ≥ 10 mg/m$^{2/}$wk, not exceeding 1 mg/kg/wk Etanercept (doses as above) + MTX (dose at physician's discretion)	594	Up to 36 mo	USA and Canada
Halbig & Horneff 2009 Rheumatol Int [77]	Registry	Etanercept (German Etanercept Registry)	437	Mean (SD): 16 (14.6) mo	Germany, Austria
Kearsley-Fleet 2014 ACR [23]	Registry (BSPAR-ETN)	Etanercept	422	1 y	UK
Minden 2012 ACR/ARHP [78]	Registry (BIKER and JUMBO)	Etanercept	368	NR	Germany
Horneff 2004 Ann Rheum Dis [79]	Prospective, registry	Etanercept 0.4 mg/kg twice weekly (max 25 mg)	322	Mean (SD): 13.4 (10.5) mo; median 12 mo	Germany, Austria
Otten 2011 JAMA [80]	Prospective, multicentre, registry (ABC register)	Etanercept	262	Up to 87 mo	Netherlands

Study ID	Study design	Intervention	Number of patients	Duration of treatment*	Location
Tarkiainen 2014 Rheumatol [81]	Observational, multicentre	Etanercept (other interventions not extracted)	213	NR	Finland
Kearsley-Fleet 2013 ACR/ARHP [82]	Registry (BSPAR)	Etanercept	191	2 y	UK
Zuber 2011 Med Scin Monit [83]	Registry	Etanercept	188	Up to 72 mo	Poland
Otten J Rheumatol 2010 (Dutch registry) [84]	Prospective, multicentre, observational, registry (Dutch registry)	Etanercept	179	≥15 mo	Netherlands
Solari et al 2013 [20]	Retrospective review of patient clinical charts and data	Etanercept	173	Median, 2.2 y	Italy
Prince 2009 Ann Rheum Dis [85]	Prospective, observational, multicentre, registry	Etanercept 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly	146	Median 1.7 y	Netherlands
Gerloni 2008 Ann Rheum Dis [86]	Open, single centre, long term prospective safety study	Etanercept 0.4 mg/kg twice weekly (max 25 mg); pts could switch to infliximab if did not respond/did not tolerate ETN	95	Mean (SD): 24.1 (17.3) mo	Italy
Sevcic 2011 Rheumatol [87]	Prospective, registry	Etanercept 0.4 mg/kg body weight twice weekly or adalimumab 40 mg every 2 weeks	72	12 mo	Hungary
Susic 2013 PReS [88]	Prospective, observational	Etanercept 0.4 mg/kg twice weekly	63	Up to 12 mo	NR
Quartier 2003 Arth Rheum [89]	Open-label, prospective, multicentre	Etanercept 0.4 mg/kg twice weekly (max 25 mg)	61	Median 13 mo	France
Klotsche 2014 Arth Care Res [28]	Prospective, registry (BIKER)	Etanercept	61	12 mo	Germany
Loskutova 2014 PReS [90]	NR	Etanercept or abatacept	54	Up to 24 mo	NR
Prince 2010 Ann Rheum Dis [26]	Prospective, registry	Etanercept 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly	53	≥ 27mo	Netherlands
Prince 2011 Rheum [91]	Prospective, registry (ABC registry)	Etanercept 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly	49	≥27 mo	Netherlands
Anink 2014 PReS [42]	Registry (Dutch ABC)	Etanercept	43	>5 y (median 8.5y; IQR: 7.7-10.3)	Netherlands

Study ID	Study design	Intervention	Number of patients	Duration of treatment*	Location
Trachana 2012 EULAR [92]	NR	Etanercept	42	2 to 5 y	Greece
Trachana 2013 Clin Rheumatol [92]	Retrospective	Etanercept	41	Mean (SD): 47 mo(15)	Greece
Nielson 2008 Clin Exp Rheum [22]	Registry (Italian ETN Registry)	Etanercept 0.4 mg/kg twice weekly	40	12 mo	Italy
Vojvodich 2007 J Rheumatol [93]	Retrospective, observational study	Etanercept	31	1 y	Sweden
De Sanctis 2013 J Rheumatol [94]	Prospective observational study	Etanercept 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly	30	Up to 12 mo	Italy
Alekseeva 2012 EULAR [95]	NR	Etanercept 0.4 mg/kg twice weekly (max 25mg) + MTX 15 mg/m2/wk	25	Up to 48 wk	NR
Lahdenne 2003 Ann Rheum Dis [96]	Non-randomised, prospective, open-label	Etanercept 0.4 mg/kg twice weekly (maximum 25 mg per dose); or infliximab 3-4 mg/kg at wk 0, 2, 6, and every 4-8 wk thereafter	24	12 mo	Finland
Kietz 2002 Ann Rheum Dis [97]	Open, prospective, observational study	Etanercept 0.4 mg/kg twice weekly	22	Mean 16.7 mo (range 4-26)	USA
Calvo 2012 EULAR [98]	Retrospective chart review	Etanercept	21	Mean 36.6 mo (SD 22)	NR
Robinson 2003 Clin Drug Invest [7]	NR	Etanercept 0.4 mg/kg (max 25 mg)	21	Up to 14 mo	USA
Otten 2011 Ann Rheum Dis [99]	Prospective, multicentre, observational	Etanercept (except 1 pt. on adalimumab)	18	NR	Netherlands
Opoka-Winiarska 2014 PReS [100]	NR	Etanercept	13	Mean 24 mo (SD 11.81)	NR
Hooper 2013 Ped Rheum [101]	Review of Amgen clinical trial (CTD) and post-marketing safety (PMD) databases	Etanercept (assumed dose of 50 mg/wk)	NR	NR	Global
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID	Study design	Intervention	Number of patients	Duration of treatment*	Location
[redacted]		[redacted]			

* refers to the duration reported in the paper; many are ongoing studies. ABC, Arthritis and Biologics in Children; BIKER, Biologika in der Kinderrheumatologie (German Biologics JIA Registry); BSPAR, British Society for Paediatric and Adolescent Rheumatology; JUMBO, juvenile arthritis methotrexate/biologics long-term observation; † study used to inform the marketing authorisation

4.12.2 Inclusion and exclusion criteria for the relevant observational studies

The inclusion and exclusion criteria are summarised in Table 19.

The majority of the studies allowed patients to receive concomitant medications, either methotrexate or other DMARDs. The inclusion and exclusion criteria refer to the analysis in the identified paper, not necessarily to the registry as a whole.

Table 19 Inclusion and exclusion criteria and permitted concomitant medications, observational studies

Study ID	Inclusion criteria	Exclusion criteria	Concomitant medications allowed
Horneff 2014 ACR	JIA	NR	NR
Windschall 2015 Clin Rheumatol	ERA, PsA, EOJIA, polyarticular JIA RF +ve or -ve, newly starting ttmt with etanercept who had data for at least the 3 mo visit	NR	DMARDs, steroids
Horneff 2012 EULAR	JIA	NR	NR
Geikowski 2014 J Rhematol	All pts in registry treated with ETN at least 6 mo with complete data to calculate PedACR response	NR	MTX, NSAIDs, corticosteroids
Papsdorf Rheum 2011	JIA, previously treated with NSAIDs and either corticosteroids or MTX (or both)	NR	NSAIDs and corticosteroids
Davies 2013 ACR/ARHP	NR	NR	NR

Study ID	Inclusion criteria	Exclusion criteria	Concomitant medications allowed
Horneff 2009 Ann Rheum Dis	2-18 y; JIA	Pts with diseases other than JIA. Pts treated with DMARDs other than ETN and MTX	Prednisone
Giannini 2009† Arth Rheum	2-18 yr. (3 patients <2 y were also included); Systemic, oligoarticular or polyarticular JIA ≥ 3 joints with active arthritis. Pts were eligible if their disease was under control on ≥1 DMARDs or etanercept with 0 active joints at entry. Pts were receiving etanercept, Etanercept + MTX, or MTX at entry. Pts in etanercept arm to have started etanercept ttmt within 6 months prior to enrolment. Pts in MTX arm to have started MTX within 6 months after enrolment. All must have an adequate trial of NSAIDs and/or prednisone	Serious medical condition, history of drug and/or alcohol abuse or malignancies in previous 5 y. At time of enrolment: receiving anti-TNF agent other than etanercept, or cyclophosphamide, or other experimental or biologic agents. Previous ttmts: anti-TNF antibody, anti-CD4 antibody, or IL-2 diphtheria fusion protein ttmt or participated in an investigational study of a drug or biologic agent other than etanercept ≤6 months before enrolment	Sulfasalazine, methotrexate, cyclosporine, leflunomide, injectable gold, hydroxychloroquine, and azathioprine, NSAIDs and/or prednisone
Halbig & Horneff 2009 Rheumatol Int	JIA; failed/intolerant to MTX	NR	MTX
Kearsley-Fleet 2014 ACR	Systemic, oligoarticular, polyarticular, psoriatic	Pts who stopped ttmt for AE or unknown reason	NR
Minden 2012 ACR/ARHP	NR	NR	NR
Horneff 2004 Ann Rheum Dis	Failure to respond to MTX	NR	MTX, oral corticosteroids
Otten 2011 JAMA	All JIA pts in whom etanercept was initiated as 1st biologic ttmt and who could have had ≥15 mo follow-up. No previous biological	Previous ttmt with biologicals	MTX, other DMARDs, NSAIDs and corticosteroids
Tarkiainen 2004 Rheumatol	JIA, JIA-associated uveitis or chronic anterior uveitis without arthritis	NR	DMARDs
Kearsley-Fleet 2013 ACR/ARHP	Severe JIA	NR	NR
Zuber 2011 Med Sci Monit	4-17 y; JIA unresponsive or intolerant to MTX qualifying for anti-TNF treatment in Poland	Treatment with another TNF-α inhibitor	DMARDs, NSAIDs, glucocorticosteroids
Otten 2010 J Rheumatol	JIA with active disease despite max tolerated dose of MTX who failed to respond to MTX	NR	MTX, prednisone

Study ID	Inclusion criteria	Exclusion criteria	Concomitant medications allowed
Solari 2011 J Rheumatol	JIA	NR	MTX, systemic and intra-articular corticosteroids
Prince 2009 Ann Rheum Dis	<18 y; All pts with JIA in whom etanercept use was granted	NR	DMARDS, no limitations in use of concomitant drugs
Gerloni 2008 Ann Rheum Dis	Fulfilling JIA-ILAR diagnostic criteria; not responsive or intolerant ≥DMARD, all had failed MTX	NR	Oral corticosteroids and NSAIDs, MTX and other previous DMARDs were continued if tolerated
Sevcic 2011 Rheumatol	4 to 18 y; Polyarticular failed/intolerant to MTX	NR	MTX, NSAIDS, corticosteroids
Susic 2013 PReS	Polyarticular JIA	NR	NR
Quartier 2003 Arth Rheum	JIA according to the ILAR criteria, “active” chronic polyarticular disease (≥5 swollen joints and ≥3 joints with pain and LOM ≥ 6 months). Intolerance/ lack of efficacy methotrexate (≥0.4 mg/kg/wk)	Major concurrent diseases. Ongoing infection/requirement for a live attenuated vaccine. Uncontrolled severe systemic symptoms and/or biologic features of macrophage activation syndrome. Abnormal liver function. Low WBC, neutrophil, or platelet count. Radiologic evidence of destructive, non-reversible polyarthritis (Steinbrocker class III or IV)	DMARDs, including MTX, had to be withdrawn at least 15 days before the initiation of etanercept treatment, unless justification was provided by the patient’s physician. NSAIDs/corticosteroids doses stable for at least 1 month before initiation of etanercept treatment
Klotsche 2014 Arth Care Res	JIA	NR	Corticosteroids, NSAIDs
Loskutova 2014 PReS	Polyarticular JIA	NR	NR
Prince 2010 Ann Rheum Dis	<18yrs; JIA patients eligible for treatment with etanercept in The Netherlands who completed 3 HRQoL questionnaires	NR	DMARDs and concomitant medications
Prince 2011 Rheum	<18 yr.; Polyarticular course, insufficient response to MTX at max tolerated dose	NR	MTX, other DMARDs and systemic glucocorticoids
Anink 2014 PReS	JIA refractory to MTX	NR	NR
Trachana 2012 EULAR	JIA previously resistant to conventional treatment and >2 y drug exposure	NR	NR
Trachana 2013 Clin Rheumatol	JIA	Latent TB	DMARDS, prednisolone
Nielson 2008 Clin	Polyarticular JIA pts with wrist involvement who had	NR	Methotrexate, corticosteroids

Study ID	Inclusion criteria	Exclusion criteria	Concomitant medications allowed
Exp Rheum	a standard radiograph of both hands and wrists at baseline and after 1 y. Refractory or intolerant MTX		
Vojvodich 2007 J Rheumatol	Unsatisfactory response/intolerance to MTX	Concomitant growth hormone	DMARDS
De Sanctis 2013 J Rheumatol	Polyarticular course JIA	'Classic atherosclerotic risk factors'	NSAIDS
Alekseeva 2012 EULAR	JIA	NR	NR
Lahdenne 2003 Ann Rheum Dis	Severe polyarticular course JIA refractory to standard ttmt for ≥1 y	NR	DMARDS, NSAIDs
Kietz 2002 Ann Rheum Dis	Polyarticular course JIA	NR	DMARDS (ETN was added to current regimen), NSAIDs, corticosteroids
Calvo 2012 EULAR	< 4 y; Polyarticular JIA	NR	MTX, prednisolone
Robinson 2003 Clin Drug Invest	JIA	NR	NR
Otten 2011 Ann Rheum Dis	PsA	Other JIA types without psoriatic lesions	MTX, other DMARDs and systemic glucocorticoids
Opoka-Winiarska 2014 PReS	<5 y at start of therapy	NR	DMARDS, glucocorticosteroids
Hooper 2013 Ped Rheum	≤ 30 y; CTD: All subjects participating in ETN clinical trials: PMD: registry and post-marketing data	Recurrent tumours where primary tumour occurred prior to ETN exposure	NR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

† study informed the etanercept marketing authorisation

4.12.3 Baseline characteristics in the relevant observational studies

Baseline participant characteristics are summarised in Table 20 and Table 21

Table 21. All studies reported outcomes for a mixed JIA subtype population except for Windschall 2015 and Halbig & Horneff 2009, who reported separately on eoJIA, ERA and PsA as well as polyarthritis. In tables where large numbers of data points were not reported, 'NR' has been replaced with '-' for clarity of presentation.

Table 20 Baseline characteristics of participants in the studies

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Horneff 2014 ACR	1925	NR	NR	NR	NR	NR
Windschall 2015 Clin Rheumatol ERA	238	14.8	34.0	3.7 (2.9)	ERA: 238	Corticosteroids: 89 (37.4) MTX: 173 (72.7) Sulfasalazine: 37 (15.5)
eoJIA	315	11	75.9	6.3 (4.2)	eoJIA: 315	Corticosteroids: 181 (57.5) MTX: 213 (67.6) Sulfasalazine: 8 (2.5)
PsA	127	13.6	66.9	4.4 (3.6)	PsA: 127	Corticosteroids: 31 (24.4) MTX: 94 (74.0) Sulfasalazine: 5 (3.9)
Polyarthritis (RF+)	160	15.2	88.1	3.5 (3.2)	Polyarthritis (RF+): 160	NR
Polyarthritis (RF-)	534	12.3	76.0	4.5 (3.8)	Polyarthritis (RF-): 534	NR
Horneff 2012 EULAR	1470	NR	NR	NR	NR	NR
Geikowski 2014 J Rheumatol	863	NR	65.6	NR	Systemic JIA: 82 (9.5) Polyarticular (RF-): 269 (31.2) Polyarticular (RF+): 87 (10.1) Oligoarticular persistent: 60 (7) Oligoarticular extended: 155 (18) PsA: 57 (6.6) ERA: 124 (14.4)	Corticosteroids: 382 (44.3) MTX: 640 (74.2)
Papsdorf 2011 Rheum	787	12.5 (5)	64.5	5.12 (3.9)	Polyarthritis (RF -ve): 230 (9) Polyarthritis (Rf+ve): 80 (10) Persistent oligoarthritis: 38 (5) eoJIA: 127 (16) ERA: 112 (14) PsA: 59 (8)	MTX 567 (75) Azathioprine 45 (5.7) Chloroquine 12 (1.5) Ciclosporin 37 (4.7) Leflunomide 13 (1.7) Mycophenolate mofetil: 3 (0.4) Sulfasalazine 29 (3.7)
Davies 2013 ACR/ARHP	677	10.6	NR	4.6	Systemic: 15% Non-systemic: 85%	NR
Horneff 2009 Ann Rheum Dis Etanercept	100	13.1 (at start of ttmt) Median 14.9	58	5.5 (4.6)	Systemic onset: 8 (8) Polyarticular (RF-): 24 (24) Polyarticular (RF+): 3 (3) Oligoarticular persistent: 8 (8)	Prednisone (48%)

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Etanercept + MTX	504	12.5 (at start of ttmt) Median 12.9	67	4.9 (3.6)	eoJIA: 17 (17) ERA: 27 (27) PsA: 7 (7) Unclassified JIA: 6 (6) Systemic: 57 (11.3) Polyarticular (RF-): 158 (31.3) Polyarticular (RF+): 65 (12.9) Oligoarticular persistent: 23 (4.6) eoJIA: 73 (14.5) ERA: 66 (13.1) PsA: 41 (8.1) Unclassified: 21 (4.2)	Prednisone (62%)
Giannini 2009† Arth Rheum MTX	197	9	73.6	20.2 (30.7) months	Systemic: 13 (6.6) Polyarticular, including pts with eoJIA: 184 (93.4)	MTX: 197 (100.0) Etanercept: 1 (0.5) Hydroxychloroquine: 7 (3.6) Sulfasalazine: 3 (1.5) Cyclosporine: 0 (0) Prednisone: 36 (18.3) Intra-articular corticosteroids: 22(11.2)
Etanercept	103	10.8	80.6	58.1 (44.5) months	Systemic: 8 (7.8) Polyarticular, including pts with eoJIA: 95 (92.2)	MTX: 0 (0.0) Etanercept: 102 (99.0) Hydroxychloroquine: 7 (6.8) Sulfasalazine: 3 (2.9) Cyclosporine: 4 (3.9) Prednisone: 21 (20.4) Intra-articular corticosteroids: 13 (12.6)
Etanercept + MTX	294	10.1	72.8	40.7 (41.7) months	Systemic: 37 (12.6) Polyarticular including pts with eoJIA: 256 (87.1) Unknown: 1 (0.3)	MTX: 294 (100.0) Etanercept: 292 (99.3) Hydroxychloroquine: 15 (5.1) Sulfasalazine: 9 (3.1) Cyclosporine: 3 (1.0) Prednisone: 78 (26.5) Intra-articular corticosteroids: 46 (15.6)
Halbig & Horneff 2009 Rheumatol	437	12.1 (at start	70	5.1 (4.0)	NA	MTX (82.5)

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Int		of ttmt)				
All						
Polyarthritis (RF-)	138	12.3	76.8	5.7 (4.0)	NA	MTX(79.0)
Polyarthritis (RF+)	53	14.3	84.9	3.4 (3.0)	NA	MTX (92.9)
Persistent oligoarthritis	15	9.7	60.0	3.3 (3.5)	NA	MTX (93.3)
eoJIA	73	11.0	76.7	7.0 (4.0)	NA	MTX (78.4)
ERA	51	15.0	49.0	3.2 (2.4)	NA	MTX (83.0)
PSA	31	13.5	64.5	5.0 (4.5)	NA	MTX (76.7)
Kearsley-Fleet 2014 ACR	422	Median 11	73	Median 4 y (IQR: 2-7)	All	NR
Minden 2012 ACR/ARHP	386	23	NR	14	NR	NR
Horneff 2004 Ann Rheum Dis	322	NR	NR	NR	Systemic onset: 66 (21) Polyarticular (RF-): 94 (29) Polyarticular (RF+): 39 (12) Persistent oligoarticular: 10 (3) eoJIA: 54 (17) ERA: 26 (8) PsA: 17 (5) Unclassified JIA: 16 (5)	Oral corticosteroids: 199 (68) MTX: 235 (80)
Otten 2011 JAMA	262	Median 12.4	71	Median 3	Systemic: 46 (18) Polyarticular (RF-): 102 (39) Polyarticular (RF+): 23 (9) Oligoarticular persistent 5 (2) eoJIA: 57 (22) PsA: 17 (6) ERA: 12 (5)	MTX: 234 (89) Other DMARDs: 19 (7) Corticosteroids: (intra-articular) 8 (3); (systemic) 96 (37)
Tarkiainen 2014 Rheumatol	213 (ENT)	NR	NR	NR	NR	NR
Kearsley-Fleet 2013 ACR/ARHP	191	Median 11.0	65	Median 3.5 (range 1.7-7.1)	Systemic: 25 (13%) ERA: 14 (7%) EOJIA: 41 (22%) Oligoarthritis (persistent): 7 (4%) Polyarthritis (RF-): 68 (36%) Polyarthritis (RF+): 12 (6%) PsA: 8 (4%)	Corticosteroids: 71 (38)

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					Undifferentiated: 15 (8%)	
Zuber 2011 Med Sci Monit	188	10	65	52 mo (41.7)	Systemic: 28 (15) Polyarticular (RF-): 79 (42) Polyarticular (RF+): 13 (7) Oligoarticular extended: 20 (16) Oligoarticular persistent: 27 (14) ERA: 1 (0.5) PsA: 2 (1) Unclassified: 8 (4)	Numbers NR
Otten 2010 J Rheum	179	NR	70	NR	Systemic JIA: 42 Polyarticular (RF-): 71 Polyarticular (RF+): 13 eoJIA: 37 PsA: 10 ERA: 6	NR
Solari 2013 J Rheum	173	Median 9.9 (6.7-14.3)	71.1	Median 2.2 91.1-3.5)	Systemic: 27 (15.6) Persistent oligoarthritis: 12 (6.9) eoJIA: 70 (40.5) Polyarthritis (RF-ve): 38 (22) Polyarthritis (RF-ve): 7 (4) PsA: 6 (3.5) ERA: 12 (6.9) Undifferentiated: 1 (0.6)	MTX: 116 (67.1) Systemic corticosteroids: 24 (13.9) Intra-articular corticosteroids: 38 (22.0)
Prince 2009 Ann Rheum Dis	146	Median 11.2	69	Median 4.1	Systemic: 39 (27) Polyarticular (RF+): 11 (8) Polyarticular (RF-): 55 (38) eoJIA: 28 (19) ERA: 5 (3) PsA: 8 (5) Unclassified: 0 (0)	MTX: 113 (77) Other DMARDs: 13 (9) Glucocorticosteroids: 67 (46)
Gerloni 2008 Ann Rheum Dis	95	13.7	70.5	8.4 (8.3)	NR	NR
Sevcic 2011 Rheumatol	72	12.9	69	7.4 (3.9)	Systemic JIA: (8) Polyarticular (RF-): (50) Polyarticular (RF+): (8) Oligoarticular extended: (28) PsA: (2) ERA: (4)	NR

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Susic 2013 PReS	63	Median 15	73	NR	All polyarticular	NR
Quartier 2003 Arth Rheum	61	12.2	80.3	6.6	Systemic: 22 (36) Oligoarticular: 24 (39) Polyarticular: 13 (21)	MTX: 10 (16) Prednisone: 44 (72)
Klotsche et al 2014 Arth Care Res	61	10.6	65.6	3.4(3.2)	Systemic: 1(1.6) Polyarticular (RF+):9(14.8) Polyarticular (RF-):32(52.5) eoJIA:11(18.0) ERA:3(4.9) PsA:2(3.3) Persistent oligoarthritis :2(3.3) Other:1(1.6)	Glucocorticoids 35(57.4)
Loskutova 2014 PreS	32	NR	NR	NR	NR	NR
Prince 2010 Ann Rheum Dis	53	Median 11.9	62	Median 3.0 (IQR 1.6-5.1)	Systemic JIA: 14 (26) Polyarticular (RF-): 18 (34) Polyarticular (RF+): 5 (9) eoJIA: 11 (21) PsA: 3 (6) ERA: 2 (4)	MTX: 42 (79) Other DMARDs: 5 (9) Glucocorticoids systemic: 24 (45)
Prince 2011 Rheum	49	Median 11.6	59	Median 3.6 (IQR 2.0-5.1)	Systemic: 11 (22) Polyarticular (RF+): 4 (8) Polyarticular (RF-): 18 (37) eoJIA: 11 (22) ERA: 2 (4) PsA: 3 (6)	Systemic glucocorticoids: 23 (47) MTX: 39 (80) Other DMARDs: 5 (10)
Anink 2014 PreS	43	Median 22	NR	NR	NR	NR
Trachana 2012 EULAR	42	Median 10.6	76.2	Median 4.17	Polyarthritis 32	NR
Trachana 2013 Clin Rheumatol	41	Median 10.6	76	Median 4.17	Systemic; 7 Oligo-persistent: 1 eoJIA: 9 Polyarthritis (RF-): 19 Polyarthritis (RF+): 5 ERA: 0 PSA: 0	MTX (+ prednisolone): 36 (16/36) Cyclosporine A (+ prednisolone): 5 (3/5) Prednisolone: 16

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					Unclassified: 0	
Nielson 2008 Clin Exp Rheum	40	NR	62.5	Median 4.4	eoJIA: 7 (17.5) Polyarthritis: 21 (52.5) Systemic: 11 (27.5) PsA: 1 (2.5)	MTX: 26 (87) Corticosteroids: 18 (45)
Vojvodich 2007 J Rheumatol Etanercept – Prepubertal	20	8 y 2 mo	70	NR	Systemic: 4 Polyarticular: 8 JAS:1 Polyarticular (RF+): 0 Oligoarticular extended: 6 Psoriatic: 0 Other (IBD): 1	18
Etanercept – Pubertal	11	11 y 10 mo	72	NR	Systemic: 1 Polyarticular: 4 JAS: 0 Polyarticular (RF+): 3 Oligoarticular extended: 2 Psoriatic: 1 Other (IBD): 0	10
De Sanctis 2013 J Rheumatol	30	12.3	73	Median 2.50 (IQR 1.17-5.29)	Systemic: 2 Polyarticular:15 ERA:3 PsA:3 ExOA:7	NR
Alekseeva 2012 EULAR	25	NR	68	NR	Polyarthritis: 17 (68) Oligoarthritis: 8 (32)	NR
Lahdenne 2003 Ann Rheum Dis	10	NR	NR	NR	eoJIA: 2 (20.0) Polyarthritis: 6 (60.0) Systemic: 2 (20.0)	NR
Kietz 2002 Ann Rheum Dis	22	13.9	86.4	6.3	Polyarticular: 22 (100)	MTX: 21 (95.5) Hydroxychloroquine: 13 (59.1) Sulfasalazine: 1 (4.6) Corticosteroids: 5 (22.7)
Calvo 2012 EULAR	21	NR	66.7	NR	All polyarticular	NR
Robinson 2003 Clin Drug Invest	21	6.9		63.0 mo (61.6)	Polyarticular: 13 (62)	NR

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					Systemic: 8 (38)	
Otten 2011 Ann Rheum Dis	18	NR	72	Median 24 mo (2-55)	PsA: 18 (100)	Systemic glucocorticoids: 4 (22) MTX: 15 (83) Other DMARDs: 3 (17)
Opoka-Winiarska 2014 PreS	13	NR	NR	2.46 (1.2 mo)	NR	NR
Hooper 2013 Ped Rheum	NR	NR	NR	NR	NR	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Mean (SD) unless otherwise stated; † study informed the etanercept marketing authorisation

Table 21 Baseline disease activity, observational studies

Study ID	PGA disease activity		PGA wellbeing		No. active joints		No. joints with LOM		CHAQ score		VAS pain
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Horneff 2014 ACR	-	-	-	-	-	-	-	-	-	-	-
Windschall 2015 Clin Rheumatol ERA	54.2** (27.4)	-	51.0** (26.4)	-	4.3 (5.7)	-	4.4 (5.1)	-	0.6 (0.6)	-	-
eoJIA	52.0** (26.4)	-	46.6** (28.3)	-	5.7 (5.1)	-	6.3 (5.4)	-	0.6 (0.6)	-	-
PsA	47.5** (26.6)	-	45.0** (26.9)	-	5.7 (5.4)	-	5.5 (6.3)	-	0.7 (0.6)	-	-
Polyarthritis (RF+)	57.2** (28.0)	-	45.7** (28.5)	-	10.6 (10.0)	-	10.3 (10.2)	-	0.8 (0.7)	-	-
Polyarthritis (RF-)	54.2** (27.4)	-	44.8** (27.8)	-	10.8 (11.1)	-	12.1 (12.5)	-	0.8 (0.7)	-	-
Horneff 2012 EULAR	-	-	-	-	-	-	-	-	-	-	-
Geikowski 2014 J Rheumatol	-	58.0** (IQR 36.0-80.0)	-	50.0** (IQR 30.0-73.0)	-	5 (IQR 2-11)	-	5 (IQR 2-11)	-	0.6 (IQR 0.25-1.25)	Median 41.0 (IQR 19.5-65.5)
Papsdorf 2011 Rheumatology	6 (4-8)*	-	5 (3-7)*	-	9.2 (9.4)	-	-	-	0.86 (0.7)	-	-
Davies 2013 ACR/ARHP	-	-	-	-	-	-	-	-	-	-	-
Horneff 2009 Ann Rheum Dis Etanercept	5.8* (2.6)	-	5.1* (2.7)	-	6.8 (8.2)	-	8.4 (10.70)	-	0.75 (0.63)	-	-
Etanercept + MTX	6.2* (2.6)	-	5.6* (2.60)	-	10.0 (9.7)	-	10.8 (11.1)	-	0.9 (0.72)	-	-
Giannini 2009† Arth Rheum MTX	-	4	-	-	-	6	-	-	-	-	-
Etanercept	-	3	-	-	-	4	-	-	-	-	-
Etanercept + MTX	-	4	-	-	-	6	-	-	-	-	-

Study ID	PGA disease activity		PGA wellbeing		No. active joints		No. joints with LOM		CHAQ score		VAS pain
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Halbig & Horneff 2009 Rheumatol Int All	6.5* (2.4)	-	5.6* (2.7)	-	10 (9)	-	-	-	0.9 (0.7)	-	-
Polyarthritis (RF-)	6.5* (2.3)	-	5.5* (2.7)	-	13 (10)	-	-	-	1.0 (0.8)	-	-
Polyarthritis (RF+)	6.3* (2.7)	-	5.5* (2.6)	-	13 (9)	-	-	-	1.0 (0.7)	-	-
Persistent oligoarthritis	4.7* (3.0)	-	4.5* (3.3)	-	3 (2)	-	-	-	0.3 (0.4)	-	-
eoJIA	6.6* (2.2)	-	5.4* (2.8)	-	8 (6)	-	-	-	0.8 (0.6)	-	-
ERA	6.1* (2.3)	-	5.8* (2.6)	-	5 (5)	-	-	-	0.7 (0.6)	-	-
PSA	4.9* (2.6)	-	5.5* (2.1)	-	6 (4)	-	-	-	0.6 (0.5)	-	-
Kearsley-Fleet 2014 ACR	-	-	-	-	-	-	-	-	-	-	-
Minden 2012 ACR/ARHP	-	-	-	-	-	-	-	-	-	-	-
Horneff 2004 Ann Rheum Dis	67** (25)	-	56** (27)	-	10.2 (9.5)	-	11.8 (11.8)	-	1.0 (0.8)	-	-
Otten 2011 JAMA	-	63** (IQR 45-75)	-	53** (IQR 29-75)	-	10 (IQR 6-18)	-	7 (IQR 4-13)	-	1.5 (IQR 1.0-2.1)	Median 57** (IQR 29-76)
Tarkiainen 2014 Rheumatol	-	-	-	-	-	-	-	-	-	-	-
Kearsley-Fleet 2013 ACR/ARHP	-	4 (IQR 2-6)	-	4.5 (IQR 2-6.9)	-	5.5 (IQR 3-10)	-	5 (IQR 2-10)		1.1 (IQR 0.6-1.9)	-
Zuber 2011 Med Sci Monit	7.1* (1.7)	-	7.3* (1.9)	-	10.0 (9.9)	-	7.9 (9.0)	-	1.4 (0.7)	-	-
Otten 2010 J Rheum	-	-	-	-	-	-	-	-	-	-	-

Study ID	PGA disease activity		PGA wellbeing		No. active joints		No. joints with LOM		CHAQ score		VAS pain
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Solari 2013 J Rheum	-	6 (IQR 4-8)*	-	5 (IQR 3-7)*	-	5 (IQR 2.5-10)	-	-	-	-	5 (IQR 3.1-7.2)*
Prince 2009 Ann Rheum Dis	-	68 (IQR 53-78)**	-	54 (IQR 27-76)	-	12 (IQR 7-22)	-	9 (IQR 6-14)	-	2.0 (IQR 1.2-2.4)	-
Gerloni 2008 Ann Rheum Dis	-	-	-	-	-	-	-	-	-	-	-
Sevcic 2011 Rheumatol	60.6** (14.9)	-	62.0** (20.2)	-	13.3 (11.1)	-	16.5 (12.7)	-	1.146 (0.611)	-	-
Susic 2013 PReS	-	-	-	-	-	-	-	-	-	-	-
Quartier 2003 Arth Rheum	50	-	46	-	16	-	26	-	1.81	-	-
Klotsche et al 2014 Arth Care Res	56.9** (19.5)	-	38.3** (25.5)	-	7.2(6.2)	-	-	-	0.7 (0.6)	-	Mean 36.4** (27.1)
Loskutova 2014 PreS	-	-	-	-	-	-	-	-	-	-	-
Prince 2010 Ann Rheum Dis	66.0** (SE 2.5)	-	51.6** (SE 3.3)	-	16.8 (SE 1.0)	-	11.4 (SE 0.8)	-	1.73 (SE 0.1) (CHAQ DI)	-	Mean 55.6** (SE 3.3)
Prince 2011 Rheum	66.0** (SE 2.5)	-	50.8** (SE 3.4)	-	16.7 (SE 1.0)	-	10.9 (SE 0.7)	-	1.70 (SE 0.1)	-	Mean 53.8** (SE 3.2)
Anink 2014 PreS	-	-	-	-	-	-	-	-	-	-	-
Trachana 2012 EULAR	-	-	-	-	-	-	-	-	-	-	-
Trachana 2013 Clin Rheumatol	-	-	-	-	-	-	-	-	-	-	-
Nielson 2008 Clin Exp Rheum	-	6.5*	-	6.0*	-	9.5	-	8.0	-	1.4	Median 5.7*
Vojvodich 2007 J Rheumatol	-	-	-	-	-	-	-	-	-	-	-

Etanercept – All

Study ID	PGA disease activity		PGA wellbeing		No. active joints		No. joints with LOM		CHAQ score		VAS pain
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Etanercept – Pubertal	-	-	-	-	-	-	-	-	-	-	-
De Sanctis 2013 J Rheumatol	-	-	-	-	-	8.0 (IQR 6-18.2)	-	-	-	-	-
Alekseeva 2012 EULAR	-	-	-	-	-	-	-	-	-	-	-
Lahdenne 2003 Ann Rheum Dis	-	35**	-	36**	-	10	-	-	-	1.19	-
Kietz 2002 Ann Rheum Dis	-	-	-	-	24	-	-	-	-	-	-
Calvo 2012 EULAR	71.5** (11.5)	-	70** (14.1)	-	12 (4.3)	-	3.5 (5.1)	-	1.2 (0.3)	-	-
Robinson 2003 Clin Drug Invest	-	-	-	-	-	-	8.1 (6.4)	-	-	-	-
Otten 2011 Ann Rheum Dis	-	-	-	-	-	-	-	-	-	-	-
Opoka-Winiarska 2014 PreS	-	-	-	-	-	-	-	-	-	-	-
Hooper 2013 Ped Rheum	-	-	-	-	-	-	-	-	-	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- denotes 'not reported'. PGA, physician (disease activity) or parent/patient (wellbeing) global assessment; LOM, limitation of motion; CHAQ, Childhood Health Assessment Questionnaire; VAS, visual analogue scale; † study informed the etanercept marketing authorisation

Baseline disease activity (PGA) for the mixed JIA populations, where reported, ranged from 5.4 in Windschall 2015 to 7.1 in Calvo 2012. This is comparable to the baseline activity evidenced in the interventional studies. PGA disease activity was somewhat lower in eoJIA, ERA and PsA.

Ethnicity was only reported in Giannini 2009 (approx. 75% white ethnicity) and Tachana 2013 (all Caucasian). Data on prior biological use was not generally reported, nor was information on height and weight. JADAS/DAS score was rarely reported; for those few studies that provided JADAS/DAS outcomes, baseline values are presented alongside the outcome.

4.12.4 Quality assessment of the relevant observational studies

A large proportion of the studies were publications from large national registries and as such are representative of real-world practice. No studies were assessed to be of poor quality. The summary of the quality assessment for observational/registry studies is presented in Appendix 3.

4.12.5 Clinical effectiveness results of the observational studies

Data were extracted at the following time points, where reported: 3 months, 1 year, and longest reported follow-up.

Summary of efficacy from the observational studies

Etanercept has been extensively studied in patients with JIA for over 15 years involving over 10,000 patients within the real world setting. Efficacy results in terms of improvements in response rate and reduction in disease flare are consistent from real-world evidence, including long-term follow-up with that observed in RCT

- The largest series to report JIA ACR response was Geikowski 2014 (863 patients): 81.9% had achieved JIA ACR30 at 6 months, 55.2% had achieved JIA ACR 70 and 31.3% had achieved JIA ACR 90.
- Kearsley-Fleet 2014 reported data on 407 patients from the UK: at 12 months, response rates were 75%, 70%, 59%, and 41% for JIA ACR 30, 50, 70 and 90 respectively.

[redacted]

- Sustained efficacy was reported by Halbig 2009 in the largest cohort that reported results at 24 months: of 114 patients, 96.5%, 93.8% and 90.3% achieved a PedACR score of 30, 50 and 70, respectively.
- High rates of inactive disease/remission were seen in most studies reporting these outcomes. For example, in 173 patients treated for a median of 2.2 years, 87 (50.3%) achieved inactive disease after a median of 0.6 years, and the

probability of achieving inactive disease after 6, 12 and 24 months of therapy was 24%, 46% and 57%, respectively (Solari 2013). Of 787 patients from the German etanercept registry, 47.6% met the criteria for inactive disease (Wallace criteria) and 26.6% achieved remission on medication at last observation (Papsdorf 2011).

JIA ACR response

Data on JIA ACR response were less frequently reported in observational/registry studies than in the interventional studies (Table 22**Error! Reference source not found.**). Reporting at longer follow-up times is difficult to interpret as most papers only report results for patients who are still on-treatment; reasons given for discontinuation in these real-world studies included intolerance and lack of efficacy, but also disease remission.

- The largest series to report JIA ACR results was Geikowski 2014 (863 patients): 81.9% had achieved JIA ACR30 at 6 months, 55.2% had achieved JIA ACR 70 and 31.3% had achieved JIA ACR 90.
- Kearsley-Fleet 2014 reported data on 407 patients from the UK: at 12 months, response rates were 75%, 70%, 59%, and 41% for JIA ACR 30, 50, 70 and 90 respectively.
- Sustained efficacy was reported by Halbig 2009 in the largest cohort that reported results at 24 months: of 114 patients, response rates were 96.5%, 93.8% and 90.3%.

Table 22 JIA ACR response, relevant observational studies

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Horneff 2014 ACR	1925	NR	NR	NR	NR	NR
Windschall 2015 Clin Rheumatol ERA	238	14.8	34.0	3.7 (2.9)	ERA: 238	Corticosteroids: 89 (37.4) MTX: 173 (72.7) Sulfasalazine: 37 (15.5)
eoJIA	315	11	75.9	6.3 (4.2)	eoJIA: 315	Corticosteroids: 181 (57.5) MTX: 213 (67.6) Sulfasalazine: 8 (2.5)
PsA	127	13.6	66.9	4.4 (3.6)	PsA: 127	Corticosteroids: 31 (24.4) MTX: 94 (74.0) Sulfasalazine: 5 (3.9)
Polyarthritis (RF+)	160	15.2	88.1	3.5 (3.2)	Polyarthritis (RF+): 160	NR
Polyarthritis (RF-)	534	12.3	76.0	4.5 (3.8)	Polyarthritis (RF-): 534	NR
Horneff 2012 EULAR	1470	NR	NR	NR	NR	NR
Geikowski 2014 J Rheumatol	863	NR	65.6	NR	Systemic JIA: 82 (9.5) Polyarticular (RF-): 269(31.2) Polyarticular (RF+): 87 (10.1) Oligoarticular persistent: 60 (7) Oligoarticular extended: 155 (18) PsA: 57 (6.6) ERA: 124 (14.4)	Corticosteroids: 382 (44.3) MTX: 640 (74.2)
Papsdorf 2011 Rheum	787	12.5 (5)	64.5	5.12 (3.9)	Polyarthritis (RF -ve): 230 (9) Polyarthritis (Rf+ve): 80 (10) Persistent oligoarthritis: 38 (5) eoJIA: 127 (16) ERA: 112 (14) PsA: 59 (8)	MTX 567 (75) Azathioprine 45 (5.7) Chloroquine 12 (1.5) Ciclosporin 37 (4.7) Leflunamide 13 (1.7) Mycophenolate mofetil: 3 (0.4) Sulfasalazine 29 (3.7)
Davies 2013 ACR/ARHP	677	10.6	NR	4.6	Systemic: 15% Non-systemic: 85%	NR
Horneff 2009 Ann Rheum Dis Etanercept	100	13.1 (at start of ttmt) Median 14.9	58	5.5 (4.6)	Systemic onset: 8 (8) Polyarticular (RF-): 24 (24) Polyarticular (RF+): 3 (3)	Prednisone (48%)

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Etanercept + MTX	504	12.5 (at start of ttmt) Median 12.9	67	4.9 (3.6)	Oligoarticular persistent: 8 (8) eoJIA: 17 (17) ERA: 27 (27) PsA: 7 (7) Unclassified JIA: 6 (6) Systemic: 57 (11.3) Polyarticular (RF-): 158 (31.3) Polyarticular (RF+): 65 (12.9) Oligoarticular persistent: 23 (4.6) eoJIA: 73 (14.5) ERA: 66 (13.1) PsA: 41 (8.1) Unclassified: 21 (4.2)	Prednisone (62%)
Giannini 2009† Arth Rheum MTX	197	9	73.6	20.2 (30.7) months	Systemic: 13 (6.6) Polyarticular, including pts with eoJIA: 184 (93.4)	MTX: 197 (100.0) Etanercept: 1 (0.5) Hydroxychloroquine: 7 (3.6) Sulfasalazine: 3 (1.5) Cyclosporine: 0 (0) Prednisone: 36 (18.3) Intra-articular corticosteroids: 22(11.2)
Etanercept	103	10.8	80.6	58.1 (44.5) months	Systemic: 8 (7.8) Polyarticular, including pts with eoJIA: 95 (92.2)	MTX: 0 (0.0) Etanercept: 102 (99.0) Hydroxychloroquine: 7 (6.8) Sulfasalazine: 3 (2.9) Cyclosporine: 4 (3.9) Prednisone: 21 (20.4) Intra-articular corticosteroids: 13 (12.6)
Etanercept + MTX	294	10.1	72.8	40.7 (41.7) months	Systemic: 37 (12.6) Polyarticular including pts with eoJIA: 256 (87.1) Unknown: 1 (0.3)	MTX: 294 (100.0) Etanercept: 292 (99.3) Hydroxychloroquine: 15 (5.1) Sulfasalazine: 9 (3.1) Cyclosporine: 3 (1.0) Prednisone: 78 (26.5) Intra-articular

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
						corticosteroids: 46 (15.6)
Halbig & Horneff 2009 Rheumatol Int	437	12.1 (at start of ttmt)	70	5.1 (4.0)	NA	MTX (82.5)
All						
Polyarthritis (RF-)	138	12.3	76.8	5.7 (4.0)	NA	MTX(79.0)
Polyarthritis (RF+)	53	14.3	84.9	3.4 (3.0)	NA	MTX (92.9)
Persistent oligoarthritis	15	9.7	60.0	3.3 (3.5)	NA	MTX (93.3)
eoJIA	73	11.0	76.7	7.0 (4.0)	NA	MTX (78.4)
ERA	51	15.0	49.0	3.2 (2.4)	NA	MTX (83.0)
PSA	31	13.5	64.5	5.0 (4.5)	NA	MTX (76.7)
Kearsley-Fleet 2014 ACR	422	Median 11	73	Median 4 y (IQR: 2-7)	All	NR
Minden 2012 ACR/ARHP	386	23	NR	14	NR	NR
Horneff 2004 Ann Rheum Dis	322	NR	NR	NR	Systemic onset: 66 (21) Polyarticular (RF-): 94 (29) Polyarticular (RF+): 39 (12) Persistent oligoarticular: 10 (3) eoJIA: 54 (17) ERA: 26 (8) PsA: 17 (5) Unclassified JIA: 16 (5)	Oral corticosteroids: 199 (68) MTX: 235 (80)
Otten 2011 JAMA	262	Median 12.4	71	Median 3	Systemic: 46 (18) Polyarticular (RF-): 102 (39) Polyarticular (RF+): 23 (9) Oligoarticular persistent 5 (2) eoJIA: 57 (22) PsA: 17 (6) ERA: 12 (5)	MTX: 234 (89) Other DMARDs: 19 (7) Corticosteroids: (intra-articular) 8 (3); (systemic) 96 (37)
Tarkiainen 2014 Rheumatol	213 (ENT)	NR	NR	NR	NR	NR
Kearsley-Fleet 2013 ACR/ARHP	191	Median 11.0	65	Median 3.5 (range 1.7-7.1)	Systemic: 25 (13%) ERA: 14 (7%) EOJIA: 41 (22%) Oligoarthritis (persistent): 7 (4%) Polyarthritis (RF-): 68 (36%)	Corticosteroids: 71 (38)

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					Polyarthritis (RF+): 12 (6%) PsA: 8 (4%) Undifferentiated: 15 (8%)	
Zuber 2011 Med Sci Monit	188	10	65	52 mo (41.7)	Systemic: 28 (15) Polyarticular (RF-): 79 (42) Polyarticular (RF+): 13 (7) Oligoarticular extended: 20 (16) Oligoarticular persistent: 27 (14) ERA: 1 (0.5) PsA: 2 (1) Unclassified: 8 (4)	Numbers NR
Otten 2010 J Rheum	179	NR	70	NR	Systemic JIA: 42 Polyarticular (RF-): 71 Polyarticular (RF+): 13 eoJIA: 37 PsA: 10 ERA: 6	NR
Solari 2013 J Rheum	173	Median 9.9 (6.7-14.3)	71.1	Median 2.2 91.1-3.5)	Systemic: 27 (15.6) Persistent oligoarthritis: 12 (6.9) eoJIA: 70 (40.5) Polyarthritis (RF-ve): 38 (22) Polyarthritis (RF-ve): 7 (4) PsA: 6 (3.5) ERA: 12 (6.9) Undifferentiated: 1 (0.6)	MTX: 116 (67.1) Systemic corticosteroids: 24 (13.9) Intra-articular corticosteroids: 38 (22.0)
Prince 2009 Ann Rheum Dis	146	Median 11.2	69	Median 4.1	Systemic: 39 (27) Polyarticular (RF+): 11 (8) Polyarticular (RF-): 55 (38) eoJIA: 28 (19) ERA: 5 (3) PsA: 8 (5) Unclassified: 0 (0)	MTX: 113 (77) Other DMARDs: 13 (9) Glucocorticosteroids: 67 (46)
Gerloni 2008 Ann Rheum Dis	95	13.7	70.5	8.4 (8.3)	NR	NR
Sevcic 2011 Rheumatol	72	12.9	69	7.4 (3.9)	Systemic JIA: (8) Polyarticular (RF-): (50) Polyarticular (RF+): (8) Oligoarticular extended: (28) PsA: (2)	NR

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					ERA: (4)	
Susic 2013 PReS	63	Median 15	73	NR	All polyarticular	NR
Quartier 2003 Arth Rheum	61	12.2	80.3	6.6	Systemic: 22 (36) Oligoarticular: 24 (39) Polyarticular: 13 (21)	MTX: 10 (16) Prednisone: 44 (72)
Klotsche et al 2014 Arth Care Res	61	10.6	65.6	3.4(3.2)	Systemic: 1(1.6) Polyarticular (RF+):9(14.8) Polyarticular (RF-):32(52.5) eoJIA:11(18.0) ERA:3(4.9) PsA:2(3.3) Persistent oligoarthritis :2(3.3) Other:1(1.6)	Glucocorticoids 35(57.4)
Loskutova 2014 PreS	32	NR	NR	NR	NR	NR
Prince 2010 Ann Rheum Dis	53	Median 11.9	62	Median 3.0 (IQR 1.6-5.1)	Systemic JIA: 14 (26) Polyarticular (RF-): 18 (34) Polyarticular (RF+): 5 (9) eoJIA: 11 (21) PsA: 3 (6) ERA: 2 (4)	MTX: 42 (79) Other DMARDs: 5 (9) Glucocorticoids systemic: 24 (45)
Prince 2011 Rheum	49	Median 11.6	59	Median 3.6 (IQR 2.0-5.1)	Systemic: 11 (22) Polyarticular (RF+): 4 (8) Polyarticular (RF-): 18 (37) eoJIA: 11 (22) ERA: 2 (4) PsA: 3 (6)	Systemic glucocorticoids: 23 (47) MTX: 39 (80) Other DMARDs: 5 (10)
Anink 2014 PreS	43	Median 22	NR	NR	NR	NR
Trachana 2012 EULAR	42	Median 10.6	76.2	Median 4.17	Polyarthritis 32	NR
Trachana 2013 Clin Rheumatol	41	Median 10.6	76	Median 4.17	Systemic; 7 Oligo-persistent: 1 eoJIA: 9 Polyarthritis (RF-): 19 Polyarthritis (RF+): 5 ERA: 0	MTX (+ prednisolone): 36 (16/36) Cyclosporine A (+ prednisolone): 5 (3/5) Prednisolone: 16

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
					PSA: 0 Unclassified: 0	
Nielson 2008 Clin Exp Rheum	40	NR	62.5	Median 4.4	eoJIA: 7 (17.5) Polyarthritis: 21 (52.5) Systemic: 11 (27.5) PsA: 1 (2.5)	MTX: 26 (87) Corticosteroids: 18 (45)
Vojvodich 2007 J Rheumatol Etanercept – Prepubertal	20	8 y 2 mo	70	NR	Systemic: 4 Polyarticular:8 JAS:1 Polyarticular (RF+): 0 Oligoarticular extended: 6 Psoriatic: 0 Other (IBD): 1	18
Etanercept – Pubertal	11	11 y 10 mo	72	NR	Systemic: 1 Polyarticular: 4 JAS:0 Polyarticular (RF+): 3 Oligoarticular extended: 2 Psoriatic: 1 Other (IBD): 0	10
De Sanctis 2013 J Rheumatol	30	12.3	73	Median 2.50 (IQR 1.17-5.29)	Systemic: 2 Polyarticular:15 ERA:3 PsA:3 ExOA:7	NR
Alekseeva 2012 EULAR	25	NR	68	NR	Polyarthritis: 17 (68) Oligoarthritis: 8 (32)	NR
Lahdenne 2003 Ann Rheum Dis	10	NR	NR	NR	eoJIA: 2 (20.0) Polyarthritis: 6 (60.0) Systemic: 2 (20.0)	NR
Kietz 2002 Ann Rheum Dis	22	13.9	86.4	6.3	Polyarticular: 22 (100)	MTX: 21 (95.5) Hydroxychloroquine: 13 (59.1) Sulfasalazine: 1 (4.6) Corticosteroids: 5 (22.7)
Calvo 2012 EULAR	21	NR	66.7	NR	All polyarticular	NR

Study ID and arm/reporting group	No. of patients in analysis group	Age, y*	% female	JIA duration, y*	JIA subtype, n (%)	Concomitant medication use at study start, n (%)
Robinson 2003 Clin Drug Invest	21	6.9		63.0 mo (61.6)	Polyarticular: 13 (62) Systemic: 8 (38)	NR
Otten 2011 Ann Rheum Dis	18	NR	72	Median 24 mo (2-55)	PsA: 18 (100)	Systemic glucocorticoids: 4 (22) MTX: 15 (83) Other DMARDs: 3 (17)
Opoka-Winiarska 2014 PreS	13	NR	NR	2.46 (1.2 mo)	NR	NR
Hooper 2013 Ped Rheum	NR	NR	NR	NR	NR	NR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Denotes 'not reported'; † study informed the etanercept marketing authorisation

ACR core set outcomes

Not all studies reported outcomes for individual ACR core set items. Results are summarised in Table 23. For PGA disease activity, where results are reported they show substantial percentage improvements from baseline, or (where reported as absolute values), low scores in the range of 1 to 2. There is a similar trend for the other outcomes. No data were reported from the UK studies. Few studies reported data for individual subtypes. Halbig & Horneff 2009 showed consistently low CHAQ scores for each type at 12 and 24 months.

Table 23 Outcomes for ACR core set components, observational studies

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Horneff 2014 ACR		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Windschall 2015 Clin Rheumatol	-	-	-	-65	-	-	-	-65	-	1.0 (2.4)	-	-	-	-	-	-52	-	-	-	-61	-	-
Last obs. ERA																						
Last obs. eoJIA		-	-	-56	-	-	-	-56	-	1.9 (3.5)	-	-	-	-	-	-50		-	-	-62	-	-
Last obs. PsA		-	-	-58	-	-	-	-52	-	1.8 (3.4)	-	-	-	-	-	-40		-	-	-48	-	-
Last obs. Poly. RF+		-	-	-		-	-	-	-	3.7 (6.9)	-	-		-	-	-		-	-	-	-	-
Last obs. Poly RF-		-	-	-		-	-	-	-	3.6 (6.9)	-	-		-	-	-		-	-	-	-	-
24 mo, each subtype		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Horneff 2012 EULAR		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
3 mo																						
12 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
24 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Geikowski 2014 J Rheumatol		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
6 mo																						
Papsdorf Rheum 2011	787	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Davies 2013 ACR/ARHP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Horneff 2009 Ann Rheum Dis Etanercept 12 mo	55	1.9* (2.1)	-	-	55	1.8* (1.9)	-	-	55	1.9 (3.8)	-	-	55	4.6 (6.4)	-	-	55	0.32 (0.44)	-	-	Mean (SD) 10 (10)	Mean (SD) 10 (46)
Etanercept + MTX 12 mo	376	1.7* (2.2)	-	-	376	1.5* (2.0)	-	-	376	2.3 (4.6)	-	-	376	5.0 (7.8)	-	-	376	0.38 (0.57)	-	-	Mean (SD) 14 (15)	Mean (SD) 8 (16)
Giannini 2009† Arth Rheum MTX 3 mo	175	-	2	-	175	-	-	-	175	-	-	-	-	-	-	-		-	-	-	-	-
12 mo	124	-	1	-	124	-	-	-	124	0	-	-	-	-	-	-	-	-	-	-	-	-
36 mo	67	-	1	-	67	-	-	-	67	0	-	-	-	-	-	-	-	-	-	-	-	-
Etanercept 3 mo	95	-	2	-	95	-	-	-	95	-	-	-	-	-	-	-	-	-	-	-	-	-
12 mo	68	-	1	-	68	-	-	-	68	1	-	-	-	-	-	-	-	-	-	-	-	-
36 mo	42	-	1	-	42	-	-	-	42	0	-	-	-	-	-	-	-	-	-	-	-	-
Etanercept + MTX 3 mo	270	-	2	-	270	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12 mo	200	-	1	-	200	-	-	-	200	2	-	-	-	-	-	-	-	-	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
36 mo	115	-	1	-	115	-	-	-	115	0	-	-	-	-	-	-	-	-	-	-	-	-
Halbig & Horneff 2009 Rheumatol Int 12 mo all	114	1.5* (1.9)	-	-	114	1.4* (1.5)	-	-	114	2 (5)	-	-	114	-	-	-	114	0.37 (0.51)	-	-	Mean (SD) 14 (14)	Mean (SD) 7.9 (14.8)
12 mo poly –ve		-	-	-		-	-	-		-	-	-		-	-	-	-	0.62 (0.65)	-	-	-	-
12 mo poly +ve		-	-	-		-	-	-		-	-	-		-	-	-	-	0.36 (0.47)	-	-	-	-
12 mo persistent oligo		-	-	-		-	-	-		-	-	-		-	-	-	-	0.05 (0.11)	-	-	-	-
12 mo eoJIA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.21 (0.33)	-	-	-	-
12 mo ERA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.09 (0.13)	-	-	-	-
12 mo PsA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.15 (0.34)	-	-	-	-
24 mo all	114	1.5 (2)	-	-	114	1.4 (1.7)	-	-	114	3 (6)	-	-	114	-	-	-	114	0.34 (0.52)	-	-	Mean (SD) 14 (12)	Mean (SD) 8.8 (15.7)
24 mo poly –ve		-	-	-		-	-	-		-	-	-		-	-	-	-	0.57 (0.67)	-	-	-	-
24 mo poly +ve		-	-	-		-	-	-		-	-	-		-	-	-	-	0.46 (0.6)	-	-	-	-
24 mo persistent		-	-	-		-	-	-		-	-	-		-	-	-	-	0.03 (0.06)	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score				
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
oligo																						
24 mo eoJIA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.21 (0.35)	-	-	-	-
24 mo ERA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.13 (0.27)	-	-	-	-
24 mo PsA		-	-	-		-	-	-		-	-	-		-	-	-	-	0.08 (0.12)	-	-	-	-
Kearsley-Fleet 2014 ACR 1 yr		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Minden ACR/ARHP 2012		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Horneff 2004 Ann Rheum Dis 3 mo	225	26** (26)	-	-	225	19** (19)	-	-	225	3.8 (6.3)	-	-	225	7.2 (10.6)	-	-	225	-	-	-	Mean (SD) 19 (21)	-
12 mo	152	20** (23)	-	-	152	16** (18)	-	-	152	3.1 (4.6)	-	-	152	7.1 (8.9)	-	-	152	0.4 (0.6)	-	-	Mean (SD) 17 (17)	-
30 mo	42	20** (24)	-	-	42	12** (16)	-	-	42	4.6 (6.9)	-	-	42	10.0 (10.7)	-	-	42	0.5 (0.7)	-	-	Mean (SD) 19 (17)	-
Otten 2011 JAMA 15 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
87 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Tarkiainen 2014 Rheumatol		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Kearsley-Fleet 2013 ACR/ARHP 1 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
2 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Zuber 2011 Med Sci Monit 3 mo	172	4.2 (2.1)	-	-	172	3.8 (2.2)	-	-	172	4.9 (8.6)	-	-	172	4.6 (8.1)	-	-	172	0.7 (0.7)	-	-	Mean (SD) 13 (12.3)	Mean (SD) 8.0 (19)
12 mo	146	2.9 (1.8)	-	-	146	2.7 (2.0)	-	-	146	2.5 (4.1)	-	-	146	3.1 (4.8)	-	-	146	0.5 (0.6)	-	-	Mean (SD) 12 (9.4)	Mean (SD) 4 (11.3)
48 mo	39	2.4 (1.6)	-	-	39	2.0 (1.6)	-	-	39	2.6 (3.8)	-	-	39	3.2 (4.7)	-	-	39	0.3 (0.4)	-	-	Mean (SD) 10 (6.6)	Mean (SD) 4 (6.9)
Otten 2010 J Rheum 3 mo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Solari 2013 J Rheum	173	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prince 2009 Ann Rheum Dis 3 mo, all	142	-	15** (IQR 8-29)	-	142	-	10** (IQR 2-40)	-	142	-	2 (IQR 0-6)	-	142	-	5 (IQR 2-9)	-	142	-	1.0 (IQR 0.4-1.8)	-	Median 10 (IQR 5-20)	-
15 mo, all	97	-	10** (IQR 2-	-	97	-	5** (IQR 0-	-	97	-	1 (IQR 0-	-	95	-	2 (IQR 1-	-	97	-	0.4 (IQR 0-	-	Median 8 (IQR	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
75 mo, all	5	-	23) 10** (IQR 5-35)	-	5	-	26) 30** (IQR 6-58)	-	5	-	3) 1 (IQR 0-5)	-	5	-	6) 3 (IQR 2-7)	-	5	-	1.0) 0.9 (IQR 0.5-1.6)	-	5-17) Median 16 (IQR 5-33	-
3 mo, each type		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
15 mo, each type		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
75 mo, each type		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Gerloni 2008 Ann Rheum Dis		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Sevcic 2011 Rheumatol 3 mo	71	19.7 (12.4)	-	-	71	19.8 (18.8)	-	-	71	1.5 (1.9)	-	-	71	8.5 (8.0)	-	-	71	0.624 (0.486)	-	-	Mean (SD) 17.2 (15.2)	-
12 mo	61	14.7 (11.3)	-	-	61	17.0 (14.7)	-	-	61	1.4 (2.5)	-	-	61	7.1 (7.0)	-	-	61	0.480 (0.415)	-	-	Mean (SD) 13.3 (9.1)	-
Susic 2013 PReS 12 mo	-	-	-	-80	-	-	-	-56	-	-	-	-80	-	-	-	-68	-	-	-	-60	-	-
Quartier 2003 Arth Rheum																						
3 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
12 mo		-		-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Klotsche 2014 Arth Care Res 3 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Loskutova 2014 PreS		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
24 mo																						
Prince 2010 Ann Rheum Dis 3 mo	53	**16.7 (SE 2.5)	-	-	53	18.5 (SE 3.3)	-	-	53	4.47 (SE 1.0)	-	-	53	5.93 (SE 0.8)	-	-	53	1.07 (SE 0.1)	-	-	Mean 12.2 (SE 2.0)	-
27 mo	53	**11.9 (SE 3.0)	-	-	53	15.8 (SE 4.0)	-	-	53	2.34 (SE 1.2)	-	-	53	3.13 (SE 0.9)	-	-	53	0.54 (SE 0.1)	-	-	Mean 11.3 (SE 2.5)	-
Prince 2011 3 mo	49	14.9** (SE 2.5)	-	-	49	15.7** (SE 3.4)	-	-	49	3.99 (SE 1.0)	-	-	49	5.40 (SE 0.7)	-	-	49	-	-	-	Mean 11.9 (SE 2.0)	-
27 mo	49	11.4** (SE 3.0)	-	-	49	15.2** (SE 3.9)	-	-	49	2.45 (SE 1.1)	-	-	49	2.89 (SE 0.8)	-	-	49	-	-	-	Mean 11.1 (SE 2.4)	-
Anink 2014 PreS 8.5 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Trachana 2012 EULAR 1 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
5 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Trachana 2013 Clin Rheumatol 1 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
10 y		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Nielson 2008 Clin exp Rheum 3 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Vojvodich 2007 J		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
Rheumatol Prepubertal 12 mo																						
Pubertal 12 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
De Sanctis 2013 J Rheumatol 12 mo		-	-	-		-	-	-	30	-	1.5 (IQR 0-5.0)	-		-	-	-		-	-	-	Mean (SD) 12.25 (7.97)	Median 0.33 (IQR 0.32-0.83)
Alekseeva 2012 EULAR 48 wk		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Lahdenne 2003 Ann Rheum Dis 3 mo	-	-	-	Change in score -29.0	-	-	-	Change in score - 24.5	-	-	-	Change in number - 9.5	-	-	-	-	-	-	-	Change in score - 0.81	-	-
12 mo		-	-	-		-	-	-		-	-	-		-	-	-		-	-	-	-	-
Kietz 2002 Ann Rheum Dis 24 mo		-	-	-		-	-	-	-	12.8	-	- 48.1		-	-	-		-	-	-	Mean 18.55	-
Calvo 2012 EULAR 6 mo	-	11.6** (11.2)	-	-	-	12.9** (12.4)	-	-	-	1.44 (1.77)	-	-	-	1 (1.33)	-	-	-	0.4 (0.2)	-	-	Mean (SD) 14.1 (8.3)	Mean (SD) 3 (4.

Study ID, arm & time point	PGA disease activity (VAS)				PGA wellbeing (VAS)				No. of active joints				No. of joints with LOM				CHAQ score					
	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	N	Mean (SD)	Median	% change	ESR (mm/h)	CRP mg/L
																						9)
2 y	-	-	-		-	-	-		-	-	-		-	-	-		-	-	-		-	-
Robinson 2003 Clin Drug Invest 14 mo	-	-	-		-	-	-		-	-	-	21	6.4 (5.6)	-	-		-	-	-		Mean (SD) 26.9 (17.8)	-
Otten 2011 Ann Rheum Dis 3 mo	-	-	-		-	-	-		-	-	-		-	-	-		-	-	-		-	-
15 mo	-	-	-		-	-	-		-	-	-		-	-	-		-	-	-		-	-
Opoka-Winiarska 2014 PreS 6 mo	-	-	-		-	-	-		-	-	-		-	-	-		-	-	-		-	-
Hooper 2013 Ped Rheum	-	-	-		-	-	-		-	-	-		-	-	-		-	-	-		-	-
[redacted]																						
[redacted]																						
[redacted]																						

* 1-10 scale, ** 1-100 scale; † study informed the etanercept marketing authorisation on long term safety of etanercept

Disease inactivity and remission

The numbers/proportions in remission/inactive disease may be difficult to interpret in long-term follow-up because few observational studies report ITT analyses. Notably, some patients are reported to discontinue treatment because of remission, and may not be counted in subsequent analyses.

The observational study that informed the marketing authorisation for the long term safety of etanercept (Giannini 2009) recorded the proportion of patients with a physician global assessment (PGA) disease activity of 0, and the proportion with no active joints. At 3 months, 16 (18.6%) of 86 patients receiving etanercept had PGA of 0; 18 patients had PGA=0 at 12 months and 17 at 36 months. High rates of disease inactivity were seen in the methotrexate arm, but these patients were naïve to methotrexate at baseline, whereas patients in the etanercept arms had previously failed methotrexate.

A study by Solari et al. of 173 consecutive etanercept-treated JIA patients at an Italian centre, treated for a median of 2.2 years, reported that 87 (50.3%) achieved inactive disease (Wallace criteria) after a median of 0.6 years of therapy. At last follow-up, 85 (49.1%) still had inactive disease and 70 (40.5%) were in clinical remission on medication. The probability of achieving inactive disease after 6, 12 and 24 months of therapy was 24%, 46% and 57%, respectively.

In a study of 787 patients from the German etanercept registry (Papsdorf 2011), 47.6% met the criteria for inactive disease (Wallace criteria) and 26.6% achieved remission on medication (at last observation).

In another large cohort (Otten 2011), 32% of 245 patients on etanercept had inactive disease at 15 months. Prince 2009 reported remission by modified Wallace criteria in 35 of 97 patients at 15 months. Klotsche 2014 reported inactive disease by Wallace criteria in 17 of 56 patients at 12 months and remission in 5 of 56.

A summary of disease inactivity outcomes reported in the observational/registry studies is presented in Table 24 below.

Table 24 Inactive disease and remission outcomes, observational studies

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
Horneff 2014 ACR	All	1925	NR	NR	NR
Windschall 2015 Clin Rheumatol Last obs.	Each of: eoJIA, PsA, polyarthritis(RF+, RF-)	-	NR	NR	NR
24 mo	Each of: eoJIA, PsA, polyarthritis(RF+, RF-)	-	NR	NR	NR
Horneff 2012 EULAR	All	NR	NR	NR	NR
Geikowski 2014 J Rheumatol 6 mo	All	863	NR	NR	NR
Papsdorf 2011 Rheumatology	All	787	Inactive disease and clinical remission	Wallace 2004	Inactive disease: 375 (47.6) Clinical remission: 166 (26.6)
Davies ACR/ARHP 2013	All	677	NR	NR	NR
Horneff 2009 Ann Rheum Dis Etanercept 12 mo	All	69 (ITT)	NR	NR	NR
Etanercept + MTX 12 mo	All	427 (ITT)	NR	NR	NR
Giannini 2009† Arth Rheum MTX 3 mo	All	175	No disease activity, or no active joints	PGA=0, or active joints=0	PGA 0: 21(12.0%) Active joints 0: NR
12 mo		124	“	“	PGA 0: 44 (35.5%) Active joints 0: 47 (69.1%)
36 mo		67	“	“	PGA 0: 31 (46.3%) Active joints 0: 43 (65.2%)
Etanercept 3 mo	All	86	“	“	PGA 0: 16 (18.6%) Active joints 0: NR
12 mo		68	“	“	PGA 0: 18 (26.5%) Active joints 0: 14 (40%)
36 mo		42	“	“	PGA 0: 17 (40.5%) Active joints 0: 24 (57.1%)
Etanercept + MTX 3 mo	All	246	“	“	PGA 0: 25 (10.2%) Active joints 0: NR

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
12 mo		200	"	"	PGA 0: 54 (27.0%) Active joints 0: 34 (38.2%)
36 mo		115	"	"	PGA 0: 35 (30.4%) Active joints 0: 58 (50.4%)
Halbig & Horneff 2009 Rheumatol Int All time points	All subgroups	-	NR	NR	NR
Kearsley-Fleet ACR 2014 1 yr.	All	407 included in model	NR	NR	NR
Minden 2012 ACR/ARHP		386	NR	NR	NR
Horneff 2004 Ann Rheum Dis Time point NR	All	NR	Complete remission	Morning stiffness <5 min, no tender joint, no swollen joint, normal ESR	72 (26%)
	Polyarticular (RF-)	NR	"	"	14 (17%)
	Polyarticular (RF+)	NR	"	"	11 (30%)
	Oligoarticular	NR	"	"	5 (62%)
	eoJIA	NR	"	"	14(28%)
	Other	NR	"	"	20 (40%)
Otten 2011 JAMA 15 mo	All	245	Inactive disease	No active arthritis, no systemic features, no uveitis, normal ESR (≤20 mm/h), PGA score indicating no disease activity (≤10 mm)	32% (24-40%)
87 mo		17	Inactive disease	As above	45% (13-77%)
Tarkiainen 2014 Rheumatol	All	213 (ENT)	NR	NR	NR
Kearsley-Fleet 2013 ACR/ARHP 1 y	All	191	NR	NR	NR
2 y	All	191	NR	NR	NR
Zuber 2011 Med Sci Monit 3 mo	All	172	ACR Pedi 100	ACR Pedi 100	15%
12 mo		146	ACR Pedi 100	ACR Pedi 100	19.1%
48 mo		39	ACR Pedi 100	ACR Pedi 100	23.70%
Otten 2010 J Rheum	All	179	NR	NR	NR

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
3 mo					
Solari 2013 J Rheum	All	173	Inactive disease and clinical remission	Wallace 2004	Inactive disease: 85 (49.1) Clinical remission: 70 (40.5) at last follow up
Prince 2009 Ann Rheum Dis 3 mo	All	146	Remission	Wallace 2004 [70], modified to include PGA <20mm	NR
15 mo		97	“	“	35
75 mo		5	“	“	1
3 mo	Polyarticular (RF+)	11	“	“	NR
15 mo		9	“	“	3
75 mo		3	“	“	1
3 mo	Polyarticular (RF-)	55	“	“	NR
15 mo		36	“	“	14
75 mo		1	“	“	0
3 mo	Oligoarticular	28	“	“	NR
15 mo		18	“	“	6
75 mo		1	“	“	0
3 mo	ERA	5	“	“	NR
15 mo		4	“	“	0
75 mo		0	“	“	0
3 mo	PsA	8	“	“	NR

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
15 mo		6	“	“	3
75 mo		0	“	“	0
Gerloni 2008 Ann Rheum Dis	All	95	NR	NR	NR
Sevcic 2011 Rheumatol 3 mo	All	71	NR	NR	NR
12 mo		61	NR	NR	NR
Susic 2013 PReS 12 mo	All	63	NR	NR	NR
Quartier 2003 Arth Rheum All time points	All	-	NR	NR	NR
Klotsche 2014 Arth Care Res 12 mo	All	56	Inactive disease Remission	Wallace 2004 Wallace 2004	Inactive: 17 (32.1%) Remission: 5
Loskutova 2014 PreS 24 mo	All	32	NR	NR	NR
Prince 2010 Ann Rheum Dis 3 mo	All	53	NR	NR	NR
27 mo	All	53	NR	NR	NR
Prince 2011 3 mo	All	49	NR	NR	NR
27 mo		49	NR	NR	NR
Anink 2014 PreS 8.5 y	All	43	NR	NR	NR
Trachana 2012 EULAR 1 y	All	42	Clinical remission (CR) ACR Pedi 100	Wallace 2004 [70] ACR Pedi 100	CR: 4 ACR Pedi 100: 17
5 y	All	13	Clinical remission (CR) ACR Pedi 100	Wallace2004 ACR Pedi 100	CR:1 ACR Pedi 100: 5
Trachana 2013 Clin Rheumatol 1 y	All	42	Clinical remission (CR) ACR Pedi 100	Wallace 2004 [70] ACR Pedi 100	CR: 21 ACR Pedi 100: 17

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
10 y	All	1	Clinical remission (CR) ACR Pedi 100	Wallace2004 ACR Pedi 100	CR: 0 ACR Pedi 100: 0
Nielson 2008 Clin Exp Rheum 3 mo	All	36	NR	NR	NR
Vojvodich 2007 J Rheumatol Prepubertal 12 mo	All	20	NR	NR	NR
Pubertal 12 mo	All	11	NR	NR	NR
De Sanctis 2013 J Rheumatol 12 mo	All	30	NR	NR	NR
Alekseeva 2012 EULAR 12 mo	All	25	Inactive disease	NR	86%
Lahdenne 2003 Ann Rheum Dis 3 mo	All	9	NR	NR	NR
12 mo	All	12	NR	NR	NR
Kietz 2002 Ann Rheum Dis 24 mo	All	22	NR	NR	NR
Calvo 2012 EULAR 6 mo	All	21	Clinical remission	NR	'All pts achieved clinical remission at 6 mo of ttmt'
2 y	All	191	NR	NR	NR
Robinson 2003 Clin Drug Invest 14 mo	All	21	NR	NR	NR
Otten 2011 Ann Rheum Dis	PsA	-	Inactive disease	No active arthritis, no systemic features, no uveitis, normal ESR (≤16 mm/h), PGA score indicating no disease activity (≤10 mm)	of 9 pts at 27 mo 4 of 6 pts at 39 mo
Opoka-Winiarska 2014 PreS 6 mo	All	13	NR	NR	NR
Hooper 2013 Ped Rheum	-	-	NR	NR	NR

Study ID, arm & time point	JIA subtype*	No. on arm at time point	Outcome	Definition	Patients attaining outcome, n (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† study informed the etanercept marketing authorisation on long term safety of etanercept

Pain assessment

Few studies reported assessment of pain by parent or child. Where reported, this was carried out using a VAS (not tabulated). Neilson 2008 reported an 84.7% decrease at 12 months. Prince 2010 reported 19.3 and 12.4 on a 1-100 scale at 3 and 27 months respectively. Other scores reported ranged from 9.5 to 15.7.

JADAS/DAS score

Most studies did not report JADAS/DAS scores (scores not tabulated). Windschall 2015 reported mean JADAS scores of 4.4, 5.1 and 5.0 at 3 months and 4.0, 3.0 and 5.3 at 24 months for ERA, eoJIA and PsA respectively. Trachana 2013 reported JADAS71 of 1.45 (baseline: 19.45) at 1 year in 42 patients. DeSanctis 2013 reported JADAS 27 of JADAS-27 (scale 0-57) of 26.63 at baseline and 8.04 at 12 months in 30 patients. At 24 months, Horneff 2012 reported mean and median JADAS 71 scores of 5.0 and 2 respectively, and mean and median JADAS10 scores of 4.6 and 2; baseline values were in the range of 17-20. Thus, where reported, the evidence from JADAS scores supports that from JIA ACR scores to show substantial and sustained falls with etanercept.

Disease flare

The only study to report disease flare as an outcome measure was Quartier 2003, who reported that of 31 patients who completed 12 months' treatment, 9 experienced disease flare (defined as ≥ 30% worsening of ≥3 response indicators relative to last assessment, with ≥ 2 active joints.)

Corticosteroid reduction

Only two studies reported on corticosteroid reduction during etanercept treatment. Quartier 2003 reported that median prednisolone dose was reduced from 0.22 mg/kg/day (range 0.08–0.59) to 0.10 mg/kg/day (range 0–0.34) in 26 patients at 6 months. Prince 2010 reported that glucocorticoids were discontinued in 75% of patients by 27 months.

Growth

Only one of the included studies (Vojvodich 2007) reported on growth outcomes in children with JIA treated with etanercept. The outcome measure was change in height standard deviation score over time. The authors concluded that: 'TNF inhibition with etanercept improved growth in a majority of patients with JIA. Our data demonstrates that growth improvement with etanercept was independent of the pubertal growth spurt.' These data are supported by other studies (not included in the systematic review as they did not contain extractable outcomes relating to height and weight): Kearsley-Fleet et al. 2015 reported improvement in height over the first two-years; Giannini et al. 2010 reported significant increases in mean height in children with JIA treated with etanercept; Billiau et al. 2010 reported that etanercept + MTX in polyarticular JIA was associated with significantly improved growth velocity compared with MTX alone.

Joint damage

Two studies reported measures of joint damage or radiological deterioration. Neilson 2008 reported a median Poznanski score of -1.8 at 12 months, a -16% change from baseline. Trachana 2013 reported that at 1 year, 3 of 15 patients experienced joint damage, defined as radiological deterioration in patients with radiologic abnormality at baseline.

4.12.6 Health-related quality of life

Etanercept provides sustained HRQoL improvement in patients with JIA

Due to factors such as impaired physical function, JIA can have consequences for psychological well-being and HRQoL.

- Treatment with etanercept has been shown in three studies to significantly improve HRQoL from baseline in several generic instruments.
- Rapid improvements (over 3 months) have been observed in the Child Health Questionnaire (CHQ), the Health Utility Index 3 (HUI3) and PedsQL.[26-28]
- Follow-up from these studies indicates that improvements can be maintained long term (maximum follow-up 27 months).

Four studies met the criteria for inclusion in the HRQoL review. These are shown in Table 25 along with the data extracted. Prince 2010, Prince 2011 and Klotsche 2014 all reported some efficacy or safety data and were also included in the clinical effectiveness review, where patient characteristics are tabulated.[26-28] Data were reported for the Child Health Questionnaire (CHQ), PedsQL and Health Utility Index 3 (HUI3) instruments. No disease-specific instruments were reported, though the PedsQL administered in Klotsche 2014 included the disease-specific module. No studies were identified that reported EQ-5D or mapped results to EQ-5D. The data show sustained HRQoL improvements over a range of measures in children treated with etanercept.

- Prince 2010 found improvements over baseline in CHQ physical and psychosocial summary scores at 3 months and further improvement at 27 months, in an analysis of 53 patients.[26]
- Prince 2011 reported improvement in utility as measured by HUI3 at 3 months, and further improvement at 27 months.[27]

- Klotsche 2014 measured PedsQL scores over 12 months in 61 patients. Summary score rose from 72.2 at baseline to 81.4 at 3 months and 92.0 at 12 months. All domains (physical, emotional, social and school functioning) were improved.[28]

- In addition, a study of 43 patients from the Dutch registry, with a median duration of etanercept treatment of 8.5 years (Anink 2014), reported that 'The improvement in HRQoL after start of etanercept was sustained after 8.5 years. Disability was low. On many aspects of daily life, patients functioned comparably to or better than the general population.' (This publication, a conference abstract, was included in the clinical review. It was not included in the HRQoL review because it did not report any quantitative HRQoL outcomes).[42]

- Robinson 2003 reported HRQoL data as graphs only (Figure 2). Polyarticular JIA is shown in dark circles. The authors reported that functional status and HRQoL improved; a significant difference between pre- and post etanercept functional assessment (JAFAR and CHAQ) and HRQoL assessment by parents and patients was found.[7]

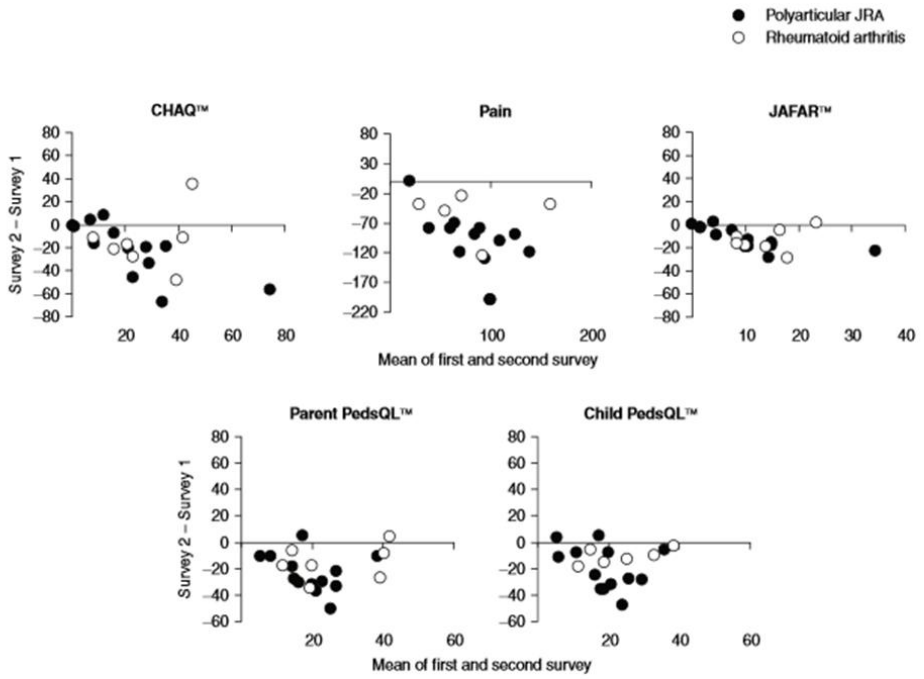


Fig. 1. Functional assessment and quality of life in patients with polyarticular and systemic juvenile rheumatoid arthritis (JRA). **CHAQ™** = Childhood Health Assessment Questionnaire; **Child PedsQL™** = Child Pediatric Quality of Life Inventory Version 4; **JAFAR™** = Juvenile Arthritis Function Assessment Report; **Parent PedsQL™** = Parent Pediatric Quality of Life Inventory Version 4.

Figure 2 Functional assessment and HRQoL, Robinson 2003

Table 25 Studies included in the HRQoL review, and data extracted

Study ID, time point and no. of patients	HRQoL, general				HRQoL, disease-specific	
	Baseline	Score at time point	Change from baseline	Instrument	Change from baseline	Instrument
Robinson 2003 Clin Drug Invest 14 mo (n=NR)	JAFAR, ParentPedsQL and ChildPedsQL were reported in graphical form - no extractable data CHAQ, pain, JAFAR, child and parent PedsQL measures were all improved in all JIA patients (p<0.001)					
Prince 2010 Ann Rheum Dis 3 mo (n=53)	**CHQ, Mean (SE)** 24.7(2.6) Physical summary Score (PhS) 45.1(1.4) Psychosocial summary score (PsS) **HUI3, Mean (SE)** 0.51(0.04)	**CHQ** 32.7(3.1)Phs 49.4(1.7)PsS **HUI3** 0.64(0.05)	NR	CHQ (0-100) HUI3(0-1)	NR	NR
27 mo (n=53)	**CHQ, Mean (SE)** 24.7(2.6) Physical summary Score (PhS) 45.1(1.4) Psychosocial summary score (PsS) **HUI3, Mean (SE)** 0.51(0.04)	**CHQ** 39.6(4.7)Phs 53.6(2.7)PsS **HUI3** 0.77(0.08**)**	NR	CHQ (0-100) HUI3(0-1)	NR	NR
Prince 2011 Rheum 3 mo (n=49)	0.53 (SE 0.04)	0.69 (SE 0.05)	NR	HUI3 multi-attribute function	NR	NR
27 mo (n=49)	0.53 (SE 0.04)	0.78 (SE 0.07)	NR	HUI3 multi-attribute function	NR	NR
Klotsche 2014 Arth Care Res 3 mo (n=61)	72.2(16.8)	81.4(16.5)	NR	PedsQL (generic and disease specific modules)	NR	NR
12 mo (n=61)	72.2(16.8)	92.0 (9.2)	NR			

CHQ: child health questionnaire; PedsQL: pediatric quality of life inventory; HUI3: health utilities index mark; JAFAR: the juvenile arthritis functional assessment report

4.13 Adverse reactions

Only data on adverse events classed as, grade 3 or 4 or, as ‘serious’ or ‘medically important ‘were extracted. Data on overall number of discontinuations in the included studies, and discontinuations due to AEs, were also extracted, as were the total number of patient-years of etanercept use.

Summary of findings: safety

Etanercept has a long-term safety and tolerability profile established through over 15 years of real-world use

- Data on the short-term and long-term safety and tolerability of etanercept are available from both clinical trials and observational/registry studies.
- Low rates of serious adverse events are reported across clinical trials. Evidence from real-world/registry analyses indicate that low rates of adverse events are evidenced in clinical practice. Exposure-adjusted rates of adverse events in selected categories of JIA were similar among the 3 treatment groups (18.3, 18.7, and 21.6 per 100 patient-years in the MTX, etanercept, and etanercept plus MTX groups respectively (Giannini 2009).
- Long-term exposure to etanercept (Lovell 2008) was not associated with any overall increased risk of serious adverse events (reported rate was 0.12 per patient per year).
- [redacted]

4.13.1 Interventional studies

Treatment discontinuation: Definitions of safety populations, where reported, are presented in Table 8. Discontinuations due to AEs in the interventional studies were low: only one patient in the pivotal study (Lovell 2000) and 3.1% in the CLIPPER study (Horneff 2014). The rate of discontinuation due to AEs in the Lovell extension study after up to 8 years of follow-up was 7% (Table 26).

Table 26 Discontinuations and patient-years of etanercept use (safety analyses), interventional studies

Study ID and arm		Overall discontinuations during treatment			Discontinuation due to AEs†		
	JIA subtype*	N	n	%	N	n	%
Lovell 2000± NEJM Etanercept (open-label phase)	All	69	-	-	69	1 in whole study (phase NR)	-
Etanercept (double-blind phase)	All	25	-	-	25		-
Placebo (double-blind phase)	All	26	-	-	26	-	-
Mori 2005 Mod Rheumatol	All	-	-	-	22	1	-
Horneff 2009 Rheumatol	All	20	0	0	20	0	0
Horneff 2014 Ann Rheum Dis (CLIPPER [Part 1)	All	127	5	-	127	4	3.1
	eoJIA	60	-	-	60	1	1.7
	ERA	38	-	-	38	2	5.3
	PsA	29	-	-	29	1	3.4
Zeng 2014 Ann Rheum Dis	Oligoarticular and polyarticular	-	-	-	-	-	-
Extension studies							
Lovell 2003 Arth Rheum	All	58	-	-	58	2	-
Lovell 2008 ±Arth Rheum	All	58	38	66	58	4	7
Mori 2011 Mod Rheumatol Etanercept (open label)	All	22	-	-	22	0	0
Etanercept (double-blind 0.4 mg/kg)	All	6	-	-	6	0	0
Mori 2012 Mod Rheumatol Etanercept (both doses)	All	32	14	-	32	2	-
Constantin 2013 ACR/ARHP (CLIPPER Part 2)	All; 215 pt.-y of exposure	127	-	-	127	5	-
	eoJIA	60	-	-	60	1	-
	ERA	38	-	-	38	3	-
	PsA	29	-	-	29	21	-

* where reporting stratified; all denotes all pts reported; † denotes treatment-emergent, otherwise relationship to treatment NR; N denotes evaluation population;± studies informing the licence

Adverse events: Studies reported very low rates of serious adverse events. In studies reporting on JIA subtypes, (Horneff 2014 and Constantin 2013) no differences in safety were observed across the groups. Rates of medically important infections, where reported, were low (0.03 per patient-year in Lovell 2008). Long-term exposure to etanercept was not associated with any overall increased risk of serious infection, malignancy, tuberculosis, demyelinating disorders, lupus, lymphomas or death (Lovell 2008).

A summary of the adverse events in the interventional studies is presented in Table 27Table 27 below.

Table 27 Adverse events, interventional studies

Study ID and arm	JIA subtype	Serious AEs*			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Lovell 2000± NEJM Etanercept (open-label phase)	All	69	2 in whole study (phase NR)	-	69	-	-	69	-	-	69	-	-	69	0	0
Etanercept (double-blind phase)	All	25	-	-	25	-	-	25	-	-	25	0	0	25	0	0
Placebo (double-blind phase)	All	26	-	-	26	-	-	26	-	-	26	0	0	26	0	0
Mori 2005 Mod Rheumatol	All	22	2	-	22	0	-	-	-	-	22	-	0	-	-	-
Horneff 2009 Rheumatol	All	20	0	0	20	-	-	20	-	-	20	-	-	20	-	-
Horneff 2014± Ann Rheum Dis	All	127	1*	0.8	127	3	2.4	127	0	0	127	0	0	127	0	0
	eoJIA	60	0*	0	60	2	3.3	60	0	0	60	0	0	60	0	0
	ERA	38	1*	2.6	38	0	0	38	0	0	38	0	0	38	0	0
	PsA	29	0*	0	29	1	3.4	29	0	0	29	0	0	29	0	0
Zeng 2014 Ann Rheum Dis	Oligoarticular and polyarticular	32	0	0	-	-	-	-	-	-	-	-	-	-	-	-
Extension studies																
Lovell 2003 Arth Rheum	All	58	9	-	58	-	-	58	-	-	58	0	0	58	-	-
Lovell 2008 ±Arth Rheum	All	69	39 in 318 pt.-years	-	69	9	-	69	0	0	69	-	-	69	0	0
Mori 2011 Mod Rheumatol	All	22	7	0	22	-	-	22	-	-	22	-	-	22	0	0

Study ID and arm	JIA subtype	Serious AEs*			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
		N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Etanercept (open label)																
Etanercept (extension 0.4 mg/kg)	All	6	0	0	6	-	-	6	-	-	6	-	-	6	0	0
Mori 2012 Mod Rheumatol Etanercept (both doses)	All	32	6 (none ≥grade 3)	18.8	32	-	-	32	-	-	32	-	-	32	0	0
Constantin 2013 ACR/ARHP	All; 215 pt.-y of exposure	127	16*	-	127	10	-	127	0	0	-	-	-	127	0	0
	eoJIA	60	2*	-	60	4	-	60	0	0	60	-	-	60	-	-
	ERA	38	11*	-	38	3	-	38	0	0	38	-	-	38	-	-
	PsA	29	3*	-	29	3	-	29	0	0	29	-	-	29	-	-

ǂ where reporting stratified; all denotes all pts reported; † denotes treatment-emergent, otherwise relationship to treatment NR; N denotes evaluation population; ± studies informing the licence

4.13.2 Observational studies

Data on the short-term and long-term safety and tolerability of etanercept are also available from observational/registry studies.

Treatment discontinuation: The majority of studies did not directly report discontinuation rates, either overall or due to adverse events. However, the Giannini 2009 study, which informed the marketing authorisation for etanercept, reported a discontinuation rate due to AEs of 1.9 % in 387 patient-years of use, similar to the rate observed with methotrexate monotherapy. Evidence from a UK cohort (483 etanercept-treated JIA patients were enrolled from 30 UK centres) followed up for a median of 2 years (maximum 5 years), indicates that the majority (69%) of patients remain on the drug (Southwood et al.).[104]

A summary of the discontinuation rates is presented in Table 28 below.

Table 28 Discontinuations and total patient-years of etanercept use (safety analyses), observational studies

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Overall discontinuations			Discontinuation due to AEs		
			N	n	%	N	n	%
Horneff 2014 ACR	All	3958	-	-	-	-	-	-
Windschall 2015 Clin Rheumatol	ERA	406.19	-	-	-	-	-	-
	eoJIA	682.29	-	-	-	-	-	-
	PsA	211.83	-	-	-	-	-	-
	Polyarthritis (RF+)	372.13	-	-	-	-	-	-
	Polyarthritis (RF-)	1132.94	-	-	-	-	-	-
	All	-	-	-	-	-	-	-
Horneff 2012 EULAR	All	-	-	-	-	-	-	-
Geikowski 2014 J Rheumatol	All	-	-	-	-	-	-	-
Papsdorf 2011 Rheumatology	All	-	-	-	-	-	-	-
Davies 2013 ACR/ARHP	All	1498	-	-	-	-	-	-
Horneff 2009 Ann Rheum Dis								
Etanercept	All	1149 across both ttmt groups	100	-	14	100	3	-
Etanercept + MTX	All	As above	504	-	10 (ETN)	504	14	-
Giannini 2009 Arth Rheum								
MTX	All	387.8	197	131	66.5	197	3	1.5
Etanercept	All	224.11	103	56	54.4	103	2	1.9
Etanercept + MTX	All	635.17	294	162	55.1	294	1	0.3
Halbig & Horneff 2009 Rheumatol Int	All	-	-	-	-	-	-	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Overall discontinuations			Discontinuation due to AEs		
			N	n	%	N	n	%
Kearsley-Fleet 2014 ACR	All	-	407	29	-	407	8	-
Minden 2012 ACR/ARHP	All	1815	-	-	-	-	-	-
Horneff 2004 Ann Rheum Dis	All	592	322	53	-	322	11	-
	Polyarticular (RF-)		94	12	13	94	1	-
	Polyarticular (RF+)		39	3	8	39	1	-
	Oligoarticular		64	9	14	64	3	-
	ERA		26	5	19	26	3	-
	PsA		17	4	24	17	1	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Overall discontinuations			Discontinuation due to AEs		
			N	n	%	N	n	%
Otten 2011 JAMA	All	683.7	262	142	54	262	25	-
Tarkiainen 2014 Rheumatol	All	710	-	-	-	-	-	-
Kearsley-Fleet 2013 ACR/ARHP	All	-	-	-	-	-	-	-
Zuber 2011 Med Sci Monit	All	393	188	51	-	188	4	-
Otten 2010 J Rheum	All	-	179	-	-	179	-	-
Solari 2013 J Rheum	All	458.8	173	36	-	-	-	-
Prince 2009 Ann Rheum Dis	All	312	146	-	-	-	-	-
Gerloni 2008 Ann Rheum Dis	All	258	-	-	-	95	18	14.2
Sevcic 2011 Rheumatol	All	-	72	-	-	72	-	-
Susic 2013 PReS	All	-	-	-	-	-	-	-
Quartier 2003 Arth Rheum	All	-	61	30 at 12 mo	-	61	12	20%
Klotsche et al 2014 Arth Care Res	All	-	61	8	-	61	1	-
Loskutova 2014 PreS	All	-	-	-	-	-	-	-
Prince 2010 Ann Rheum Dis	All	-	53	4	-	-	0	-
Prince 2011 Rheum	All	-	-	-	-	-	-	-
Anink 2014 PreS	All	-	-	-	-	-	-	-
Trachana 2012 EULAR	All	-	-	-	-	-	-	-
Trachana 2013 Clin Rheumatol	All	-	-	-	-	-	-	-
Nielson 2008 Clin Exp Rheum	All	-	-	-	-	-	-	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Overall discontinuations			Discontinuation due to AEs		
			N	n	%	N	n	%
Vojvodich 2007 J Rheumatol	Prepubertal	-	-	-	-	-	-	-
	Pubertal	-	-	-	-	-	-	-
De Sanctis 2013 J Rheumatol	All	-	-	-	-	-	-	-
Alekseeva 2012 EULAR	All	-	-	-	-	25	0	0
Lahdenne 2003 Ann Rheum Dis	All	-	10	1	-	-	-	-
Kietz 2002 Ann Rheum Dis	All	-	22	0	0	22	0	0
Calvo 2012 EULAR	All	-	21	2	-	-	-	-
Robinson 2003 Clin Drug Invest	All	-	21	0	0	21	0	0
Otten 2011 Ann Rheum Dis	All	-	18	6	-	-	-	-
Opoka-Winiarska 2014 PreS	All	-	-	-	-	-	-	-
Hooper 2013 Ped Rheum	All ETN-exposed pts (any disease)	231,404 (estimated)	-	-	-	-	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N denotes number of patients in evaluation population. – denotes not reported

Adverse events: The Giannini 2009 study indicated relatively similar rates of medically important infections (1.3, 1.8, and 2.1 per 100 patient-years) during long-term therapy of etanercept monotherapy, etanercept plus methotrexate, or methotrexate monotherapy, respectively [15]. Rates of malignancies, autoimmune events and deaths, where reported, were zero or very low over long-term follow-up across the included studies. [redacted]

A summary of the adverse events, observational studies is presented in Table 29.

Table 29 Summary of adverse events, observational studies

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Horneff 2014 ACR	All	3958	1925	149	-	-	-	-	-	-	-	-	-	-	-	-	-
Windschall 2015 Clin Rheumatol																	
	ERA	406.19	238	17	-	-	2	-	-	2	-	-	-	-	-	0	-
	eoJIA	682.29	315	31	-	-	4	-	-	0	-	-	-	-	-	0	-
	PsA	211.83	127	11	-	-	1	-	-	0	-	-	-	-	-	0	-
	Polyarthritis (RF+)	372.13	160	16	-	-	-	-	-	-	-	-	-	-	-	-	-
	Polyarthritis (RF-)	1132.94	534	33	-	-	-	-	-	-	-	-	-	-	-	-	-
	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Horneff 2012 EULAR	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Geikowski 2014 J Rheumatol	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Papsdorf 2011 Rheumatology	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Davies 2013 ACR/ARHP	All	1498	-	-	-	677	134	-	-	-	-	-	-	-	-	-	-
Horneff 2009 Ann Rheum Dis																	
Etanercept	All	1149 across both ttmt groups	100	4	-	100	1	-	100	0	-	100	-	-	100	0	0
Etanercept + MTX	All	As above	504	48	-	504	25	-	504	3	-	504	-	-	504	0	0
Giannini 2009± Arth Rheum	All	387.8	197	-	-	197	5	1.29	197	0	0	197	17	-	197	0	0
MTX																	
Etanercept	All	224.11	103	-	-	103	4	1.78	103	0	0	103	12	-	103	0	0
Etanercept + MTX	All	635.17	294	-	-	294	13	2.05	294	0	0	294	15	-	294	0	0
Halbig &	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Horneff 2009 Rheumatol Int All																	
Kearsley-Fleet 2014 ACR	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Minden 2012 ACR/ARHP	All	1815	386	77	-	386	20	-	386	2	-	386	17	-	-	2 in pts treated with ETN in previous 3 mo	-
Horneff 2004 Ann Rheum Dis All	All	592	322	12	-	-	-	-	322	1	-	-	-	-	-	-	-
Polyarticular (RF-)	Polyarticular (RF-)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Polyarticular (RF+)	Polyarticular (RF+)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oligoarticular	Oligoarticular		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ERA	ERA		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PsA	PsA		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Otten 2011 JAMA	All	683.7	262	31	-	262	7	-	262	0	0	262	9	-	262	2 deaths 4.8 y and 0.7 y after ETN discontinuation	-
Tarkiainen 2014 Rheumatol	All	710	213	55	25.8	213	21	13.6	213	0	0	-	-	-	213	2	-
Kearsley-Fleet 2013 ACR/ARHP	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zuber 2011 Med Sci Monit	All	393	188	6	-	188	16 severe resp	-	188	0	0	188	-	-	188	0	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
							tract infections; 1 infectious SAE										
Otten 2010 J Rheum	All	-	179	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Solari 2013 J Rheum	All	458.8	173	-	-	173	2	-	-	-	-	-	-	-	173	1	-
Prince 2009 Ann Rheum Dis	All	312	146	9	-	146	4	-	146	0	-	146	-	-	146	3 (all systemic JIA; all ≥6 mo after discontinuing ETN due to lack of response	-
Gerloni 2008 Ann Rheum Dis	All	258	-	-	-	95	2	-	95	1	-	95	-	-	-	-	-
Sevcic 2011 Rheumatol	All	-	72	-	-	72	-	-	72	0	0	-	-	-	-	-	-
Susic 2013 PReS	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quartier 2003 Arth Rheum	All	-	61	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Klotsche et al 2014 Arth Care Res	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Loskutova 2014 PReS	All	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-
Prince 2010 Ann Rheum Dis	All	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Prince 2011 Rheum	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anink 2014 PReS	All	-	-	-	-	-	-	-	43	0	0	-	-	-	-	-	-
Trachana 2012 EULAR	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trachana 2013 Clin Rheumatol	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nielson 2008 Clin Exp Rheum	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vojvodich 2007 J Rheumatol	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prepubertal																	
Pubertal	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
De Sanctis 2013 J Rheumatol	All	-	30	0	-	-	-	-	-	-	-	-	-	-	-	-	-
Alekseeva 2012 EULAR	All	-	25	-	0	-	-	-	-	-	-	-	-	-	-	-	-
Lahdenne 2003 Ann Rheum Dis	All	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kietz 2002 Ann Rheum Dis	All	All	-	-	-	-	22	0	0	-	-	-	-	-	-	-	-
Calvo 2012 EULAR	All	All	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Robinson 2003 Clin Drug Invest	All	All	-	-	-	-	21	0	0	-	-	-	-	-	-	-	-
Otten 2011 Ann Rheum Dis	All	All	-	18	-	-	-	-	-	-	-	-	-	-	-	-	-

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Opoka-Winiarska 2014 PReS	All	All	-	-	-	-	-	-	-	13	0	0	-	-	13	0	0
Hooper 2013 Ped Rheum	All ETN-exposed pts (any disease)	All ETN-exposed pts (any disease)	231,404 (estimated)	-	-	-	-	-	-	-	CTD: 2 (1 not in ETN arm); PMD: 103 total, 20 in JIA pts	-	-	-	-	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	28 experienced a total of 65 AEs. 22 experienced a total of 36 TRAEs	27.45% AEs [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID and arm	JIA subtype*	Total patient-years of ETN use	Serious AEs			Medically important infection/ sepsis			Malignancies			Autoimmune events			Deaths		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
[redacted]																	

± study informing the etanercept licence

4.14 Interpretation of clinical effectiveness and safety evidence

Etanercept is an effective treatment in the respective licensed JIA subtypes both in the short-term and long term in terms of improvement in ACR response; reduction in disease flare and radiographic progression. A range of generic instruments have shown that this leads to an improvement in HRQoL. Furthermore, etanercept has a long term-term safety and tolerability profile established in at least 15 years of real-world use. Etanercept should continue to be recommended by NICE as an effective treatment for JIA and the recommendation extended to include eoJIA, ERA and PsA subtypes.

A large body of evidence has shown that etanercept is an effective and well tolerated treatment for JIA in all the subgroups within its licensed indication. The pivotal trial (Lovell 2000) had a unique design allowing for patients to try a new treatment (etanercept); only those who had a response to treatment were enrolled in the randomised phase of the study. This design reflected ethical considerations for trials of a novel agent in a paediatric population. During the appraisal of etanercept in TA35 it was identified as a high quality trial and its findings have subsequently been supported by 8 years of follow-up data.

A further key strength of the evidence base is the fact that a large number of high-quality real-world registry studies are available, and these confirm the efficacy and safety of etanercept in JIA seen in the clinical trials. Amongst these the CLIPPER study was notable as the first prospective study to specifically investigate a biologic DMARD in eoJIA, ERA and PsA subtypes (Horneff 2014). Importantly a number of registry studies have been conducted in the UK and the results can therefore be considered generalizable to the population included in scope.

Nonetheless, there are several limitations to the evidence base available. Registry studies by the nature of their design more closely reflect clinical practice. Consequently a large number of studies reported in this submission allowed for the use of varying concomitant therapies (DMARDs, NSAIDs), which may have influenced estimates of treatment effect. Furthermore, the inception of most registry studies pre-dates the current ILAR classification of JIA. Variation in subtypes may influence estimates of treatment effect (Quartier 2003 and Horneff 2004). In addition,

although other biologic DMARDs are within the scope of this appraisal, no head to head studies have been published comparing recently introduced biologics to etanercept in JIA or associated subtypes.

Despite these limitations, the large number of registry studies and the fact that these data span over 15 years of real-world use, means that etanercept has the most comprehensive evidence base of any of any biological treatment for JIA consistently demonstrating clinical benefit across all JIA subtypes included in scope. Together these data demonstrate that etanercept is an effective treatment for JIA across a range of outcomes and disease subtypes, providing rapid and sustained improvements in disease activity, physical functioning and health-related quality of life, with a well-defined safety profile. On this basis etanercept should continue to be recommended by NICE as an effective treatment for JIA and the recommendation extended to include eoJIA, ERA and PsA subtypes.

4.15 Ongoing studies

A summary of the relevant on-going studies is presented below

- B1801308 (UK) Lianne Kearsley-Fleet, Rebecca Davies, Mark Lunt, Taunton R. Southwood, and Kimme L. Hyrich on behalf of the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). Factors Associated with Improvement in Disease Activity Following Initiation of Etanercept in Children and Young People with Juvenile Idiopathic Arthritis: Results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN); anticipated study end-date: Dec 31, 2015

- B1801310 (BIKER German JIA registry: Biologika in der Kinderrheumatologie-Register) PI: Prof. Dr. med. Gerd Horneff, Asklepios Klinik Sankt Augustin GmbH, Germany; anticipated study end-date: Nov 30, 2015

- B1801023 (extension-study of Horneff 2014): an open-label extension study to assess the long-term safety and clinical benefit of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-

related arthritis, or psoriatic arthritis who were previously enrolled in Protocol 0881A1-3338-WW(B1801014)

- 0881A-101393: Evaluating safety and quality of life in patients treated with etanercept
- 0881A-102356: Safety and efficacy of etanercept in children with juvenile idiopathic arthritis, a retrospective review of the Spanish experience

Note: The interim results (improvement in disease activity outcome) of the BSPAR-ETN and B1801023 (Constantin 2014 CLIPPER Part 2 ACR abstract) studies have been included in this MTA submission, where relevant.

5 Cost-effectiveness

Etanercept is clinically effective and represents value for money to the NHS

- Etanercept has previously been found by NICE (TA35) to be a cost-effective treatment for polyarticular-course JIA. This is consistent with decisions made by the SMC and AWMSG.
- Previous technology appraisals (TA35 and TA238) have challenged data limitations and approaches to conducting cost-effectiveness analyses of JIA and systemic JIA, respectively.
- Pfizer undertook a feasibility assessment which identified that limitations remain with data for key model attributes such as utilities and natural history data required to model a life-time time horizon, as per the NICE Reference Case.
- For these reasons any cost-effectiveness evidence submitted would continue to be associated with considerable and unresolvable uncertainty. Therefore, Pfizer have not submitted a cost-effectiveness model for this appraisal.

We have undertaken a targeted review of publications and major HTA bodies that report cost-effectiveness analyses for etanercept in JIA. Our findings confirm that there is a paucity of robust data in this area and since the original publication of NICE guidance from TA35 in 2002, we have identified only one relevant, peer-reviewed publication [Ungar 2011] and one further published NICE technology appraisal (TA238).[105]

Ungar et al in their published economic analysis investigated the cost-effectiveness of biologics in polyarticular-course JIA patients who had previously failed DMARDs from a Canadian health care perspective. The results of their analysis estimated an incremental cost-effectiveness ratio (ICER) of CDN$26,061 per additional ACR Pedi 30 response for etanercept versus methotrexate (no formal indirect comparison was undertaken). The authors noted that limitations in the utility evidence available prevented a cost-utility analysis from being undertaken. Furthermore, the authors concluded that despite calculating ICERs for other biologics vs methotrexate, comparisons across biologics were inappropriate due to differences in study populations.

Identification of only one published cost-effectiveness studies for etanercept in JIA indicates that there are inherent problems with economic modelling of JIA. There is a lack of utility data and as such, there were multiple assumptions made in both TA35 and TA238. This is consistent with the decision to adapt an adult rheumatoid arthritis model to estimate cost-effectiveness of etanercept for polyarticular-course JIA in TA35. This adapted model produced an ICER of £16,082/QALY for etanercept versus placebo, and £24,000/QALY following revisions by the Evidence Review Group (ERG).

Although etanercept was recommended as a cost-effective treatment for polyarticular-course JIA the ERG identified several key limitations with the evidence necessary for economic modelling. Similar limitations were identified in the later appraisal of tocilizumab for systemic JIA (TA238). Indeed the assessors in TA238 stated there were, “fundamental problems in the model structure and use of effectiveness evidence” (NICE 2006). The key modelling issues raised during these appraisals are summarised in Table 30Table 31.

Table 30 Limitations with the models in TA35 & TA238 (NICE 2002, NICE 2006)

	TA35 modelling key areas of uncertainty	**TA238 modelling issues**
HRQoL data	Assumption that CHAQ was equivalent to HAQ Assumption that JRA30 could be equated to ACR20 Relationship between HAQ and utility and mortality in rheumatoid arthritis being applied to children with JIA	Assumption that ACR responses could be related to CHAQ scores. The mapping of utilities was based on an adult rheumatoid arthritis population and un-validated
Efficacy and safety data	Limited evidence on long-term outcomes and the effectiveness of treatments Model required a lifetime horizon but with a lack of long-term data the extrapolation of the model beyond the evidence was purely an assumption	Insufficient long term data on the natural course of disease

Notwithstanding, the increase in the availability of longer term clinical outcomes for etanercept, some fundamental gaps still exist in the dataset required to populate an economic model. This means that uncertainties raised during the previous two NICE appraisals still remain. These are primarily related to the long term CHAQ and utility data available to Pfizer, particularly within JIA subtypes. This most likely reflects the

broader challenges faced when conducting health related quality of life research in paediatric populations.[106]

Furthermore to model JIA according to the NICE Reference Case, with a life-time time horizon, the impact of JIA in adulthood must also be understood. Data on disease progression into adulthood necessary to model the transition is not available to Pfizer. For these reasons any cost-effectiveness evidence submitted would continue to be associated with considerable and unresolvable uncertainty. Therefore, Pfizer have not submitted a cost-effectiveness model for this appraisal.

6 Assessment of factors relevant to the NHS and other parties

6.1 Cost analysis

Previous technology appraisals (TA35 and TA238) have challenged data limitations and approaches to conducting cost-effectiveness analyses of polyarticular JIA and systemic JIA, respectively. Nonetheless, to inform decision making Pfizer have undertaken a cost analysis to demonstrate that etanercept is a cost saving treatment option (see below). To illustrate this, an analysis has been conducted comparing etanercept, adalimumab and tocilizumab for the indication of polyarticular JIA (first-line bDMARD). Annual costs for the first year of treatment were estimated based upon respective product licenses and published list prices for adalimumab and tocilizumab. Where relevant, doses were estimated using the distribution of patient weights considered in TA238.

The cost analysis for polyarticular JIA (Table 31) demonstrated that for the majority of ages in scope, etanercept is the biologic treatment with the lowest acquisition cost. Specifically, etanercept was the cheapest treatment option for polyarticular JIA up to 11 years of age. In selecting treatments for the management of JIA the NHS should also consider the cost of drug administration. Etanercept and adalimumab are administered subcutaneously, which can be undertaken by a carer at home. This offers flexibility to patients and their families and has no cost impact for the NHS. Tocilizumab is administered intravenously in a hospital setting on a monthly basis. Based technology appraisal for tocilizumab administration, the administration cost in a hospital setting has been estimated to cost £179.83 per infusion [TA238] (inflated to 2015) for tocilizumab (equates to £2,338 per annum).

Table 31 Cost analysis

		Dose (mg)			
		Etanercept			
Age	Weight (Kg) Ave	0.4mg/kg twice weekly	0.8mg/kg weekly	Adalimumab	Tocilizumab
2 years	13.25	5.3	10.6	NR*	132.5
3 years	15	6	12	NR*	150
4 years	16.75	6.7	13.4	NR*	167.5
5 years	18.5	7.4	14.8	NR*	185
6 years	20.25	8.1	16.2	NR*	202.5
7 years	22.75	9.1	18.2	NR*	227.5
8 years	25	10	20	NR*	250
9 years	27.5	11	22	NR*	275
10 years	31	12.4	24.8	NR*	248
11 years	34.75	13.9	27.8	NR*	278
12 years	39.25	15.7	31.4	NR*	314
13 years	44.5	17.8	35.6	NR*	356
14 years	49	19.6	39.2	NR*	392
15 years	52	20.8	41.6	NR*	416
16 years	55.75	22.3	44.6	NR*	446
17 years	59.5	23.8	47.6	NR*	476

*Adalimumab is dosed on body surface area and is only available as a single strength, hence dose does not influence cost per dose and is not shown in this table.

	Etanercept†	Adalimumab	Tocilizumab‡
2 years	£1,859.00	£9,155.64	£5,000.19
3 years	£3,718.00	£9,155.64	£5,000.19
4 years	£3,718.00	£9,155.64	£5,665.79
5 years	£3,718.00	£9,155.64	£5,665.79
6 years	£3,718.00	£9,155.64	£6,331.39
7 years	£3,718.00	£9,155.64	£6,331.39
8 years	£3,718.00	£9,155.64	£6,996.99
9 years	£4,647.76	£9,155.64	£6,996.99
10 years	£4,647.76	£9,155.64	£6,996.99
11 years	£9,295.00	£9,155.64	£6,996.99
12 years	£9,295.00	£9,155.64	£8,328.19
13 years	£9,295.00	£9,155.64	£8,993.79
14 years	£9,295.00	£9,155.64	£8,993.79
15 years	£9,295.00	£9,155.64	£8,993.79
16 years	£9,295.00	£9,155.64	£10,324.99
17 years	£9,295.00	£9,155.64	£10,324.99

To reflect clinical practice and avoidance of drug wastage, doses were rounded down to the nearest available combination of vial strengths to a maximum of 10% variation from estimated dose.

†Where relevant the cheapest dosage regimen was assumed to be used in selecting between once weekly and twice weekly options. ‡Includes cost of administration in hospitals.

7 Reference List

1. Shepherd J. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology Assessment Report Protocol. 2014.

Ref Type: Online Source

2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P, International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *The Journal of Rheumatology* 2004;**31**:390-2.

3. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. *Arthritis Care and Research* 2011;**63**:January.

4. Martin K. Juvenile Idiopathic Arthritis (JIA) explained. Childrens Chronic Arthritis Association. 2014.

Ref Type: Online Source

5. NHS England Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis. NHS England. 2015.

Ref Type: Online Source

6. Espinosa M, Gottlieb BS. Juvenile Idiopathic Arthritis. *Pediatrics in Review* 2012;**33**:303-13.

7. Robinson RF, Nahata MC, Hayes JR, Rennebohm R, Higgins G. Quality-of-life measurements in juvenile rheumatoid arthritis patients treated with etanercept. *Clinical Drug Investigation* 2003;**23**:2003.

8. Beresford MW. Juvenile idiopathic arthritis: New insights into classification, measures of outcome, and pharmacotherapy. *Pediatric Drugs* 2011;**13**:2011.

9. NICE. NICE technology appraisal guidance [TA35]: Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. NICE. 2015. 2002.

Ref Type: Online Source

10. Summary of opinion for Enbrel. European Medicines Agency. 26-6-2014.

Ref Type: Online Source

11. Enbrel: Summary of Product characteristics. Pfizer Limited. 27-10-2014.

Ref Type: Online Source

12. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000;**342**:16.

13. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, Dehoorne J, Panaviene V, Susic G, Stanevica V, Kobusinska K, Zuber Z, Mouy R, Rumba-Rozenfelde I, Breda L, Dolezalova P, Job-Deslandre C, Wulffraat N, Alvarez D, Zang C, Wajdula J, Woodworth D, Vlahos B, Martini A, Ruperto N. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and

psoriatic arthritis: Part 1 (week 12) of the CLIPPER study. *Annals of the Rheumatic Diseases* 2014;**73**:June.

14. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin S-L, Baumgartner SW, Giannini EH. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis and rheumatism* 2008;**58**:May.

15. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, Higgins G, Gottlieb B, Singer NG, Chon Y, Lin S-L, Baumgartner SW. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. *Arthritis and rheumatism* 2009;**60**:September.

16. Kosmac M, Toplak N, Simonini G, Pagnini I, Pagnini R, Curin Serbec V, and Avcin T. Anti-Drug Antibodies Are Associated with Diminished Drug Levels and Treatment Failure. ACR/ARHP Scientific meeting, Washington, USA. 2012.

Ref Type: Conference Proceeding

17. Geikowski T, Becker I, Horneff G. Predictors of response to etanercept in polyarticular-course juvenile idiopathic arthritis. *Rheumatology (United Kingdom)* 2014;**53**:ket490.

18. Southwood TR, Foster HE, Davidson JE, Hyrich KL, Cotter CB, Wedderburn LR, Hull RG, Venning HE, Rahman JK, Cummins CL. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. *Rheumatology* 2011;**50**:January.

19. Constantin T, Foeldvari I, Vojinovic J, Horneff G, Burgos-Vargas R, Nikishina I, Akikusa J, Avcin T, Chaitow J, Koskova E, Lauwerys B, Bukowski J, Zang C, Wajdula J, Woodworth D, Vlahos B, Martini A, Ruperto N. Long-term safety and efficacy of etanercept in paediatric subjects with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis. *Arthritis and Rheumatism Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2013 San Diego, CA United States Conference Start: 20131025 Conference End: 20131030 Conference P* 2013;S117-S118.

20. Solari N, Palmisani E, Consolaro A, Pistorio A, Viola S, Buoncompagni A, Gattorno M, Picco P, Ruperto N, Malattia C, Martini A, Ravelli A. Factors associated with achievement of inactive disease in children with juvenile idiopathic arthritis treated with etanercept. *Journal of Rheumatology* 2013;**40**:February.

21. Papsdorf V, Horneff G. Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis. *Rheumatology* 2011;**50**:January.

22. Nielsen S, Ruperto N, Gerloni V, Simonini G, Cortis E, Lepore L, Alpigiani MG, Zulian F, Corona F, Alessio M, Barcellona R, Gallizzi R, Rossi F, Magni-Manzoni S, Lombardini G, Filocamo G, Raschetti R, Martini A, Ravelli A. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. *Clinical and Experimental Rheumatology* 2008;**26**:July/August.

23. Kearsley-Fleet, L., Davies, R., Lunt, M., Taunton, R, and Southwood, T. Predicting treatment response to etanercept in juvenile idiopathic arthritis: Results from the British Society for Paediatric and adolescent Rheumatology Etanercept Cohort syudy(BSPAR-ETN). Arthritis and Rheumatism.Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2014.

Ref Type: Conference Proceeding

24. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, Higgins G, Gottlieb B, Chon Y, Zhang N, Baumgartner SW. Effects of long-term etanercept treatment on growth in children with selected categories of juvenile idiopathic arthritis. *Arthritis and rheumatism* 2010;**62**:November.

25. Kearsley-Fleet Lianne, Davies Rebecca, Lunt Mark, Southwood Taunton R., and Hyrich Kimme L. Factors Associated with Improvement in Disease Activity Following Initiation of Etanercept in Children and Young People with Juvenile Idiopathic Arthritis: Results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). 2015.

Ref Type: Unpublished Work

26. Prince FHM, Geerdink LM, Borsboom GJJM, Twilt M, van Rossum MAJ, Hoppenreijs EPAH, Ten CR, Koopman-Keemink Y, Van Santen-Hoeufft M, Raat H, van Suijlekom-Smit LWA. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases* 2010;**69**:January.

27. Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, ten CR, Koopman-Keemink Y, Gorter SL, Raat H, van Suijlekom-Smit LW. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children register. *Rheumatology (Oxford, England)* 2011;**50**:Jun.

28. Klotsche J, Minden K, Thon A, Ganser G, Urban A, Horneff G. Improvement in health-related quality of life for children with juvenile idiopathic arthritis after start of treatment with etanercept. *Arthritis Care and Research* 2014;**66**:February.

29. Otten MH, Anink J, Spronk S, van Suijlekom-Smit LWA. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. *Annals of the Rheumatic Diseases* 2013;**72**:1806-12.

30. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. *Arthritis Care and Research* 2011;**63**:January.

31. Eberhard BA, Laxer RM, Andersson U, Silverman ED. Local synthesis of both macrophage and T cell cytokines by synovial fluid cells from children with juvenile rheumatoid arthritis. *Clin Exp Immunol* 1994;**96**:260-6.

32. Enbrel Summary of Product characteristics. Pfizer Limited. 27-10-2014.

Ref Type: Online Source

33. Etanercept_Enbrel. Scottish Medicines Consortium (SMC). 2012. 12-3-2015.

Ref Type: Online Source

34. etanercept (Enbrel). All Wales Medicines Stategy Group (AWMSG). 6-12-2013. 13-3-2015.

Ref Type: Online Source

35. Enbrel: 50 mg solution for injection in pre-filled pen - Summary of Product Characteristics. Pfizer Limited. 27-10-2014.

Ref Type: Online Source

36. Borrís-Blasco Jn, Gracia-Perez A, Caster+í MD-E, Rosique-Robles JD, Abad J. Educational session as a tool to increase patient satisfaction of switching etanercept from the prefilled syringe to the autoinjection pen. *Expert Opin Biol Ther* 2013;**13**:1103-8.

37. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. *Rheumatology* 2010;**49**:1406-8.

38. Ringold S, Grant S, Girdish C, Wallace CA, Sullivan SD. Methotrexate and injectable tumor necrosis factor-alpha inhibitor adherence and persistence in children with rheumatic diseases. *Journal of Rheumatology* 2013;**40**:January.

39. Klein A, Horneff G. Long-term experience with biologic therapies for the treatment of polyarticular juvenile idiopathic arthritis. *Clinical Investigation* 2013;**3**:May.

40. Hanson H, Hart R, Thompson B, Tattersall R, Jordan A, McDonagh J, Foster HE. 160.ΓÇâWorking on it: A Qualitative Study Exploring Factors Associated with Positive Vocational Outcomes in Young Adults with Juvenile Idiopathic Arthritis. *Rheumatology* 2014;**53**:i120.

41. van Royen-Kerkhof A, Vastert BS, Swart JF, Wulffraat NM. Biologic treatment of pediatric rheumatic diseases: are we spoilt for choice? *Immunotherapy* 2014;**6**:1-3.

42. Anink J, Prince FHM, Dijkstra M, Otten H, Twilt M, Ten CR, Gorter SL, Koopman-Keemink Y, van Rossum MAJ, Hoppenreijs EPA, van Suijlekom-Smit LWA. Long term functional outcome and quality of life of patients with refractory juvenile idiopathic arthritis treated with etanercept: Results of the Dutch arthritis and biologicals in children register. *Pediatric Rheumatology Conference: 21st European Pediatric Rheumatology, PReS Congress Belgrade Serbia Conference Start: 20140917 Conference End: 20140921 Conference Publication: (var pagings) 12 , 2014 Date of Publication: 17 Sep 2014* 2014.

43. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *The Lancet* 2011;**377**:2138-49.

44. Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. *Health Technology Assessment* 2002;**6**:43.

45. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, Maldonado-Cocco J, Suarez-Almazor M, Orozco-Alcala J, Prieur AM. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *The Journal of Rheumatology* 1998;1991-4.

46. Thierry S, Fautrel B, Lemelle In, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: A systematic review. *Joint Bone Spine* 2014;**81**:112-7.

47. Prakken BJ, Albani S. Using biology of disease to understand and guide therapy of JIA. *Best Practice & Research Clinical Rheumatology***23**:599-608.

48. Prince FHM, Otten MH, Suijlekom-Smit LWA. Diagnosis and management of juvenile idiopathic arthritis. *BMJ* 2010;**341**.

49. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002;**109**:2002.

50. NHS STANDARD CONTRACT PAEDIATRIC MEDICINE: RHEUMATOLOGY . NHS commissioning board. 2013.

Ref Type: Online Source

51. Davies R, Kearsley-Fleet L, Baildam E, Beresford MW, Foster H, Southwood TR, Thomson W, Hyrich KL. Factors associated with choice of first biologic among children with juvenile idiopathic arthritis: A combined analysis from two UK paediatric biologic registers. *Pediatric Rheumatology Conference: 21st European Pediatric Rheumatology, PReS Congress Belgrade Serbia Conference Start: 20140917 Conference End: 20140921 Conference Publication: (var pagings) 12 , 2014 Date of Publication: 17 Sep 2014* 2014.

52. Davies, R., Southwood TR, Kearsley-Fleet, Lianne, and Hyrich, K. L. Baseline co-morbidities in patients with JIA starting etanercept or methotrexate: Results from the BSPAR Etanercept Register. BSPAR annual conference. Rheumatology(51), viii7-viii8. 2012.

Ref Type: Conference Proceeding

53. ORENCIA 250 mg powder for concentrate for solution for infusion - Summary of Product Characteristics. Bristol-Myers Squibb Pharmaceutical Limited. 29-9-2014.

Ref Type: Online Source

54. Humira: Summary of Product characteristics. Abbvie Ltd. 27-11-2014.

Ref Type: Online Source

55. RoActemra 20mg/ml Concentrate for Solution for Infusionn - Summary of Product Characteristics. Roche Products Limited. 15-9-2014.

Ref Type: Online Source

56. McErlane F, Foster HE, Davies R, Lunt M, Watson KD, Symmons DPM, Hyrich KL. Biologic treatment response among adults with juvenile idiopathic arthritis: Results from the British society for rheumatology biologics register. *Rheumatology (United Kingdom)* 2013;**52**:ket248.

57. Assessing, managing and monitoring biologic therapies for inflammatory arthritis. Guidance for rheumatology practitioners. Royal College of Nursing (RCN). 2003.

Ref Type: Online Source

58. Bringing Networks to Life - An RCPCH guide to implementing Clinical Networks. Royal College of Paediatrics and Child Health (RCPCH). 2012.

Ref Type: Online Source

59. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**.

60. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *New England Journal of Medicine* 2000;**342**:763-9.

61. Mori M, Takei S, Imagawa T, Imanaka H, Maeno N, Kurosawa R, Kawano Y, Yokota S. Pharmacokinetics, efficacy, and safety of short-term (12 weeks) etanercept for methotrexate-refractory polyarticular juvenile idiopathic arthritis in Japan. *Modern Rheumatology* 2005;**15**:December.

62. Horneff G, Ebert A, Fitter S, Minden K, Foeldvari I, Kummerle-Deschner J, Thon A, Girschick HJ, Weller F, Huppertz HI. Safety and efficacy of once weekly etanercept 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. *Rheumatology* 2009;**48**:2009.

63. Zeng H, Zeng P, Xie Y, Tang Y, Li F. A randomized controlled clinical trial to evaluate the efficacy of recombinant human tumor necrosis factor-alpha receptor ii fusion protein in juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases* 2014;**73**.

64. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Lange M, Finck BK, Burge DJ. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile

rheumatoid arthritis: Interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis and rheumatism* 2003;**48**:01.

65. Lovell DJ, Reiff A, Jones OY, Schneider R, Nocton J, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore JB, White B, Giannini EH. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis and rheumatism* 2006;**54**:June.

66. Mori M, Takei S, Imagawa T, Imanaka H, Nerome Y, Kurosawa R, Kawano Y, Yokota S, Sugiyama N, Yuasa H, Fletcher T, Wajdula JS. Etanercept in the treatment of disease-modifying anti-rheumatic drug (DMARD)-refractory polyarticular course juvenile idiopathic arthritis: Experience from Japanese clinical trials. *Modern Rheumatology* 2011;**21**:December.

67. Mori M, Takei S, Imagawa T, Imanaka H, Nerome Y, Higuchi R, Kawano Y, Yokota S, Sugiyama N, Yuasa H, Fletcher T, Wajdula JS. Safety and efficacy of long-term etanercept in the treatment of methotrexate-refractory polyarticular-course juvenile idiopathic arthritis in Japan. *Modern Rheumatology* 2012;**22**:September.

68. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, and Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2014.

Ref Type: Online Source

69. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;**40**:1202-9.

70. WALLACE CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization, Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *The Journal of Rheumatology* 2004;**31**:2290-4.

71. Wallace C, Giannini EH, Spalding SJ, Hashkes P, O'Neil KM, Zeft AS, Szer IS. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis and rheumatism* 2011;**63**.

72. Horneff, G., Huppertz, H. I., Ganser, G., Haas, J. P., Foeldvari, I., and Minden, K. Drug safety in Treatment of Juvenile Idiopathic Arthritis (JIA): Biologic Therapy Compared with MTX. ACR/ARHP, Boston, Massachusetts, United States . 2014.

Ref Type: Conference Proceeding

73. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. *Clinical Rheumatology* 2015;**34**:61-9.

74. Horneff G, Kaul I. Definition of improvement thresholds in juvenile idiopathic arthritis using the JADAS. *Arthritis and Rheumatism Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals 2012 Washington, DC United States Conference Start: 20121109 Conference End: 20121114 Conference* 2012;S492-S493.

75. Davies R, Southwood T, Kearsley-Fleet L, Lunt M, Hyrich KL. Medically significant infections are increased in patients with juvenile idiopathic arthritis treated with etanercept: Results from the british society for paediatric and adolescent rheumatology etanercept cohort study. *Rheumatology (United Kingdom) Conference: Rheumatology 2014 Liverpool United Kingdom Conference Start: 20140429 Conference End: 20140429 Conference Publication: (var pagings) 53 ()(pp i166-i167), 2014 Date of Publication: April 2014* 2014;i166-i167.

76. Horneff G, De Bock FD, Foeldvari I, Girschick HJ, Michels H, Moebius D, Schmeling H, German T. Safety and efficacy of combination of Etanercept and methotrexate compared to treatment with Etanercept only in patients with juvenile idiopathic arthritis (jia): Preliminary data from the german JIA registry. *Annals of the Rheumatic Diseases* 2009;**68**:April.

77. Halbig M, Horneff G. Improvement of functional ability in children with juvenile idiopathic arthritis by treatment with etanercept. *Rheumatology International* 2009;**30**:December.

78. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, Ganser G, Horneff G. Long-term outcome of patients with jia treated with etanercept, results of the biologic register jumbo. *Rheumatology (United Kingdom)* 2012;**51**:kes019.

79. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, Hospach T, Huppertz HI, Keilzer R, Kuster RM, Michels H, Moebius D, Rogalski B, Thon A. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases* 2004;**63**:December.

80. Otten MH, Prince FHM, Armbrust W, Ten CR, Hoppenreijs EPAH, Twilt M, Koopman-Keemink Y, Gorter SL, Dolman KM, Swart JF, van den Berg JM, Wulffraat NM, van Rossum MAJ, van Suijlekom-Smit LWA. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. *JAMA - Journal of the American Medical Association* 2011;**306**:07.

81. Tarkiainen M, Tynjala P, Vahasalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. *Rheumatology (Oxford)* 2014.

82. Kearsley-Fleet L, Davies R, Lunt M, Hyrich KL, Southwood TR. Growth in children and adolescents with juvenile idiopathic arthritis (JIA) after 2 years of treatment with etanercept: Results from the British society for paediatric and adolescent rheumatology (BSPAR) etanercept cohort study. *Arthritis and Rheumatism Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2013 San Diego, CA United States Conference Start: 20131025 Conference End: 20131030 Conference P* 2013;S122-S123.

83. Zuber Z, Rutkowska-Sak L, Postepski J, Dobrzyniecka B, Opoka-Winiarska V, Kobusinska K, Gietka P, Osinska V, Turowska-Heydel D, Szczygielska I, Kolodziejczyk B, Swiatek-Baczkowska A, Gazda A, Wiland P, Tlustochowicz W, Tuszkiewicz-Misztal E. Etanercept treatment in juvenile idiopathic arthritis: The Polish registry. *Medical Science Monitor* 2011;**17**:2011.

84. Otten MH, Prince FHM, Twilt M, van Rossum MAJ, Armbrust W, Hoppenreijs EPAH, Kamphuis S, Koopman-Keemink Y, Wulffraat NM, Gorter SL, Ten CR, van Suijlekom-Smit LWA. Delayed clinical response in patients with juvenile

idiopathic arthritis treated with etanercept. *Journal of Rheumatology* 2010;**37**:March.

85. Prince FHM, Twilt M, Ten CR, van Rossum MAJ, Armbrust W, Hoppenreijs EPAH, Van Santen-Hoeufft M, Koopman-Keemink Y, Wulffraat NM, van Suijlekom-Smit LWA. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: The Dutch national register. *Annals of the Rheumatic Diseases* 2009;**68**:May.

86. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. *Annals of the Rheumatic Diseases* 2008;**67**:August.

87. Sevcic K, Orban I, Brodszky V, Bazso A, Balogh Z, Poor G, Kiss E. Experiences with tumour necrosis factor-alpha inhibitors in patients with juvenile idiopathic arthritis: Hungarian data from the National Institute of Rheumatology and Physiotherapy Registry. *Rheumatology* 2011;**50**:ker103.

88. Susic G, Radunovic G, Damjanov N, Novakovic D, Djurovic N, Stojanovic R. PReS-FINAL-2144: Bone mineral status in patients with juvenile idiopathic arthritis after 12 months of treatment with etanercept. *Pediatric Rheumatology Conference: 20th Pediatric Rheumatology European Society, PReS Congress Ljubljana Slovenia Conference Start: 20130925 Conference End: 20130929 Conference Publication: (var pagings) 11 , 2013 Date of Publication: 05 Dec 2013* 2013.

89. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, Sibilia J, Kone-Paut I, Gandon-Laloum S, LeBideau M, Bader-Meunier B, Mouy R, Debre M, Landais P, Prieur A-M. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis and rheumatism* 2003;**48**:01.

90. Loskutova OU, Zholobova ES, Nikolaeva MN, Galstian LA. Indirect comparison of etanercept and abatacept efficacy and safety in patients with polyarticular juvenile idiopathic arthritis. *Pediatric Rheumatology Conference: 21st European Pediatric Rheumatology, PReS Congress Belgrade Serbia Conference Start: 20140917 Conference End: 20140921 Conference Publication: (var pagings) 12 , 2014 Date of Publication: 17 Sep 2014* 2014.

91. Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, Ten CR, Koopman-Keemink Y, Gorter SL, Raat H, van Suijlekom-Smit LW. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children register. *Rheumatology (Oxford, England)* 2011;**50**:Jun.

92. Trachana M, Pratsidou-Gertsi P, Badouraki M, Haidich AB, Pardalos G. Achievement of clinical remission in patients with juvenile idiopathic arthritis under a 2-10-year Etanercept exposure. *Clinical Rheumatology* 2013;**32**:August.

93. Vojvodich PF, Hansen JB, Andersson U, Savendahl L, Hagelberg S. Etanercept treatment improves longitudinal growth in prepubertal children with juvenile idiopathic arthritis. *Journal of Rheumatology* 2007;**34**:December.

94. De SS, Marcovecchio ML, Gaspari S, Del TM, Mohn A, Chiarelli F, Breda L. Etanercept improves lipid profile and oxidative stress measures in patients with juvenile idiopathic arthritis. *Journal of Rheumatology* 2013;**40**:June.

95. Alekseeva E, Bzarova T, Fetisova A, Valieva S, Isayeva K, Denisova R, Sleptsova T, Mitenko E, Chistyakova E. Efficacy and safety of etanercept in combination with methotrexate in the patients with early and late juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2013 Madrid Spain Conference Start: 20130612 Conference End: 20130615 Conference Publication: (var pagings) 72 , 201* 2013.

96. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Annals of the Rheumatic Diseases* 2003;**62**:245-7.

97. Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. *Annals of the Rheumatic Diseases* 2002;**61**:2002.

98. Calvo I, Lopez B, Marco A, Henriquez S, Rodriguez Y, Avino J, Martinez R, Harto M. Biological therapy in patients with chronic juvenile idiopathic arthritis-associated uveitis: Results of follow-up in a multidisciplinary unit. *Annals of the Rheumatic Disease Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2012 Berlin Germany Conference Start: 20120606 Conference End: 20120609 Conference Publication: (var pagings) 71 , 20* 2013.

99. Otten MH, Prince FHM, Ten CR, van Rossum MAJ, Twilt M, Hoppenreijs EPAH, Koopman-Keemink Y, Oranje AP, De Waard-van Der Spek, Gorter SL, Armbrust W, Dolman KM, Wulffraat NM, van Suijlekom-Smit LWA. Tumour necrosis factor (TNF)-blocking agents in juvenile psoriatic arthritis: Are they effective? *Annals of the Rheumatic Diseases* 2011;**70**:February.

100. Opoka-Winiarska V, Postepski J, Korobowicz-Markiewicz A, Szabat A, Emeryk A. Effectiveness of tnf inhibitors therapy in children with juvenile idiopathic arthritis aged 2 to 5 years. *Pediatric Rheumatology Conference: 21st European Pediatric Rheumatology, PReS Congress Belgrade Serbia Conference Start: 20140917 Conference End: 20140921 Conference Publication: (var pagings) 12 , 2014 Date of Publication: 17 Sep 2014* 2014.

101. Hooper M, Wenkert D, Bitman B, Dias VC, Bartley Y. Malignancies in children and young adults on etanercept: summary of cases from clinical trials and post marketing reports. *Pediatric Rheumatology Online Journal* 2013;**11**:35.

102. FINAL NON-INTERVENTIONAL SYNOPSIS STUDY REPORT: ENBREL PROTOCOL B1801130 LEGACY NUMBER 0881Y-4689: Enbrel-Juvenile Idiopathic Arthritis (JIA) Use Results Survey [All-Case Surveillance] (Enbrel-JIA). Pfizer Limited. 30-6-2014.

Ref Type: Unpublished Work

103. CSR for Study 0881 X1-4665: RISK OF CANCER IN THE PEDIATRIC POPULATION WITH JUVENILE IDIOPATHIC ARTHRITIS WHO HAVE RECEIVED TREATMENT WITH ETANERCEPT COMPARED TO THE RISK IN THE GENERAL POPULATION-INSIGHT FROM THREE REGISTRIES. Pfizer Limited. 2009.

Ref Type: Unpublished Work

104. Southwood TR, Foster HE, Davidson JE, Hyrich KL, Cotter CB, Wedderburn LR, Hull RG, Venning HE, Rahman JK, Cummins CL. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. *Rheumatology* 2011;**50**:January.

105. NICE technology appraisal guidance [TA238]: Tocilizumab for the treatment of systemic juvenile idiopathic arthritis. NICE. 2011. 16-3-2015.

Ref Type: Online Source

106. Ungar W. Challenges in Health State Valuation in Paediatric Economic Evaluation. *Pharmacoeconomics* 2011;**29**:641-52.

8 Appendices

The following appendices have been provided as separate documents to the main submission

Appendix 1: Systematic review search strategies

Appendix 2: Reference list for excluded studies

Appendix 3: Quality assessment for observational studies

Appendix 4: Summary of Product Characteristics (SmPc), Enbrel