Clinical trial results:
SWITCH: Randomised-controlled trial of switching to alternative tumour-necrosis factor (TNF)-blocking drugs or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-blocking drug.

Summary

EudraCT number	2010-023880-17
Trial protocol	GB
Global end of trial date	23 November 2015

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	RR10/9589

Additional study identifiers

ISRCTN number	ISRCTN89222125
ClinicalTrials.gov id (NCT number)	NCT01295151
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Hyde Terrace, Leeds, United Kingdom, LS2 9LN
Public contact	Regulatory Affairs and Governance Manager, CTRU QA Department, Leeds Institute of Clinical Trials Research, ctruq@leeds.ac.uk
Scientific contact	Regulatory Affairs and Governance Manager, CTRU QA Department, Leeds Institute of Clinical Trials Research, ctruq@leeds.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	15 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2015
Global end of trial reached?	Yes
Global end of trial date	23 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare alternative-mechanism-TNF-inhibitor and abatacept to rituximab in terms of disease response, quality of life, cost-effectiveness, and toxicity and safety over a 12 month period.

Protection of trial subjects:

The randomised treatments in the study are all licensed having demonstrated health benefits with well characterised safety profiles. In addition, in order to be eligible for the trial patients must have already have been established on a biological therapy. Patients were monitored closely throughout the trial and were asked to attend regular outpatient appointments.

CTRU prepared annual safety reports containing anonymised data to the MHRA, main REC and sponsor. The Data Monitoring and Ethics Committee reviewed un-blinded periodic safety data to determine patterns and trends of events or to identify safety issues which would not be apparent on an individual case basis.

Trial data was collected on paper CRFs and was sent to CTRU where it was entered into a trial database application - MACRO. The database is stored on a private network protected by a firewall. Access is restricted to staff working on the trial by login and password. The trial data was then filed in locked filing cabinets.

CTRU comply with all aspects of the Data Protection Act 1998. All information collected during the trial has been kept strictly confidential. Patient names were collected on the Consent Form and sent to CTRU and patients were informed in the Patient Information Sheet that their names were processed this way. For all other data collection forms that were transferred to or from CTRU, the data was coded with a trial number, the patients initials and date of birth.

Background therapy:

All participants were required to be on a stable dose of methotrexate for 4 weeks prior to the screening visit and were expected to continue on this therapy for the duration of the study. Interruption of dose was permitted however.

The protocol indicated participants would receive standard folic acid as per local policy. In addition, methylprednisolone was administered intravenously at a dose of 100mg prior to each rituximab infusion.

Evidence for comparator: -	
Actual start date of recruitment	31 July 2012
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: 122

Worldwide total number of subjects	122
EEA total number of subjects	122

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)	0
Adults (18-64 years)	90
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between July 2012 and December 2014, 678 patients were pre-screened for the trial across 35 centres. Of these, 149/678 patients appeared suitable for and consented to pre-randomisation tests to confirm eligibility. Of these, 122/149 patients were confirmed eligible, maintained their consent, and proceeded to randomisation.

Pre-assignment

Screening details:

Of the 678 patients screened 529 patients were excluded pre-registration. 417 failed to meet the eligibility criteria. The main reasons were: had not failed an initial TNFi agent (95 patients), were not on a stable dose of methotrexate over the over the previous 28 days (92) and had received more than one TNFi drug or other biological agent (72)

Pre-assignment period milestones

Number of subjects started	678[1]
Number of subjects completed	122

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Declined to consent (pre-consent): 90
Reason: Number of subjects	Other reason for non-registration (pre-consent): 22
Reason: Number of subjects	Ineligible to be randomised (pre-consent): 417
Reason: Number of subjects	Ineligible to be randomised (post-consent): 19
Reason: Number of subjects	Other reason for non-randomisation (post consent): 6
Reason: Number of subjects	Withdrew consent (post-consent): 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: "Numbers started pre-assignment period" is the total number considered for enrolment, including those that were not approached due to being clearly ineligible, those that did not consent to trial specific tests, those that consented to tests, but were not randomised, and those that were randomised. "Worldwide number enrolled" is the number of patients randomised and took part in the SWITCH trial.

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:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Alternative mechanism TNFi

Arm description:

a. Etanercept if initial failure to a monoclonal antibody: infliximab, adalimumab, certolizumab or golimumab
OR
b. Infliximab, adalimumab, certolizumab or golimumab if initial failure to the receptor fusion protein, etanercept (choice of TNFi at investigator's discretion)

Arm type	Experimental

Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etanercept was administered at either a dose of 50mg by subcutaneous injection per week or as two 25mg injections per week for a minimum of 24 weeks (unless not tolerated). For participants who were responding to treatment at week 24, treatment was continued following the same regimen until week 48. Following week 48 treatment was at the discretion of the treating clinician.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection/infusion, Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Adalimumab was given at a dose of 40mg by subcutaneous injection every 2 weeks for a minimum of 24 weeks (unless not tolerated). For participants who were responding to treatment at week 24 treatment was continued following the same regimen until week 48. Following week 48 treatment was at the discretion of the treating clinician.

Investigational medicinal product name	Certolizumab Pegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Certolizumab pegol was given at a dose of 400mg by subcutaneous injection at weeks 0, 2, 4 and then at a dose of 200mg every 2 weeks thereafter for a minimum of 24 weeks. For participants who were responding to treatment at week 24 treatment was continued at the same 200mg every 2 weeks regimen until week 48. Following week 48 treatment was at the discretion of the treating clinician.

Investigational medicinal product name	Golimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled pen, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Golimumab will be given at a dose of 50mg by subcutaneous injection every 4 weeks for a minimum of 24 weeks. For participants who were responding to treatment at week 24 treatment was continued following the same regimen until week 48. Following week 48 treatment is at the discretion of the treating clinician.

Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infliximab was given at a dose of 3mg/kg per intravenous infusion. The intravenous infusions were administered at week 0, 2 (+/- 2 days), 6 (+/- 2 days) and then 8-weekly thereafter (+/- 7 days) for a minimum of 24 weeks. For participants who were responding to treatment at week 24 treatment was continued at the same 8-weekly regimen until week 48. Following week 48 treatment was at the discretion of the treating clinician.

Arm title	Abatacept

Arm description:

Subcutaneous abatacept. Dose=125mg at week 0 and then once a week thereafter for a minimum of 24 weeks. Trial specific supplies were provided by Bristol Myers Squibb.

Arm type	Experimental
Investigational medicinal product name	abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept was given at a dose of 125 mg by subcutaneous injection at week 0 and once weekly thereafter for a minimum of 24 weeks. For participants who are responding to treatment at week 24 treatment will continue following the same regimen until week 48. Following week 48 treatment is at the discretion of the treating clinician.

Arm title	Rituximab

Arm description:

Rituximab IV at weeks 0 and 2, and then at weeks 24 and 26 if necessary.

Arm type	Active comparator
Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab will be given at a dose of 1g; 2 intravenous infusions will be administered at days 0 (week 0) and 15 (week 2; +5 days).

In line with standard practice, a participant who loses an initial 6 month (week 24) response as per NICE guidance may receive a further cycle of rituximab after a minimum of 6 months following the first dose. The second cycle of rituximab will be given at a dose of 1g; 2 intravenous infusions will be administered at a 2 week interval (+5 days) e.g. week 24 and 26 (+5 days).

Subsequent treatment following week 48 will be at the discretion of the treating clinician. Prior to receiving rituximab, intravenous methylprednisolone 100mg will also be given.

Number of subjects in period 1	Alternative mechanism TNFi	Abatacept	Rituximab
Started	41	41	40
Completed	31	34	31
Not completed	10	7	9
Consent withdrawn by subject	2	1	-
Physician decision	2	1	3
Death	-	1	1
Lost to follow-up	2	1	1
Trial termination	4	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Alternative mechanism TNFi
Reporting group description:	
a. Etanercept if initial failure to a monoclonal antibody: infliximab, adalimumab, certolizumab or golimumab OR b. Infliximab, adalimumab, certolizumab or golimumab if initial failure to the receptor fusion protein, etanercept (choice of TNFi at investigator's discretion)	

Reporting group title	Abatacept
Reporting group description:	
Subcutaneous abatacept. Dose=125mg at week 0 and then once a week thereafter for a minimum of 24 weeks. Trial specific supplies were provided by Bristol Myers Squibb.	

Reporting group title	Rituximab
Reporting group description:	
Rituximab IV at weeks 0 and 2, and then at weeks 24 and 26 if necessary.	

Reporting group values	Alternative mechanism TNFi	Abatacept	Rituximab
Number of subjects	41	41	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	27	27
From 65-84 years	5	14	13
85 years and over	0	0	0
Age continuous Units: years			
median	56.9	60.5	57
inter-quartile range (Q1-Q3)	45.5 to 59.8	45.2 to 66.9	52.4 to 67.4
Gender categorical Units: Subjects			
Female	33	39	30
Male	8	2	10
Disease Duration Category Units: Subjects			
< 5 years	16	15	14
≥5 years	25	26	26
Rheumatoid Factor / Anti-citrullinated protein antibody status Units: Subjects			
RF seropositive or ACPA positive	36	31	33

Both RF seronegative and ACPA negative	5	10	7
Non-Response category Units: Subjects			
Primary	15	15	15
Secondary	26	26	25
Smoking status Units: Subjects			
Non-smoking (Never smoked)	12	17	21
Past smoker	18	13	11
Current smoker	11	11	8
Previous TNFi agent Units: Subjects			
Adalimumab	10	10	8
Certolizumab pegol	11	9	5
Etanercept	16	18	18
Golimumab	2	0	4
Infliximab	2	4	5
Disease Duration			
Years between Rheumatoid Arthritis diagnosis and randomisation.			
Units: Years			
median	5.9	6.9	7
inter-quartile range (Q1-Q3)	3.9 to 12.3	4 to 15.4	3.9 to 15.6
Body Mass Index Units: Kg/m2			
median	28.7	28.4	29
inter-quartile range (Q1-Q3)	25 to 34	24.3 to 34.5	25.4 to 33.5

Reporting group values	Total		
Number of subjects	122		
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)	90		
From 65-84 years	32		
85 years and over	0		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical Units: Subjects			
Female	102		
Male	20		

Disease Duration Category Units: Subjects			
< 5 years	45		
≥5 years	77		
Rheumatoid Factor / Anti-citrullinated protein antibody status Units: Subjects			
RF seropositive or ACPA positive	100		
Both RF seronegative and ACPA negative	22		
Non-Response category Units: Subjects			
Primary	45		
Secondary	77		
Smoking status Units: Subjects			
Non-smoking (Never smoked)	50		
Past smoker	42		
Current smoker	30		
Previous TNFi agent Units: Subjects			
Adalimumab	28		
Certolizumab pegol	25		
Etanercept	52		
Golimumab	6		
Infliximab	11		
Disease Duration			
Years between Rheumatoid Arthritis diagnosis and randomisation.			
Units: Years median inter-quartile range (Q1-Q3)	- -		
Body Mass Index Units: Kg/m2 median inter-quartile range (Q1-Q3)	- -		

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised

Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients who deviated from the protocol or failed to comply with the required treatment regimen were excluded from the per-protocol population. Analysis was conducted by treatment received

Reporting group values	Intention-to-treat	Per-protocol population	
Number of subjects	122	41	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	90	31	
From 65-84 years	32	10	
85 years and over	0	0	
Age continuous Units: years			
median	57.3	57.7	
inter-quartile range (Q1-Q3)	46.7 to 65.4	45.6 to 64.7	
Gender categorical Units: Subjects			
Female	20	30	
Male	102	11	
Disease Duration Category Units: Subjects			
< 5 years	45	11	
≥5 years	77	30	
Rheumatoid Factor / Anti-citrullinated protein antibody status Units: Subjects			
RF seropositive or ACPA positive	100	33	
Both RF seronegative and ACPA negative	22	8	
Non-Response category Units: Subjects			
Primary	45	18	
Secondary	77	23	
Smoking status Units: Subjects			
Non-smoking (Never smoked)	50	16	
Past smoker	42	15	
Current smoker	30	10	
Previous TNFi agent Units: Subjects			
Adalimumab	28	9	
Certolizumab pegol	25	9	
Etanercept	52	16	
Golimumab	6	2	
Infliximab	11	5	
Disease Duration			
Years between Rheumatoid Arthritis diagnosis and randomisation.			
Units: Years			
median	6.7	8	
inter-quartile range (Q1-Q3)	3.9 to 14.2	4.4 to 14.3	
Body Mass Index			

Units: Kg/m2			
median	29	29	
inter-quartile range (Q1-Q3)	24.9 to 34.1	25.3 to 34.9	

End points

End points reporting groups

Reporting group title	Alternative mechanism TNFi

Reporting group description:

a. Etanercept if initial failure to a monoclonal antibody: infliximab, adalimumab, certolizumab or golimumab
OR
b. Infliximab, adalimumab, certolizumab or golimumab if initial failure to the receptor fusion protein, etanercept (choice of TNFi at investigator's discretion)

Reporting group title	Abatacept

Reporting group description:

Subcutaneous abatacept. Dose=125mg at week 0 and then once a week thereafter for a minimum of 24 weeks. Trial specific supplies were provided by Bristol Myers Squibb.

Reporting group title	Rituximab

Reporting group description:

Rituximab IV at weeks 0 and 2, and then at weeks 24 and 26 if necessary.

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised

Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients who deviated from the protocol or failed to comply with the required treatment regimen were excluded from the per-protocol population. Analysis was conducted by treatment received

Primary: Absolute reduction in DAS28 at 24 weeks post randomisation

End point title	Absolute reduction in DAS28 at 24 weeks post randomisation

End point description:

Endpoint description:
DAS28 is a measure of disease activity in RA. The composite score is calculated as a function of the number of tender and swollen joints (total 28 joints), the erythrocyte sedimentation rate (ESR) and the patient's global assessment of their arthritis measured
- Tender Joint Count (TJC: Range 0-28)
- Swollen Joint Count (SJC: Range 0-28)
- Erythrocyte Sedimentation Rate (ESR: Range 0-99)
- Patient-completed Visual Analogue Scale of Global Assessment of Arthritis

With these four items, the DAS28 score is calculated in the following manner:
$DAS28=(0.56\times\sqrt{TJC})+(0.28\times\sqrt{SJC})+(0.7\times\log[e]\ ESR)+(0.014\times VAS(mm))$

Where log[e] is the natural logarithm function.

End point type	Primary

End point timeframe:

Baseline to 24 weeks post randomisation

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[1]	41[2]	40[3]	
Units: units				
arithmetic mean (standard deviation)	1.4 (± 1.28)	1.2 (± 1.72)	1.3 (± 1.94)	

Notes:

[1] - Prior to multiple imputation of missing values, 36/41 patients had complete data at weeks 0 and 24.
[2] - Prior to multiple imputation of missing values, 34/41 patients had complete data at weeks 0 and 24.
[3] - Prior to multiple imputation of missing values, 32/40 patients had complete data at weeks 0 and 24.

Statistical analyses

Statistical analysis title	Primary endpoint analysis (ITT - TNFi vs RTX)

Statistical analysis description:

Mixed-effects linear regression model. Outcome: Reduction in DAS28 between Weeks 0 and 24. Adjusted for covariates used to balance the randomisation system: disease duration category, RF/ACPA seropositivity category and Primary/Secondary Non-response category (all as fixed effects) and randomising centre (random effect). Same model fit to all fully-imputed datasets, resulting parameter estimates combined by Rubin's rules. Non-Inferiority concluded if 95% CI lies wholly above NI margin of -0.6.

Comparison groups	Alternative mechanism TNFi v Rituximab
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.0094 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	1.05

Notes:

[4] - Non-inferiority margin: -0.6 units of DAS28 score. Position of 2-sided 95% confidence interval judged in relation to margin. If 2-sided interval lies wholly above -0.6, NI conclusion reached in ITT population (must be matched by similar conclusion in Per-protocol population). If 2-sided interval lies wholly above 0, superiority conclusion reached in ITT population.
[5] - One-sided P-Value, corresponding to a one-sided 97.5% test, using non-inferiority margin of -0.6. Must be less than 0.025 to conclude non-inferiority to rituximab.
Per-Protocol population P-value=0.489; non-inferiority to rituximab not demonstrated

Statistical analysis title	Primary endpoint analysis (ITT - ABT vs RTX)

Statistical analysis description:

Mixed-effects linear regression model. Outcome: Reduction in DAS28 between Weeks 0 and 24. Adjusted for covariates used to balance the randomisation system: disease duration category, RF/ACPA seropositivity category and Primary/Secondary Non-response category (all as fixed effects) and randomising centre (random effect). Same model fit to all fully-imputed datasets, resulting parameter estimates combined by Rubin's rules. Non-Inferiority concluded if 95% CI lies wholly above NI margin of -0.6.

Comparison groups	Abatacept v Rituximab

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.0493 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.79

Notes:

[6] - Non-inferiority margin: -0.6 units of DAS28 score. Position of 2-sided 95% confidence interval for (abatacept - rituximab) judged in relation to margin. If 2-sided interval lies wholly above -0.6, Non-inferiority conclusion reached in ITT population (must be matched by similar conclusion in Per-protocol population). If 2-sided interval lies wholly above 0, superiority conclusion reached in ITT population.
[7] - One-sided P-Value, corresponding to a one-sided 97.5% test, using non-inferiority margin of -0.6. Must be less than 0.025 to conclude non-inferiority to rituximab.
Per-Protocol Population P-value=0.216; non-inferiority to rituximab not demonstrated.

Secondary: ACR20 Response at 24 weeks

End point title	ACR20 Response at 24 weeks

End point description:

The ACR20 (American College of Rheumatology) response criterion is a composite endpoint. To achieve response, a patient must achieve between baseline and 24 weeks:
20% reduction in Tender Joint Counts and 20% reduction in Swollen Joint Counts and 20% reduction in 3 of the following 5 criteria:
Patient-completed Pain VAS (Range 0-100mm)
Patient-completed general health VAS (Range 0-100mm)
Patient-completed assessment of disability (HAQ-DI, Range 0-3)
Physician-completed assessment of disease activity (Range 0-100mm)
Either C-reactive Protein or Erythrocyte Sedimentation Rate measure.

End point type	Secondary

End point timeframe:

From baseline to 24 weeks.

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[8]	41[9]	40[10]	
Units: Number of patients responding				
Achieved ACR20 Response	16	11	10	
Non-Response	20	24	27	

Notes:

[8] - Prior to multiple imputation of missing values, 36/41 patients had complete data for ACR Response.
[9] - Prior to multiple imputation of missing data, 35/41 patients had complete data for ACR20 Response.
[10] - Prior to multiple imputation of missing data, 37/40 patients had complete data for ACR20 Response.

Statistical analyses

Statistical analysis title	ACR20 Response at 24 weeks (ITT - TNFi v RTX)

Statistical analysis description:

Fixed-effects logistic regression model. Outcome: ACR20 Response at week 24. Adjusted for covariates used to balance the randomisation system: disease duration category, RF/ACPA seropositivity category and Primary/Secondary Non-response category (all as fixed effects). Randomising centre not fitted due to non-convergence. Same model fit to all fully-imputed datasets, resulting parameter estimates combined by Rubin's rules. ITT analysis population.

Comparison groups	Alternative mechanism TNFi v Rituximab
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15 [11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	5.53

Notes:

[11] - 2-sided P-Value for null hypothesis that ACR20 response rates at 24 weeks are equal.

Statistical analysis title	ACR20 Response at 24 weeks (ITT - ABT v RTX)

Statistical analysis description:

Fixed-effects logistic regression model. Outcome: ACR20 Response at week 24. Adjusted for covariates used to balance the randomisation system: disease duration category, RF/ACPA seropositivity category and Primary/Secondary Non-response category (all as fixed effects). Randomising centre not fitted due to non-convergence. Same model fit to all fully-imputed datasets, resulting parameter estimates combined by Rubin's rules. ITT analysis population.

Comparison groups	Abatacept v Rituximab
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	3.21

Secondary: DAS28 Score

End point title	DAS28 Score

End point description:

For a description of the derivation of the DAS28 score, please refer to description given under Primary Endpoint.

NB: Values of mean and Std dev given here are at Week 48.

End point type	Secondary

End point timeframe:

Baseline to 48 weeks. Measured at baseline, weeks 12, 24, 36 and 48.

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[12]	41[13]	40[14]	
Units: Units of DAS28				
arithmetic mean (standard deviation)	4.1 (± 1.58)	4.8 (± 1.24)	4.8 (± 1.42)	

Notes:

[12] - Prior to multiple imputation of missing data, 26/41 patients had complete data at all timepoints.

[13] - Prior to multiple imputation of missing data, 24/41 patients had complete data at all timepoints.

[14] - Prior to multiple imputation of missing data, 21/40 patients had complete data at all timepoints.

Statistical analyses

Statistical analysis title	DAS28 Score (ITT TNFi vs RTX)

Statistical analysis description:

Mixed-effects linear regression model. Outcome: DAS28 over 48 weeks. Adjusted for covariates used to balance the randomisation system (except for centre) and additionally baseline DAS28. Treatment, Time and Time-by-treatment effects fitted as fixed effects. Within-patient correlation in outcomes modelled using unstructured covariance pattern-model. Values reported are differences at 48 weeks. P-Values for interaction between trt-time are P=0.338 (24weeks), P=0.071 (36 weeks), P=0.552 (48 weeks).

Comparison groups	Alternative mechanism TNFi v Rituximab
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.249
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.27

Statistical analysis title	DAS28 Score (ITT - ABT vs RTX)

Statistical analysis description:

Mixed-effects linear regression model. Outcome: DAS28 over 48 weeks. Adjusted for covariates used to balance the randomisation system (except for centre) and additionally baseline DAS28. Treatment, Time and Time-by-treatment effects fitted as fixed effects. Within-patient correlation in outcomes modelled using unstructured covariance pattern-model. Values reported are differences at 48 weeks. P-Values for interaction between trt-time are P=0.976 (24weeks), P=0.871 (36 weeks), P=0.755 (48 weeks).

Comparison groups	Abatacept v Rituximab

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.859
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.71

Secondary: DAS28 Response

End point title	DAS28 Response

End point description:

Response defined as the achievement of a reduction in DAS28 of 1.2 or more (ie a change of -1.2 or less) since baseline.

NB: The reported number of patients responding given here are for Week 48.

End point type	Secondary

End point timeframe:

Baseline to 48 weeks. DAS28 measured at baseline, 12, 24, 36 and 48 weeks.

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[15]	41[16]	40[17]	
Units: Number of patients responding				
Response (DAS28 reduced by 1.2 or more)	19	18	13	
Non-Response	11	12	10	

Notes:

[15] - Prior to multiple imputation of missing data, 26/41 patients had complete data at all timepoints.

[16] - Prior to multiple imputation of missing data, 24/41 patients had complete data at all timepoints.

[17] - Prior to multiple imputation of missing data, 21/40 patients had complete data at all timepoints.

Statistical analyses

Statistical analysis title	DAS28 Response over 48 weeks (ITT - TNFi vs RTX)

Statistical analysis description:

Mixed-effects logistic regression model. Outcome: Response over 48 weeks. Adjusted for covariates used to balance the randomisation system (except for centre) and additionally baseline DAS28. Treatment, Time and Time-by-treatment effects fitted as fixed effects. Within-patient correlation in outcomes modelled using unstructured covariance pattern-model. Values reported are ORs at 48 weeks. P-Values for
interaction between trt-time are P=0.116 (24weeks), P=0.327 (36weeks), P=0.699 (48weeks).

Comparison groups	Alternative mechanism TNFi v Rituximab

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.543
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	4.19

Statistical analysis title	DAS28 Response over 48 weeks (ITT - ABT vs RTX)

Statistical analysis description:

Mixed-effects logistic regression model. Outcome: Response over 48 weeks. Adjusted for covariates used to balance the randomisation system (except for centre) and additionally baseline DAS28. Treatment, Time and Time-by-treatment effects fitted as fixed effects. Within-patient correlation in outcomes modelled using unstructured covariance pattern-model. Values reported are ORs at 48 weeks. P-Values for
interaction between trt-time are P=0.930 (24weeks), P=0.888 (36weeks), P=0.675 (48weeks).

Comparison groups	Abatacept v Rituximab
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.869
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.73

Secondary: HAQ-DI

End point title	HAQ-DI

End point description:

HAQ-DI questionnaire (See: Pincus T, Summey JA, Soraci SA, et al. Assessment of patient satisfaction in activities of daily living using a modified stanford health assessment questionnaire. Arthritis & Rheumatism. 1983;26(11):1346-53.). Patients respond to 20 questions across 8 domains relating to physical function, and the need for any help or aids to undertake daily activities. The extent of disability is scored from 0 (no disability) to 3 (severe disability) for each item relating to rising, dressing, walking and other activities. The use of help or aids increases the category score from 0 or 1 to a 2. If the category score is already a 2 or 3, no adjustment is made. The total score is derived by taking the maximum score across all domains and dividing by 8 to provide an average score in the range 0-3.

NB: the median and IQR given here corresponds to Week 48

End point type	Secondary

End point timeframe:

HAQ-DI questionnaire completed by the patient at baseline and weeks 12, 24, 36, 48.

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	34	30	
Units: Units of HAQDI				
median (inter-quartile range (Q1-Q3))	1.5 (1.1 to 1.9)	1.6 (1 to 2.1)	1.7 (1.1 to 2.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: RAQOL

End point title	RAQOL

End point description:

See de Jong Z, van der Heijde D, McKenna SP, Whalley D. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. Rheumatology. 1997 August 1, 1997;36(8):878-83.

Thirty item questionnaire, each item having a Yes (score as 1) / No (score as 0) response to ascertain the extent of rheumatoid arthritis symptoms experienced, maximum score 30.

NB: the median and IQR given here corresponds to Week 48

End point type	Secondary

End point timeframe:

Baseline and weeks 12, 24, 36, 48.

End point values	Alternative mechanism TNFi	Abatacept	Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	34	30	
Units: Units of RAQoL				
median (inter-quartile range (Q1-Q3))	19 (9 to 23)	17.5 (11.4 to 24)	19.5 (12 to 25)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs/ARs and SAEs were monitored from randomisation until a minimum of 30 days* post last dose of randomised treatment during the interventional phase (week 48 max). Monitoring for SARs and SUSARs continued during the observational phase (week 96 max).

Adverse event reporting additional description:

At each clinical assessment visit (weeks 12, 24, 36, 48) patients were asked to reported adverse events. Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions were subject to expedited reporting.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Alternative TNFi

Reporting group description:

All participants randomised to receive alternative TNFi.

One participant was withdrawn prior to receiving any IMP due to eligibility randomisation, this patient reported no Adverse Events.

Reporting group title	Abatacept

Reporting group description:

All participants randomised to abatacept.

All participants received at least one injection of abatacept.

Reporting group title	Rituximab

Reporting group description:

All patients randomised to receive rituximab.

All participants received at least one infusion of rituximab.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

Serious adverse events	Alternative TNFi	Abatacept	Rituximab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	4 / 41 (9.76%)	4 / 40 (10.00%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Melanoma			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			

Epigastric chest pain			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Left Basal Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flare of Rheumatoid Arthritis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Collapse, broken coccyx			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Chest Infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Alternative TNFi	Abatacept	Rituximab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2012	Inclusion of the option for subcutaneous IMPs to be sourced and delivered to participants homes by a third party home healthcare providers as per local hospital practice.
01 March 2012	Amendment from intravenous formulation of abatacept to subcutaneous formulation following agreement from manufacturers of abatacept to provide trial supplies. This also required changes to other documentation to i) include a further vendor responsible for packaging and labelling of the abatacept trial supplies and ii) amend wording on the labels for sub-cutaneous abatacept.
06 March 2012	Wording added to the label for subcutaneous abatacept as requested by Bristol Myers Squibb (the manufacturers of abatacept).
29 May 2012	Addition of Almac Limited as the responsible party for the packaging, labelling and batch release of abatacept. Also, addition of trial identifier (the word 'SWITCH') to the already approved label for abatacept.
15 May 2013	Clarification included in the proptocol that where local practice indicates the use of a home healthcare provider for the delivery of subcutaneous IMPs, the trial procedures will map onto the established, standard care practices in place at each individual site in terms of services and record keeping and retention requirements.
09 October 2013	Approval was obtained for a letter to provide to participants that explained a discrepancy between the expiry date given on the internal and external packaging of abatacept. Amendment was submitted to ethics committee only as competent authority
09 October 2013	Addition of a Patient Advert designed to advertise the trial directly to patients, with the intention that sites display the patient advert in patient waiting rooms etc. In addition, information contained within the advert was intended to be used via various means e.g. patient websites, e-bulletins, social media for the purpose of advertising the trial to the wider rheumatoid arthritis community. Submitted to Main Research Ethics Committee only as related only to information to be provided to the participant.
10 December 2013	Addition of golimumab to alternative mechanism TNFi arm following feedback from sites that use of golimumab was becoming more commonplace and therefore the ability to use this may expand the field of potential patients/increase pragmatism of study/would reflect standard practice more closely.
10 December 2013	Modification of the primary endpoint from a dichotomous endpoint (whether or not the patient achieved a reduction of greater than 1.2 units in DAS28 with no toxicity) to a continuous endpoint (change in DAS28 score).
02 May 2014	R&D form amended to enable the use of Participant Identification Centres in order to identify further participants. Submitted to Main Research Ethics Committee only.
16 May 2014	Corrections of errors noted in the Research Ethics Committee form and the Patient Information Sheet relating to the amount of radiation patients would be exposed to as part of the imaging aspects of the study. Submitted to Main Research Ethics Committee only as related to information provided on the Patient Information Sheet.

08 August 2014	A Participant Information Summary Sheet was created to summarise and complement the main Participant Information Sheet & Informed Consent Document before the patient reads the main Participant Information Sheet and Informed Consent Form following feedback from patient and public involvement representatives that the current Participant Information Sheet and Informed Consent Form was lengthy and a supplementary summary sheet would be beneficial. Submitted to Main Research Ethics Committee only as related to information provided on the Patient Information Sheet.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 December 2014	A temporary halt to recruitment was necessary following the withdrawal of funding by the NIHR Health Technologies Assessment programme. The halt was considered temporary at the time as the Chief Investigator sought alternative sources of funding. This was submitted as a Substantial Amendment to the Medicines and Healthcare Products Regulatory Authority and the Main Research Ethics Committee on 16th December 2014 and approvals received on 9th January 2015 and 30th December 2014 respectively. Unfortunately, discussions to secure an alternative funding source were not successful and the need for a permanent halt was conveyed to participating sites on 9th February 2015. This was followed by submission of a substantial amendment on 9th April 2015 to update the protocol accordingly .	-

Notes:

Limitations and caveats

None reported