Clinical trial results:
A Randomised Controlled Trial Assessing the Effectiveness, Safety and Cost-effectiveness of Methotrexate versus Ciclosporin in the Treatment of Severe Atopic Eczema in Children: The TREatment of Severe Atopic Eczema Trial (TREAT)

Summary

EudraCT number	2015-002013-29
Trial protocol	GB IE
Global end of trial date	14 May 2020

Results information

Result version number	v1 (current)
This version publication date	15 December 2023
First version publication date	15 December 2023

Trial information

Trial identification

Sponsor protocol code	TREAT

Additional study identifiers

ISRCTN number	ISRCTN15837754
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Carsten Flohr, Kings College London, 44 07806514078, carsten.flohr@kcl.ac.uk
Scientific contact	Carsten Flohr, Kings College London, 44 07806514078, carsten.flohr@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE1 9RT
Public contact	Carsten Flohr, Guy's and St Thomas' Foundation NHS Trust, 44 07806514078, carsten.flohr@kcl.ac.uk
Scientific contact	Carsten Flohr, Guy's and St Thomas' Foundation NHS Trust, 44 07806514078, carsten.flohr@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2020
Global end of trial reached?	Yes
Global end of trial date	14 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There are two co-primary endpoints:
To assess the change in atopic ezcema severity between baseline visit and 12 weeks of treatment with Methotrexate or Ciclosporin treatment, using the 0SCORAD index
and
Time to first significant flare up during the 24 weeks after the end of treatment with either Methotrexate or Ciclosporin.

Protection of trial subjects:

The drug dosing for MTX and CyA as well as the frequency of the study visits and safety assessments, including safety bloods, are in keeping with SmPC guidance and the American Academy of Dermatology guidelines for the use of systemic immuno-suppressive therapy in children and young people with severe atopic eczema.

The trial was was overseen by the Trial Management Group, the Trial Steering Group and Independent Data and Safety Monitoring Committee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 98
Country: Number of subjects enrolled	Ireland: 5
Worldwide total number of subjects	103
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	65
Adolescents (12-17 years)	38
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants will be identified by the clinical team at each centre via a search of the patient database/s either electronically or manually or clinic list review to find potentially eligible patients. At the routine clinic visit, the patient and/or parent/guardian will be asked whether they would be willing to participate in the study.

Pre-assignment

Screening details:

Participants will be identified by the clinical team at each centre via a search of the patient database/s either electronically or manually or clinic list review to find potentially eligible patients. At the routine clinic visit, the patient and/or parent/guardian will be asked whether they would be willing to participate in the study.

Period 1

Period 1 title	Main Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

As the trial interventions are at different frequencies (daily vs once weekly), have rather different side effect profiles and since no placebo is used as part of the study, blinding of the local investigator and research nurse will not be possible. However, the assessor who will perform the severity assessments (o-SCORAD, EASI & IGA), will be blinded to the trial allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin

Arm description:

Patients should remain on the full treatment dose (4mg/kg/day for CyA) for the 12 weeks. After that, dose increases to a maximum of 5mg/kg/day or dose decreases are allowed, according to the treatment response.

Arm type	Active comparator
Investigational medicinal product name	Ciclosporin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2mg/kg (total: 4mg/kg/day)
(rounded to the nearest whole capsule where applicable)

Arm title	Methotrexate

Arm description:

Patients will start on an initial test dose (0.1/mg/kg/week) for MTX (week 0) and then continue on the full treatment dose (0.4mg/kg/week for MTX – maximum dose of 25mg/week) from the following week (week 1), providing there have not been any significant side effects and the results from the safety bloods are acceptable.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:
Initial dose of 0.1mg/kg/week, then 0.4mg/kg/week from week 1 (maximum 25mg/week)

Notes:
[1] - The roles blinded appear inconsistent with a simple blinded trial.
Justification: Only the assessor in the trial was blinded.

Number of subjects in period 1	Ciclosporin	Methotrexate
Started	52	51
Completed	47	44
Not completed	5	7
Physician decision	2	4
Consent withdrawn by subject	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Ciclosporin
Reporting group description:	
Patients should remain on the full treatment dose (4mg/kg/day for CyA) for the 12 weeks. After that, dose increases to a maximum of 5mg/kg/day or dose decreases are allowed, according to the treatment response.	
Reporting group title	Methotrexate
Reporting group description:	
Patients will start on an initial test dose (0.1/mg/kg/week) for MTX (week 0) and then continue on the full treatment dose (0.4mg/kg/week for MTX – maximum dose of 25mg/week) from the following week (week 1), providing there have not been any significant side effects and the results from the safety bloods are acceptable.	

Reporting group values	Ciclosporin	Methotrexate	Total
Number of subjects	52	51	103
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age in years			
Units: years			
arithmetic mean	10.34	9.82	
standard deviation	± 4.21	± 4.01	-
Gender categorical			
Sex			
Units: Subjects			
Female	21	28	49
Male	31	23	54
Ethnicity			
Ethnicity			
Units: Subjects			
White British	27	27	54
Black British	6	4	10
Indian	2	3	5
Mixed	2	3	5
Other White	2	3	5
Pakistani	2	3	5
Asian	1	2	3
Asian (Philippines)	0	1	1

Asian (Other)	1	0	1
Bangladeshi	0	1	1
Black African	1	0	1
Brazilian	0	1	1
British Bangladeshi	0	1	1
British Pakistani	1	0	1
Filipino	1	0	1
German, Czech	1	0	1
Latin American	0	1	1
Mixed White	1	0	1
South East Asian	1	0	1
Sri Lankan	1	0	1
White Irish	1	0	1
Chinese	1	1	2
IGA			
IGA			
Units: Subjects			
Mild	0	1	1
Moderate	16	18	34
Severe	31	29	60
Very Severe	5	3	8
Weight			
Weight			
Units: kg			
arithmetic mean	38.12	37.04	
standard deviation	± 20.32	± 18.08	-
Height			
Height - n=51 for CyA group			
Units: cm			
arithmetic mean	137.82	133.75	
standard deviation	± 24.66	± 22.62	-
BMI			
BMI - n = 51 for CyA group			
Units: kg/m			
arithmetic mean	18.80	19.30	
standard deviation	± 4.16	± 4.15	-
EASI			
EASI does have units.			
Units: EASI			
arithmetic mean	28.97	27.12	
standard deviation	± 12.53	± 11.62	-
o-SCORAD			
o-SCORAD does not have units.			
Units: o-SCORAD			
arithmetic mean	48.34	45.25	
standard deviation	± 11.35	± 9.60	-
POEM			
POEM does not have units. There were 50 pts who had POEM at baseline in the CyA group and 49 in the MTX group.			
Units: POEM			
arithmetic mean	20.40	20.84	

standard deviation	± 5.26	± 5.47	-
DFI			
DFI doe not have units. 51 pts in the CyX group had a baseline value.			
Units: DFI			
arithmetic mean	15.24	15.59	
standard deviation	± 7.89	± 7.67	-
IDQoL - Dermatitis			
IDQoL-Dermatitis (under 4s only)does not have units. 3 pts in the CyA group and 5 pts in the MTX group reported this outcome.			
Units: IDQoL			
arithmetic mean	3	2.80	
standard deviation	± 0	± 0.84	-
IDQoL - Life Quality Index			
IDQoL - Life Quality Index (under 4s only) has no units. n-=3 in the CyA group and n=5 in the MTC group.			
Units: IDQoL			
arithmetic mean	16	13	
standard deviation	± 8.19	± 7.91	-
CDLQI			
CDLQI does not have any units. n=48 in the CyA group and n=47in the MTC group.			
Units: CDLQI			
arithmetic mean	14.67	15.26	
standard deviation	± 6.96	± 6.57	-

End points

End points reporting groups

Reporting group title	Ciclosporin

Reporting group description:

Patients should remain on the full treatment dose (4mg/kg/day for CyA) for the 12 weeks. After that, dose increases to a maximum of 5mg/kg/day or dose decreases are allowed, according to the treatment response.

Reporting group title	Methotrexate

Reporting group description:

Patients will start on an initial test dose (0.1/mg/kg/week) for MTX (week 0) and then continue on the full treatment dose (0.4mg/kg/week for MTX – maximum dose of 25mg/week) from the following week (week 1), providing there have not been any significant side effects and the results from the safety bloods are acceptable.

Primary: O-SCORAD

End point title	O-SCORAD

End point description:

End point type	Primary

End point timeframe:

Change in atopic eczema severity between baseline and 12 weeks

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[1]	51[2]		
Units: O-SCORAD				
arithmetic mean (standard deviation)	25.84 (± 10.79)	30.86 (± 12.14)		

Notes:

[1] - Values at 12 weeks.

[2] - Values at 12 weeks.

Statistical analyses

Statistical analysis title	Change in atopic eczema severity using o-SCORAD
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0131
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	-5.69

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-10.81
upper limit	-0.57
Variability estimate	Standard error of the mean
Dispersion value	2.25

Statistical analysis title	Sensitivity analysis
Statistical analysis description: Inclusion of centre as a random effect in a linear mixed model.	
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0115
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-5.47
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-10.31
upper limit	-0.64
Variability estimate	Standard error of the mean
Dispersion value	2.12

Primary: Time to first significant Flare	
End point title	Time to first significant Flare
End point description:	
End point type	Primary
End point timeframe: During the 24 weeks after treatment cessation	

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Events				
Flare	25	18		
No Flare	27	33		

Statistical analyses

Statistical analysis title	Time to first significant flare
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1529 [3]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.55
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.77
upper limit	3.1

Notes:

[3] - P-value based on log-rank test

Statistical analysis title	Sensitivity analysis 1

Statistical analysis description:

The analysis will be carried out in the subset of those who completed 36 weeks treatment.

Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1948
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	5.14
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.03
upper limit	25.62

Statistical analysis title	Sensitivity analysis 2

Statistical analysis description:

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 con-med as recorded on the con-med form.

Comparison groups	Ciclosporin v Methotrexate

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1538
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.54
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.77
upper limit	3.09

Secondary: EASI

End point title	EASI

End point description:

End point type	Secondary

End point timeframe:

EASI was measured at baseline and Weeks 4, 8, 12,20, 28,36,48 and 60.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[4]	51[5]		
Units: EASI				
arithmetic mean (standard error)				
Week 12	12.36 (± 0.86)	15.49 (± 0.87)		
Week 36	12.81 (± 0.82)	11.19 (± 0.84)		
Week 48	13.03 (± 0.93)	9.04 (± 0.94)		
Week 60	13.25 (± 1.09)	6.89 (± 1.10)		

Notes:

[4] - Week 36 n=48
Week 48 n=47
Week 60 n=46

[5] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	Linear Mixed Model for EASI

Statistical analysis description:

Linear Mixed Model parameter estimates - EASI

Comparison groups	Ciclosporin v Methotrexate

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-5.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.27
upper limit	-2.74
Variability estimate	Standard error of the mean
Dispersion value	1.4

Secondary: IGA

End point title	IGA
End point description:	
IGA does not have units.	
End point type	Secondary
End point timeframe:	
IGA was measured at baseline and Weeks 4, 8, 12,20, 28,36,48 and 60.	

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: IGA				
arithmetic mean (standard deviation)	1099.02 (± 290.37)	1043.16 (± 293.10)		

Statistical analyses

Statistical analysis title	IGA Area Under the Curve
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3785
Method	Area Under the Curve

Secondary: O-SCORAD - Secondary

End point title	O-SCORAD - Secondary

End point description:

End point type	Secondary

End point timeframe:

O-SCORAD was measured at baseline and Weeks 4, 8, 12,20, 28,36,48 and 60.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[6]	51[7]		
Units: o-SCORAD				
arithmetic mean (standard error)				
Week 12	26.53 (± 1.13)	31.32 (± 1.15)		
Week 36	27.09 (± 1.10)	25.64 (± 1.11)		
Week 48	27.37 (± 1.21)	22.80 (± 1.23)		
Week 60	27.64 (± 1.39)	19.96 (± 1.41)		

Notes:

[6] - Week 36 n=48
Week 48 n=47
Week 60 n=46

[7] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	Linear Mixed Model for O-SCORAD
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-7.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	-4.33
Variability estimate	Standard error of the mean
Dispersion value	1.82

Secondary: POEM

End point title	POEM

End point description:

End point type	Secondary

End point timeframe:

All patients and/or parent/legal guardian will be asked to complete a diary during treatment and a separate diary during follow up.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	51		
Units: POEM				
arithmetic mean (standard error)				
Week 12	9.28 (± 0.72)	12.01 (± 0.72)		
Week 36	10.10 (± 0.72)	9.89 (± 0.72)		
Week 48	10.52 (± 0.73)	8.82 (± 0.73)		
Week 60	10.93 (± 0.75)	7.76 (± 0.75)		

Statistical analyses

Statistical analysis title	Linear Mixed Model parameter estimates – POEM
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.27
upper limit	-2.15
Variability estimate	Standard error of the mean
Dispersion value	1.04

Statistical analysis title	POEM AUC results
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3773
Method	Area Under the Curve
Parameter estimate	Mean difference (final values)
Point estimate	-375.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1214.61
upper limit	464.14
Variability estimate	Standard error of the mean
Dispersion value	423.08

Secondary: Number of parent-reported flares after treatment cessation

End point title	Number of parent-reported flares after treatment cessation

End point description:

The following analyses were restricted to those who completed more than 80% of each respective question within the participant diaries during the 24 weeks following treatment cessation.

End point type	Secondary

End point timeframe:

Number of flares reported after treatment cessation.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: Flares				
arithmetic mean (standard deviation)	9.41 (± 5.40)	6.19 (± 4.22)		

Statistical analyses

Statistical analysis title	Mean number of patient/parent flares

Statistical analysis description:

T-test comparing the mean number of patient/parent-reported flares between treatment groups following trial treatment cessation.

Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0251
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	6.01

Secondary: Number of participants who re-flared

End point title	Number of participants who re-flared

End point description:

End point type	Secondary

End point timeframe:

Number of participants who re-flared according to co-primary outcome 2 definition during the 24 weeks after treatment cessation.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Re-flares				
Re-flare	25	18		
No re-flare	27	33		

Statistical analyses

Statistical analysis title	Chi-square test comparing number of participants

Statistical analysis description:

Chi-square test comparing number of participants who re-flared according to co-primary outcome 2 definition

Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1884
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	3.74

Secondary: Proportion of participants achieving 50% improvement in the o-SCORAD index

End point title	Proportion of participants achieving 50% improvement in the o-SCORAD index

End point description:

End point type	Secondary

End point timeframe:

Proportion of participants achieving 50% improvement in the o-SCORAD index at 12, 36, 48, and 60 weeks

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[8]	51[9]		
Units: Participants				
Week 12	25	14		
Week 36	27	24		
Week 48	16	23		
Week 60	22	24		

Notes:

[8] - Week 12 n=52
Week 36 n=48
Week 48 n=47
Week 60 n=46

[9] - Week 12 n=51
Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	Proportion of participants with 50% improvement
Comparison groups	Methotrexate v Ciclosporin
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [10]
Method	GLMM
Parameter estimate	Treatment Difference
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.34
Variability estimate	Standard error of the mean
Dispersion value	0.44

Notes:

[10] - P-value from the 50% improvement GLMM parameter estimates

Secondary: Participants who withdraw from treatment because of AEs

End point title	Participants who withdraw from treatment because of AEs

End point description:

End point type	Secondary

End point timeframe:

Throughout the trial.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Participants				
Withdrew	4	6		
Did not withdraw	48	45		

Statistical analyses

Statistical analysis title	Withdraw from treatment because of AE

Statistical analysis description:

Proportion of participants who withdraw from treatment because of AEs

Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5256
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	2.36

Secondary: Quality of Life using CDLQI

End point title	Quality of Life using CDLQI

End point description:

End point type	Secondary

End point timeframe:

Measured at Weeks 12, 36, 48 and 60.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[11]	49[12]		
Units: CDLQI				
arithmetic mean (standard error)				
Week 12	7.09 (± 0.76)	8.45 (± 0.76)		
Week 36	7.63 (± 0.58)	7.80 (± 0.59)		
Week 48	7.90 (± 0.61)	7.48 (± 0.62)		
Week 60	8.17 (± 0.70)	7.15 (± 0.72)		

Notes:

[11] - Week 12 n=49
Week 36 n=48
Week 48 n=46
Week 60 n=47
[12] - Week 12 n=49
Week 36 n=42
Week 48 n=41
Week 60 n=43

Statistical analyses

Statistical analysis title	CDLQI score

Statistical analysis description:

Linear Mixed Model mean estimated differences CDLQI score

Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1351
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.53
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	1.31

Secondary: IDQOL

End point title	IDQOL

End point description:

Due to the low numbers no formal statistical testing was carried out.

End point type	Secondary

End point timeframe:

Measured at baseline, week 12, week 36, week 48 and Week 60

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[13]	9[14]		
Units: IDQOL				
arithmetic mean (standard deviation)				
Week 12	12.33 (± 5.51)	10.22 (± 4.84)		
Week 36	6.75 (± 8.18)	9.5 (± 6.66)		
Week 48	9.33 (± 3.51)	10.80 (± 6.53)		
Week 60	0 (± 0)	12.50 (± 0.71)		

Notes:

[13] - Week 12 n=3
Week 36 n=4
Week 48 n=3
Week 60 n=0
[14] - Week 12 n=9
Week 36 n=6
Week 48 n=5
Week 60 n=2

Statistical analyses

No statistical analyses for this end point

Secondary: DFI

End point title	DFI

End point description:

End point type	Secondary

End point timeframe:

Measured at baseline, Week 12, Week 36, Week 48 and Week 60.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[15]	51[16]		
Units: DFI				
arithmetic mean (standard error)				
Week 12	7.59 (± 0.88)	8.56 (± 0.88)		
Week 36	8.50 (± 0.73)	7.96 (± 0.73)		
Week 48	8.95 (± 0.75)	7.66 (± 0.76)		
Week 60	9.40 (± 0.83)	7.36 (± 0.85)		

Notes:

[15] - Week 12 n=51
Week 36 n=48
Week 48 n=47
Week 60 n=47
[16] - Week 12 n=51
Week 36 n=44
Week 48 n=44
Week 60 n=60

Statistical analyses

Statistical analysis title	Linear Mixed Model parameter estimates – DFI
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2369
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.57
upper limit	1.13
Variability estimate	Standard error of the mean
Dispersion value	1.45

Secondary: Association between FLG carriage and treatment response (EASI)	
End point title	Association between FLG carriage and treatment response (EASI)
End point description:	
End point type	Secondary
End point timeframe:	
FLG measured at 12 , 36 and 60 weeks	

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[17]	43[18]		
Units: EASI				
arithmetic mean (standard error)	27.42 (± 12.27)	23.46 (± 10.09)		

Notes:

[17] - For EASI at week 12 n=46
For EASI at week 36 n=43
For EASI at week 60 n=42
result is for baseline

[18] - For EASI at week 12 n=43
For EASI at week 36 n=39
For EASI at week 60 n=37
result is for baseline

Statistical analyses

Statistical analysis title	Linear model estimates for EASI score at 12 weeks
Comparison groups	Ciclosporin v Methotrexate

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-0.644
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.354
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.357

Statistical analysis title	Linear model estimates for EASI score at 36 weeks
Statistical analysis description:	
This analysis has 82 patients included	
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.572
Method	Mixed models analysis
Parameter estimate	Treatment Diffe
Point estimate	0.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.515
upper limit	0.925
Variability estimate	Standard error of the mean
Dispersion value	0.362

Notes:

[19] - A total of 82 participants were included in this analysis.

Statistical analysis title	Linear model estimates for EASI score at 60 weeks
Statistical analysis description:	
There were 79 patients included in this analysis	
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.041
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	0.877

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	1.718
Variability estimate	Standard error of the mean
Dispersion value	0.422

Notes:

[20] - A total of 79 participants included in this analysis.

Secondary: Association between FLG carriage and treatment response (OSCORAD)

End point title	Association between FLG carriage and treatment response (OSCORAD)

End point description:

End point type	Secondary

End point timeframe:

Analysis performed at 12,36 and 60 weeks

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[21]	43[22]		
Units: OSCORAD				
arithmetic mean (standard deviation)	46.83 (± 11.97)	42.77 (± 9.42)		

Notes:

[21] - results are for Yes in CYA at baseline

[22] - results are for Yes in MTX at baseline

Statistical analyses

Statistical analysis title	Linear model estimate for O-SCORAD at 12 weeks
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-6.838
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.631
upper limit	-0.046
Variability estimate	Standard error of the mean
Dispersion value	3.416

Statistical analysis title	Linear model estimate for O-SCORAD at 36 weeks
Statistical analysis description: There are 82 patients in this analysis	
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	1.922
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.067
upper limit	8.91
Variability estimate	Standard error of the mean
Dispersion value	3.51

Statistical analysis title	Linear model estimate for O-SCORAD at 60 weeks
Statistical analysis description: There are 79 patients included in this analysis	
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	8.827
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.287
upper limit	16.366
Variability estimate	Standard error of the mean
Dispersion value	3.784

Post-hoc: Proportion of participants achieving at least 50% improvement in EASI 50	
End point title	Proportion of participants achieving at least 50% improvement in EASI 50
End point description:	

End point type	Post-hoc

End point timeframe:

Proportion of participants achieving at least 50% improvement in EASI score at 12, 16, 36, 48 and 60 weeks

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[23]	51[24]		
Units: Patients				
Week 12	35	27		
Week36	34	40		
Week 48	23	35		
Week 60	32	34		

Notes:

[23] - Week 36 n=48
Week 48 n=47
Week 60 n= 46

[24] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	50% improvement in EASI - GLMM parameter estimates
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0044
Method	GLMM
Parameter estimate	Treatment Difference
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.92
Variability estimate	Standard error of the mean
Dispersion value	0.4

Post-hoc: Proportion of participants achieving at least 50% improvement in EASI 75

End point title	Proportion of participants achieving at least 50% improvement in EASI 75

End point description:

End point type	Post-hoc

End point timeframe:

Proportion of participants achieving at least 75% improvement in EASI score at 12, 16, 36, 48 and 60 weeks.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[25]	51[26]		
Units: Patients				
Week 12	23	10		
Week 36	20	21		
Week 48	14	21		
Week 60	16	21		

Notes:

[25] - Week 36 n=48
Week 48 n=47
Week 60 n=46
[26] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	75% improvement in EASI - GLMM parameter estimates
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0003
Method	GLMM
Parameter estimate	Treatment Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.41

Post-hoc: Proportion of participants achieving at least 50% improvement in EASI 90

End point title	Proportion of participants achieving at least 50% improvement in EASI 90

End point description:

End point type	Post-hoc

End point timeframe:

Proportion of participants achieving at least 90% improvement in EASI score at 12, 16, 36, 48 and 60 weeks

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[27]	51[28]		
Units: Patients				
Week 12	4	1		
Week 36	5	9		
Week 48	3	7		
Week 60	2	7		

Notes:

[27] - Week 36 n=48
Week 48 n=47
Week 60 n=46
[28] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

Statistical analysis title	90% improvement in EASI - GLMM parameter estimates
Comparison groups	Methotrexate v Ciclosporin
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0011
Method	GLMM
Parameter estimate	Treatment Difference
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	0.69

Post-hoc: O-SCORAD-75

End point title	O-SCORAD-75

End point description:

End point type	Post-hoc

End point timeframe:

Proportion of participants achieving at least 75% improvement in O-SCORAD score at 12, 16, 36, 48 and 60 weeks.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[29]	51[30]		
Units: Patients				
Week 12	6	1		
Week 36	3	6		
Week 48	3	7		
Week 60	6	1		

Notes:

[29] - Week 36 n=47
Week 48 n=46
Week 60 n=52

[30] - Week 36 n=45
Week 48 n=44
Week 60 n=51

Statistical analyses

Statistical analysis title	75% improvement in O-SCORAD - GLMM parameter estim
Comparison groups	Ciclosporin v Methotrexate
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0307
Method	GLMM
Parameter estimate	Treatment difference
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	3.31
Variability estimate	Standard error of the mean
Dispersion value	0.8

Post-hoc: O-SCORAD-90

End point title	O-SCORAD-90

End point description:

End point type	Post-hoc

End point timeframe:

Proportion of participants achieving at least 90% improvement in O-SCORAD score at 12, 16, 36, 48 and 60 weeks.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[31]	51[32]		
Units: Patients				
Week 12	0	0		
Week 36	1	2		
Week 48	0	1		
Week 60	0	1		

Notes:

[31] - Week 36 n=48
Week 48 n=47
Week 60 n=46
[32] - Week 36 n=46
Week 48 n=45
Week 60 n=44

Statistical analyses

No statistical analyses for this end point

Post-hoc: EASI sensitivity analysis

End point title	EASI sensitivity analysis

End point description:

EASI, excluding those who restarted a systemic treatment

End point type	Post-hoc

End point timeframe:

EASI Collected at as described in protocol.

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[33]	50[34]		
Units: EASI				
arithmetic mean (standard error)				
Week 12	12.30 (± 0.89)	15.43 (± 0.90)		
Week 36	12.83 (± 0.90)	10.97 (± 0.90)		
Week 48	13.10 (± 1.05)	8.74 (± 1.03)		
Week 60	13.36 (± 1.25)	6.51 (± 1.22)		

Notes:

[33] - Week 36 n=44
Week 48 n=35
Week 60 n=28
[34] - Week 36 n=44
Week 48 n=37
Week 60 n=32

Statistical analyses

Statistical analysis title	Linear Mixed Model parameter estimates – EASI,

Statistical analysis description:

Linear Mixed Model parameter estimates – EASI, excluding those who restarted a systemic treatment

Comparison groups	Ciclosporin v Methotrexate

Number of subjects included in analysis	101
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-5.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.51
upper limit	-2.76
Variability estimate	Standard error of the mean
Dispersion value	1.46

Post-hoc: o-SCORAD sensitivity analysis

End point title	o-SCORAD sensitivity analysis
End point description:	
End point type	Post-hoc
End point timeframe:	
o-SCORAD collected at	

End point values	Ciclosporin	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[35]	50[36]		
Units: o-SCORAD				
arithmetic mean (standard error)				
Week 12	26.44 (± 1.17)	31.32 (± 1.18)		
Week 36	26.76 (± 1.18)	25.27 (± 1.18)		
Week 48	26.91 (± 1.34)	22.25 (± 1.32)		
Week 60	27.07 (± 1.57)	19.23 (± 1.54)		

Notes:

[35] - Week 36 n=44
Week 48 n=35
Week 60 n=28

[36] - Week 36 n= 44
Week 48 n=37
Week 60 n=32

Statistical analyses

Statistical analysis title	Linear Mixed Model parameter estimates – o-SCORAD

Statistical analysis description:

Linear Mixed Model mean estimated differences in o-SCORAD score, excluding those who restarted a systemic treatment

Comparison groups	Ciclosporin v Methotrexate

Number of subjects included in analysis	101
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment Difference
Point estimate	-8.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.76
upper limit	-4.35
Variability estimate	Standard error of the mean
Dispersion value	1.88

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Ciclosporin

Reporting group description:

Patients should remain on the full treatment dose (4mg/kg/day for CyA) for the 12 weeks. After that, dose increases to a maximum of 5mg/kg/day or dose decreases are allowed, according to the treatment response.

Reporting group title	Methotrexate

Reporting group description:

Patients will start on an initial test dose (0.1/mg/kg/week) for MTX (week 0) and then continue on the full treatment dose (0.4mg/kg/week for MTX – maximum dose of 25mg/week) from the following week (week 1), providing there have not been any significant side effects and the results from the safety bloods are acceptable.

Serious adverse events	Ciclosporin	Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	7 / 51 (13.73%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness bilateral			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 51 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Eczema herpeticum			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral tonsillitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shingles			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ciclosporin	Methotrexate	
Total subjects affected by non-serious adverse events subjects affected / exposed	48 / 51 (94.12%)	47 / 51 (92.16%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 51 (5.88%)	12 / 51 (23.53%)	
occurrences (all)	4	35	
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)	5 / 51 (9.80%)	
occurrences (all)	6	7	
Feeling cold			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	3	
Chest pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Malaise			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Swelling			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Chest discomfort			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Feeling hot			

subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Seasonal allergy			
subjects affected / exposed	0 / 51 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Food allergy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Menstruation irregular			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Balanoposthitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Menstruation delayed			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Testicular swelling			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 51 (9.80%)	6 / 51 (11.76%)	
occurrences (all)	6	7	
Oropharyngeal pain			
subjects affected / exposed	4 / 51 (7.84%)	4 / 51 (7.84%)	
occurrences (all)	6	6	
Rhinorrhoea			
subjects affected / exposed	2 / 51 (3.92%)	2 / 51 (3.92%)	
occurrences (all)	3	2	
Wheezing			
subjects affected / exposed	0 / 51 (0.00%)	4 / 51 (7.84%)	
occurrences (all)	0	5	
Asthma			
subjects affected / exposed	1 / 51 (1.96%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Epistaxis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Productive cough			
subjects affected / exposed	0 / 51 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nasal congestion			

subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Mood swings			
subjects affected / exposed	1 / 51 (1.96%)	2 / 51 (3.92%)	
occurrences (all)	1	13	
Mood altered			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	3	2	
Enuresis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	4	
Insomnia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	3	
Irritability			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Investigations			
Glomerular filtration rate abnormal			
subjects affected / exposed	14 / 51 (27.45%)	8 / 51 (15.69%)	
occurrences (all)	17	14	
Neutrophil count decreased			
subjects affected / exposed	3 / 51 (5.88%)	2 / 51 (3.92%)	
occurrences (all)	3	7	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	3 / 51 (5.88%)	
occurrences (all)	1	5	
Blood creatine increased			

subjects affected / exposed	2 / 51 (3.92%)	2 / 51 (3.92%)	
occurrences (all)	2	4	
Lymphocyte count decreased			
subjects affected / exposed	3 / 51 (5.88%)	2 / 51 (3.92%)	
occurrences (all)	3	3	
Liver function test abnormal			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	4	
Haemoglobin decreased			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Weight decreased			
subjects affected / exposed	1 / 51 (1.96%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Haematocrit decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	2	
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood alkaline phosphatase abnormal			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood creatine decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood sodium increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Lymphocyte count increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Mean cell volume abnormal			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Red blood cell count decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Foot fracture			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Immunisation anxiety related reaction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 51 (27.45%)	11 / 51 (21.57%)	
occurrences (all)	24	27	
Dizziness			
subjects affected / exposed	4 / 51 (7.84%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Lethargy			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	6	
Syncope			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Cluster headache			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	2	
Burning sensation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	4	
Hypoacusis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	0	
Eye disorders			
Eye discharge			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Eye irritation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Eye swelling			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Eyelid pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Ocular hyperaemia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 51 (17.65%)	22 / 51 (43.14%)	
occurrences (all)	12	35	
Abdominal pain upper			
subjects affected / exposed	9 / 51 (17.65%)	22 / 51 (43.14%)	
occurrences (all)	12	35	
Abdominal pain			
subjects affected / exposed	7 / 51 (13.73%)	22 / 51 (43.14%)	
occurrences (all)	10	35	
Vomiting			
subjects affected / exposed	9 / 51 (17.65%)	9 / 51 (17.65%)	
occurrences (all)	13	11	
Diarrhoea			
subjects affected / exposed	8 / 51 (15.69%)	7 / 51 (13.73%)	
occurrences (all)	10	8	
Mouth ulceration			
subjects affected / exposed	0 / 51 (0.00%)	6 / 51 (11.76%)	
occurrences (all)	0	12	
Abdominal distension			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Faeces discoloured			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Lip swelling			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Abdominal discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Abdominal pain lower			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Duodenogastric reflux			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Gingival pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Lip pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Retching			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	22 / 51 (43.14%)	15 / 51 (29.41%)	
occurrences (all)	45	19	
Pruritus			
subjects affected / exposed	3 / 51 (5.88%)	2 / 51 (3.92%)	
occurrences (all)	4	4	
rash			
subjects affected / exposed	4 / 51 (7.84%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Alopecia			

subjects affected / exposed	4 / 51 (7.84%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Acne			
subjects affected / exposed	3 / 51 (5.88%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	3 / 51 (5.88%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Blister			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Dermatitis atopic			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 51 (5.88%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Flank pain			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 51 (13.73%)	9 / 51 (17.65%)	
occurrences (all)	8	9	
Eczema infected			
subjects affected / exposed	6 / 51 (11.76%)	6 / 51 (11.76%)	
occurrences (all)	8	8	
Lower respiratory tract infection			
subjects affected / exposed	5 / 51 (9.80%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 51 (7.84%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Molluscum contagiosum			
subjects affected / exposed	3 / 51 (5.88%)	3 / 51 (5.88%)	
occurrences (all)	3	3	
Viral infection			
subjects affected / exposed	0 / 51 (0.00%)	6 / 51 (11.76%)	
occurrences (all)	0	6	
Folliculitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Skin infection			
subjects affected / exposed	2 / 51 (3.92%)	3 / 51 (5.88%)	
occurrences (all)	2	3	

Tonsillitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Herpes simplex			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Oral herpes			
subjects affected / exposed	1 / 51 (1.96%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Staphylococcal infection			
subjects affected / exposed	3 / 51 (5.88%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Ear infection			
subjects affected / exposed	1 / 51 (1.96%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Herpes zoster			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	2	
Conjunctivitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Localised infection			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 51 (0.00%)	
occurrences (all)	2	0	

Sinusitis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Varicella			
subjects affected / exposed	0 / 51 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Body tinea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Campylobacter infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Croup infectious			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Eczema herpeticum			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Erythema infectiosum			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Helicobacter infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Infected bite			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Lice infestation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Varicella zoster virus infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Viral rash			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Vulvitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 51 (5.88%)	8 / 51 (15.69%)	
occurrences (all)	4	11	
Iron deficiency			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2015	page 2 & 7 – change from Senior Lecturer to Reader for Dr Carsten Flohr page 22 – change to exclusion criteria 7 to include males and to say that an acceptable method of contraception must be used for 6 months after the last dose of study drug page 23 – addition of the following to the exclusion criteria: - Receiving treatment with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) for which elevated plasma concentrations are associated with serious and/or life-threatening events; this includes bosentan, dabigatran etexilate and aliskiren. - Receiving treatment with products containing Hypericum perforatum (St. John's wort) - Receiving oral treatment with tacrolimus - Receiving oral treatment with everolimus and sirolimus - Receiving oral treatment with lercanidipine page 26 – section 6.5.2 has been amended to say that patients who develop an unacceptable toxicity based on the investigator's judgement will be withdrawn. page 31 – text added to explain the dosing regimen for methotrexate page 34-36 – Details have been added to section 7.7.2 to describe any medications that are not permitted and any precautions that are required to be taken with regards to administration of concomitant medications.
23 October 2015	Page 2 – addition of qualifications for Carsten Flohr and Ashley Jones. Page 5 – title altered to 'Professor' for Leonie Taams Page 11 – Progressive Multifocal Leukoencephalopathy (PML), Tuberculosis (TB) and Thiopurine Methyltransferase (TPMT) added to Glossary Page 15 – schematic of study design altered to reflect new schedule and figures for recruitment corrected Page 16-17 – Further details added on why we are comparing ciclosporin with methotrexate. Page 18-20 – Further detail on risk:benefit ratio of trial interventions added Page 24 – Exclusion to reflect abnormal chest x-ray added to the exclusion criteria Page 27 – Details on steps in place to ensure blinding is maintained added Page 29 – Details added on the drug dosing for the trial Investigational Medicinal Products and information regarding chest x-rays required for patients with a risk of TB Page 31 – Information on when occasional monitoring of ciclosporin is recommended added Page 32-33 – Further details on precautions to be taken when prescribing and dispensing methotrexate added Page 34 – 'New or worsening unexplained dyspnoea or cough' added to the monitoring parameters for Methotrexate Page 36 – Information added with regards to avoiding ibuprofen whilst taking methotrexate and management of this if it occurs. Page 39 – window added for week 1 and 2. Page 40 – Table of study procedures altered to reflect new schedule. Page 41-45 – Visit summary altered to reflect new schedule Page 45 – Details on what is recorded in patient diary added Page 45 – Procedures for assessing safety updated to reflect new schedule Page 46 – Details on what is recorded in patient diary added Page 46 – 'intervention vs control' changed to 'MTX vs CyA' Page 59 – Patient information leaflets changed to patient information sheets

17 October 2016	- Minor clarifications and corrections - Clarification and further information added to eligibility criteria - Clarification to consent and screening process - Clarification of sample collection - Further detail added regarding treatment regimes - Addition of pregnancy CRF - Clarification of AE and SAE reporting period - Visit summary amended to reflect new summary -
29 June 2017	- Addition of pregnancy test during the baseline visit to confirm patient eligibility at the point of randomisation - Addition of POEM baseline questionnaire used to capture POEM data at baseline visit only - Addition of adverse event reporting procedures for patients discontinued from trial treatment but remain to be treated by their clinician on one of the trial interventions - Clarification of safety reporting - Addition of adverse event reporting procedures for patients discontinued from trial treatment but remain to be treated by their clinician on one of the trial interventions
18 February 2019	- Text added to refine co-primary outcome - Text added to refine the secondary endpoints - Addition of text highlighting importance of eligibility - Detail added to clarify collection of data for patients who discontinue trial treatment - Further detail added to the monitoring parameter table, to allow for temporary interruption to MTX - Text added to indicate which hospital collects tape striping and mechanistic samples. - Reference to Creatinine, Cystatin C, and urine NAG as being safety bloods removed - Additional text added to allow research nurses to contact patients in order to collect missing health resource use data. Addition of GP questionnaire to collect health resource use data. - Text added to refine the analysis of the co primary outcome

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37722926

http://www.ncbi.nlm.nih.gov/pubmed/29727479