Clinical trial results:
Adjuvant rituximab – a potential treatment for the young patient with Graves' hyperthyroidism .

Summary

EudraCT number	2016-000209-35
Trial protocol	GB
Global end of trial date	27 August 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2021
First version publication date	30 April 2021

Trial information

Trial identification

Sponsor protocol code	7805

Additional study identifiers

ISRCTN number	ISRCTN20381716
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Dr Timothy Cheetham, Newcastle University, 0191 282 9562, timothy.cheetham@ncl.ac.uk
Scientific contact	Dr Timothy Cheetham, Newcastle University, 0191 282 9562, timothy.cheetham@ncl.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	23 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2020
Global end of trial reached?	Yes
Global end of trial date	27 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal question is to establish whether a single 500mg dose of RTX, when administered together with a short 12 month course of 'conventional' anti-thyroid drug (ATD), is likely to result in a meaningful improvement in the proportion of young people with Graves' hyperthyroidism entering disease remission.

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

Young people with Graves' hyperthyroidism are managed with anti-thyroid drugs (ATD) initially but only 25% of young patients remit after a two-year course. Novel approaches to management are needed and B lymphocyte depletion with Rituximab (RTX) has shown promise in adults with Graves' hyperthyroidism. The aim of this trial is to establish whether a single dose of RTX, administered with a short course of ATD therapy, is likely to improve remission rates in young people with Graves' hyperthyroidism. 27 subjects with newly-diagnosed Graves' hyperthyroidism aged 12 to 20 years will receive a single dose of 500mg RTX within 6 weeks of commencing ATD. ATD will be stopped 12 months post RTX. Thyroid function tests, immunological markers including thyroid stimulating hormone receptor (TSHR) and peroxidase antibodies, serum immunoglobulin levels and peripheral blood lymphocyte subset analysis (including B cells [CD19]+ and class Switch memory B cells [CD27+ IgD-]) will be measured throughout the trial. The primary end-point will be the proportion of patients who are in remission off ATD 2 years post RTX. 40% or more patients in remission at 2 years following a single dose of RTX and a 12 month course of ATD would constitute a clinically meaningful improvement in outcome, above that normally observed, that would provide the foundation for a definitive trial.

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	24
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period ran from 4 November 2016 and 8 August 2018, at nine NHS hospital sites in the United Kingdom. Sites were in Birmingham (Paediatric), Leeds (Paediatric and Adult), Newcastle upon Tyne (Paediatric and Adult), Sheffield (Paediatric and Adult) and Southampton (Paediatric) in England, and Edinburgh (Adult) in Scotland.

Pre-assignment

Screening details:

The pre-screening assessment comprises:
• Patient has excess TH concentration: elevated FT3 and/or free thyroxine
• Suppressed TSH level
• Elevated TRAb, including TBII ± raised TPO antibody titre
• Patient (12-20 years, inclusive) has not received ATD for longer than 6 weeks at time of RTX treatment

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Rituximab

Arm description:

All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.

Arm type	Single arm trial
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:

The Rituximab infusion will be prepared by the respective pharmacy department or according to local trust policy as per section 6.6 of the SmPC for "MabThera 500mg Concentrate for Solution for Infusion". Each participant will receive a single dose of 500mg of Rituximab administered as an intravenous infusion at visit 1.

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

Dosage and administration details:

An initial dose of 20mg CBZ once daily is suggested for most participants in the initial phase, until the participant is euthyroid or mildly hyperthyroid, at which point the dose can be reduced.

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

Dosage and administration details:

CBZ is the first choice ATD in this trial but in the event of significant side-effects with CBZ (other than liver dysfunction) then participants can be switched to PTU. The increased risk of liver dysfunction with PTU will be discussed with participants and their families prior to commencing this treatment. Whilst on PTU, liver function tests should be checked at each clinic visit and PTU stopped immediately if the ALT or bilirubin are 2X outside the upper limit of the local reference range. If participants cannot tolerate or be treated with either CBZ or PTU during the first 12 months post-RTX, other potential means of maintaining a euthyroid state can be discussed with the trial management team.

Number of subjects in period 1	Rituximab
Started	27
Baseline	27
Completed	27

Period 2

Period 2 title	28 weeks post-Rituximab administration
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rituximab

Arm description:

All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.

Arm type	Single arm trial
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:

The Rituximab infusion will be prepared by the respective pharmacy department or according to local trust policy as per section 6.6 of the SmPC for "MabThera 500mg Concentrate for Solution for Infusion". Each participant will receive a single dose of 500mg of Rituximab administered as an intravenous infusion at visit 1.

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

Dosage and administration details:

An initial dose of 20mg CBZ once daily is suggested for most participants in the initial phase, until the participant is euthyroid or mildly hyperthyroid, at which point the dose can be reduced.

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

Dosage and administration details:

CBZ is the first choice ATD in this trial but in the event of significant side-effects with CBZ (other than liver dysfunction) then participants can be switched to PTU. The increased risk of liver dysfunction with PTU will be discussed with participants and their families prior to commencing this treatment. Whilst on PTU, liver function tests should be checked at each clinic visit and PTU stopped immediately if the ALT or bilirubin are 2X outside the upper limit of the local reference range. If participants cannot tolerate or be treated with either CBZ or PTU during the first 12 months post-RTX, other potential means of maintaining a euthyroid state can be discussed with the trial management team.

Number of subjects in period 2	Rituximab
Started	27
28 weeks	27
Completed	27

Period 3

Period 3 title	52 weeks post-Rituximab administration
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rituximab

Arm description:

All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.

Arm type	Single arm trial
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:

The Rituximab infusion will be prepared by the respective pharmacy department or according to local trust policy as per section 6.6 of the SmPC for "MabThera 500mg Concentrate for Solution for Infusion". Each participant will receive a single dose of 500mg of Rituximab administered as an intravenous infusion at visit 1.

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

Dosage and administration details:

An initial dose of 20mg CBZ once daily is suggested for most participants in the initial phase, until the participant is euthyroid or mildly hyperthyroid, at which point the dose can be reduced.

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

Dosage and administration details:

CBZ is the first choice ATD in this trial but in the event of significant side-effects with CBZ (other than liver dysfunction) then participants can be switched to PTU. The increased risk of liver dysfunction with PTU will be discussed with participants and their families prior to commencing this treatment. Whilst on PTU, liver function tests should be checked at each clinic visit and PTU stopped immediately if the ALT or bilirubin are 2X outside the upper limit of the local reference range. If participants cannot tolerate or be treated with either CBZ or PTU during the first 12 months post-RTX, other potential means of maintaining a euthyroid state can be discussed with the trial management team.

Number of subjects in period 3	Rituximab
Started	27
52 weeks	27
Completed	27

Period 4

Period 4 title	104 weeks post-Rituximab administration
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rituximab

Arm description:

All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.

Arm type	Single arm trial
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:

The Rituximab infusion will be prepared by the respective pharmacy department or according to local trust policy as per section 6.6 of the SmPC for “MabThera 500mg Concentrate for Solution for Infusion”. Each participant will receive a single dose of 500mg of Rituximab administered as an intravenous infusion at visit 1.

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

Dosage and administration details:

An initial dose of 20mg CBZ once daily is suggested for most participants in the initial phase, until the participant is euthyroid or mildly hyperthyroid, at which point the dose can be reduced.

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

Dosage and administration details:

CBZ is the first choice ATD in this trial but in the event of significant side-effects with CBZ (other than liver dysfunction) then participants can be switched to PTU. The increased risk of liver dysfunction with PTU will be discussed with participants and their families prior to commencing this treatment. Whilst on PTU, liver function tests should be checked at each clinic visit and PTU stopped immediately if the ALT or bilirubin are 2X outside the upper limit of the local reference range. If participants cannot tolerate or be treated with either CBZ or PTU during the first 12 months post-RTX, other potential means of maintaining a euthyroid state can be discussed with the trial management team.

Number of subjects in period 4	Rituximab
Started	27
Completed	27

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	15.3		
standard deviation	± 2.39	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	3	3	
Goitre size Units: Subjects			
Neither palpable nor visible	6	6	
Palpable only, not visible	10	10	
Palpable and visible	8	8	
Large goitre	2	2	
Not available	1	1	
Height Units: cm			
arithmetic mean	162.9		
standard deviation	± 6.86	-	
Weight Units: kg			
arithmetic mean	58.2		
standard deviation	± 15.99	-	
BMI Units: Units			
arithmetic mean	21.7		
standard deviation	± 4.26	-	
BMI SD Score			

Units: Score			
arithmetic mean	0.43		
standard deviation	± 1.19	-	
Systolic blood pressure			
Units: mmHg			
arithmetic mean	116.3		
standard deviation	± 9.88	-	
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	70.3		
standard deviation	± 8.07	-	
TSH			
Units: mU/L			
arithmetic mean	0.08		
standard deviation	± 0.23	-	
FT3			
Units: pmol/L			
arithmetic mean	10.85		
standard deviation	± 7.12	-	
FT4			
Units: pmol/L			
arithmetic mean	23.66		
standard deviation	± 14.46	-	
Thyroid antibodies: TPO			
Units: kU/L			
arithmetic mean	326.2		
standard deviation	± 450.4	-	
Thyroid antibodies: TRAb			
Units: U/L			
arithmetic mean	14.6		
standard deviation	± 14.59	-	
Blood count: Hb			
Units: g/L			
arithmetic mean	129.6		
standard deviation	± 13.6	-	
Blood count: Platelets			
Units: 10^9/L			
arithmetic mean	306.9		
standard deviation	± 60.8	-	
Blood count: Neutrophils			
Units: 10^9/L			
arithmetic mean	3.38		
standard deviation	± 1.13	-	
Blood count: Lymphocytes			
Units: 10^9/L			
arithmetic mean	2.07		
standard deviation	± 0.66	-	
Blood count: White cell			
Units: cells/microlitre			
arithmetic mean	6208		
standard deviation	± 1325	-	
Lymphocyte: CD19			

Units: cells/microlitre			
arithmetic mean	392		
standard deviation	± 166	-	
Lymphocyte: CD27			
Units: cells/microlitre			
arithmetic mean	55.5		
standard deviation	± 79.4	-	
Liver function: ALT			
Units: U/L			
arithmetic mean	99.0		
full range (min-max)	99.0 to 99.0	-	
Liver function: Bilirubin			
Units: micromole(s)/litre			
arithmetic mean	10.0		
full range (min-max)	10.0 to 10.0	-	

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.	
Reporting group title	Rituximab
Reporting group description:	
All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.	
Reporting group title	Rituximab
Reporting group description:	
All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.	
Reporting group title	Rituximab
Reporting group description:	
All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.	

Primary: Number of participants in remission

End point title	Number of participants in remission[1]
End point description:	
End point type	Primary
End point timeframe:	
104 weeks post-Rituximab administration	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Statistical analysis cannot be entered, as the EudraCT report does not allow data entry for single-arm trials. The number of subjects in remission 2 years after a single dose of Rituximab and a 12-month course of ATD is 13. The proportion of subjects in remission is 0.481 (13/27); 90% lower one-sided confidence interval (0.345, 1.00). As the number of patients in remission, 13, exceeds the critical number, 9 (A'Hern design), the null hypothesis that the remission rate is ≤ 20% is rejected.	

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Number of participants				
Yes	13			
No	14			

Statistical analyses

No statistical analyses for this end point

Secondary: TRAb titre and remission status

End point title	TRAb titre and remission status

End point description:

End point type	Secondary

End point timeframe:

24 months plus or minus 14 days post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: units per litre				
median (standard deviation)				
Relapse Remission	9.65 (± 18.6) 6.5 (± 11.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: B cell number expressed as a percentage of baseline and remission status 28 weeks post-Rituximab administration

End point title	B cell number expressed as a percentage of baseline and remission status 28 weeks post-Rituximab administration

End point description:

End point type	Secondary

End point timeframe:

28 weeks plus or minus 14 days, post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage				
median (standard deviation)				
Remission Relapse	18.0 (± 16.3) 46.5 (± 49.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: B cell number expressed as a percentage of baseline and remission status at 52 weeks post-Rituximab administration

End point title	B cell number expressed as a percentage of baseline and remission status at 52 weeks post-Rituximab administration

End point description:

End point type	Secondary

End point timeframe:

52 weeks plus or minus 14 days, post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage				
median (standard deviation)				
Remission	48.9 (± 27.8)			
Relapse	62.8 (± 21.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative dose of ATD to 12 months

End point title	Cumulative dose of ATD to 12 months

End point description:

End point type	Secondary

End point timeframe:

104 weeks post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: mg/kg				
median (standard deviation)				
Remission	54.6 (± 35.8)			
Relapse	60.5 (± 57.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time taken for TSH to no longer be suppressed

End point title	Time taken for TSH to no longer be suppressed

End point description:

End point type	Secondary

End point timeframe:

104 weeks post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Days				
median (standard deviation)				
Remission	46.0 (± 170.6)			
Relapse	93.0 (± 88.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time taken for FT4 to normalise

End point title	Time taken for FT4 to normalise

End point description:

End point type	Secondary

End point timeframe:

104 weeks post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Days				
median (standard deviation)				
Remission	31.0 (± 42.5)			
Relapse	44.0 (± 77.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time taken for FT3 to normalise

End point title	Time taken for FT3 to normalise

End point description:

End point type	Secondary

End point timeframe:

104 weeks post-Rituximab administration.

End point values	Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Days				
median (standard deviation)				
Remission	27.0 (± 46.4)			
Relapse	58.0 (± 83.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non-SAEs/SARs occurring during drug treatment were reported on the eCRF system within four weeks of the form being due.

Adverse event reporting additional description:

All Adverse Events were recorded. PIs were responsible for managing all AEs/ARs according to local protocols.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Rituximab

Reporting group description:

All participants receive an infusion of Rituximab, along with their standard treatment, at the start of the trial.

Serious adverse events	Rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cyst			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Surgical and medical procedures			
Dental care			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dental operation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nail operation			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Thyroidectomy			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	8		
Feeling hot			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Swelling			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	6		
Food allergy			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	7		
Menorrhagia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Menstruation delayed			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Metrorrhagia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Polymenorrhagia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Choking sensation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Cough			

subjects affected / exposed	12 / 27 (44.44%)		
occurrences (all)	14		
Dry throat			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	15 / 27 (55.56%)		
occurrences (all)	20		
Productive cough			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Throat irritation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Aggression			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

Depressed mood subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3			
Depression subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Insomnia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4			
Lethargy subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Mood swings subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2			
Panic attack subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Investigations Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Blood folate decreased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Vitamin D decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2			
Weight increased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1			
Weight decreased				

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Back injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Blister			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Foot fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Limb injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	12		
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Epilepsy			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	16 / 27 (59.26%)		
occurrences (all)	29		
Hyperaesthesia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Lethargy			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Loss of consciousness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Memory impairment			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Migraine without aura			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

Poor quality sleep subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Tremor subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4		
Vocal cord paralysis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Eye disorders Eye pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Ocular hyperaemia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Eye inflammation subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Eye swelling subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2		
Diplopia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Exophthalmos subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	3			
Abdominal pain upper				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Ageusia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Coeliac disease				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	5 / 27 (18.52%)			
occurrences (all)	6			
Dyspepsia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Dysphagia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Gingival bleeding				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Lip dry				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			

Oral herpes			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hirsutism			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Rash pruritic			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Endocrine disorders			
Toxic goitre			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hyperthyroidism			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Exophthalmos			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Costochondritis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Hypermobility syndrome			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal pain			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Rheumatoid arthritis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Infections and infestations			
Coxsackie viral infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nail infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	15 / 27 (55.56%)		
occurrences (all)	24		
Otitis media			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Parvovirus infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

Pharyngitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 7		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4		
Viral infection subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 11		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2017	The following changes have been made: 1. Additional blood sample at three visits for exploratory analyses of the immune system. 2. Re-structured primary endpoint/outcome measure, to cover all relapse eventualities. 3. Updated wording of a secondary outcome measure, as there is no appropriate "normal reference range" for this group of patients, to define 'recovery'. 4. More flexibility at pre-screening/consent visit. 5. Additional NHS sites: Cardiff and Vale University Health Board and University Hospital Southampton NHS Foundation Trust 6. Permission to use pre-prepared Rituximab infusion bags from site-approved manufacturers, labelled locally according to Annex 13. 7. Participants to give consent for a copy of their consent form to be sent securely to the NCTU trial team. 8. Use of latest version of SmPCs for Rituximab and Carbimazole, and update of RSI for Carbimazole in line with the Innovator product. 9. Use of any brand of Rituximab. 10. Update and correction of protocol and consent form with information, and clarification of terminology.
24 January 2018	The following changes have been made: 1. Update of STM, on documents. 2. Clarification of protocol on SAE follow-up to end of trial; Trial Medication section, to ensure one brand of IMP used; and web link. 3. Update of PIS and GP Letter on administration of live vaccine; update of web link on PIS. 4. Update of Consent Form to remove use of fax.
11 June 2018	The following changes have been made: 1. Use of latest version of Rituximab SmPC as RSI; a single SmPC to replace a joint SmPC. Use of latest version of Carbimazole SmPC. 2. Clarification of timing for primary end point for Visit 10. 3. Update of protocol to clarify requirement for liver function test at baseline. 4. Other administrative changes to protocol: change of Trial Manager, updated Sponsor contact details and change of Co-investigator. Planned trial period increased to 60 months, due to approved extension.
14 February 2019	New Acting Principal Investigator at trial site.
05 September 2019	The following changes have been made: • Clarification of the secondary objective of the trial • Correction of Adverse Event coding procedure • Correction of typos • Consistency of punctuation and grammar

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No secondary analyses are entered, as EudraCT does not permit reporting of single-arm trials.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30670519