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Synopsis

Effectiveness, safety and cost-effectiveness of methotrexate versus ciclosporin for severe childhood atopic dermatitis: a synopsis of the TREAT RCT

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Published January 2026
DOI: 10.3310/AHDR8524

Abstract

Parts of this abstract have been reproduced from Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F, *et al.*; TREAT Trial Investigators. Efficacy and safety of ciclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): a multicentre parallel-group assessor-blinded clinical trial. *Br J Dermatol* 2023;189:674–84. https://doi.org/10.1093/bjd/ljad281. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Background: Atopic dermatitis is a chronic, inflammatory skin disease characterised by intensely itchy skin. Atopic dermatitis has the highest disease burden among cutaneous diseases as measured by disability-adjusted life-years and approximately 20% of United Kingdom children experience atopic dermatitis, of whom 16% have moderate or severe forms. Treatment options for severe childhood atopic dermatitis are limited, and this is compounded by the lack of widely available information regarding short- and long-term side effects and cost-effectiveness of different treatments. Ciclosporin is the most commonly used systemic treatment for severe paediatric atopic dermatitis, but methotrexate is being increasingly used as an alternative first-line systemic treatment. Although these medications are regularly used off-licence in children with severe atopic dermatitis, there had been no firm evidence about the effectiveness, safety, cost-effectiveness, or impact on quality of life from an adequately powered randomised controlled trial using systemic medication in children.

Design and methods: The TREatment of severe Atopic dermatitis Trial addressed this gap, assessing potential differences in the speed of onset, effectiveness, side-effect profiles and reduction in flares post treatment between ciclosporin and methotrexate, and the cost-effectiveness of the drugs. Treatment impact on quality of life was also examined in addition to whether filaggrin genotype influences treatment response. Furthermore, the trial studied the immunological effects of ciclosporin and methotrexate. TREatment of severe Atopic dermatitis Trial was a multicentre,

parallel-group, assessor-blind randomised controlled trial of 15 months duration (9-month treatment phase, 6-month follow-up period). In total, 103 children aged 2–16 years with moderate to severe atopic dermatitis, unresponsive to topical treatment were randomised (1 : 1) to receive methotrexate (0.4 mg/kg/week) or ciclosporin (4 mg/kg/day).

Objectives: The trial had two primary outcomes: change from baseline to 12 weeks in Objective Severity Scoring of Atopic Dermatitis and time to first significant flare following treatment cessation.

Results: The TREatment of severe Atopic dermatitis Trial found that ciclosporin had a faster onset of results compared to methotrexate up until approximately 20 weeks on treatment, with a mean difference in change between baseline and 12 weeks of −5.69 (97.5% CI −10.81 to −0.57, $p = 0.013$). Following this time point, methotrexate became more effective up to the end of treatment and showed better longer-term disease control; however, there was no statistically significant difference between treatment groups in the time to first significant flare after treatment cessation (log-rank test $p = 0.15$; HR = 1.55; 97.5% CI 0.77 to 3.10, $p = 0.16$). These results were supported by the immunological readouts measured during the study, suggesting the methotrexate-driven strengthening of the skin barrier.

The data also suggest no significant benefit for increased kidney monitoring to detect renal dysfunction. A reduced need for renal monitoring would reduce both financial and carbon costs of care for patients moving forward.

Limitations: The primary limitations for this project include missing data from patient diaries, a small sample size for a randomised controlled trial comparing two active treatments, and a lack of hepatotoxicity marker collection.

Conclusions: The results of the TREatment of severe Atopic dermatitis Trial have changed the treatment paradigm for the use of conventional systemic medication, favouring methotrexate, especially because the health economics analysis found that methotrexate is more cost-effective than ciclosporin. The findings of the TREatment of severe Atopic dermatitis Trial have been incorporated into updates of international treatment guidelines for atopic dermatitis.

Future work: Looking forward, it would be clinically useful to conduct longer-term, real-world studies to determine the optimal duration of methotrexate treatment for atopic dermatitis. It will also be useful to take advantage of atopic dermatitis registers for future research – these provide a wealth of real-world data that can be harnessed for clinical knowledge.

Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme as award number 13/50/12.

A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/AHDR8524.

Introduction

Background and rationale

Atopic dermatitis (AD, also called 'atopic eczema') is a skin disease affecting around 20% of UK children, 16% of whom have moderate to severe disease.[3] Global prevalence varies due to a variety of factors, but developing countries are experiencing a rising incidence.[3] AD is associated with a high-cost burden to patients, families, and healthcare systems.[4,5] Severe AD is associated with sleep disturbance, poor school attendance and social withdrawal, attention-deficit hyperactivity disorder, anxiety and clinical depression. AD skin often becomes infected, and this can be a reason for hospital admission. Although many cases of AD can be treated with emollients, topical anti-inflammatory treatments, and/or ultraviolet (UV) therapy,[6] around 5% of children require oral immunosuppressive treatment to induce and maintain disease control.[7,8] The most conventional systemic agent used for paediatric patients with moderate to severe AD is ciclosporin (CyA), but methotrexate (MTX) has emerged as an increasingly used alternative.[8,9]

Ciclosporin is a calcineurin inhibitor with rapid onset of action in AD that decreases production of the inflammatory cytokines associated with AD and inhibiting T-cell activation by blocking nuclear factor of activated T cells (NFAT)-dependent cytokine production. Long-term use of CyA increases risk of hypertension and renal toxicity and the recommended maximum treatment duration is 1 year.[10,11] Unfortunately, patients on CyA are quick to relapse following treatment cessation.[10] In addition, the economic burden of CyA is great on patients, their families, and the exchequer. For a child weighing 38 kg a 36-week treatment course of CyA (4 mg/kg/day orally) without dose modifications would be £875.70 (or £24.33 per week) in the UK, excluding dispensing costs or National Health Service (NHS) discount.[12]

Methotrexate is a folic acid antagonist that acts as an immunosuppressant by modulating immune system activity and hindering cell division, DNA/RNA synthesis and repair, and protein synthesis. The mechanism of action of MTX in immune-mediated inflammatory diseases is not fully understood, but one putative additional mechanism of action is inhibition of the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway,[13,14] which have been associated with decreased filaggrin (FLG) production. MTX is considered safe for use in paediatric patients,[14,15] but typical side effects include nausea, fatigue, deranged liver enzymes and, rarely, bone marrow suppression. Patients may take MTX indefinitely, as long as safety parameters are not of concern. MTX has shown a slower onset of action than CyA. Clinical experience suggests that MTX may have disease-modifying potential, but this has not been formally assessed with an adequately powered trial. The cost of a 36-week treatment course of MTX (0.4/kg/week equating to 15 mg weekly) without dose modifications is a fraction of the cost of the 36-week CyA treatment cost; £19.65 (or £0.55 per week) for a child weighing 38 kg, excluding the cost of folic acid, dispensing costs or NHS discount.[12]

Atopic dermatitis is characterised by a disruption in the epidermal barrier driven primarily by a T-helper 2 (Th2)/T-helper 22 (Th22) inflammatory response.[16] Although it is known that the disease pathogenesis is driven by genetic predisposition, immunological dysregulation and environmental factors,[17] there is a significant knowledge gap in understanding the interaction of immune biomarkers and their modulation throughout disease course.[18] New, minimally invasive techniques, such as tape strips for stratum corneum sampling, present the opportunity to investigate skin immune biomarkers, especially for paediatric patients, where skin biopsying poses a challenge.[17] Furthermore, tape stripping offers the opportunity to monitor dynamic changes in immune biomarkers over time due to the possibility of repeated sampling. The longitudinal approach allows for the study of various treatment options on the skin's immune profile in addition to providing insight into disease modulation. This will further the current understanding of various treatment efficacies in AD management.

While MTX is not regarded as being nephrotoxic in low doses, both CyA and MTX can affect kidney function. As such, frequent renal profile measurements are routinely undertaken as part of safety monitoring during AD treatment.[10,19] However, these standard tests are not very sensitive tools, since serum creatinine may change late in the evolution of acute kidney injury (AKI). There is some suggestion that cystatin-c (CysC), a protein encoded by the CST3 gene, may identify AKI earlier in children,[20] and a combination strategy incorporating serum creatinine, CysC and urinary N-acetyl-beta-D-glucosaminidase (UNAG) measurement has also been shown to identify AKI earlier.[21] UNAG is an enzyme found in the lysosomes of proximal tubule epithelial cells, and a raised level likely indicates proximal tubular damage.[22] Symmetric dimethylarginine (SDMA) has also been identified as a clinically useful biomarker for chronic kidney disease (CKD) and can be raised in CKD irrespective of the creatinine level.[23] As far as we are aware, no clinical trial has assessed a combination of these sensitive renal function biomarkers in the context of MTX and CyA to date.

There is concern about the potential short- and long-term side effects of CyA and MTX due to a general lack of randomised control trial (RCT) data on treatment effectiveness, cost-effectiveness and side-effect profiles. With increasing interest and prevalence in AD globally, there is a need for cost-effective treatment and increased information on current drugs available for healthcare providers to make informed decisions for their patients.

The TREatment of severe Atopic dermatitis Trial (TREAT, www.treat-trial.org.uk/) was started to address key clinical questions for the management of children with severe AD using systemic medication, looking specifically at any differences in speed of onset, effectiveness, side-effect profiles and reduction in flares post treatment between CyA and MTX, and the cost-effectiveness of the drugs. The reported risk of rebound flares with the use of CyA warranted an especially robust evaluation of CyA as a first-line treatment against a comparator drug that is not only efficacious and safe but potentially also can alter the natural history of the disease. We proposed that MTX fulfils all three requirements. As the anti-inflammatory action of MTX is poorly understood, this trial included laboratory research that aimed to shed further light on how MTX achieves its anti-inflammatory effect with the potential to explain re-programming of the disease process.

Objectives

The primary objectives of the TREAT were to assess the change in AD severity between baseline and 12 weeks of treatment in the two treatment arms and to examine disease remission (as measured by time to first significant flare) following treatment cessation in the MTX versus CyA groups (*Report Supplementary Material 1*).

The secondary objectives were as follows: (1) to examine AD severity using the Eczema Area and Severity Index (EASI), validated Investigator's Global Assessment scale (v-IGA), Objective Severity Scoring of Atopic Dermatitis

(o-SCORAD), and Patient-Oriented Eczema Measure (POEM) scores between 0 and 12, 36, 48, 60 weeks; (2) to compare the number of flares in each study arm as well as the proportion of children who re-flared after treatment cessation; (3) to study the impact on quality of life: change in Children's Dermatology Life Quality Index (CDLQI)/ Infants Dermatitis Quality of Life (IDQoL) and Dermatitis Family Impact (DFI) scores between 0, 12, 36, 48 and 60 weeks; (4) to determine the proportion of participants achieving 50% improvement in the o-SCORAD and EASI index at 12, 36, 48, and 60 weeks; (5) to capture the proportion of participants who withdraw from treatment because of adverse events (AEs); (6) to assess the cost-effectiveness of CyA versus MTX, based on utility measured using the Child Health Utility Instrument (CHU-9D); (7) to study the immuno-metabolic effects of MTX and CyA, especially in markers of glycolytic activation and T-cell cytokine signature, at baseline, and after treatment cessation; (8) to compare the drug side effects/toxicity profiles of both MTX and CyA; and (9) to study the impact of FLG carriage on reduction in AD severity (*Report Supplementary Material 1*). A health economic assessment comparing the cost-effectiveness of the two medications was added, supported by additional funding through the NIHR Research for Patient Benefit Programme.

Methods

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TREatment of severe Atopic dermatitis Trial was a multicentre, parallel-group, assessor-blinded RCT conducted across paediatric dermatology centres in the UK (12) and Ireland (1). Patients were identified through paediatric dermatology clinics. Eligible patients were aged 2–16 years with a diagnosis of severe recalcitrant AD defined as o-SCORAD ≥ 30, and a history of inadequate clinical response to potent topical corticosteroids (TCSs) on the body and moderate strength TCSs on the face as determined by the treating clinician (see *Appendix 1*, *Figure 1*). Other inclusion criteria were usage of a highly effective method of contraception for females of childbearing potential and sexually active males, living within travelling distance of the recruiting centre, willingness to comply with study events, and a baseline visit < 2 weeks from the screening visit. AD was diagnosed using the UK refinement of Hanifin and Rajka criteria.[24] Patients were disqualified from participating in TREAT if they had a serious medical condition that would compromise patient safety, an active or chronic infection at screening or baseline, moderate to severe impaired renal function, liver disease or injury, received systemic corticosteroids within 14 days prior to the screening visit and 28 days of baseline visit, received phototherapy within 4 weeks prior to screening visit and 6 weeks of the baseline visit, or had previous exposure to any biologic agents or systemic immunosuppressive therapy, except for oral corticosteroids (CS) for acute flare management.

Random assignment occurred at a 1 : 1 ratio at the baseline visit using a web-based randomisation programme, which concealed for allocation and was controlled centrally by the Liverpool Clinical Trials Centre (LCTC). Due to the nature of the trial interventions, blinding of the local investigator, research nurse and participants was not possible, but the assessors performing the severity assessments were blinded to treatment group allocation. The screening visit included a full medical history and concomitant medication review, a pregnancy test where applicable, height, safety bloods, collection of demographic data and o-SCORAD completion. Eligible patients returned for the baseline visit, where baseline assessor-blinded o-SCORAD, EASI and v-IGA assessments were conducted, and POEM questionnaires completed. Once all baseline assessments had been performed, participants were randomised to the study drug, which was then dispensed by the local hospital pharmacy.

Participants randomised to the CyA arm (Neoral®, Novartis Pharmaceuticals UK Ltd) were prescribed 4 mg/kg/day orally in two divided doses for the treatment period of 36 weeks. After 12 weeks, dose increases (to a maximum of 5 mg/kg/day) or decreases were allowed, dependent on individual treatment response. Participants randomised to the MTX arm (any brands with UK/EU marketing authorisation) were prescribed a single test dose of 0.1 mg/kg at week 0 and then 0.4 mg/kg/week orally (maximum dose 25 mg/week) until week 36. Only the 2.5 mg strength of MTX tablets was dispensed. Participants in the MTX arm were also prescribed oral folic acid 1 mg once daily apart from on the day of MTX administration.

Patients receiving MTX were followed up at week 1 to monitor for potential myelosuppression. All participants were seen at weeks 2, 4, 8, 12, 20, 28, 36, 48 and 60 for efficacy and safety parameters. Quality-of-life questionnaires were collected at weeks 12, 36, 48 and 60.

All participants were given participant diaries to complete weekly throughout the course of the study. Information on resource use was collected with the diaries.

Samples for skin immune profile analysis were collected at baseline, 12, 36, and 60 weeks, using tape strips. Round, adhesive tapes (3.8 cm^2, DSquame; CuDerm, Dallas, TX, USA) were attached to the skin and pressed for five seconds with a standardised force applied by a disc pressure applicator (CuDerm). Six successive tapes were taken from each patient and stored at −80°C. The strips were removed with tweezers and placed in 2-ml cryogenic vials. The natural moisturisation factor (NMF) analysis was completed using the fifth tape and the cytokine analysis was completed using the sixth tape. The MESO QuickPlex SQ 120MM was used to measure the concentrations of eleven cytokines: TNF-α, IL-1α, IL-1b, IL-1 receptor antagonist (IL-1RA), IL-5, IL-18, CCL27 (CTACK), CCL17 (Thymus and activation-regulated chemokine, TARC), CXCL8 (IL-8), CXCL10 (IP10) and IL-17A.

Analyses

TREatment of severe Atopic dermatitis Trial was powered to detect a minimal clinically important difference (MCID) of 8 o-SCORAD points[25] assuming a standard deviation (SD) of 10, in the change from baseline to 12 weeks for each participant for the coprimary outcome of assessing the change in AD severity. A sample size of 41 per group, increasing to 49 per group to allow for an estimated 18% loss to follow-up, would be required to provide 90% power using a *t*-test with a 0.025 two-sided significance level. The method of analysis of covariance (ANCOVA) was used for this outcome. The outcome measure was o-SCORAD score at 12 weeks post randomisation (± 2 weeks) and the explanatory variables were treatment group and baseline o-SCORAD score. The mean o-SCORAD at baseline (week 0) and at week 12 and the mean change from baseline to week 12 (week 12–0) is presented by treatment group. The mean difference in change from baseline between the two groups is reported with 97.5% confidence intervals. A two-sided *p*-value of 0.025 (2.5% level) is used to declare statistical significance and is reported alongside the 97.5% confidence interval.

For the second primary outcome of examining disease remission as defined by time to the first significant flare following treatment cessation, the study was powered to detect a difference of 30% (from 86% to 56%) based on the results reported by Harper *et al.*,[10] which indicated that 86% of participants re-flared after the first 3 months of CyA pulse treatment. A sample size of 43 per group, increasing to 51 per group to allow for an estimated 18% loss to follow-up, would be required to provide 80% power to detect a reduction in re-flare of 30% (from 86% to 56%), using a two-sided test with a 0.025 significance level.

For the skin immune profile assessment, the baseline level of cytokines was used as standard and the amount of cytokine on the tape was normalised for protein content. Cytokines were excluded from data analysis if, for a specific marker, the majority was below detection level. The NMF components analysed were histidine, pyrrolidone carboxylic acid, trans-urocanic acid and cis-urocanic acid. High-performance liquid chromatography with a UV detector was used to perform the analysis of NMF compounds. NMF was normalised by protein amount. The analyses for the skin immune profile are not included in the statistical analysis plan (SAP) (*Report Supplementary Material 2*).

For the statistical analysis of the skin immune profile, the distribution of biomarker concentrations was checked with QQ plots against normal and exponential distributions, with the median and interquartile range obtained as summary statistics. We used the Spearman's correlation to test for any association between EASI and biomarker concentrations and the Wilcoxon matched-pairs signed-rank test to compare biomarker concentrations at each planned follow-up. Lastly, we used a repeated-measures analysis with generalised estimating equations to study the effects of MTX and CyA on biomarker concentrations with the predictors of separate time effect contrasts at the planned follow-up visits with respect to baseline, a treatment effect contrast comparing the MTX group to the CyA group, and a follow-up visit by treatment interaction.

Although not originally listed under the study objectives, the additional outcome of studying the potential impact of CyA versus MTX on renal function was comprehensively assessed through an evaluation of both functional (serum creatinine, SDMA, CysC) and kidney injury (UNAG) markers at baseline, weeks 2, 12, 36 (9 months on treatment from baseline) and 60 (6 months off treatment).[1] The difference at each time point was assessed using linear mixed models, including a random intercept, to allow for within-participant correlations at different visits. The covariates in the models were the baseline value and an interaction between treatment group and visit in order to estimate the treatment effect at each time point. The total number and percentage of potentially clinically relevant treatment emergent decreases in estimated glomerular filtration rate (eGFR) are reported. This was defined as a drop in eGFR > 20% from baseline, with eGFR calculated using the formula eGFR = height (in cm) × 40/plasma creatinine.

The within-trial economic analysis was undertaken using individual patient-level data from the TREAT trial using

the intention-to-treat (ITT) principle. A health economic analysis plan (HEAP) (*Report Supplementary Material 3*) was written and signed before analysis began and the primary analytical approach taken was cost–utility analysis, with secondary analysis taking a cost-effectiveness analysis approach. The evaluation has been undertaken in keeping with published guidelines for the economic evaluation of health care interventions at the time the analysis plan was written.[26–30]

The economic evaluation takes a UK NHS and Personal Social Services (PSS) perspective to reflect the funder and location of most of the work. The study did include one Irish centre in Dublin, which recruited 5 (< 5%) participants. In Ireland, although a large percentage of health care funding is via the public system, individuals are often required to subsidise certain types of care at the point of use. The process of care for the drugs being considered is not dissimilar between the UK and Ireland; therefore, participants data from the Irish centre were included in the analysis and costed from a UK perspective. Data on time off work for parents/carers are presented in a separate sensitivity analysis to reflect the broader perspective of these costs.

In accordance with the National Institute for Health and Care Excellence (NICE) guidance,[29] the data collection tools were designed to capture resource use from the perspective of the NHS. The clinical team did not feel this group of patients were likely to incur any PSS because of their AD. Resource use data were compiled from two sources. Intervention costs including visits, safety monitoring and medication [both intervention drugs and concomitant medications (i.e. any drug or substance administered between the screening visit and the visit at week 60)] were sourced from Clinical Report Form (CRF) data. Wider NHS resource use [general practitioner (GP) and practice nurse visits in primary care and secondary care hospital contacts with doctors, nurses or accident and emergency] related to the child's AD was collected via diaries (hereon referred to as diary data) completed by the main guardian/carer. Some resource use incurred because adverse events were collected via CRFs as part of safety monitoring but, because these data might overlap with the diary, data were not analysed together with the diary data. Costs of any pregnancy tests undertaken during monitoring were not included because they were not routine in this aged population and represent a very small cost. Parents were asked to record time-off work because of their child's AD (i.e. either to attend appointments or look after them when off school unwell due to their AD) and children's time off school due to their AD as part of the diary data. Study diaries were designed for completion at 4, 8, 12, 20, 28, 36, 48 and 60 weeks – these diaries were designed to be self-completed and returned either to the trial research nurses at clinic visits or via the post and entered into the database by the central research team at the University of Liverpool. Consent was also sought to contact participants GP practices in order to collect resource use data.

Given the low response and completion rates of diary data and GP questionnaire on wider (non-trial) health resource use data, the resource use data collected as part of the CRF on adverse events and serious adverse events were used to cost additional health care visits. These data were only collected for the duration a participant was taking trial treatment plus 4 weeks post treatment cessation and are analysed together with intervention resource use and concomitant medication to provide what has been termed a partial NHS perspective in the base-case analysis.

All unit costs were valued in Great British pounds for 2022. The cost of the intervention medications were estimated using the published unit costs in the Prescription Cost Analysis.[31] Other resource use relevant to the NHS perspective was valued using unit costs identified from published sources, including Prescription Cost Analysis,[32] Unit Costs of Health and Social Care[32] and NHS Reference Costs.[33] A table of unit costs, together with their sources and assumptions, is presented in the results section. Assessment appointments were costed using the Paediatric Dermatology Service – Consultant led Non-Admitted Face-to-Face Attendance Follow-up rate after the first visit which was costed using the first visit unit cost. When more than one product existed for a particular medicine name, the unit cost for that most frequently prescribed drug was used.

Parental time off work to look after their child due to appointments or illness as a result of AD was sought in the participant diaries and costed using the human capital approach using published average wages.[34] Time off school due to AD was captured for the child participants and is reported in units of time as there is not agreed approach to costing children's time.[35,36] The cost of all reported resource use was calculated for each participant and a total cost for each participant was estimated along with a mean (SD) cost per participant by treatment group.

For full reports on the statistical analysis plan and the health economics analysis plan, refer to *Report Supplementary Materials 2* and *3*.

Discussion/interpretation

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Findings

Three hundred and thirty-three potential participants were screened between May 2016 and February 2019, of whom 103 were deemed eligible and underwent randomisation to receive CyA (n = 52) or MTX (n = 51) for the 36-week treatment period. Recruitment closed once target was reached. One participant randomised to the CyA group did not receive study treatment for religious reasons (alcohol in the CyA solution). Seven (13%) and 13 (25%) participants prematurely discontinued CyA and MTX treatment, respectively. All 103 participants randomised were included in the ITT analysis and the health economic analysis. The baseline demographics, clinical characteristics of participants, and biomarker scores were well balanced across both groups (see *Appendix 1*, *Figures 2*–*13*, and *Appendix 2*, *Tables 1*–*3*), including the disease severity and quality-of-life scores. The final follow-up visit was conducted on 14 May 2020.

The CyA group saw a statistically significant improvement in disease severity based on o-SCORAD compared to the MTX group at week 12, with a mean difference in change between baseline and 12 weeks of −5.69 (97.5% CI −10.81 to −0.57, p = 0.013; using ANCOVA; see *Appendix 1*, *Figure 2*). MTX produced better disease control at week 36 compared to CyA, with a estimated difference in mean o-SCORAD of 1.44 (estimated mean score for the MTX cohort minus the CyA cohort; p-value 0.3606). By weeks 48 and 60, the estimated difference was 4.56 (p-value 0.0093) and 7.68 (p-value 0.0001), respectively (see *Appendix 2*, *Table 4*). A total of 43 participants experienced a significant flare (relapse) after treatment cessation, 25 (48%) in the CyA group and 18 (35%) in the MTX group. There was no statistically significant difference between treatment groups in the second coprimary outcome, time to first significant flare after treatment cessation (log-rank test p = 0.15; HR = 1.55; 97.5% CI 0.77 to 3.10, p = 0.16; see *Appendix 1*, *Figure 14*). Sensitivity analyses yielded comparable results (see *Appendix 2*, *Tables 5*–*7*).

Regarding the secondary outcomes, mean profile plots showed greater improvement in disease severity scores in the CyA group at 12 weeks, no difference at 36 weeks, and in favour of MTX at 48 (12 weeks post treatment) and 60 weeks (24 weeks post treatment) (see *Appendix 2*, *Table 8*). The linear mixed models confirmed these findings (see *Appendix 2*, *Tables 9*–*11*).

The proportion of participants achieving o-SCORAD-50 was significant at 12 weeks in favour of the CyA group (OR = 2.60; 95% CI 1.23 to 5.49, p = 0.012). There were no significant differences between treatment groups at 36 or 48 weeks, but by 60 weeks the proportion of participants achieving o-SCORAD-50 was in favour of the MTX group (OR = 0.33; 95% CI 0.13 to 0.85, p = 0.022) (see *Appendix 2*, *Tables 2* and *9*). These results were confirmed in the secondary analysis of the primary outcome (see *Appendix 2*, *Table 12*).

Comparison of the mean number of participant-reported flares following trial treatment cessation showed a significant difference between the two groups (3.22; 95% CI 0.42 to 6.01, p = 0.025), with a higher number in the CyA group (9.41) compared with the MTX group (6.19). There was no evidence that FLG mutation status modified treatment effect at 12, 36 or 60 weeks (see *Appendix 2*, *Table 13*).

Post hoc analysis indicated that the proportion of participants achieving EASI-50, EASI-75 and EASI-90 at week 12 in the CyA group was significantly higher than those in the MTX group, though by week 60 this effect had reversed (see *Appendix 2*, *Table 8*). Proportion of participants achieving v-IGA 0 or 1 was higher in the CyA group at week 12 [6/52 (11.5%)] compared to the MTX group [1/51 (2.96%)], similar at week 36 and then higher in the MTX group at weeks 48 and 60 (see *Appendix 1*, *Figure 3* and *Appendix 2*, *Table 14*).

Quality of life, as estimated by CDLQI, DFI and IDQoL, improved post baseline to a level of the MCID in both treatment groups (see *Appendix 1*, *Figures 5*–*7*). There were no significant differences in these scores between the treatment groups at any time point (see *Appendix 2*, *Tables 10* and *11*).

Overall, participants in the CyA group reported a higher number of days on topical anti-inflammatory treatments than those in the MTX group over the course of the trial. The mean (SD) total number of days on TCS was 94.50 (37.36) in the CyA group compared with 78.72 (56.46) in the MTX group. The mean total number of days on topical calcineurin inhibitors (TCI) was 51.16 (56.60) in the CyA group compared with 26.09 (35.46) in the MTX group. A higher number of mean (SD) total days on emollients [159.52 (67.86)] was reported in the MTX group compared with the CyA group [142.00 (35.25)].

A total of 369 AEs were experienced by 48 (94.1%) participants in the CyA cohort and 407 AEs by 47 (92.2%) participants in the MTX arm. The five most frequently reported AEs in the CyA group were AD flares (43.1%), headache (27.5%), abnormal eGFR (27.5%), upper abdominal pain (17.6%) and vomiting (17.6%). In the MTX group, the five most frequently reported AEs were nausea (43.1%), AD flares (29.4%), fatigue (23.5%), headache (21.6%) and vomiting (17.6%) (see *Appendix 2*, *Tables 15* and *16*).

Serious adverse events (SAEs) were experienced by five participants in the CyA group (10%) and seven participants in the MTX group (14%) (see *Appendix 2*, *Table 17*). Of the five SAEs reported in the CyA group, two were deemed either possibly or probably related to study treatment by the investigator. One participant developed a bacterial lower respiratory tract infection of moderate severity, and one participant developed eczema herpeticum of moderate severity, requiring hospital admission. The latter participant subsequently withdrew from the study. Of the seven SAEs reported in the MTX group, two were deemed either possibly or probably related to study treatment by the investigator. One participant developed herpes zoster shingles infection of mild severity, and one participant developed eczema herpeticum classified as severe. Both required hospital admission and were withdrawn from study treatment. Overall, 10 participants withdrew from study medication due to an AE: 7.7% in the CyA group and 11.8% in the MTX group (OR = 0.63, $p = 0.53$). Two participants in the MTX arm discontinued treatment because of nausea. There were no blood abnormalities recorded as SAEs and even among non-serious adverse events, excluding abnormal eGFR, these were rare (see *Appendix 2*, *Table 17*).

Samples from patients in both the MTX and CyA arms showed significant changes in cytokine levels from baseline, but the number of cytokines showing significant change was higher in the MTX arm than the CyA arm (see *Appendix 1*, *Figures 12* and *13* and *Appendix 2*, *Table 3*). Other than IL-1α, both treatment arms showed an increase in cytokine levels. Significant changes at week 60 were found for IL1a (MTX), IL-18 (MTX and CyA), CXCL8 (MTX and CyA), CXCL10 (MTX), CCL17 (MTX and CyA) and CCl27 (MTX). No significant changes were observed at any time point for IL-1β with either therapy. NMF showed a significant increase only after MTX treatment, at weeks 12 and 36. NMF is considerably reduced in severe AD cases, independent of FLG loss-of-function status.[37,38] The skin barrier biomarker profile data concluded that MTX induces more NMF production and better corrects inhibition of FLG expression compared to CyA, possibly explaining the better long-term disease control, as seen at the 60-week mark of TREAT. Although there were missing data (only 43/103 participants had available biomarker data), the patterns of missingness were fairly evenly distributed across both cohorts (see *Appendix 2*, *Table 18*).

The Spearman's correlation matrix between EASI and biomarker levels shows that, except IL-1a and NMF, all biomarkers showed positive association with EASI (see *Appendix 1*, *Figure 15*). The best correlation between EASI and biomarkers has been found for CXCL8 ($r = 0.50$; $p < 0.0001$). Although there were no statistically significant differences observed between the two treatment arms for any of the biomarkers, it is worthwhile to note that MTX induced significant changes in baseline levels in a greater number of biomarkers and at more time points than CyA. Importantly, the levels of NMF and IL-1α only increased after MTX, but not CyA, which might explain the prolonged disease control seen in that treatment arm. The findings of the skin immune profile study in the TREAT trial indicate a distinct effect of MTX in modulation of certain pathways associated with Th-2 suppression and normalisation of skin barrier function.

Our study findings show that CyA was not associated with decreased renal function compared to baseline nor did it produce worse renal outcomes than MTX over a 36-week treatment period. The median values for serum creatinine, CysC, UNAG and SDMA remained stable and within normal range in both trial arms. The median values were comparable between the treatment groups at all evaluated time points (see *Appendix 1*, *Figures 6–11*) and using the estimated difference in means between treatment groups at each time point demonstrated no statistically significant differences. The total number of samples of serum creatinine, CysC, UNAG, and SDMA available at each time point varied in the CyA (n = 47, 50, 41, 39 at 2, 12, 36 and 60 weeks) and MTX (n = 44, 47, 34, 31 at 2, 12, 36 and 60 weeks) arms.

Across all time points, 17 events affecting 14 (26.9%) participants in the CyA arm and 14 events affecting 8 (15.7%) participants in the MTX arm demonstrated a 20% decrease in eGFR. In all these events, the eGFR reverted to baseline values when participants were encouraged to hydrate prior to a repeat test, which suggests that these were not treatment emergent incidents. No patients were required to stop treatment due to renal impairment during the study.

These data provide reassurance to clinicians that both drugs can be used as treatments in severe AD, especially where access to newer biological agents is limited. Further,

our data suggest no added benefit with more frequent monitoring to detect kidney dysfunction. Reducing the number of blood tests would make the drugs more acceptable to children and young people who may be put off by the treatment due to the frequency of blood tests. Moreover, fewer blood tests would reduce the overall cost of treatment to healthcare providers, and we suggest monitoring 6-monthly once on a stable treatment regimen. To avoid potentially spurious drops in eGFR, children should be encouraged to maintain hydration when MTX or CyA is prescribed.

In the health economics analysis, the adjusted analyses estimated an incremental cost of −£489.67 (95% CI −685.78 to −293.36) with MTX being significantly cost saving compared to CyA and incremental quality-adjusted life-years (QALYs) of −0.0057 (95% CI −0.0384 to 0.0270) (a loss equivalent of just over 2 days of perfect health, where 1 day of perfect health equals 0.002738. This was not statistically significant). The resulting net monetary benefit (NMB) at a willingness to pay per QALY threshold of £20,000 (£30,000) was £375.49 (£38.45). Since the NMB was positive, methotrexate is likely to be cost-effective compared to ciclosporin. The probability of methotrexate being cost-effective was 85.5% (73.1%) for a £20,000 (£30,000) threshold. The results were similar in unadjusted analyses and those analyses taking a wider perspective. Combined with the results of the treatment analysis, it was found that MTX was superior to CyA since it was both cost saving and resulted in greater clinical improvement of disease severity.

A complete case analysis for the partial NHS perspective was undertaken as stated in the HEAP (*Report Supplementary Material 3*; see *Appendix 2*, *Tables 19–24*). Given the amount of missing utility data, the sample size for this analysis was only 53% of the sample. The adjusted analysis estimated incremental costs of −£282.32 (95% CI −511.41 to −53.24) and incremental QALYs of −0.0104 (95% CI −0.0578 to 0.0369), producing an ICER of £27,102 per QALY and NMB of £73.98 (−£30.19) at a £20,000 and £30,000 threshold. This suggests MTX is likely cost-effective at £20,000 but not £30,000 if the threshold is the same in the Southwest quadrant as the Northeast quadrant of the cost-effectiveness plane. The probability of cost-effectiveness is much lower at 55.7% (48.4%) at a £20,000 (£30,000) threshold, suggesting there is greater uncertainty about the decision to recommend MTX in this analysis. This reflects the sample size and level of missing outcome data in this analysis. The unadjusted analysis of the complete case found cost savings and gains to QALYs suggesting that MTX dominates CyA, but this is likely to reflect that the factors associated with QALYs were not adjusted for, rather than being a realistic estimate. No threshold analysis was undertaken on drug cost because MTX was found to be effective for disease control and cost-effective. It is clear from the results that the cost of CyA would need to be similar or less than that to MTX to appear cost-effective given all other cost categories and outcomes are not significantly different between treatment groups. The secondary analysis for cost-effectiveness with inclusion of data from flares was not completed due to missing data in patient diaries.

The health economics analysis extends the clinical findings of the primary RCT by indicating that MTX and CyA perform similarly in terms of costs for visits/monitoring, adverse events, and concomitant medications and QALYs, but that MTX drug costs are significantly cheaper than CyA drug costs in terms of the mean per participant cost. These findings support the conclusion of the clinical study that MTX is an effective, low-cost alternative to CyA for patients where first-line novel systemic biologics and small molecules prescribing is restricted by health funding bodies.

Contributions to existing knowledge

Currently, neither CyA nor MTX is licensed for the treatment of AD in children and young people, and it is unlikely that this will change in the future, as there is little interest from the pharmaceutical industry in pursuing this for this indication. CyA has a treatment label for AD in adults in the UK/EU and was the most widely prescribed conventional systemic for European and North American children in 2017, despite its significantly higher cost.[8,9,39] Higher drug costs restrict the use of CyA in middle- and lower-income settings, where MTX is the only affordable systemic AD medication. TREAT demonstrates that, as predicted, MTX is a safe and more cost-effective alternative to CyA. Both MTX and CyA demonstrated similar disease improvement above the MCID after week 36 for all severity scores, indicating that both drugs are appropriate treatment options for paediatric patients with severe AD, but CyA acts more quickly to establish disease control, as measured by o-SCORAD; however, MTX demonstrated greater long-term disease control following treatment cessation. Furthermore, although both treatment options carry some semblance of risk for altering kidney function, the data collected in this study can reassure prescribing clinicians that both drugs can safely be used as treatment for severe AD. The data also demonstrate that there is no added benefit to more frequent monitoring for kidney dysfunction. A less rigorous schedule for blood draws may also encourage paediatric patients who would be put off by the frequency of blood tests. Fewer blood tests would also reduce the cost of treatment. TREAT has contributed

greatly to the existing amount of knowledge on the usage of CyA and MTX to treat severe AD in children and young people by addressing key clinical questions regarding any differences in speed of onset, effectiveness, side-effect profile, reduction in flares post treatment and the cost-effectiveness of the drugs.

Strengths, weaknesses, challenges and limitations

TREAT was the first adequately powered RCT in this age group to evaluate available conventional systemic therapies, and the proposed study population was calculated to ensure proper statistical robustness prior to the start of the study. The representativeness of the sample was enhanced by having study sites across the UK and Ireland, and the trial outcomes followed the core outcome set recommended by Harmonising Outcome Measures for Eczema (HOME).[40] These include EASI as a measurement of clinical signs, POEM to track patient-reported symptoms, and CDLQI to evaluate quality of life. Furthermore, TREAT studied active treatment for a relatively long period of time (9 months) and included 6 months of follow-up to evaluate disease control and potential relapse after treatment cessation. Another strength of the study was that there was a good level of complete data collected via CRF including intervention drug use, concomitant medication, safety monitoring and adverse events, enabling the costs of the partial NHS perspective to be robustly estimated.

However, there were missing data, especially for resource use questions, which were discovered at the end of the diary period. A full exploration into the missing data can be found with the health economics analysis. This may have been due to the quantity of questions in the diary and quality-of-life questionnaire in addition to the irregular amounts of time between visits during the trial. Looking back, completion rates for the resource use questions in the diaries ought to have been more closely monitored earlier in the trial so investigators could have made greater attempts to remedy this issue. This meant that the base-case analysis had to be undertaken with a narrower health sector perspective than originally planned in the HEAP. The missing utility data also mean that there is uncertainty around the QALY estimates. The amounts and patterns of missing data were similar in both treatment groups and patterns of missingness were properly investigated to ensure appropriate data evaluation. However, non-random missingness, which is missing data that depend on unobserved variables, cannot be truly ruled out as a mechanism of missingness, meaning that the estimates based on the missing at random (MAR) assumption may be biased.

Second, the sample size is small for the comparison of two active treatments. Although the study size was appropriately powered to detect the published MCID, it is still difficult to interpret within person MCID calculations in the context of between-group comparisons. As such, meeting the MCID between therapies is a large effect to base a power calculation on. Another limitation lies with the time frame of the trial. Since the economic evaluation was contained within the clinical RCT, the results are limited to concluding that MTX is likely to be more cost-effective than CyA over the 60-week time frame of the trial and more long-term effectiveness cannot be inferred from this data set. Another challenge encountered was that when an alternative approach of eliciting wider NHS resource use data from GP practices was adopted, GP practices were struggling with COVID issues. This approach then failed and contributed to delays in conducting the economic analysis. Finally, the study focused on markers for nephrotoxicity, but did not address any markers for hepatotoxicity, which is a main concern with long-term MTX treatment. This should be addressed in future studies using real-world data. Further, since concerns with CyA-associated nephrotoxicity are with long-term continuous use for more than 52 weeks, longer-term follow-up with new markers would be helpful to identify any early signs of nephrotoxicity to warn clinicians about stopping or switching treatment. This longer-term exploration of nephrotoxicity markers needs to be addressed with real-world data.

Take-home messages

Methotrexate is a cost-effective alternative to CyA for the treatment of severe AD in paediatric patients, especially when access to newer biologics is limited. CyA was not associated with decreased renal function compared to baseline or with worse renal outcomes than MTX during the treatment period. Although MTX and CyA performed similarly in terms of costs for visits/monitoring, adverse events and concomitant medications and QALYs, the drug costs for MTX are significantly cheaper than those for CyA, making MTX the first-choice conventional systemic medication for children with severe AD. Due to the cost-effectiveness of MTX, this is highly relevant for middle- and low-income settings, now also reflected in treatment guidelines.[41]

Engagement with partners and stakeholders

We identified the trial sites with support from the UK Dermatology Clinical Trials Network (UK DCTN), as well as the network of the British Society for Paediatric Dermatology (BSPD), ensuring a geographical spread and

balance between highly specialised tertiary paediatric dermatology centres as well as more general secondary care settings. Both organisations had previously contributed to a national and international survey on the use of systemic medication in children with AD, which informed the choice of mediations to be compared in a RCT.[8]

Patient and public involvement

Patient experts were part of the TREAT trial from study conception, including protocol writing, study oversight committees and publication of the results. A national research priority setting exercise was run by the James Lind alliance in conjunction with the National Eczema Society and the Centre of Evidence Based Dermatology in Nottingham in 2012. This brought patients, nurses, and dermatologists together. 'What is the best and safest way of using drugs that suppress the immune system?' was one of five key priority areas for healthcare professionals to address. This topic included questions about ciclosporin and methotrexate. We discussed whether a placebo-controlled trial with systemic immunosuppressive medication was acceptable both at the UK Dermatology Clinical Trials Steering Group, which included an eczema patient and carer and a representative from the National Eczema Society, and at our own St John's Institute of Dermatology PPI panel. There was clear feedback for an active comparator (rather than a placebo arm), as the latter was considered unethical. The National Eczema Society (NES) was also involved in raising awareness of the study during recruitment through their national membership and contributed to the trial design.

The Trial Management Group and Trial Steering Committee allowed two PPI representatives to provide peer support, to provide a broader patient perspective, and to ensure representation at each meeting if one cannot attend. User involvement was sought during the development of information and consent forms, protocol and feedback to the participants through the trial PPI panel comprised of five parents and five young people. This group met regularly and offered advice on other aspects of the trial as needed, including retention of participants.

Finally, the results were published in a format accessible to patients and their families in the NES magazine and on the NES website and then also presented in a national patient and public webinar, hosted by the St John's Institute of Dermatology DermAcademy, chaired by the TREAT trial Chief Investigator and cohosted by the Chief Executive Officer of the NES. The findings from TREAT have also been published on publicly accessible platforms, such as the *British Journal of Dermatology*, which is open access. This ensures that affected communities can access high-quality information and results from this trial. The official lay summary can be found on the TREAT website (www.treat-trial.org.uk/) and the video summary of the results can be viewed here: www.youtube.com/watch?v=n1Lm_fmAEio.

Equality, diversity and inclusion

We recruited from 13 sites in a broad range of settings across the UK and Ireland, not only including highly specialised centres, but also District General Hospitals, with some hospitals having a catchment area with a very diverse set of ethnicities and social backgrounds. Participants were recruited from smaller District General Hospitals, secondary care hospitals, and highly specialised centres (St. John's Institute of Dermatology, Glasgow Children's Hospitals, and centres in Dublin, Bristol, and Birmingham). The demographic characteristics were distributed similarly across both treatment arms, with approximately 60% of patients in each arm identifying as White (see *Appendix 2*, *Table 1*). In the CyA arm, 13% of patients identified as Black, 21% as Asian and 6% as other. In the MTX arm, 8% of patients identified as Black, 24% as Asian and 10% as other; 40% of the CyA arm was female, compared to 55% in the MTX arm.

Among the research team, there were 17 male and 32 female (65%) collaborators and investigators. The TREAT team made great efforts to recruit a diverse participant pool to be as reflective of the general population as possible.

Impact and learning

The findings of the TREAT trial will be significantly impactful for clinical decision-makers, especially those in low-income and low-resource settings, having already been included the international treatment guidelines for AD management.[41] MTX is more cost-effective and can establish better long-term control for severe AD compared to CyA. The long-term control with MTX was further confirmed by the skin immune profile study, which found significant increases in NMF and IL-1α. The TREAT trial also found reassuring data in the renal function assessment for sensitive renal tubular markers, with the findings concluding that there is no added benefit for a rigorous blood sampling schedule.

TREAT was made possible by excellent collaboration among research centres and hospitals throughout the UK and Ireland, in close collaboration with the UK DCTN, who helped to identify trial sites, and the British Society for Paediatric and Adolescent Dermatology, who made

dermatology colleagues across the country aware of the study.

Implications for decision-makers

The TREAT trial concluded that MTX has better treatment efficacy than CyA at 9 months, but that CyA initially works faster (12 weeks). However, even early in the treatment phase, the differences between the treatments were below the MCID, measured using the o-SCORAD and EASI scores, making MTX the preferred choice therapy unless the baseline disease severity is very severe. Moreover, there was better disease control in the MTX versus the CyA group following treatment cessation, indicating the potential for disease modification. This potential was underlined by the cutaneous immune profiles, especially the sustained upregulation of NMF. MTX had a particularly pronounced effect on certain biomarkers compared to CyA, which is a potential indicator of differing mechanisms of action.

The safety parameters collected, including a detailed renal function assessment with sensitive renal tubular markers, during the study were reassuring. Based on the results of our study, we concluded that there is no added benefit to having a rigorous blood sampling schedule to detect kidney dysfunction. A less frequent blood draw schedule would both decrease the overall cost for treatment and make these drugs more appealing to paediatric patients who would otherwise be put off by the frequent blood draws.

The health economics analysis found that MTX also has a favourable cost profile, making it the natural first choice systemic treatment medication in healthcare settings where a conventional immune-modulatory treatment needs to be tried prior to a novel systemic treatment being prescribed. This benefit also makes MTX the preferred conventional systemic treatment choice in clinical settings without licensing considerations, such as most middle- and low-income nations. This was also reflected in the latest update of the living EuroGuiDerm Guideline for the systemic treatment of atopic eczema,[41] which is produced and maintained by the European Dermatology Forum.

Lastly, the International League of Dermatological Societies (ILDS) has proposed that MTX be included in the WHO list of essential medicine for AD and psoriasis.[42] The Global Atopic Dermatitis Atlas (GADA) inaugural report calls for the same, to improve drug accessibility through inclusion on the WHO's essential medicines list and involvement of drug manufacturers. This will be especially impactful for low- and middle-income countries and healthcare centres with low resource availability.

Research recommendations

Although this RCT had a fairly long treatment period of 36 weeks, it would be clinically useful to determine the optimal duration for MTX therapy in a future study, especially as those on MTX appeared to consistently improve from a disease severity point of view, until treatment was stopped. The full treatment potential of MTX was therefore probably not seen, and an even longer trial is needed.

We also recommend that future research take full advantage of AD registers, such as the UK-Irish Atopic Dermatitis Eczema Systemic Therapy Register (A-STAR, https://ppopderm.org/project/a-star/), which provide prospective 'real world' cohorts, from which further comparative analyses can be done. The collection of real-world data on treatment effectiveness and safety of systemic agents holds the potential to enrich the pool of evidence on systemic treatment patterns in AD and fill in the gaps in the representation of AD patients. In recent years, real-world evidence has proven to be an important source of information on treatment outcomes in routine clinical care, complementing RCT data. Patient registers provide close monitoring of long-term medication safety and effectiveness in routine care for the post-marketing phase.[43] Other benefits of register-based studies include generation of evidence to support regulatory decision-making,[44] evaluation of real-world costs of treatments, and optimisation of existing therapeutic regimens.[45] A-STAR UK and A-STAR Ireland are part of a larger consortium of AD registers, DREAM TO TREAT AD, which is compiling data on abrocitinib and conventional systemic therapy use across several countries in Europe. All of these will contribute towards the current database of real-world evidence to inform treatment decisions for AD patients.

Conclusions

TREAT was a multicentre, parallel-group, assessor-blinded RCT conducted across thirteen paediatric dermatology centres in the UK and Ireland with the primary objectives of assessing changes in AD disease severity between baseline and 12 weeks of treatment in two treatment arms, MTX and CyA, and examining disease remission following treatment cessation. The study recruited 103 paediatric participants with severe AD and randomised 52 patients to the CyA arm and 51 to the MTX arm. The trial reported

that CyA at a dose of 4 mg/kg/day demonstrated a greater improvement in severity scoring at 12 weeks, but this was reversed in favour of MTX at a dose of 0.4 mg/kg/week by weeks 48 and 60, showing that MTX established better long-term disease control while CyA established faster onset of disease improvement. Improvements in severity were measured with o-SCORAD. Both MTX and CyA arms exhibited similar improvements in quality-of-life measures post baseline to MCID, as measured by CDLQI/IDQoL. Furthermore, TREAT investigated potential nephrotoxicity of both CyA and MTX by monitoring safety and kidney injury biomarkers, which showed that CyA was not associated with decreased kidney function compared to baseline levels or worse renal outcomes compared to MTX. In addition, based on the data collected during the safety monitoring portion of TREAT, we suggest that there is no additional benefit with more frequent monitoring to detect kidney damage. The health economic analysis conducted within TREAT found that MTX is significantly more cost-effective compared to CyA in the drug cost comparison.

TREAT contributes to the body of evidence on drug and cost-effectiveness for severe AD, allowing physicians to make more informed treatment decisions for their patients. Specifically, this study has confirmed that MTX provides a safe, effective, and cost-effective alternative to CyA for the treatment of severe AD in paediatric patients. The NICE clinical guidance for the diagnosis and management of AD in patients under 12 years of age was originally published in 2007 and was appropriately updated in June 2023 with new evidence on emollients.[46] The current recommendation is to use systemic treatments only after all other options have failed but lack guidance on which systemic therapy to use due to the lack of evidence to inform that recommendation. Therefore, TREAT contributes necessary evidence to inform future updates on this section of the guidance since it is the best evidence available to address this question. Claxton argued that resource allocation decisions should only be based on mean net benefit estimates, even when differences are statistically insignificant as this is the best utilisation of available evidence.[47]

In summary, TREAT found that both CyA and MTX are effective treatments for severe paediatric AD, with CyA acting more quickly and MTX producing better long-term disease control following treatment cessation. The health economic analysis extended the clinical findings by demonstrating that methotrexate and ciclosporin are similar in terms of cost for visits/monitoring, adverse events, and concomitant medications, but that methotrexate drug costs are significantly lower. Therefore, MTX provides a low-cost alternative to CyA, which is particularly useful for healthcare settings with limited financial and drug monitoring resources, where novel therapeutics, such as small molecule therapies and biologic therapies, are out-of-reach for most patients due to the high cost. The findings of the TREAT trial are nuanced, as CyA and MTX were both effective treatments, with advantages to each. The differences between the two drugs may be somewhat irrelevant in clinical practice – patient and parent choice may favour cost-effectiveness over faster response or vice versa. This study contributes to the body of evidence on drug and cost-effectiveness for severe AD, allowing physicians to make more informed treatment decisions for their patients. The optimal duration of treatment with MTX as well as a comparison of conventional systemic therapies to newer biologics and small molecules warrant future research and investigation.

Additional information

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This synopsis should be referenced as follows:
Flohr C, Chan K, Ahmed A, Ashoor F, Beattie PE, Browne F, *et al.* Effectiveness, safety and cost-effectiveness of methotrexate versus ciclosporin for severe childhood atopic dermatitis: a synopsis of the TREAT RCT. *Efficacy Mech Eval* 2026;**13**(1):1–50. https://doi.org/10.3310/AHDR8524

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Acknowledgements

We would like to thank all our study participants and their families for their support. We are grateful to Edel O'Toole and her team (Royal London Hospital and Genome Centre, Blizard Institute, Queen Mary University of London) for their assistance in testing participants' blood samples for mutations in the FLG gene. Bjorn Thomas and the FLG gene analysis pipeline was funded by a Barts Charity grant (MGU0376) to Professor Edel O'Toole. The study was developed with support from the UK Dermatology Clinical Trials Network (UK DCTN) and the UK Translational Research Network in Dermatology (UK TREND). The UK DCTN and UK TREND are grateful to the British Association of Dermatologists for financial support of their Networks. The UK DCTN is also supported by the University of Nottingham.

The TREAT trial was funded by the UK Medical Research Council/National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) Board (grant code 15/EE/0328). The TREAT trial was also supported by the South London NIHR Comprehensive Research Network (CRN) and the core facilities of the NIHR Biomedical Research Centre at Guy's and St. Thomas' NHS Foundation Trust and King's College London. The economic study presented independent research funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit Programme (PB-PG-1215-20019).

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Laboratory investigations: Nicholas Webb (Manchester Royal Infirmary) – provision of expertise on measurement and assessment of renal function relating to study drug administration; Leonie Taams (King's College London) – immunology work; Luke O'Neil (Trinity College Dublin) – metabolomics; Irwin Mclean (University of Dundee) – FLG mutation analyses.

Data-sharing statement

Data collected for the study, including deidentified individual participant data, can be made available to researchers who

provide a methodologically sound proposal to the Principal Investigator for TREAT (CF) with a signed data access agreement. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

All study subjects gave their informed consent for inclusion prior to study participation. The study protocol was approved by the Cambridge Central Research Ethics Committee (REC reference 15/EE/0328) on 5 December 2015.

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/AHDR8524

Primary conflicts of interest: Carsten Flohr was funded through a National Institute for Health and Care Research (NIHR) Career Development Fellowship (CDF-2014-07-037). Carsten Flohr is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (ClinicalTrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principal Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium. His department has received funding from Sanofi-Genzyme and Pfizer for skin microbiome work. He has also received compensation from the British Journal of Dermatology (reviewer and Section Editor) and EuroGuiDerm (guidelines lead). Tracey Sach was funded through an NIHR Career Development Fellowship (CDF-2014-07-006) at the start of the study. Tracey Sach is a member of the UK Dermatology Clinical Trials Network Steering Committee and was chair of the NIHR Research for Patient Benefit East of England Research Advisory Committee between 1 January 2020 and 31 December 2023. Tracey Sach was also a member of the following NIHR funding committees: PHR Funding Committee, PHCSA selection committee, HTA Additional Capacity Funding Board, HTA Antimicrobial Resistance Themed Call Board, HTA Efficient Study Designs, HTA Efficient Study Designs Board, HTA End of Life Care and Add on Studies, HTA Primary Care Themed Call board, HTA General Committee. Mandy Wan is a steering committee member of the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918). Alan D Irvine has received consulting fees from Almirall, Abbvie, Eli Lilly, LEO, Pfizer, Sanofi, and Regeneron and is a Director of the International Eczema Council. Amina Ahmed, Farhiya Ashoor and Catherine Spowart UK Medical Research Council/National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Board (grant code 15/EE/0328). The other authors have no conflicts of interest to declare.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Efficacy and Mechanism Evaluation programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications

Irvine AD, Jones AP, Beattie P, Baron S, Browne F, Ashoor F, *et al.*; TREAT Trial Investigators. A randomized controlled trial protocol assessing the effectiveness, safety and cost-effectiveness of methotrexate vs. ciclosporin in the treatment of severe atopic eczema in children: the TREatment of severe Atopic eczema Trial (TREAT). *Br J Dermatol* 2018;**179**:1297–306. https://doi.org/10.1111/bjd.16717

Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F, *et al.*; TREAT Trial Investigators. 'Efficacy and safety of ciclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): a multicentre, parallel group, assessor-blinded clinical trial'. Abstracts for the British Association of Dermatologists 102nd Annual Meeting, 5–7 July 2022, SEC Glasgow, Scotland. *Br J Dermatol* 2022;**187**:3. https://doi.org/10.1111/bjd.21644

Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F, *et al.*; TREAT Trial Investigators. Efficacy and safety of ciclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): a multicentre, parallel group, assessor-blinded clinical trial. *Br J Dermatol* 2023;**189**:674–84. https://doi.org/10.1093/bjd/ljad281

Bruce G, Rosala-Hallas A, Jones AP, Turner C, Dalton N, Hilger E, *et al*. The effects of ciclosporin and methotrexate on kidney function in the treatment of severe atopic dermatitis in children – results from the TREAT trial. *Br J Dermatol* 2024;**191**:851–2. https://doi.org/10.1093/bjd/ljae276

Olsson A, Steel K, Cooper R, Jones AP, Chan KR, Ogg G, *et al*. Methotrexate and ciclosporin both reduce levels of circulating interleukin (IL)-4 and IL-13 expressing CD4+ memory T cells in childhood atopic dermatitis. *Clin Exp Dermatol* 2025;**50**(11): 2249–54. https://doi.org/10.1093/ced/llaf301

Trial registration

This trial is registered as ISRCTN15837754.

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme as award number 13/50/12.

This synopsis provided an overview of the research award *Assessing the efficacy and safety of methotrexate vs ciclosporin in the treatment of severe atopic eczema in children: the TREatment of severe Atopic eczema in children Taskforce (TREAT) randomised controlled trial*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/13/50/12).

About this article

The contractual start date for this research was in May 2015. This article began editorial review in August 2024 and was accepted for publication in July 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Efficacy and Mechanism Evaluation editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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List of supplementary material

Report Supplementary Material 1
Protocol for the TREAT trial

Report Supplementary Material 2
Statistical analysis plan for the TREAT trial

Report Supplementary Material 3
Health economic analysis plan for the TREAT trial

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/AHDR8524).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

AD	atopic dermatitis
AE	adverse event
AKI	acute kidney injury
ANCOVA	analysis of covariance

BSPD	British Society for Paediatric Dermatology
CDLQI	Children's Dermatology Life Quality Index
CHU-9D	Child Health Utility Instrument
CKD	chronic kidney disease
CRF	clinical report form
CyA	ciclosporin
CysC	cystatin C
DFI	Dermatitis Family Impact
EASI	Eczema Area and Severity Index
eGFR	estimated glomerular filtration rate
FLG	filaggrin
GADA	Global Atopic Dermatitis Atlas
GP	general practitioner
HEAP	health economics analysis plan
HR	hazard ratio
IDQoL	Infants Dermatitis Quality of Life
ILDS	International League of Dermatological Societies
ITT	intention-to-treat
JAK	Janus kinase
MAR	missing at random
MCID	minimal clinically important difference
MTX	methotrexate
NES	National Eczema Society
NFAT	nuclear factor of activated T cells
NHS	National Health Service
NMB	net monetary benefit
OR	odds ratio
o-SCORAD	Objective Severity Scoring of Atopic Dermatitis
POEM	patient-oriented eczema measure
PPI	patient and public involvement
PSS	Personal Social Services
QALY	quality-adjusted life-years
RCT	randomised controlled trial
SAE	severe adverse event
SD	standard deviation
SDMA	symmetric dimethylarginine
STAT	signal transducer and activator of transcription
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
UK DCTN	UK Dermatology Clinical Trials Network
UNAG	urinary N-acetyl-beta-D-glucosaminidase
UV	ultraviolet
v-IGA	validated Investigator's Global Assessment

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This synopsis should be referenced as follows:
Flohr C, Chan K, Ahmed A, Ashoor F, Beattie PE, Browne F, *et al.* Effectiveness, safety and cost-effectiveness of methotrexate versus ciclosporin for severe childhood atopic dermatitis: a synopsis of the TREAT RCT. *Efficacy Mech Eval* 2026;**13**(1):1–50. https://doi.org/10.3310/AHDR8524

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Appendix 1 Figures

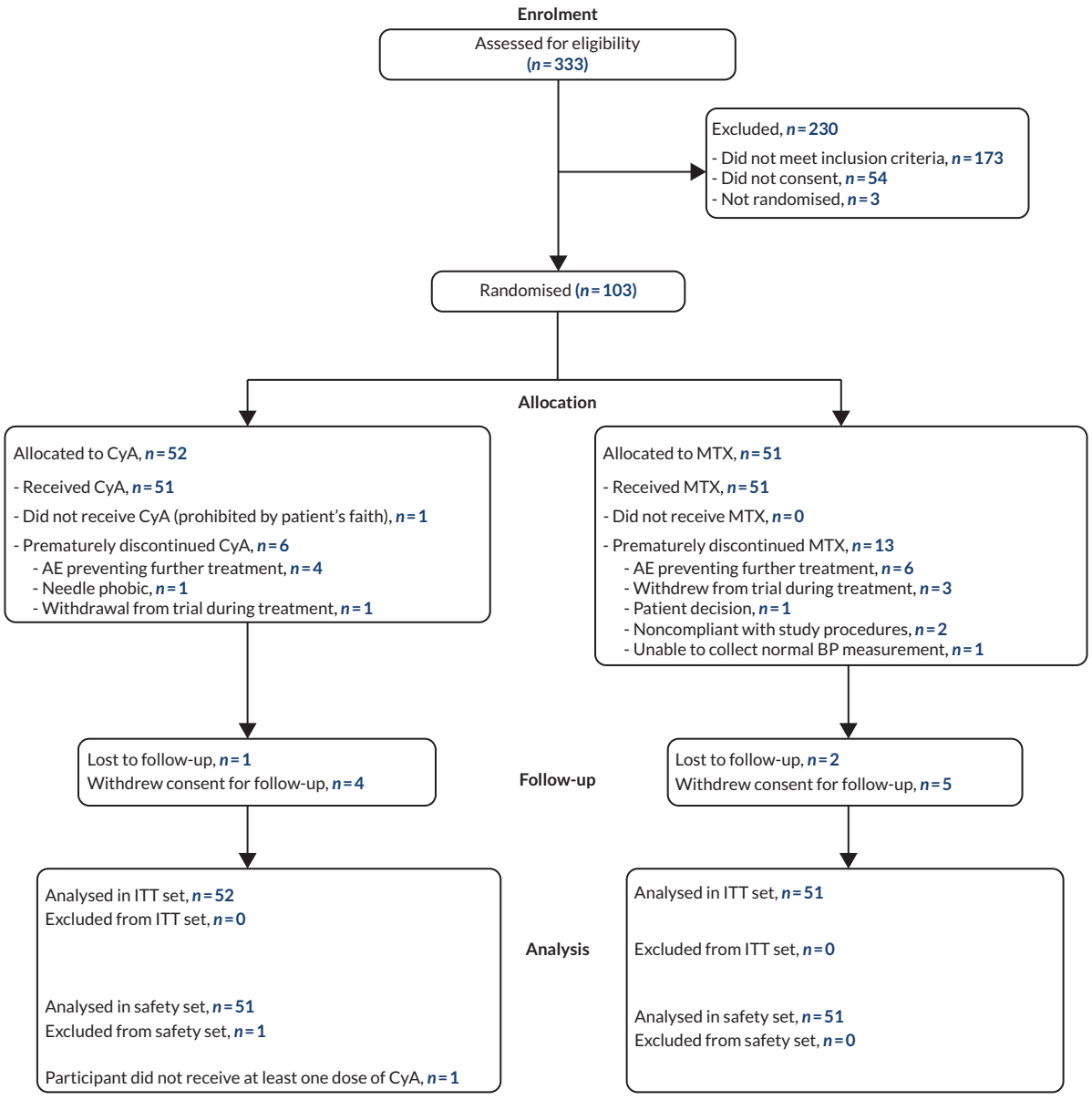

FIGURE 1 CONSORT trial profile. This figure is reproduced from Flohr *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

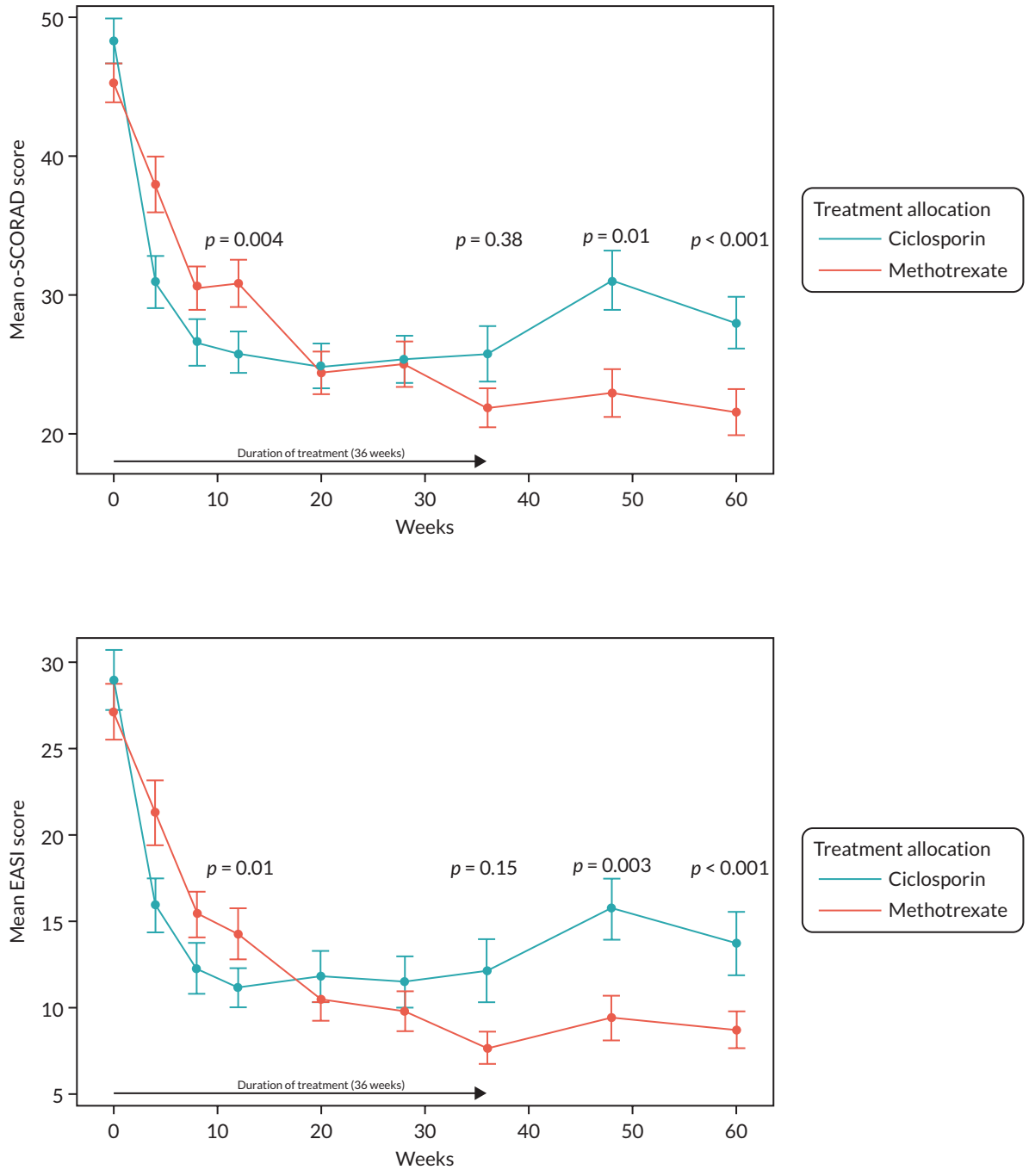

FIGURE 2 Mean profile plot of o-SCORAD and EASI over time. Point estimates at each time point are means with standard error bars; *p*-values are taken from linear mixed-model estimates. This figure is reproduced from Flohr *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

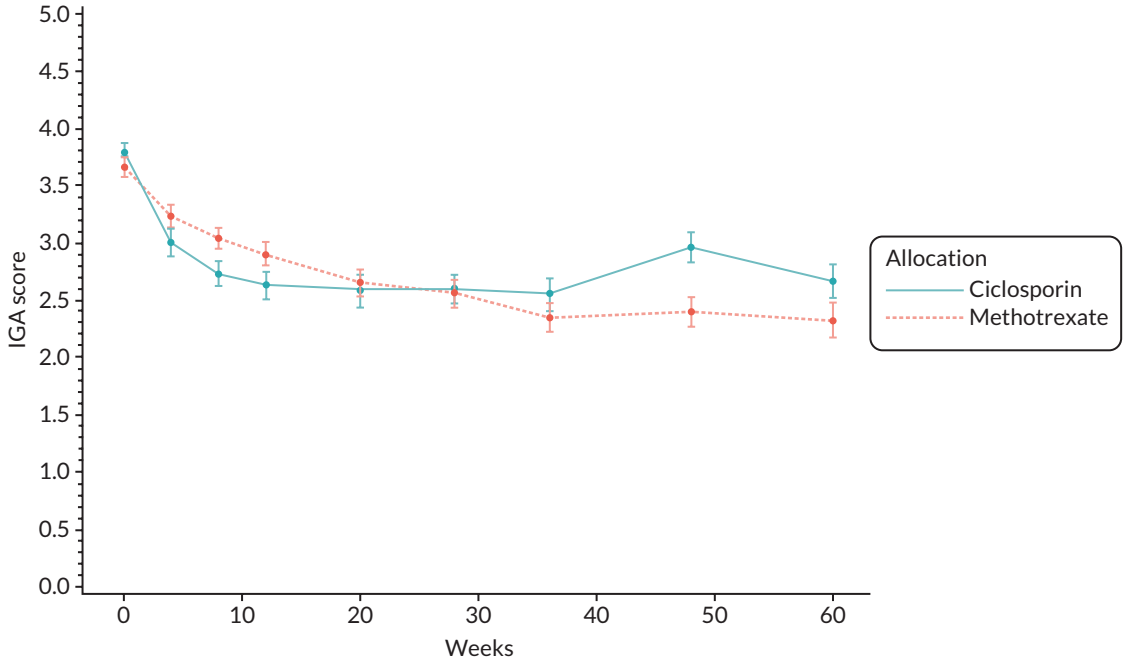

FIGURE 3 Mean profile plots for IGA over times. Raw mean estimates with standard error bars.

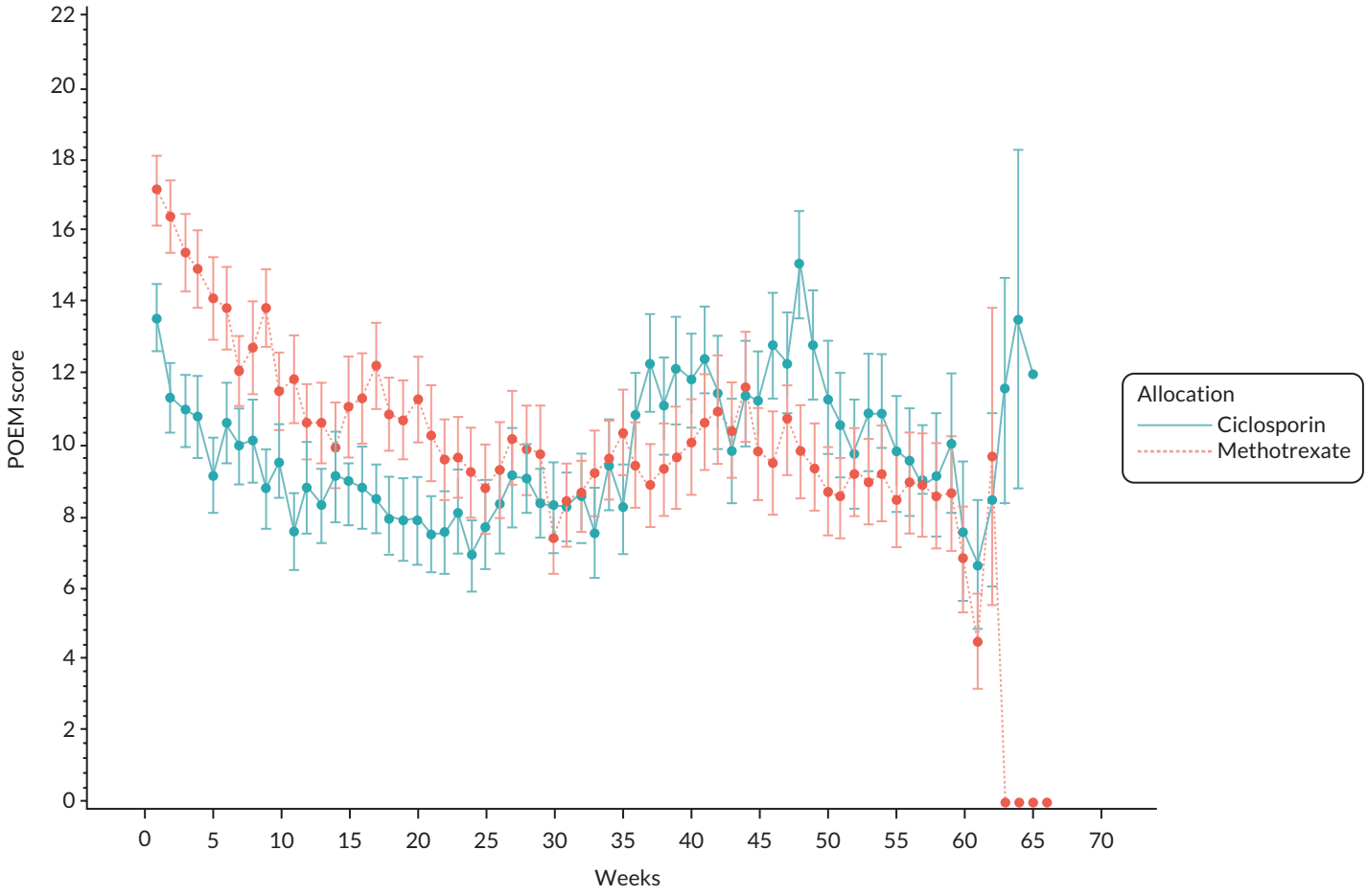

FIGURE 4 Mean profile plots for POEM over time. Raw mean estimates with standard error bars (data are presented after 60 weeks due to participant completion of diaries). The values depicted begin at week 1 of the study, rather than baseline.

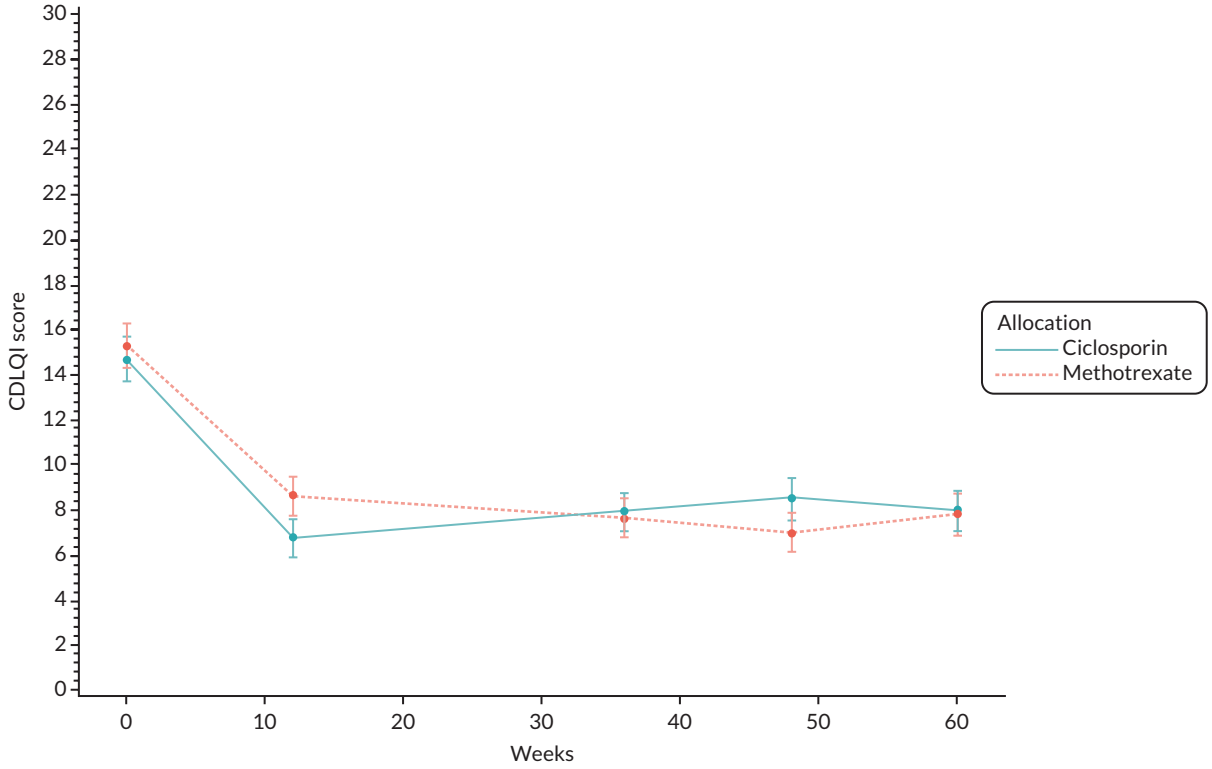

FIGURE 5 Mean profile plot of CDLQI over time. Raw mean estimates with standard error bars.

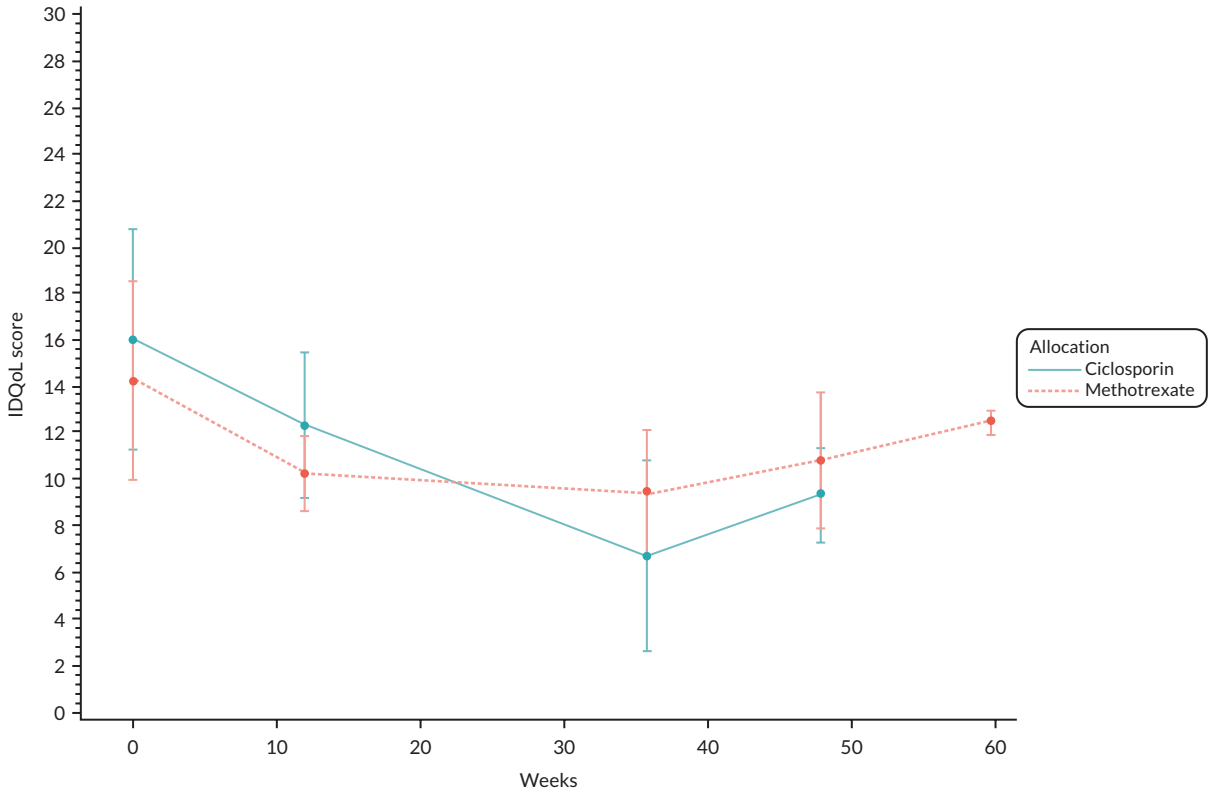

FIGURE 6 Mean profile plot of IDQoL over time. Raw mean estimates with standard error bars.

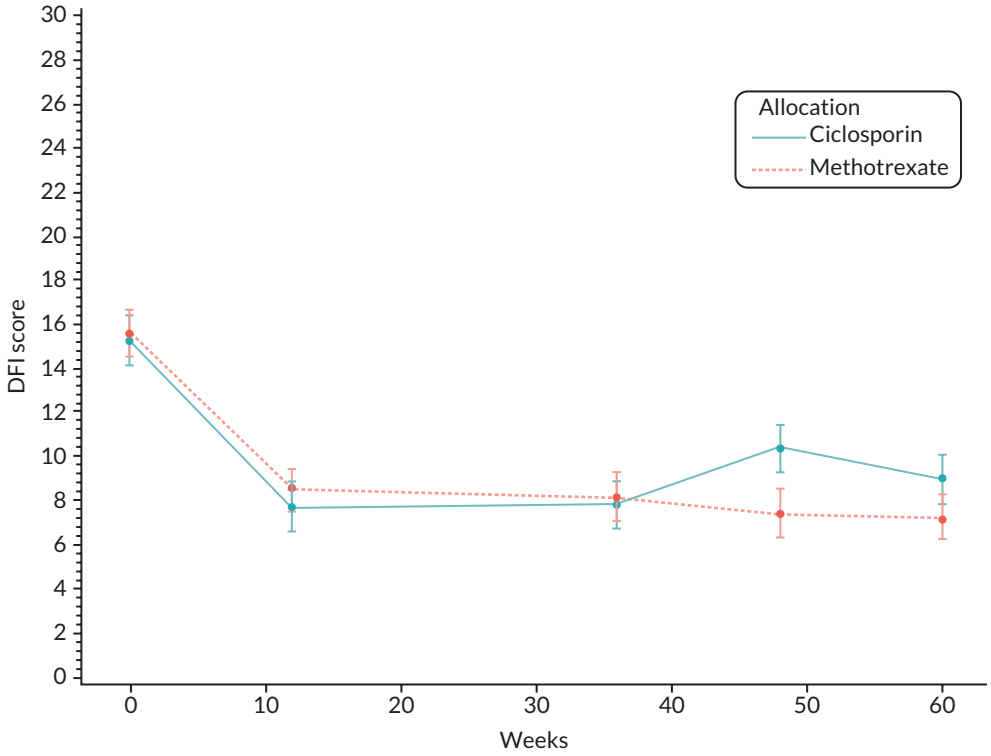

FIGURE 7 Mean profile plot of DFI over time. Raw mean estimates with standard error bars.

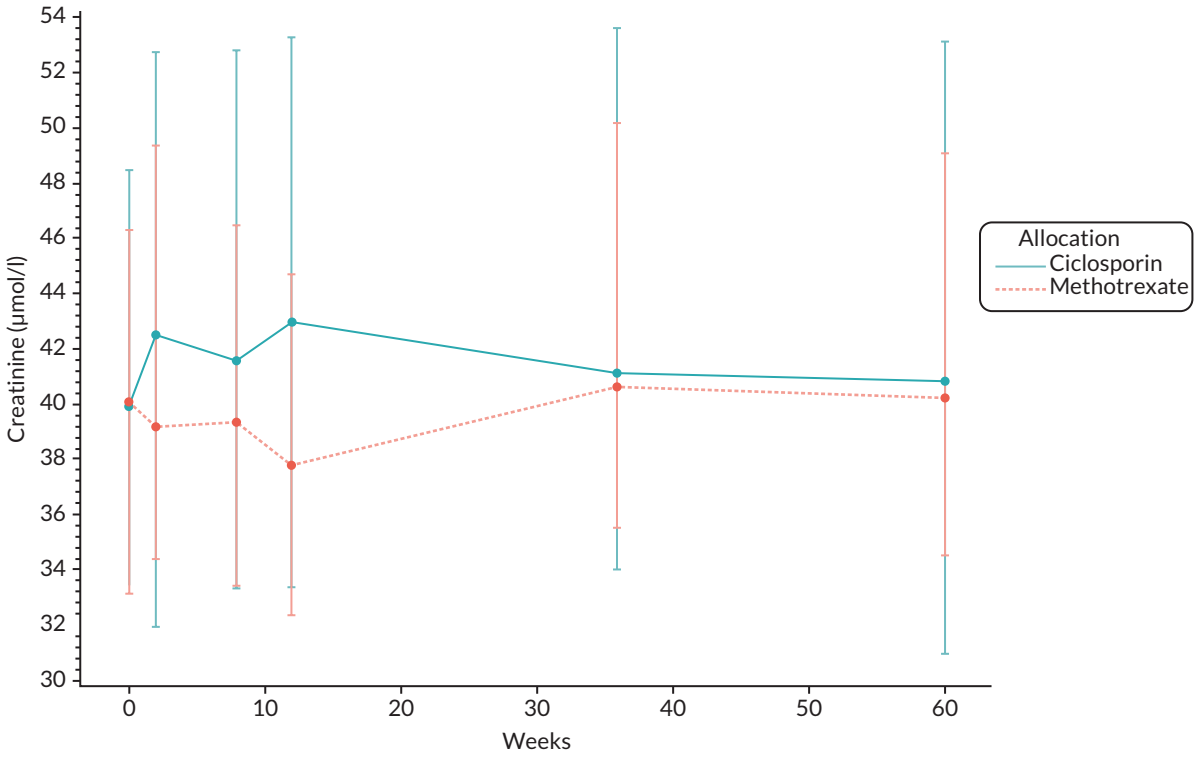

FIGURE 8 Creatinine plot.

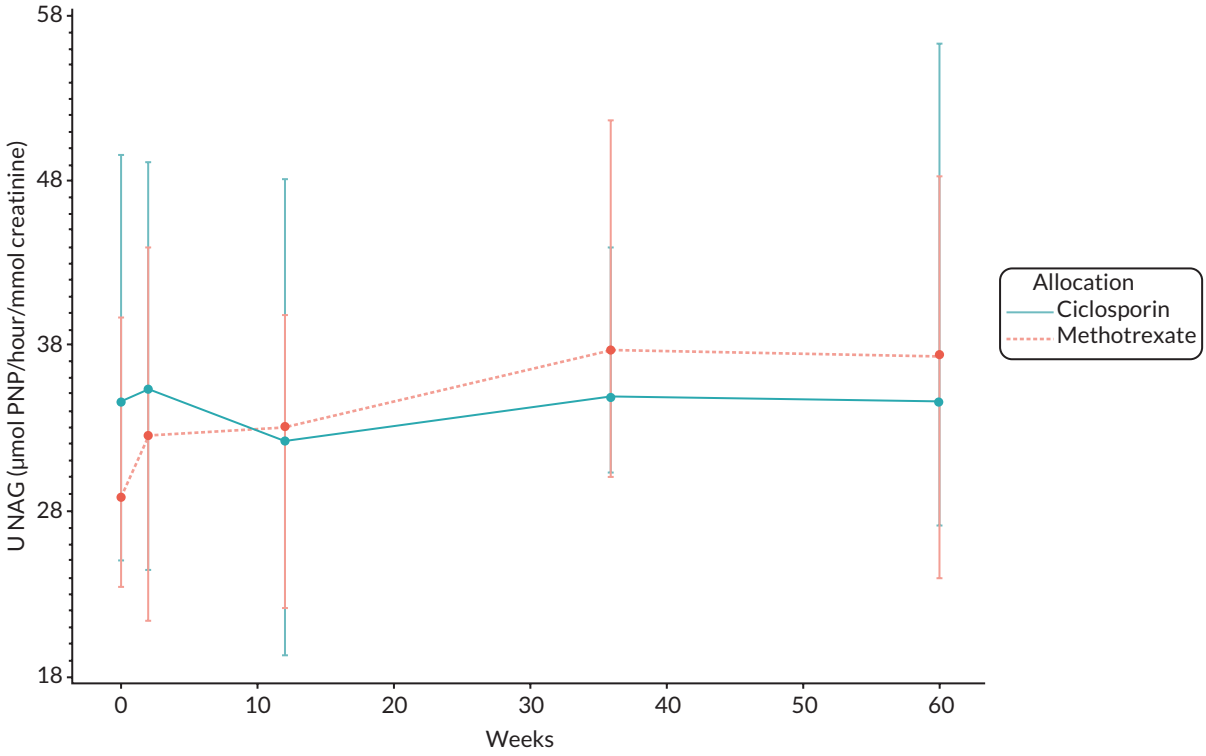

FIGURE 9 Urinary N-acetyl-beta-D-glucosaminidase plot.

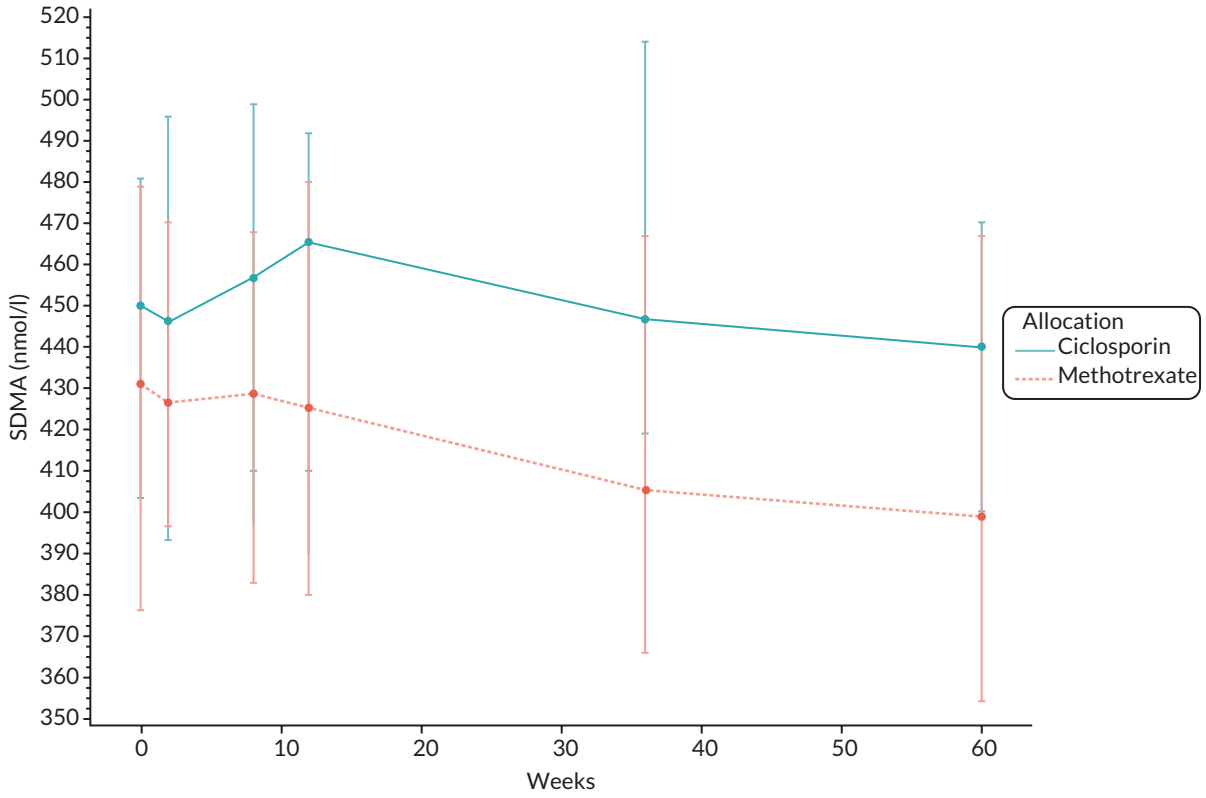

FIGURE 10 SDMA plot.

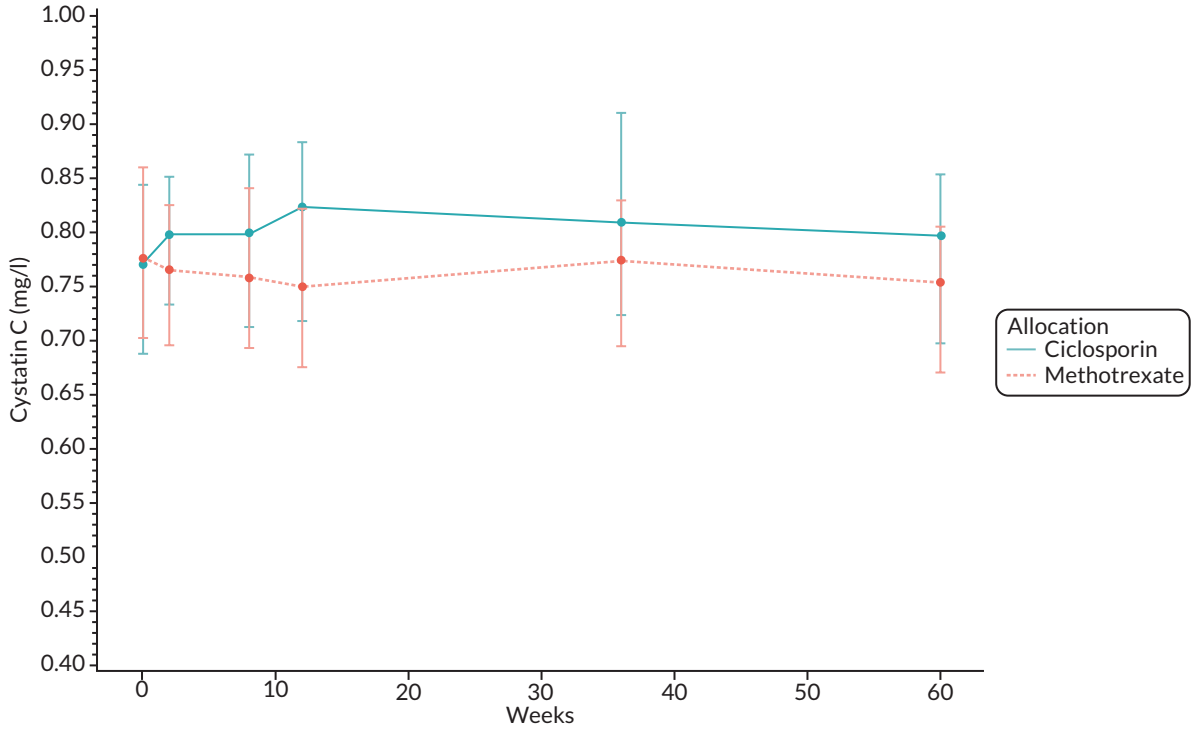

FIGURE 11 Cystatin C plot.

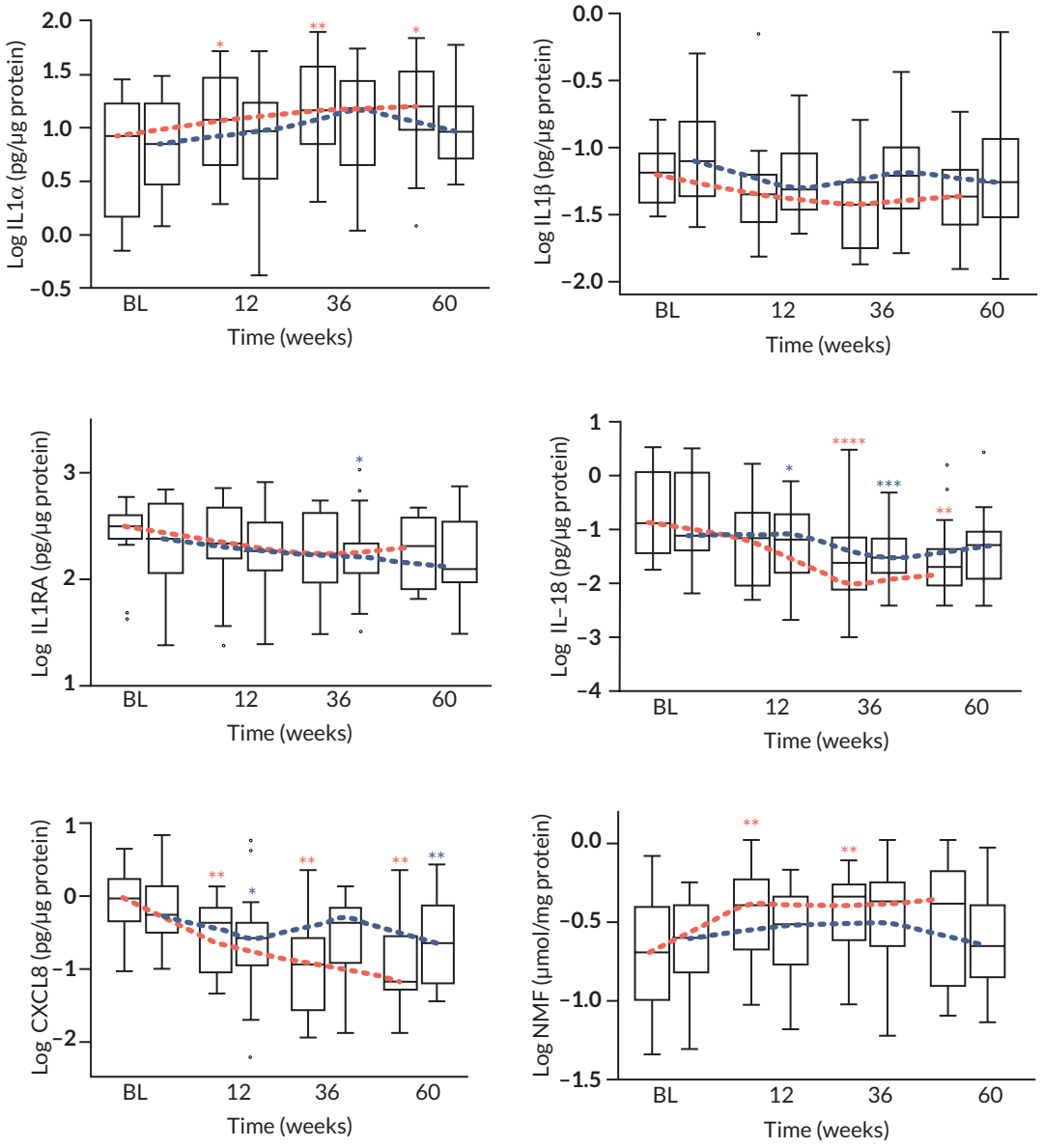

FIGURE 12 Stratum corneum levels of cytokines of innate immunity (IL-1a, IL-1b, IL-1RA, IL-18, CXCL8) and NMF at baseline and during therapy with MTX and CyA.

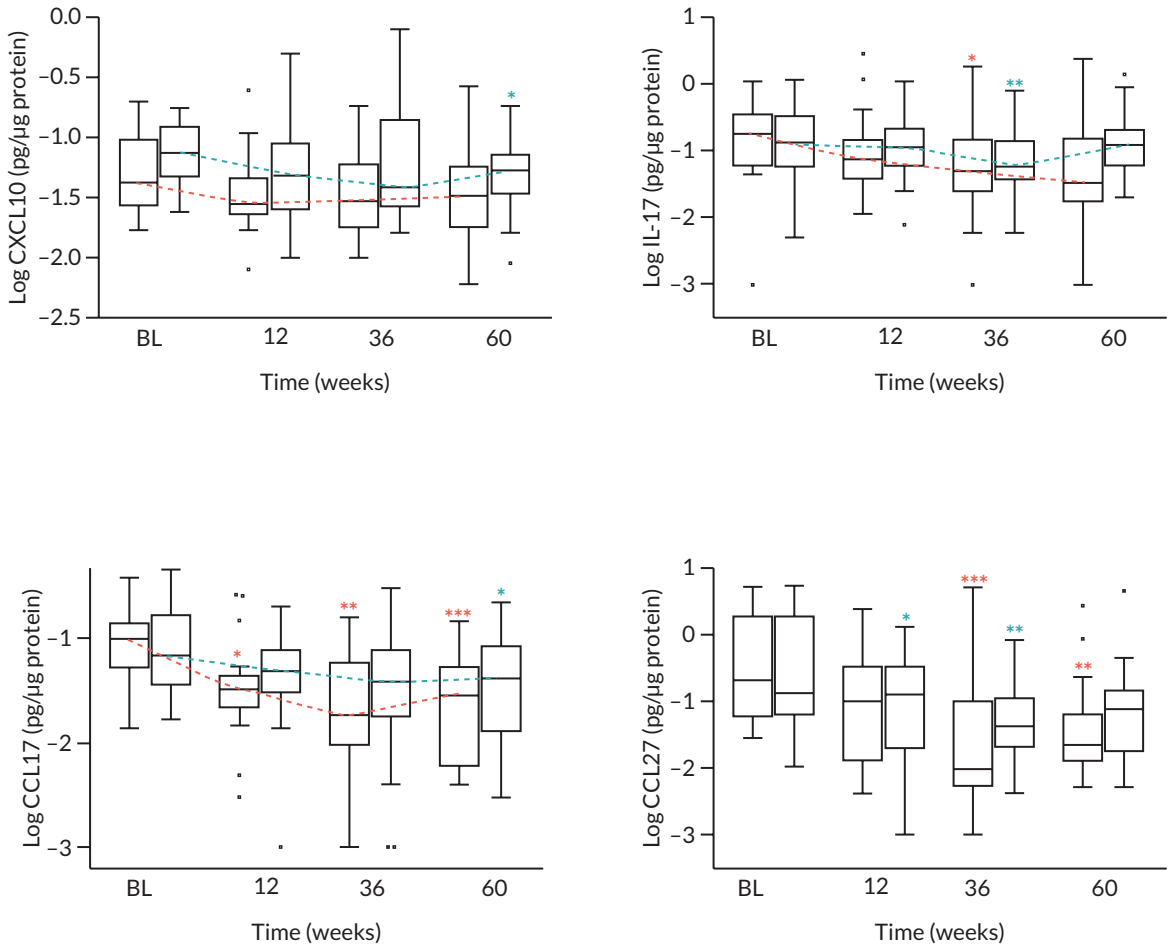

FIGURE 13 Stratum corneum levels of cytokines of Th1 (CXCL10), Th17 (IL-17A), and Th2 (CCL17, CCL27) immunity at baseline and during therapy with MTX and CyA.

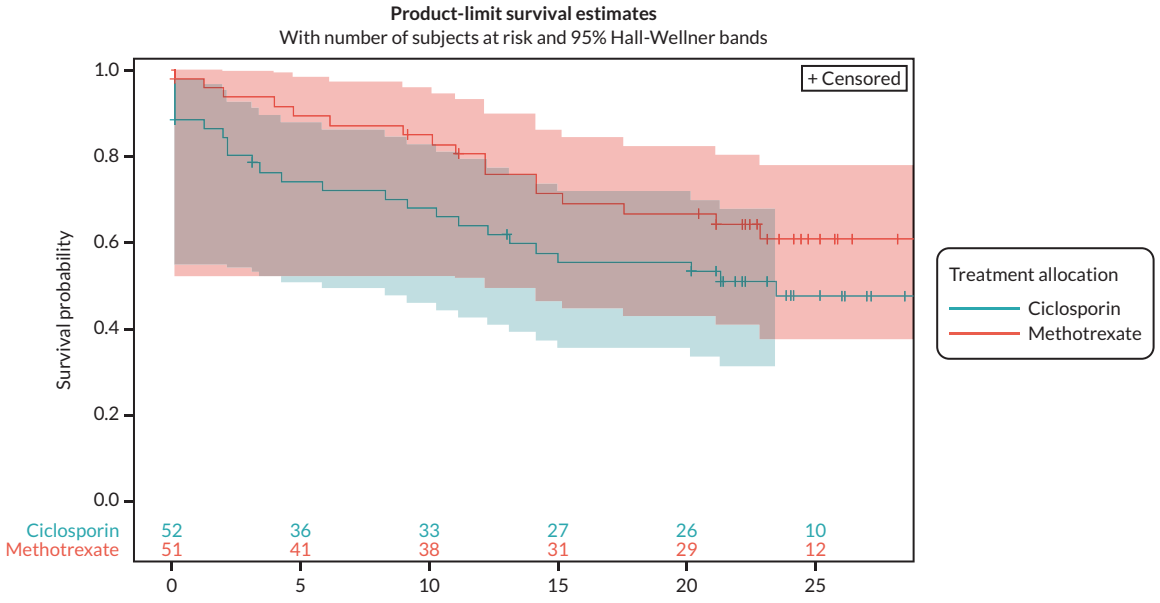

FIGURE 14 Kaplan–Meier curve comparing the time to significant re-flares of disease in the two treatment arms [CyA (blue) vs. MTX (red)].

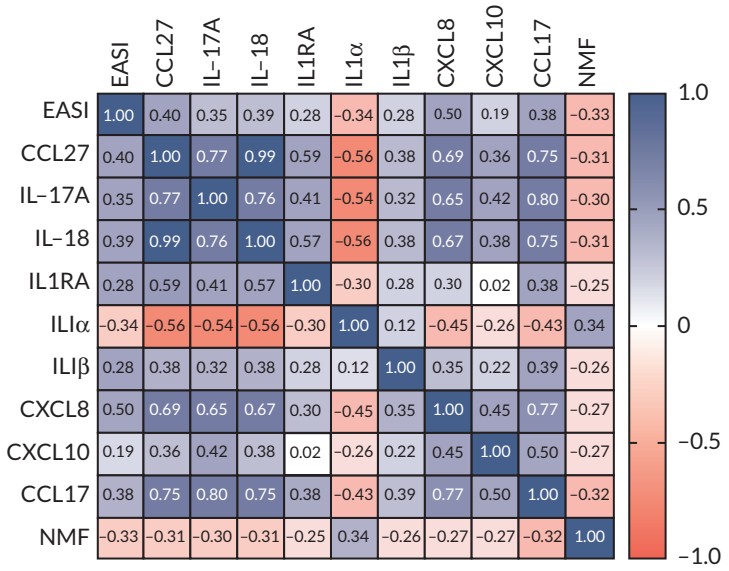

FIGURE 15 Spearman's correlation matrix showing correlation coefficient for EASI and investigated biomarkers.

Appendix 2 Tables

TABLE 1 Demographic and baseline characteristics

	CyA, *N* = 52	MTX, *N* = 51
Sex, n (%)		
Female	21 (40%)	28 (55%)
Male	31 (60%)	23 (45%)
Ethnicity, n (%)		
White	31 (60%)	30 (59%)
Black	7 (13%)	4 (8%)
Asian	11 (21%)	12 (24%)
Other	3 (6%)	5 (10%)
Age in years [mean (SD)]	10.34 (4.21)	9.82 (4.01)
BMI (kg/m^2)[a]	18.80 (4.16)	19.30 (4.15)
o-SCORAD [mean (SD)]	48.34 (11.35)	45.25 (9.60)
EASI [mean (SD)]	28.97 (12.53)	27.12 (11.62)
v-IGA, n (%)		
Mild	0 (0%)	1 (2%)
Moderate	16 (31%)	18 (35%)
Severe	31 (60%)	29 (57%)
Very severe	5 (10%)	3 (6%)
POEM [mean (SD)][b]	20.40 (5.26)	20.84 (5.47)
DFI [mean (SD)][a]	15.24 (7.89)	15.59 (7.67)
CDLQI [mean (SD)][c]	14.67 (6.96)	15.26 (6.57)

a One missing CyA measurement.
b Two missing CyA and two missing MTX assessments.
c Three excluded and one missing CyA assessment; four missing MTX assessments.

Source

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TABLE 2 Participants using anti-inflammatory concomitant medications during and after the treatment phase

	TCSs		TCIs		Topical anti-inflammatory	
Time point	**CyA, *N* (% of 52)**	**MTX, *N* (% of 51)**	**CyA, *N* (% of 52)**	**MTX, *N* (% of 51)**	**CyA, *N* (% of 52)**	**MTX, *N* (% of 51)**
While on randomised systemic therapy	43 (82.7%)	36 (70.6%)	17 (32.7%)	16 (30.8%)	44 (84.6%)	36 (70.6%)
Off randomised systemic therapy	40 (76.9%)	31 (60.8%)	23 (44.2%)	13 (25.5%)	43 (82.7%)	33 (64.7%)

TABLE 3 Median and IQR of stratum corneum biomarkers at baseline and after therapy with MTX and ciclosporin (CyA) at 12, 36 and 60 weeks, and the per cent change from baseline

pg/µg protein, Median (IQR)	Baseline		12 weeks		36 weeks		60 weeks	
	MTX (*n* = 17)	CyA (*n* = 20)	MTX (*n* = 19)	CyA (*n* = 21)	MTX (*n* = 16)	CyA (*n* = 21)	MTX (*n* = 15)	CyA (*n* = 19)
IL-1α	8.22 (1.75–13.10)	7.07 (3.13–16.27)	11.73 (4.40–29.64)*	9.25 (3.37–16.57)	14.86 (7.37–34.06)**	15.08 (4.66–26.22)	15.88 (9.26–33.41)*	9.14 (5.13–15.79)
IL-1b	0.06 (0.04–0.08)	0.08 (0.04–0.15)	0.04 (0.03–0.06)	0.05 (0.03–0.08)	0.04 (0.02–0.05)	0.06 (0.03–0.10)	0.04 (0.03–0.07)	0.05 (0.03–0.12)
IL1RA	309.0 (256.8–385.4)	236.4 (119.2–511.7)	215.1 (155.7–478.1)	181.6 (137.1–356.6)	169.1 (96.6–394.6)	162.8 (113.2–206.9)*	203.6 (79.1–385.6)	123.8 (89.4–342.4)
IL-18	0.13 (0.04–0.77)	0.09 (0.05–1.23)	0.07 (0.01–0.22)	0.08 (0.02–0.13)*	0.01 (0.01–0.06)****	0.03 (0.02–0.07)***	0.01 (0.01–0.04)**	0.05 (0.01–0.10)
CXCL8	1.00 (0.47–1.68)	0.56 (0.35–1.34)	0.23 (0.09–0.76)**	0.26 (0.12–0.45)*	0.13 (0.03–0.24)**	0.52 (0.12–0.72)	0.07 (0.05–0.28)**	0.23 (0.06–0.79)**
CXCL10	0.042 (0.037–0.090)	0.074 (0.048–0.121)	0.028 (0.023–0.046)	0.048 (0.027–0.085)	0.029 (0.018–0.053)	0.038 (0.027–0.114)	0.033 (0.018–0.057)	0.053 (0.034–0.072)*
CCL17	0.100 (0.059–0.142)	0.069 (0.036–0.165)	0.033 (0.022–0.045)*	0.050 (0.034–0.075)	0.018 (0.010–0.057)**	0.039 (0.025–0.078)	0.029 (0.006–0.055)***	0.042 (0.013–0.086)*
CCL27	0.20 (0.06–1.19)	0.13 (0.06–1.76)	0.10 (0.01–0.32)	0.12 (0.02–0.20)*	0.01 (0.01–0.08)***	0.04 (0.03–0.10)**	0.02 (0.01–0.06)***	0.07 (0.02–0.14)
IL-17A	0.18 (0.06–0.36)	0.13 (0.06–0.33)	0.07 (0.04–0.15)	0.11 (0.03–0.18)	0.05 (0.03–0.14)*	0.05 (0.04–0.13)**	0.03 (0.02–0.15)	0.11 (0.02–0.19)
NMF	0.21 (0.11–0.38)	0.25 (0.17–0.39)	0.41 (0.21–0.59)**	0.31 (0.17–0.45)	0.40 (0.25–0.55)**	0.31 (0.23–0.55)	0.45 (0.13–0.66)	0.22 (0.14–0.41)

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; **** $p \leq 0.0001$.

Source

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This synopsis should be referenced as follows: Flohr C, Chan K, Ahmed A, Ashoor F, Beattie PE, Browne F, *et al.* Effectiveness, safety and cost-effectiveness of methotrexate versus ciclosporin for severe childhood atopic dermatitis: a synopsis of the TREAT RCT. *Efficacy Mech Eval* 2026;**13**(1):1–50. https://doi.org/10.3310/AHDR8524

TABLE 4 o-SCORAD-50, o-SCORAD-75 and o-SCORAD-90 – generalised linear mixed model results

	CyA (*N* = 52)		MTX (*N* = 51)			
Visit	***N***	**≥ 50% improvement**	***N***	**≥ 50% improvement**	**Estimated OR (95% CI)**	***p*-value**
Week 12	52	25 (48.1%)	51	14 (27.5%)	2.60 (1.23 to 5.49)	0.0124
Week 36	48	27 (56.3%)	46	24 (52.2%)	0.93 (0.46 to 1.88)	0.8455
Week 48	47	16 (34.0%)	45	23 (51.1%)	0.56 (0.25 to 1.23)	0.1488
Week 60	46	22 (47.8%)	44	24 (54.5%)	0.33 (0.13 to 0.85)	0.0216
(Post hoc)	**≥ 75% improvement**		**≥ 75% improvement**			
Week 12	52	6 (11.5%)	51	1 (2.0%)	2.89 (0.77 to 10.84)	0.1157
Week 16[a]	–	–	–	–	2.31 (0.66 to 8.11)	0.1919
Week 36	48	5 (10.4%)	46	7 (15.2%)	0.75 (0.24 to 2.32)	0.6169
Week 48	47	3 (6.4%)	45	6 (13.3%)	0.38 (0.11 to 1.31)	0.1262
Week 60	46	3 (6.5%)	44	7 (15.9%)	0.19 (0.05 to 0.83)	0.0268
(Post hoc)	**≥ 90% improvement**		**≥ 90% improvement**			
Week 12	52	0 (0.0%)	51	0 (0.0%)	2.60 (1.23 to 5.49)	0.0124
Week 16[a]	–	–	–	–	0.93 (0.46 to 1.88)	0.8455
Week 36	48	1 (2.1%)	46	2 (4.3%)	0.56 (0.25 to 1.23)	0.1488
Week 48	47	0 (0.0%)	45	1 (2.2%)	0.33 (0.13 to 0.85)	0.0216
Week 60	46	0 (0.0%)	44	1 (2.3%)	2.60 (1.23 to 5.49)	0.0124

a There was no week 16 visit, ORs for week 16 are estimated by the GLMM.

TABLE 5 Coprimary outcome 2 – sensitivity analysis 1[a]

Treatment	*N*	Flare, *N* (%)	Censored, *N* (%)	Log-rank, χ^2 statistic	Log-rank, *p*-value
Ciclosporin	45	21 (47%)	24 (53%)	1.68	0.1948
Methotrexate	38	14 (37%)	24 (63%)		
Total	**83**	**35**	**48**		

a Sensitivity analysis 1 included only those who completed 36 weeks of treatment.

TABLE 6 Coprimary outcome 2 – sensitivity analysis 2[a]

Treatment	*N*	Flare, *N* (%)	Censored, *N* (%)	Log-rank, χ^2 statistic	Log-rank, *p*-value
Ciclosporin	52	25 (48%)	27 (52%)	2.03	0.1538
Methotrexate	51	18 (35%)	33 (65%)		
Total	**103**	**43**	**60**		

a In sensitivity analysis 2 those who stopped trial treatment early but continued to take MTX or CyA begin the 24-week follow-up period from the end date of the MTX or CyA as recorded on the con-med form.

TABLE 7 Coprimary outcome 2 – sensitivity analysis 3

Treatment	*N*	Flare, *N* (%)	Censored, *N* (%)	HR (97.5% CI)	*p*-value
Ciclosporin	52	25 (48%)	27 (52%)	1.54 (0.77 to 3.09)	0.1606
Methotrexate	51	18 (35%)	33 (65%)		
Total	**103**	**43**	**60**		

TABLE 8 EASI-50, EASI-75 and EASI-90 – generalised linear mixed model results (post hoc)

	CyA (*N* = 52)		MTX (*N* = 51)			
Visit	***N***	**≥ 50% improvement**	***N***	**≥ 50% improvement**	**Estimated OR (95% CI)**	***p*-value**
Week 12	52	35 (67.3%)	51	27 (52.9%)	1.77 (0.92 to 3.42)	0.0888
Week 16[a]	–	–	–	–	1.47 (0.78 to 2.76)	0.2362
Week 36	48	34 (70.8%)	46	40 (87.0%)	0.57 (0.29 to 1.11)	0.096
Week 48	47	23 (48.9%)	45	35 (77.8%)	0.32 (0.15 to 0.71)	0.0051
Week 60	46	32 (69.6%)	44	34 (77.3%)	0.18 (0.07 to 0.48)	0.0006
	≥ 75% improvement		**≥ 75% improvement**			
Week 12	52	23 (44.2%)	51	10 (19.6%)	2.66 (1.37 to 5.19)	0.0040
Week 16[a]	–	–	–	–	2.24 (1.19 to 4.22)	0.0125
Week 36	48	20 (41.7%)	46	21 (45.7%)	0.94 (0.52 to 1.71)	0.8487
Week 48	47	14 (29.8%)	45	21 (46.7%)	0.56 (0.28 to 1.11)	0.0988
Week 60	46	16 (34.8%)	44	21 (47.7%)	0.33 (0.15 to 0.77)	0.0097
	≥ 90% improvement		**≥ 90% improvement**			
Week 12	52	4 (7.7%)	51	1 (2.0%)	4.19 (1.39 to 12.67)	0.0113
Week 16[a]	–	–	–	–	3.19 (1.12 to 9.05)	0.0295
Week 36	48	5 (10.4%)	46	9 (19.6%)	0.81 (0.32 to 2.08)	0.6667
Week 48	47	3 (6.4%)	45	7 (15.6%)	0.36 (0.12 to 1.04)	0.0587
Week 60	46	2 (4.3%)	44	7 (15.9%)	0.16 (0.04 to 0.57)	0.0051

a There was no week 16 visit; ORs for week 16 are estimated by the GLMM.

TABLE 9 Patient-oriented eczema measure results from a linear mixed model[a]

Time (weeks)	CYA – estimated mean POEM score (SE)	MTX – estimated mean POEM score (SE)	Estimated difference in means (SE)	95% CI	*p*-value
12	9.28 (0.72)	12.01 (0.72)	−2.73 (1.02)	−4.75 to −0.71	0.0085
36	10.10 (0.72)	9.89 (0.72)	0.22 (1.01)	−1.79 to 2.23	0.8308
48	10.52 (0.73)	8.82 (0.73)	1.69 (1.03)	−0.35 to 3.74	0.1040
60	10.93 (0.75)	7.76 (0.75)	3.17 (1.06)	1.06 to 5.28	0.0035

a 50 CyA and 49 MTX participants were included in the model.

TABLE 10 Children's Dermatology Life Quality Index linear mixed model results

	CyA		MTX				
Time (weeks)	*N*	Estimated mean CDLQI score (SE)	*N*	Estimated mean CDLQI score (SE)	Estimated difference in means (SE)	95% CI	*p*-value
12	49	7.09 (0.76)	49	8.45 (0.76)	−1.36 (1.08)	−3.49 to 0.77	0.2085
36	48	7.63 (0.58)	42	7.80 (0.59)	−0.17 (0.83)	−1.82 to 1.48	0.8345
48	46	7.90 (0.61)	41	7.48 (0.62)	0.42 (0.87)	−1.30 to 2.14	0.6299
60	47	8.17 (0.70)	43	7.15 (0.72)	1.01 (1.01)	−0.98 to 3.01	0.3164

TABLE 11 Dermatitis family impact linear mixed model results

	CyA		MTX				
Time (weeks)	*N*	Estimated mean DFI score (SE)	*N*	Estimated mean DFI score (SE)	Estimated difference in means (SE)	95% CI	*p*-value
12	51	7.59 (0.88)	51	8.56 (0.88)	−0.96 (1.25)	−3.42 to 1.49	0.4394
36	48	8.50 (0.73)	44	7.96 (0.73)	0.54 (1.04)	−1.51 to 2.59	0.6035
48	47	8.95 (0.75)	44	7.66 (0.76)	1.29 (1.07)	−0.82 to 3.41	0.2288
60	47	9.40 (0.83)	44	7.36 (0.85)	2.04 (1.19)	−0.30 to 4.39	0.0873

TABLE 12 Estimates from the random-effects models for longitudinal secondary outcomes o-SCORAD and EASI at each time point

		CyA		MTX				
	Time (weeks)	*N*	Estimated mean score (SE)	*N*	Estimated mean score (SE)	Estimated difference in means (SE)	95% CI	*p*-value
o-SCORAD	12	52	26.53 (1.13)	51	31.32 (1.15)	−4.80 (1.62)	−8.00 to −1.59	0.0036
	36	48	27.09 (1.10)	46	25.64 (1.11)	1.44 (1.57)	−1.67 to 4.56	0.3606
	48	47	27.37 (1.21)	45	22.80 (1.23)	4.56 (1.74)	1.14 to 7.99	0.0093
	60	46	27.64 (1.39)	44	19.96 (1.41)	7.68 (1.99)	3.77 to 11.60	0.0001
EASI	12	52	12.36 (0.86)	51	15.49 (0.87)	−3.13 (1.22)	−5.55 to −0.72	0.0113
	36	48	12.81 (0.82)	46	11.19 (0.84)	1.61 (1.18)	−0.72 to 3.94	0.1727
	48	47	13.03 (0.93)	45	9.04 (0.94)	3.99 (1.33)	1.37 to 6.60	0.0030
	60	46	13.25 (1.09)	44	6.89 (1.10)	6.36 (1.55)	3.31 to 9.41	< 0.0001

TABLE 13 Linear regression results exploring treatment modification effect of FLG carriage

Variable	Parameter estimate (SE)	95% confidence interval	*p*-value
EASI 12 weeks			
Intercept	2.417 (0.421)	1.58 to 3.253	< 0.001
Baseline EASI score	0.048 (0.012)	0.025 to 0.071	< 0.001
FLG carriage	−0.413 (0.373)	−1.154 to 0.328	0.271
CyA vs. MTX	−0.644 (0.357)	−1.354 to 0.067	0.075
FLG carriage in CyA vs. FLG carriage in MTX	0.406 (0.514)	−0.615 to 1.428	0.431

TABLE 13 Linear regression results exploring treatment modification effect of FLG carriage (*continued*)

Variable	Parameter estimate (SE)	95% confidence interval	*p*-value
EASI 36 weeks			
Intercept	0.799 (0.416)	−0.028 to 1.627	0.058
Baseline EASI score	0.062 (0.011)	0.039 to 0.085	< 0.001
FLG carriage	0.239 (0.375)	−0.508 to 0.986	0.526
CyA vs. MTX	0.205 (0.362)	−0.515 to 0.925	0.572
FLG carriage in CyA vs. FLG carriage in MTX	0.441 (0.517)	−0.587 to 1.47	0.396
EASI 60 weeks			
Intercept	1.736 (0.478)	0.784 to 2.688	0.001
Baseline EASI score	0.035 (0.013)	0.009 to 0.062	0.01
FLG carriage	−0.27 (0.435)	−1.137 to 0.597	0.536
CyA vs. MTX	0.877 (0.422)	0.037 to 1.718	0.041
FLG carriage in CyA vs. FLG carriage in MTX	−0.024 (0.596)	−1.212 to 1.163	0.968
o-SCORAD 12 weeks			
Intercept	20.313 (6.363)	7.66 to 32.967	0.002
Baseline o-SCORAD	0.238 (0.123)	−0.006 to 0.483	0.056
FLG carriage	−1.871 (3.566)	−8.962 to 5.219	0.601
CyA vs. MTX	−6.838 (3.416)	−13.631 to −0.046	0.049
FLG carriage in CyA vs. FLG carriage in MTX	3.915 (4.916)	−5.86 to 13.69	0.428
o-SCORAD 36 weeks			
Intercept	1.656 (6.337)	−10.963 to 14.275	0.795
Baseline o-SCORAD	0.403 (0.122)	0.161 to 0.645	0.001
FLG carriage	2.244 (3.661)	−5.046 to 9.534	0.542
CyA vs. MTX	1.922 (3.51)	−5.067 to 8.91	0.586
FLG carriage in CyA vs. FLG carriage in MTX	3.297 (5.018)	−6.696 to 13.289	0.513
o-SCORAD 60 weeks			
Intercept	13.904 (6.686)	0.582 to 27.226	0.041
Baseline o-SCORAD	0.14 (0.131)	−0.121 to 0.401	0.288
FLG carriage	−0.435 (3.907)	−8.22 to 7.35	0.912
CyA vs. MTX	8.827 (3.784)	1.287 to 16.366	0.022
FLG carriage in CyA vs. FLG carriage in MTX	−0.322 (5.34)	−10.962 to 10.318	0.952

TABLE 14 Proportion of participants achieving IGA 0 or 1 at each visit

	CyA		MTX	
Visit	***N***	**IGA 0/1, *N* (%)**	***N***	**IGA 0/1, *N* (%)**
Week 12	52	6 (11.54)	51	1 (1.96)
Week 36	48	7 (14.58)	46	7 (15.22)
Week 48	47	3 (6.38)	45	8 (17.78)
Week 60	45	4 (8.89)	44	9 (20.45)

TABLE 15 Non-serious adverse events

		CyA (*N* = 51)		MTX (*N* = 51)	
System organ class	**Preferred term**	**Events**	**Participants (%)**	**Number of events**	**Participants (%)**
Blood and lymphatic system disorders	Anaemia	1	1 (2.0)	1	1 (2.0)
	Lymphadenopathy	1	1 (2.0)	0	0 (0)
Ear and labyrinth disorders	Ear pain	0	0 (0)	4	3 (5.9)
	Hypoacusis	0	0 (0)	1	1 (2.0)
Eye disorders	Eye discharge	2	1 (2.0)	0	0 (0)
	Vision blurred	2	1 (2.0)	0	0 (0)
	Eye irritation	1	1 (2.0)	0	0 (0)
	Eye swelling	1	1 (2.0)	0	0 (0)
	Eyelid oedema	1	1 (2.0)	0	0 (0)
	Eyelid pain	0	0 (0)	1	1 (2.0)
	Ocular hyperaemia	1	1 (2.0)	0	0 (0)
Gastrointestinal disorders	Nausea	12	9 (17.6)	35	22 (43.1)
	Abdominal pain upper	18	9 (17.6)	11	3 (5.9)
	Abdominal pain	10	7 (13.7)	14	2 (3.9)
	Vomiting	13	9 (17.6)	11	9 (17.6)
	Diarrhoea	10	8 (15.7)	8	7 (13.7)
	Mouth ulceration	0	0 (0)	12	6 (11.8)
	Abdominal distension	2	1 (2.0)	1	1 (2.0)
	Dyspepsia	1	1 (2.0)	1	1 (2.0)
	Faeces discoloured	1	1 (2.0)	1	1 (2.0)
	Lip swelling	2	2 (3.9)	0	0 (0)
	Abdominal discomfort	1	1 (2.0)	0	0 (0)
	Abdominal pain lower	0	0 (0)	1	1 (2.0)
	Aphthous ulcer	1	1 (2.0)	0	0 (0)
	Constipation	0	0 (0)	1	1 (2.0)
	Duodenogastric reflux	0	0 (0)	1	1 (2.0)

TABLE 15 Non-serious adverse events (*continued*)

System organ class	Preferred term	CyA (*N* = 51)		MTX (*N* = 51)	
		Events	Participants (%)	Number of events	Participants (%)
	Frequent bowel movements	0	0 (0)	1	1 (2.0)
	Gingival pain	1	1 (2.0)	0	0 (0)
	Lip pain	1	1 (2.0)	0	0 (0)
	Retching	1	1 (2.0)	0	0 (0)
General disorders and administration site conditions	Fatigue	4	3 (5.9)	35	12 (23.5)
	Pyrexia	6	3 (5.9)	7	5 (9.8)
	Feeling cold	0	0 (0)	3	1 (2.0)
	Chest pain	1	1 (2.0)	1	1 (2.0)
	Influenza like illness	2	2 (3.9%)	0	0 (0)
	Malaise	2	1 (2.0)	0	0 (0)
	Swelling	2	1 (2.0)	0	0 (0)
	Chest discomfort	0	0 (0)	1	1 (2.0)
	Feeling hot	1	1 (2.0)	0	0 (0)
	Pain	1	1 (2.0)	0	0 (0)
	Pallor	1	1 (2.0)	0	0 (0)
	Peripheral swelling	1	1 (2.0)	0	0 (0)
Immune system disorders	Hypersensitivity	2	2 (3.9)	0	0 (0)
	Seasonal allergy (hayfever)	0	0 (0)	2	2 (3.9)
	Food allergy	1	1 (2.0)	0	0 (0)
Infections and infestations	Nasopharyngitis	8	7 (13.7)	9	9 (17.6)
	Eczema infected	8	6 (11.8)	8	6 (11.8)
	Lower respiratory tract infection	5	5 (9.8)	3	3 (5.9)
	Upper respiratory tract infection	4	4 (7.8)	3	3 (5.9)
	Molluscum contagiosum	3	3 (5.9)	3	3 (5.9)
	Viral infection	0	0 (0)	6	6 (11.8)
	Folliculitis	4	2 (3.9)	1	1 (2.0)
	Skin infection	2	2 (3.9)	3	3 (5.9)
	Tonsillitis	4	3 (5.9)	1	1 (2.0)
	Herpes simplex	3	2 (3.9)	1	1 (2.0)
	Oral herpes	2	1 (2.0)	2	2 (3.9)
	Staphylococcal infection	3	3 (5.9)	1	1 (2.0)
	Ear infection	1	1 (2.0)	2	2 (3.9)

continued

TABLE 15 Non-serious adverse events (*continued*)

		CyA (*N* = 51)		MTX (*N* = 51)	
System organ class	**Preferred term**	**Events**	**Participants (%)**	**Number of events**	**Participants (%)**
	Gastroenteritis	2	2 (3.9)	1	1 (2.0)
	Herpes zoster	2	2 (3.9)	1	1 (2.0)
	Rhinitis	2	2 (3.9)	1	1 (2.0)
	Urinary tract infection	1	1 (2.0)	2	1 (2.0)
	Conjunctivitis	2	1 (2.0)	0	0 (0)
	Localised infection	2	2 (3.9)	0	0 (0)
	Pharyngitis	2	2 (3.9)	0	0 (0)
	Sinusitis	1	1 (2.0)	1	1 (2.0)
	Varicella	0	0 (0)	2	2 (3.9)
	Viral upper respiratory tract infection	2	1 (2.0)	0	0 (0)
	Body tinea	0	0 (0)	1	1 (2.0)
	Campylobacter infection	1	1 (2.0)	0	0 (0)
	Croup infectious	1	1 (2.0)	0	0 (0)
	Eczema herpeticum	1	1 (2.0)	0	0 (0)
	Erythema infectiosum	0	0 (0)	1	1 (2.0)
	Furuncle	1	1 (2.0)	0	0 (0)
	Gingivitis	0	0 (0)	1	1 (2.0)
	Helicobacter infection	1	1 (2.0)	0	0 (0)
	Infected bite	1	1 (2.0)	0	0 (0)
	Lice infestation	0	0 (0)	1	1 (2.0)
	Otitis media	0	0 (0)	1	1 (2.0)
	Rash pustular	1	1 (2.0)	0	0 (0)
	Respiratory tract infection viral	1	1 (2.0)	0	0 (0)
	Staphylococcal skin infection	0	0 (0)	1	1 (2.0)
	Varicella zoster virus infection	0	0 (0)	1	1 (2.0)
	Viral rash	1	1 (2.0)	0	0 (0)
	Vulvitis	1	1 (2.0)	0	0 (0)
Injury, poisoning and procedural complications	Contusion	1	1 (2.0)	0	0 (0)
	Foot fracture	0	0 (0)	1	1 (2.0)
	Immunisation anxiety-related reaction	1	1 (2.0)	0	0 (0)
	Sunburn	0	0 (0)	1	1 (2.0)

TABLE 15 Non-serious adverse events (*continued*)

		CyA (*N* = 51)		MTX (*N* = 51)	
System organ class	**Preferred term**	**Events**	**Participants (%)**	**Number of events**	**Participants (%)**
Investigations	Abnormal (decrease of > 20% from baseline) eGFR	17	14 (27.5)	14	8 (15.7)
	Neutrophil count decreased	3	3 (5.9)	7	2 (3.9)
	Alanine aminotransferase increased	1	1 (2.0)	5	3 (5.9)
	Serum creatinine increased	2	2 (3.9)	4	2 (3.9)
	Lymphocyte count decreased	3	3 (5.9)	3	2 (3.9)
	Liver function test abnormal	0	0 (0)	4	1 (2.0)
	Haemoglobin decreased	0	0 (0)	3	3 (5.9)
	Weight decreased	1	1 (2.0)	2	2 (3.9)
	Haematocrit decreased	0	0 (0)	2	1 (2.0)
	Aspartate aminotransferase abnormal	1	1 (2.0)	0	0 (0)
	Aspartate aminotransferase increased	0	0 (0)	1	1 (2.0)
	Serum alkaline phosphatase abnormal	1	1 (2.0)	0	0 (0)
	Serum alkaline phosphatase decreased	0	0 (0)	1	1 (2.0)
	Serum creatinine decreased	1	1 (2.0)	0	0 (0)
	Serum potassium increased	0	0 (0)	1	1 (2.0)
	Blood pressure increased	1	1 (2.0)	0	0 (0)
	Serum sodium increased	0	0 (0)	1	1 (2.0)
	Serum urea increased	1	1 (2.0)	0	0 (0)
	Cardiac murmur	0	0 (0)	1	1 (2.0)
	Lymphocyte count increased	0	0 (0)	1	1 (2.0)
	Mean cell volume abnormal	0	0 (0)	1	1 (2.0)
	Platelet count increased	1	1 (2.0)	0	0 (0)
	Red blood cell count decreased	0	0 (0)	1	1 (2.0)
	White blood cell count decreased	0	0 (0)	1	1 (2.0)

continued

TABLE 15 Non-serious adverse events (*continued*)

		CyA (*N* = 51)		MTX (*N* = 51)	
System organ class	**Preferred term**	**Events**	**Participants (%)**	**Number of events**	**Participants (%)**
Metabolism and nutrition disorders	Decreased appetite	4	3 (5.9)	11	8 (15.7)
	Iron deficiency	0	0 (0)	1	1 (2.0)
Musculoskeletal and connective tissue disorders	Muscle spasms	3	3 (5.9)	0	0 (0)
	Back pain	1	1 (2.0)	1	1 (2.0)
	Pain in extremity	1	1 (2.0)	1	1 (2.0)
	Arthralgia	0	0 (0)	1	1 (2.0)
	Flank pain	0	0 (0)	1	1 (2.0)
	Joint swelling	1	1 (2.0)	0	0 (0)
	Myalgia	0	0 (0)	1	1 (2.0)
	Neck pain	0	0 (0)	1	1 (2.0)
Nervous system disorders	Headache	24	14 (27.5)	27	11 (21.6)
	Dizziness	5	4 (7.8)	3	3 (5.9)
	Lethargy	0	0 (0)	6	3 (5.9)
	Syncope	3	1 (2.0)	0	0 (0)
	Cluster headache	0	0 (0)	2	1 (2.0)
	Burning sensation	1	1 (2.0)	0	0 (0)
	Hypoaesthesia	1	1 (2.0)	0	0 (0)
	Migraine	1	1 (2.0)	0	0 (0)
	Paraesthesia	0	0 (0)	1	1 (2.0)
Psychiatric disorders	Mood swings	1	1 (2.0)	13	2 (3.9)
	Mood altered	3	2 (3.9)	2	1 (2.0)
	Enuresis	0	0 (0)	4	1 (2.0)
	Insomnia	0	0 (0)	3	2 (3.9)
	Irritability	0	0 (0)	1	1 (2.0)
	Sleep disorder	1	1 (2.0)	0	0 (0)
	Stress	1	1 (2.0)	0	0 (0)
Renal and urinary disorders	Micturition urgency	1	1 (2.0)	0	0 (0)
	Polyuria	1	1 (2.0)	0	0 (0)
Reproductive system and breast disorders	Menorrhagia	3	2 (3.9)	0	0 (0)
	Menstruation irregular	2	1 (2.0)	0	0 (0)
	Balanoposthitis	0	0 (0)	1	1 (2.0)
	Dysmenorrhoea	1	1 (2.0)	0	0 (0)
	Menstruation delayed	0	0 (0)	1	1 (2.0)
	Testicular swelling	1	1 (2.0)	0	0 (0)
	Vulvovaginal pruritus	0	0 (0)	1	1 (2.0)

TABLE 15 Non-serious adverse events (*continued*)

		CyA (*N* = 51)		MTX (*N* = 51)	
System organ class	**Preferred term**	**Events**	**Participants (%)**	**Number of events**	**Participants (%)**
Respiratory, thoracic, and mediastinal disorders	Cough	6	5 (9.8)	7	6 (11.8)
	Oropharyngeal pain	6	4 (7.8)	6	4 (7.8)
	Rhinorrhoea	3	2 (3.9)	2	2 (3.9)
	Wheezing	0	0 (0)	5	4 (7.8)
	Asthma	1	1 (2.0)	3	3 (5.9)
	Epistaxis	2	2 (3.9)	1	1 (2.0)
	Productive cough	0	0 (0)	2	2 (3.9)
	Dyspnoea	0	0 (0)	1	1 (2.0)
	Nasal congestion	1	1 (2.0)	0	0 (0)
Skin and subcutaneous tissue disorders	Eczema flare	45	22 (43.1)	19	15 (29.4)
	Pruritus	4	3 (5.9)	4	2 (3.9)
	Rash	4	4 (7.8)	2	2 (3.9)
	Alopecia	4	4 (7.8)	1	1 (2.0)
	Acne	3	3 (5.9)	0	0 (0)
	Urticaria	3	3 (5.9)	0	0 (0)
	Blister	2	2 (3.9)	0	0 (0)
	Dermatitis atopic	2	2 (3.9)	0	0 (0)
	Dry skin	0	0 (0)	2	2 (3.9)
	Dyshidrotic eczema	0	0 (0)	1	1 (2.0)
	Erythema	0	0 (0)	1	1 (2.0)
	Hirsutism	1	1 (2.0)	0	0 (0)
	Hypertrichosis	1	1 (2.0)	0	0 (0)
	Impetigo	1	1 (2.0)	0	0 (0)
	Ingrowing nail	1	1 (2.0)	0	0 (0)
	Miliaria	1	1 (2.0)	0	0 (0)
	Night sweats	1	1 (2.0)	0	0 (0)
	Skin reaction	1	1 (2.0)	0	0 (0)
Total		**369**	**48 (94.1)**	**407**	**47 (92.2)**

TABLE 16 Most common non-serious adverse events occurring in at least 10% of participants

		CyA (*n* = 51)		MTX (*n* = 51)		Total (*n* = 102)	
		Events	Participants (%)	Events	Participants (%)	Events	Participants (%)
	Any non-serious adverse event	**369**	**48 (94.1)**	**407**	**47 (92.2)**	**776**	**95 (93.1)**
	Most common non-serious adverse events						
Skin and subcutaneous tissue disorders	Eczema	45	22 (43.1)	19	15 (29.4)	64	37 (36.3)
Nervous system disorders	Headache	24	14 (27.5)	27	11 (21.6)	51	25 (24.5)
Gastrointestinal disorders	Abdominal pain upper	18	9 (17.6)	11	3 (5.9)	29	12 (11.8)
	Vomiting	13	9 (17.6)	11	9 (17.6)	24	18 (17.6)
	Nausea	12	9 (17.6)	35	22 (43.1)	47	31 (30.4)
	Abdominal pain	10	7 (13.7)	14	2 (3.9)	24	9 (8.8)
	Diarrhoea	10	8 (15.7)	8	7 (13.7)	18	15 (14.7)
	Mouth ulceration	0	0 (0)	12	6 (11.8)	12	6 (5.9)
Investigations	Glomerular filtration rate abnormal	17	14 (27.5)	14	8 (15.7)	31	22 (21.6)
Infections and infestations	Nasopharyngitis	8	7 (13.7)	9	9 (17.6)	17	16 (15.7)
	Eczema infected	8	6 (11.8)	8	6 (11.8)	16	12 (11.8)
General disorders and administration site conditions	Fatigue	4	3 (5.9)	35	12 (23.5)	39	15 (14.7)
Metabolism and nutrition disorders	Decreased appetite	4	3 (5.9)	11	8 (15.7)	15	11 (10.8)

TABLE 17 Serious adverse events

	CyA (*n* = 51)		MTX (*n* = 51)		Total (*n* = 102)	
	Events	Participants (%)	Events	Participants (%)	Events	Participants (%)
Skin and subcutaneous tissue disorders	1	1 (2.0)	0	0 (0)	1	1 (1.0)
Infections and infestations	3	3 (5.9)	4	4 (7.8)	7	7 (6.9)
Ear and labyrinth disorders	1	1 (2.0)	1	1 (2.0)	2	2 (2.0)
Respiratory, thoracic and mediastinal disorders	0	0 (0)	2	2 (3.9)	2	2 (2.0)

TABLE 18 Demographic and baseline characteristics of a subgroup of patients (*n* = 43) from the TREAT cohort with available biomarker data

	Ciclosporin (*n* = 22)	Methotrexate (*n* = 21)	Overall (*n* = 43)
Ethnicity			
Black British	5 (22.7%)	4 (19.0%)	9 (20.9%)
Chinese	1 (4.5%)	1 (4.8%)	2 (4.7%)
Mixed	1 (4.5%)	2 (9.5%)	3 (7.0%)
Other (specify)	5 (22.7%)	7 (33.3%)	12 (27.9%)
Other White	1 (4.5%)	0 (0%)	1 (2.3%)
Pakistani	1 (4.5%)	0 (0%)	1 (2.3%)
White British	8 (36.4%)	7 (33.3%)	15 (34.9%)
Sex			
Female	11 (50.0%)	14 (66.7%)	25 (58.1%)
Male	11 (50.0%)	7 (33.3%)	18 (41.9%)
Age			
Mean (SD)	8.68 (3.64)	9.00 (4.72)	8.84 (4.16)
Median (minimum, maximum)	7.00 (4.00, 16.0)	8.00 (2.00, 16.0)	8.00 (2.00, 16.0)
EASI			
Mean (SD)	26.4 (13.0)	26.9 (11.4)	26.7 (12.1)
Median (minimum, maximum)	26.4 (7.40, 55.2)	23.7 (12.6, 56.6)	25.5 (7.40, 56.6)

TABLE 19 Unit costs table (£ Great British pounds, 2022)

Cost item	Unit cost (£)	Assumption	Source
Intervention			
Methotrexate (MTX)	0.08 per 2.5 mg tablet	Doses made up of 2.5 mg tablets as per protocol	PCA, 2022[18]
Folic acid	0.06 per ml	1 ml/day except day of MTX administration	PCA, 2022[18]
Ciclosporin (CyA)	0.30 per 10 mg up to 2.28 per 100 mg capsule	Neoral used as per protocol	PCA, 2022[18]
Paediatric dermatologist first visit	200.21	Paediatric Dermatology Service – Consultant Led Non-Admitted Face-to-Face Attendance, First Visit	NHS reference costs, 2022[20]
Paediatric dermatologist f/up visit	180.49	Paediatric Dermatology Service – Consultant Led Non-Admitted Face-to-Face Attendance, Follow-Up	NHS reference costs, 2022[20]
Blood test	4.70		NHS reference costs, 2022[20]
Adverse event – hospital admission	538.26	Non-Elective Inpatient – Short Stay, currency code PJ35D, Paediatric Skin Disorders with CC Score 0	NHS reference costs, 2022[20]
Medication	Various		PCA, 2022[18]
NHS primary care			
GP	41.00	Including direct care staff costs with qualification costs for a 9.22-minute appointment	Jones *et al.*, 2022[19]

continued

TABLE 19 Unit costs table (£ Great British pounds, 2022) (*continued*)

Cost item	Unit cost (£)	Assumption	Source
Practice nurse	17.33	Assumes 20-minute appointment (£52/3) and Including qualification costs	Jones *et al.*, 2022[19]
NHS secondary care			
Hospital doctor	180.49	Paediatric Dermatology Service – Consultant Led Non-Admitted Face-to-Face Attendance, Follow-Up	NHS reference costs, 2022[20]
Hospital nurse	34.50	Assumed band 7 nurse for 30 minute consultation	Jones *et al.*, 2022[19]
Accident and emergency (A&E) visit	242.03	Weighted average of total costs across all attendances in the Emergency Care section divided by total number of attendances	NHS reference costs, 2022[20]
Time off work (parents)	18.71	Mean gross hourly pay for all employee jobs	ASHE, 2022[21]

TABLE 20 Mean (SD) resource use and mean (95% CI) difference in resource use at 60 weeks (available case data)

	MTX (*n* = 51)		CyA (*n* = 52)		
Resource item	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
Intervention					
Methotrexate (doses)	33.95 (7.71)	51	0.00 (0.00)	52	33.95 (31.83 to 36.07)
Folic acid (doses)	203.71 (46.29)	51	0.00 (0.00)	52	203.71 (190.98 to 216.45)
Ciclosporin (doses)	0.00 (0.00)	51	412.54 (107.96)	52	−412.54 (−442.53 to −382.55)
Paediatric dermatologist (number of visits)	9.24 (2.30)	51	8.23 (1.71)	52	1.00 (0.21 to 1.80)
Blood tests[a] (number)	10.12 (2.37)	51	9.29 (2.30)	52	0.83 (−0.08 to 1.74)
Total adverse events (AE)	**8.12 (9.68)**	**51**	**7.19 (6.45)**	**52**	**0.93 (−2.28 to 4.13)**
GP visit for adverse event	0.41 (0.73)	51	0.52 (0.92)	52	−0.11 (−0.43 to 0.22)
Admission for adverse event	0.14 (0.40)	51	0.06 (0.24)	52	0.08 (−0.05 to 0.21)
Accident and emergency (A&E) visit for adverse event	0.14 (0.45)	51	0.06 (0.24)	52	0.08 (−0.06 to 0.22)
All medication (number of)	13.35 (6.30)	51	14.98 (8.28)	52	−1.63 (−4.51 to 1.25)
NHS primary care (diary data)					
GP (number of visits)	0.89 (1.36)	9	0.44 (0.53)	9	0.44 (−0.59 to 1.48)
Practice nurse (number of visits)	0.11 (0.33)	9	0.00 (0.00)	9	0.11 (−0.12 to 0.35)
NHS secondary care (diary data)					
Hospital doctor (number of visits)	1.33 (1.80)	9	0.11 (0.33)	9	1.22 (−0.07 to 2.52)
Hospital nurse (number of visits)	0.56 (1.33)	9	0.00 (0.00)	9	0.56 (−0.39 to 1.50)
A&E visit (number of visits)	0.00 (0.00)	9	0.11 (0.33)	9	−0.11 (−0.35 to 0.12)
Time off work (number of hours)	1.89 (3.76)	9	0.00 (0.00)	9	1.89 (−0.77 to 4.54)
Time off school (number of hours)	5.67 (6.40)	9	3.78 (7.05)	9	1.89 (−4.84 to 8.62)

a Includes any taken for adverse events.

TABLE 21 Mean (S) cost and mean (95% CI) difference in cost at 60 weeks (UK£2022) (available case data)

Cost item	MTX (*n* = 51)		CyA (*n* = 52)		Mean difference (95% CI)
	Mean (SD)	*n*	Mean (SD)	*n*	
Total intervention	**1761.24 (421.31)**	**51**	**2314.07 (469.99)**	**52**	**−552.83 (−727.41 to −378.25)**
Methotrexate + folic acid	27.09 (8.69)	51	0.00 (0.00)	52	27.09 (24.70 to 29.48)
Methotrexate alone	14.86 (7.16)	51	0.00 (0.00)	52	14.86 (12.89 to 16.83)
Folic acid alone	12.22 (2.78)	51	0.00 (0.00)	52	12.22 (11.46 to 12.99)
Ciclosporin	0.00 (0.00)	51	765.12 (316.14)	52	−765.12 (−852.94 to −677.30)
Paediatric dermatologist	1686.60 (415.66)	51	1505.29 (308.74)	52	181.31 (38.38 to 324.26)
Blood tests[a]	47.55 (11.15)	51	43.66 (10.83)	52	3.90 (−0.40 to 8.19)
Total adverse events	**123.98 (292.32)**	**51**	**66.30 (142.50)**	**52**	**57.67 (−31.95 to 147.30)**
GP visit for adverse event	16.88 (29.77)	51	21.29 (37.64)	52	−4.41 (−17.69 to 8.87)
Admission for adverse event	73.88 (215.83)	51	31.05 (126.73)	52	42.83 (−26.20 to 111.85)
Accident and emergency (A&E) visit for adverse event	33.22 (108.44)	51	13.96 (56.98)	52	19.25 (−14.51 to 53.02)
All medications	159.70 (152.72)	51	153.79 (108.49)	52	5.91 (−45.79 to 57.61)
NHS primary care (diary data)					
GP	36.44 (55.93)	9	18.22 (21.61)	9	18.22 (−24.15 to 60.59)
Practice nurse	1.93 (5.78)	9	0.00 (0.00)	9	1.93 (−2.16 to 6.01)
NHS secondary care (diary data)					
Hospital doctor	240.65 (325.38)	9	20.05 (60.16)	9	220.60 to (−13.23 to 454.43)
Hospital nurse	19.17 (46.00)	9	0.00 (0.00)	9	19.17 (−13.34 to 51.67)
A&E visit	0.00 (0.00)	9	26.89 (80.68)	9	−26.89 (−83.90 to 30.12)
Total NHS cost (excluding diary data)	2044.92 (580.59)	51	2534.16 (500.85)	52	−489.2454 (−701.06 to −277.43)
Time off work (diary data)	35.34 (70.29)	9	0.00 (0.00)	9	35.34 (−14.32 to 85.01)

a Includes any taken for adverse events.

TABLE 22 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (UK£2022) (available case data)

Cost item (diary data)	MTX (*n* = 51)		CyA (*n* = 52)		Mean difference (95% CI)
	Mean (SD)	*n*	Mean (SD)	*n*	
4 weeks					
GP	1.41 (7.61)	29	0.00 (0.00)	32	1.41 (−1.28 to 4.10)
Practice nurse	0.60 (3.22)	29	0.00 (0.00)	32	0.60 (−0.54 to 1.74)
Hospital doctor	37.34 (147.73)	29	22.56 (99.92)	32	14.75 (−49.30 to 78.86)
Hospital nurse	4.76 (25.63)	29	0.00 (0.00)	32	4.76 (−4.30 to 13.82)
A&E visit	0.00 (0.00)	29	0.00 (0.00)	32	0.00 (0.00 to 0.00)
Time off work (parent)	5.16 (27.80)	29	3.51 (19.85)	32	1.65 (−10.63 to 13.94)

continued

TABLE 22 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (UK£2022) (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item (diary data)	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
8 weeks					
GP	5.86 (21.51)	28	4.56 (17.37)	27	1.30 (−9.29 to 11.90)
Practice nurse	0.00 (0.00)	28	0.00 (0.00)	27	0.00 (0.00 to 0.00)
Hospital doctor	12.89 (47.34)	28	0.00 (0.00)	27	12.89 (−5.39 to 31.17)
Hospital nurse	1.23 (6.52)	28	1.28 (6.64)	27	−0.05 (−3.60 to 3.51)
A&E visit	0.00 (0.00)	28	0.00 (0.00)	27	0.00 (0.00 to 0.00)
Time off work (parent)	6.68 (25.06)	28	44.30 (113.19)	27	−37.61 (−81.58 to 6.35)
12 weeks					
GP	1.41 (7.61)	29	3.32 (14.90)	37	−1.91 (−7.98 to 4.16)
Practice nurse	0.00 (0.00)	29	0.00 (0.00)	37	0.00 (0.00 to 0.00)
Hospital doctor	24.90 (79.62)	29	19.51 (70.98)	37	5.38 (−31.72 to 42.48)
Hospital nurse	0.00 (0.00)	29	2.80 (12.54)	37	−2.80 (−7.46 to 1.86)
A&E visit	0.00 (0.00)	29	0.00 (0.00)	37	0.00 (0.00 to 0.00)
Time off work (parent)	12.56 (37.18)	29	17.98 (65.09)	37	−5.72 (−32.81 to 21.36)
20 weeks					
GP	3.32 (14.90)	37	5.56 (14.56)	35	−2.53 (−9.46 to 4.40)
Practice nurse	0.00 (0.00)	37	0.00 (0.00)	35	0.00 (0.00 to 0.00)
Hospital doctor	4.88 (29.67)	37	0.00 (0.00)	35	4.88 (−5.13 to 14.89)
Hospital nurse	0.00 (0.00)	37	0.00 (0.00)	35	0.00 (0.00 to 0.00)
A&E visit	6.54 (39.79)	37	0.00 (0.00)	35	6.54 (−6.88 to 19.96)
Time off work (parent)	3.03 (18.46)	37	10.69 (51.80)	35	−7.66 (−25.74 to 10.42)
28 weeks					
GP	3.51 (15.31)	35	1.17 (6.93)	35	2.34 (−3.33 to 8.01)
Practice nurse	0.50 (2.93)	35	0.00 (0.00)	35	0.50 (−0.50 to 1.48)
Hospital doctor	5.16 (30.51)	35	5.16 (30.51)	35	0.00 (−14.55 to 14.55)
Hospital nurse	0.00 (0.00)	35	0.00 (0.00)	35	0.00 (0.00 to 0.00)
A&E visit	6.92 (40.91)	35	0.00 (0.00)	35	6.92 (−6.88 to 20.71)
Time off work (parent)	23.52 (121.12)	35	0.00 (0.00)	35	25.52 (−17.33 to 64.38)
36 weeks					
GP	7.03 (21.06)	35	14.47 (33.30)	34	−7.44 (−20.79 to 5.91)
Practice nurse	0.00 (0.00)	35	0.51 (2.97)	34	−0.51 (−1.51 to 0.49)
Hospital doctor	5.16 (30.51)	35	21.23 (73.88)	34	−16.08 (−43.10 to 10.94)
Hospital nurse	0.00 (0.00)	35	0.00 (0.00)	34	0.00 (0.00 to 0.00)
A&E visit	0.00 (0.00)	35	0.00 (0.00)	34	0.00 (0.00 to 0.00)
Time off work (parent)	0.00 (0.00)	35	550.87 (2919.92)	34	−550.87 (−1535.80 to 434.06)

TABLE 22 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (UK£2022) (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item (diary data)	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
48 weeks					
GP	10.25 (30.01)	36	5.86 (14.56)	35	4.39 (−6.83 to 15.61)
Practice nurse	0.00 (0.00)	36	0.50 (2.92)	35	−0.50 (−1.47 to 0.48)
Hospital doctor	5.01 (30.08)	36	5.16 (30.51)	35	−0.14 (−14.49 to 14.20)
Hospital nurse	1.92 (8.01)	36	0.00 (0.00)	35	1.92 (−0.79 to 4.62)
A&E visit	6.72 (40.34)	36	0.00 (0.00)	35	6.72 (−6.88 to 20.33)
Time off work (parent)	5.20 (23.50)	36	0.00 (0.00)	35	5.20 (−2.73 to 13.12)
60 weeks (undiscounted)					
GP	1.64 (8.20)	25	1.46 (7.75)	28	0.18 (−4.22 to 4.58)
Practice nurse	0.00 (0.00)	25	0.62 (3.28)	28	−0.62 (−1.94 to 0.70)
Hospital doctor	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)
Hospital nurse	0.00 (0.00)	25	1.23 (6.52)	28	−1.23 (−3.85 to 1.39)
A&E visit	0.00 (0.00)	25	8.64 (45.74)	28	−8.64 (−27.03 to 9.74)
Time off work (parent)	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)
60 weeks (discounted)					
GP	1.68 (8.39)	25	1.50 (7.93)	28	0.18 (−4.32 to 4.68)
Practice nurse	0.00 (0.00)	25	0.63 (3.35)	28	−0.63 (−1.98 to 0.71)
Hospital doctor	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)
Hospital nurse	0.00 (0.00)	25	1.26 (6.67)	28	−1.26 (−3.94 to 1.42)
A&E visit	0.00 (0.00)	25	8.85 (46.81)	28	−8.85 (−27.66 to 9.97)
Time off work (parent)	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)

a The cost from week 60 diary was divided by 12 weeks and 8 weeks of this were discounted and added to the undiscounted 4 weeks as date the resource was incurred was unknown within this period.

TABLE 23 Mean (SD) outcomes and mean (95% CI) difference in outcomes over 60 weeks (available case data)

	MTX (*n* = 51)		CyA (*n* = 52)		
	Mean (SD)	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
Child participants (all ages n = 103)					
CHU-9D baseline	0.7264 (0.1505)	41	0.7242 (0.1434)	41	0.0022 (−0.0624 to 0.0668)
CHU-9D at 12 weeks	0.8374 (0.1341)	41	0.8738 (0.1183)	44	−0.0364 (−0.0909 to 0.0181)
CHU-9D at 36 weeks	0.8642 (0.1084)	42	0.8567 (0.1120)	46	0.0075 (−0.0393 to 0.0543)
CHU-9D at 48 weeks	0.8300 (0.1412)	42	0.8292 (0.1410)	41	0.0004 (−0.0616 to 0.0624)
CHU-9D at 60 weeks	0.8754 (0.1040)	41	0.8274 (0.1479)	45	0.0480 (−0.0073 to 0.1033)
QALYs[a] (undiscounted, all ages)	0.9848 (0.0951)	26	0.9691 (0.1008)	29	0.0157 (−0.0375 to 0.0689)

continued

TABLE 23 Mean (SD) outcomes and mean (95% CI) difference in outcomes over 60 weeks (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
	Mean (SD)	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
QALYs[a] (discounted, all ages)	**0.9803 (0.0947)**	**26**	**0.9648 (0.1004)**	**29**	**0.0155 (−0.0374 to 0.0685)**
QALYs with missing[b] (discounted, all ages)	**0.9166 (0.1768)**	**32**	**0.9560 (0.1142)**	**37**	**−0.0393 (−0.1100 to 0.0313)**
Child participants (aged < 7 years, proxy completed, n = 26)					
CHU-9D (under 7) baseline	0.6891 (0.1198)	10	0.6748 (0.1443)	9	0.0143 (−0.1135 to 0.1422)
CHU-9D (under 7) at 12 weeks	0.8115 (0.1171)	11	0.8483 (0.1423)	9	−0.0368 (−0.1585 to 0.0850)
CHU-9D (under 7) at 36 weeks	0.8479 (0.1004)	10	0.8675 (0.0924)	9	−0.0196 (−0.1134 to 0.0741)
CHU-9D (under 7) at 48 weeks	0.8801 (0.0999)	9	0.9089 (0.1296)	8	−0.0288 (−0.1476 to 0.0900)
CHU-9D (under 7) at 60 weeks	0.8810 (0.0944)	11	0.8399 (0.1589)	10	0 0.0411 (−0.0769 to 0.1591)
QALYs (< 7 years)	**0.9644 (0.0821)**	**6**	**0.9909 (0.0648)**	**5**	**−0.0266 (−0.1292 to 0.0760)**
Child participants (aged 7 years or over, participant completed, n = 77)					
CHU-9D (over 7) baseline	0.7384 (0.1590)	31	0.7381 (0.1423)	32	0.0003383 (−0.0756 to 0.0763)
CHU-9D (over 7) at 12 weeks	0.8469 (0.1407)	30	0.8804 (0.1127)	35	−0.0335 (−0.0964 to 0.0293)
CHU-9D (over 7) at 36 weeks	0.8693 (0.1119)	32	0.8560 (0.1183)	36	0.0134 (−0.0426 to 0.0693)
CHU-9D (over 7) at 48 weeks	0.8158 (0.1488)	33	0.8117 (0.1424)	32	0.0041 (−0.0681 to 0.0764)
CHU-9D (over 7) at 60 weeks	0.8734 (0.1087)	30	0.8212 (0.1482)	34	0.0522 (−0.0136 to 0.1179)
QALYs (7 + years)	**0.9851 (0.0996)**	**20**	**0.9594 (0.1066)**	**24**	**0.0257 (−0.0375 to 0.0890)**
Child participants (all ages n = 103) (Lower o-SCORAD score indicates milder severity)					
o-SCORAD at baseline	45.25 (9.60)	51	48.34 (11.35)	52	−3.09 (−7.20 to 1.02)
O_SCORAD at 60 weeks	21.55 (10.89)	44	28.00 (12.76)	46	−6.45 (−11.43 to −1.47)
Change in O_SCORAD	23.04 (14.39)	44	20.86 (15.96)	46	2.18 (−4.19 to 8.56)
Child participants (all ages n = 103)					
No. flares over 60 weeks[c]	12.71 (9.03)	7	34.5 (17.68)	2	−21.79 (−42.08 to −1.49)

a QALYs estimated for only those with utility data at all five time points.
b QALYs estimated for those with at least utility data at baseline and 60 months.
c Number of flares over 60 weeks estimated for those with complete data only.

TABLE 24 Cost–utility analyses and cost-effectiveness analyses results, including sensitivity analyses

Cost–utility analysis (CUA) (Nm, Nc)	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER	Net monetary benefit (NMB) £20,000 (£30,000) threshold	Probability MTX cost-effective at £20,000 (£30,000) threshold
Partial NHS perspective, multiple imputation, adjusted[a] (51, 52)	−489.67 (−685.78 to −293.36)	−0.0057 (−0.0384 to 0.0270)	85,828[b] MTX cost-effective	375.49 (318.45)	85.5% (73.1%)
Partial NHS perspective, multiple imputation, unadjusted (51, 52)	−489.25 (−696.48 to −282.01)	−0.0019 (−0.0435 to 0.0396)	254,722[b] MTX cost-effective	450.83 (431.62)	84.2% (74.4%)
Full NHS perspective, multiple imputation, adjusted[a] (51, 52)	−522.13 (−717.01 to −327.25)	−0.0034 (−0.0361 to 0.0292)	152,301[b] MTX cost-effective	453.57 (419.29)	90.2% (79.4%)
Full NHS perspective, multiple imputation, unadjusted (51, 52)	−530.32 (−734.94 to −325.70)	−0.0020 (−0.0427 to 0.0386)	261,463[b] MTX cost-effective	489.76 (469.47)	87.0% (76.9%)
CUA partial complete case, adjusted[a] (26, 29)	−282.32 (−511.41 to −53.24)	−0.0104 (−0.0578 to 0.0369)	27,102 MTX cost-effective at £20k but not £30K	73.98 (−30.19)	55.7% (48.4%)
CUA partial complete case, unadjusted (26, 29)	−404.02 (−638.93 to −169.12)	0.0155 (−0.0353 to 0.0663)	MTX dominant	714.32 (869.47)	90.9% (86.4%)
CEA analysis (*N s*, *N p*)	**Incremental cost (95% CI)**	**Incremental o-SCORAD change (95% CI)**	**Incremental cost per unit change**		
Secondary analysis, multiple imputation, adjusted[a] (51, 52)	−492.20 (−688.40 to −296.00)	5.67 (1.52 to 9.82)	MTX dominant	NMB and probability of cost-effectiveness are not estimated for the cost-effectiveness analysis (CEA) because the decision-maker's willingness to pay per unit change on the o-SCORAD is unknown.	
Secondary analysis, multiple imputation, unadjusted (51, 52)	−489.25 (−696.48 to −282.01)	3.09 (−2.76 to 8.94)	MTX dominant		

CEA, cost-effectiveness analysis; CUA, cost–utility analysis; ICER, incremental cost-effectiveness ratio; Nc, number of participants allocated to ciclosporin; Nm, number of participants allocated to methotrexate; NMB, net monetary benefit; TOW, time off work.

a In adjusted analyses, costs were adjusted for treatment group, sex, age, site, ethnic group and baseline o_SCORAD and outcomes were for treatment group, sex, age, site, ethnic group and baseline utility (CUA) or baseline o_SCORAD (CEA).

b The ICERs from the CUA are in the Southwest quadrant of the cost-effectiveness plane where an ICER larger than £20,000 (£30,000) means MTX is cost-effective compared to CyA.[36]