Clinical trial results:
RITUXILUP - An open label randomised multicentre controlled trial of RITUXImab and mycophenolate mofetil (MMF) without oral steroids for the treatment of LUPus nephritis

Summary

EudraCT number	2012-004893-25
Trial protocol	GB
Global end of trial date	13 December 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2019
First version publication date	02 June 2019

Trial information

Trial identification

Sponsor protocol code	CRO2035

Additional study identifiers

ISRCTN number	ISRCTN84054592
ClinicalTrials.gov id (NCT number)	NCT01773616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London; Joint Research Compliance Office
Sponsor organisation address	Room 221, Medical School Building, St Mary’s Campus, Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Professor Liz Lightstone, Imperial College London, l.lightstone@imperial.ac.uk
Scientific contact	Professor Liz Lightstone, Imperial College London, l.lightstone@imperial.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	17 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2017
Global end of trial reached?	Yes
Global end of trial date	13 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The trial aimed to demonstrate that a regimen free of oral steroids but with rituximab and MMF is non-inferior to a regimen based on oral steroids and MMF in achieving the primary outcome of complete renal response at one year.

Protection of trial subjects:

Data Monitoring Committee
Pharmacovigilance
On-site and remote monitoring including source data verification
Detailed informed consent process

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2014
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	24
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential patients were identified in clinics and screened against the inclusion and exclusion criteria for the study. Recruitment took place across 11 sites in the UK from May 2015 to April 2017. Recruitment to the trial was halted prematurely in April 2017 at N=25, following withdrawal of funding due to slower than anticipated recruitment.

Pre-assignment

Screening details:

Patients were screened for eligibility according to the trial inclusion and exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable - this is an open label trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Control arm / Standard of care:
1. Mycophenolate mofetil
2. Methyl prednisolone
3. Oral prednisolone

Arm type	Active comparator
Investigational medicinal product name	Mycophenolate Mofetil (MMF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing in adults: start MMF 500mg bd and increase weekly by 250mg bd to a maximum dose of 1g bd if 60kg or less and 1.5g bd if >60kg. Within these guidelines the maximum dose will be titrated against white blood cells, tolerability or trough mycophenolic acid levels where available but should be no less than 500mg bd. At 6 months, if patients have responded, as defined by stabilisation of serum creatinine, and proteinuria non nephrotic and >50% reduction from baseline, the maximum dose of MMF will be reduced to 1g bd in those on higher dose initially.

Dosing in children aged 12-18: Commence MMF dosing at 600mg/m2 for 3 days up to a maximum of 1g and then increased to 600mg/m2 bd.

Investigational medicinal product name	Oral prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral prednisolone commencing at 0.5mg/kg/day (max 60mg/day, minimum 20mg/day) tapered thus:
o From week 2: if commencing on >45mg/day, decreased by 10mg/day every 2 weeks to 40mg/day followed by decrease by 5mg/day every 2 weeks until down to 20mg/day if clinical status permits.
o From week 2: if commencing on 45mg/day or less, decreased by 5mg/day every 2 weeks until down

to 20mg/day if clinical status permits.
o However, the dose should be no more than 20mg/day at 12 -13 weeks.
o Once down to a dose of 20mg/day, this should be maintained for 4 weeks.
o Thereafter, reduced by 2.5mg/day every week down to 10mg/day if clinical status permits.
o However, the dose should be no more than 10mg/day once daily by 26 weeks at the latest
o Once down to a dose of 10mg/day, this should be maintained for a minimum of 6 weeks.
o Thereafter, the steroid dose can be tapered according to clinical status and at a rate determined by clinician.

Investigational medicinal product name	Methyl prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500mg Methyl prednisolone IV at Infusion 1/Visit 1 and Infusion 2/Visit 3. If patients have received methyl prednisolone within the 4 weeks prior to randomisation, the dose will be modified to ensure maximum methyl prednisolone given will not exceed 3g in total.

Arm title	Rituximab

Arm description:

Intervention arm:
1. Rituximab
2. Mycophenolate mofetil
3. Methyl prednisolone

Arm type	Experimental
Investigational medicinal product name	Mycophenolate Mofetil (MMF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing in adults: start MMF 500mg bd and increase weekly by 250mg bd to a maximum dose of 1g bd if 60kg or less and 1.5g bd if >60kg. Within these guidelines the maximum dose will be titrated against white blood cells, tolerability or trough mycophenolic acid levels where available but should be no less than 500mg bd. At 6 months, if patients have responded, as defined by stabilisation of serum creatinine, and proteinuria non nephrotic and >50% reduction from baseline, the maximum dose of MMF will be reduced to 1g bd in those on higher dose initially.

Dosing in children aged 12-18: Commence MMF dosing at 600mg/m2 for 3 days up to a maximum of 1g and then increased to 600mg/m2 bd.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 1g infusion at Infusion 1/Visit 1 and Infusion 2/Visit 3 (The dose in children will be 750mg/m2 (maximum 1g) at Infusion 1/Visit 1 and Infusion 2/Visit 3). Concomitant IV or oral antihistamines and IV or oral paracetamol will be administered prior to administration of Rituximab.

Investigational medicinal product name	Methyl prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500mg Methyl prednisolone IV at Infusion 1/Visit 1 and Infusion 2/Visit 3. If patients have received methyl prednisolone within the 4 weeks prior to randomisation, the dose will be modified to ensure maximum methyl prednisolone given will not exceed 3g in total.

Number of subjects in period 1	Control	Rituximab
Started	12	13
Completed	9	11
Not completed	3	2
Consent withdrawn by subject	2	1
Non-compliance with protocol visits	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Control arm / Standard of care: 1. Mycophenolate mofetil 2. Methyl prednisolone 3. Oral prednisolone	

Reporting group title	Rituximab
Reporting group description:	
Intervention arm: 1. Rituximab 2. Mycophenolate mofetil 3. Methyl prednisolone	

Reporting group values	Control	Rituximab	Total
Number of subjects	12	13	25
Age categorical			
Age in years			
Units: Subjects			
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	12	12	24
Age continuous			
Age in years			
Units: years			
median	35.5	32	
inter-quartile range (Q1-Q3)	29 to 40.5	25 to 45	-
Gender categorical			
Units: Subjects			
Female	11	11	22
Male	1	2	3
Ethnicity			
Units: Subjects			
Asian	5	6	11
Black	3	2	5
Mixed	0	1	1
White	4	4	8
Smoking status			
Units: Subjects			
Never	8	11	19
Current Smoker	1	1	2
Ex smoker	3	1	4
Lupus Nephritis Class			
Units: Subjects			
III or IV + V	4	11	15
"pure" class V	8	2	10

Height Units: cm median inter-quartile range (Q1-Q3)	 162.3 158 to 170.5	 164 160.5 to 170	 -
Waist Units: cm median inter-quartile range (Q1-Q3)	 76 70 to 95	 84 75 to 87	 -
Hip Units: cm median inter-quartile range (Q1-Q3)	 94 86 to 106	 97 93 to 99	 -
Weight Units: kg median inter-quartile range (Q1-Q3)	 62.6 53 to 82.1	 66.7 54.9 to 76.9	 -
Body Mass Index Units: NA median inter-quartile range (Q1-Q3)	 23.4 20.95 to 28.82	 22.3 20.02 to 28.94	 -
Temperature Units: degrees Celsius median inter-quartile range (Q1-Q3)	 36.5 36.2 to 36.9	 36.5 36.2 to 37.1	 -
Heart rate Units: bpm median inter-quartile range (Q1-Q3)	 90.5 72 to 98	 86 78 to 93	 -
Systolic Blood Pressure - lying Units: mmHg median inter-quartile range (Q1-Q3)	 123 118 to 148	 119 110 to 127	 -
Diastolic Blood Pressure - lying Units: mmHg median inter-quartile range (Q1-Q3)	 82 72 to 86	 75.5 71 to 78	 -
Systolic Blood Pressure - standing Units: mmHg median inter-quartile range (Q1-Q3)	 129 116 to 143	 130 120 to 140	 -
Diastolic Blood Pressure - standing Units: mmHg median inter-quartile range (Q1-Q3)	 82 74 to 90	 87 73 to 89	 -

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Control arm / Standard of care: 1. Mycophenolate mofetil 2. Methyl prednisolone 3. Oral prednisolone	

Reporting group title	Rituximab
Reporting group description:	
Intervention arm: 1. Rituximab 2. Mycophenolate mofetil 3. Methyl prednisolone	

Primary: Complete renal response (CR) at week 52 (or closest timepoint)

End point title	Complete renal response (CR) at week 52 (or closest timepoint)
End point description:	
CR is defined as: - uPCR ≤50mg/mmol (=<0.5mg/mg) in a spot urine AND - eGFR ≥60ml/min, or if <60ml/min at screening, not fallen by >20% compared to screening/randomisation (whichever worse) AND - In the rituximab arm without the need to prescribe oral steroids within 1 year (beyond the first 8 wks depending on duration of prior steroids), except for 1 course of oral prednisolone max 30mg for a maximum of 14 d OR one intramuscular, one intravenous injection or two intra-articular injections of steroids, each maximum 120mg methylprednisolone or equivalent (in addition to the planned IV methyl prednisolone in the protocol) OR - in the steroid arm without the need for additional steroids over and above the prescribed taper, except for one course of oral prednisolone maximum 30mg for a maximum of 14d OR one intramuscular, one intravenous injection or two intra-articular injections of steroids, maximum 120mg methylprednisolone or equivalent (in addition to planned IV methyl pred)	
End point type	Primary
End point timeframe:	
Week 52 or closest visit	

End point values	Control	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: N(%)				
CR	4	6		
Non-CR	8	7		

Statistical analyses

Statistical analysis title	Primary outcome analysis
Comparison groups	Control v Rituximab
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	3.74

Secondary: Partial response (PR) at week 52 or closest visit

End point title	Partial response (PR) at week 52 or closest visit

End point description:

The proportion of patients achieving partial renal response (PR) at week 52 where PR is defined as:
- eGFR - no more than a 20% decrease from the baseline value,
AND
- if not nephrotic at baseline (urine PCR <300mg/mmol (3mg/mg)), 50% improvement in spot urine PCR
OR
- if nephrotic at baseline (urine PCR >300mg/mmol (3mg/mg)), 50% improvement in spot urine PCR AND urine PCR <300mg/mmol

End point type	Secondary

End point timeframe:

52 weeks or closest visit

End point values	Control	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: N(%)				
PR	9	11		
Non-PR	3	2		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Control v Rituximab

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the consent form up to the final study visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Control

Reporting group description:

Control arm / Standard of care:
1. Mycophenolate mofetil
2. Methyl prednisolone
3. Oral prednisolone

Reporting group title	Rituximab

Reporting group description:

Intervention arm:
1. Rituximab
2. Mycophenolate mofetil
3. Methyl prednisolone

Serious adverse events	Control	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	13 / 13 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Hernia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Malaise			

subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	8	
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Stress fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Seasonal allergy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Breast pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	11	
Galactorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Pleuritic pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Upper respiratory tract infection			

subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Loss of libido			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Headache			

subjects affected / exposed	1 / 12 (8.33%)	5 / 13 (38.46%)	
occurrences (all)	2	7	
Migraine			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Poor quality sleep			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Transient ischaemic attack			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
occurrences (all)	3	5	
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Eye pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	3 / 13 (23.08%)	
occurrences (all)	1	4	
Noninfective gingivitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Alopecia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	0 / 12 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	6	
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 12 (25.00%)	2 / 13 (15.38%)	
occurrences (all)	4	3	
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	0	
Joint swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Muscle spasms			

subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Foot and mouth disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	3 / 13 (23.08%)	
occurrences (all)	1	3	
Oral candidiasis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	4	
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Skin infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	2 / 13 (15.38%)	
occurrences (all)	5	4	
Urinary tract infection			
subjects affected / exposed	4 / 12 (33.33%)	3 / 13 (23.08%)	
occurrences (all)	11	4	
Vaginal infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2014	Version 1.1: first approved version - minor changes following Ethics Committee review; clarification about informing patients' GPs
06 March 2016	V2.2: clarification regarding MMF recommendations, change of prior steroid use from 4 weeks to 12 weeks (inclusion criteria), increase for allowed methyl prednisolone pre-trial from 1g to 2g (inclusion criteria), clarifications on study assessments including timing of standard care visits, clarifications regarding trial sample handling, inclusion of definition of Adverse Event of Special Interest, clarification for reporting of pregnancy and Adverse Events, clarifications regarding steroid taper (if oral steroids taken before trial entry)
30 June 2017	V 3.0: administrative changes, amendment to final study visit following decision to terminate trial early – patients to be followed up for a minimum of 6 months and last study visit to be modified to include annual visit procedures, clarification regarding definition of withdrawal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 September 2016	The RITUXILUP study was temporarily on halt as a reassessment of study feasibility was required. The Study Team entered into discussion with the funder (ARUK) regarding how to proceed in order to reach the required recruitment target and to answer the current relevant question. Those who were randomised prior to the halt (n=18) continued to be followed up as per the study protocol.	11 October 2017
27 March 2017	The RITUXILUP study received an official notification from Arthritis Research UK (the Funder) that their financial support to complete trial recruitment "to target" will be stopped and with the Sponsor's agreement, recruitment to the trial has been suspended. The funder has reviewed the Study's progress in detail and concluded that the target number of patients cannot be recruited within a realistic time period that is considered value for money.	-

Notes:

Limitations and caveats

None reported