



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 ≤ 50 mg/mmol ($= < 0.5$ mg/mg) in a spot urine | |
| AND | |
| - eGFR ≥ 60 ml/min, or if < 60 ml/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 occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 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 | <p>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.</p> <p>Those who were randomised prior to the halt (n=18) continued to be followed up as per the study protocol.</p> | 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