Clinical trial results:
Combined Immunotherapy and Trophic Adrenocortical Stimulation in New Onset Autoimmune Addison's Disease

Summary

EudraCT number	2012-001682-33
Trial protocol	GB
Global end of trial date	16 May 2017

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	6176/RADS2

Additional study identifiers

ISRCTN number	ISRCTN20220821
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, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Prof. Simon Pearce, Newcastle University, 44 01912418674, simon.pearce@ncl.ac.uk
Scientific contact	Prof. Simon Pearce, Newcastle University, 44 01912418674, simon.pearce@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	03 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to restore adrenal function in patients with recent onset autoimmune Addison's disease. This study will answer the following questions:

In people with new-onset autoimmune Addison’s disease will the therapeutic regimen of rituximab and ACTH allow improvement or recovery of adrenal function?

Protection of trial subjects:

Rituximab infusion can be associated with transient adverse reactions in 50% of people including rash, flushing, shivers, fever, runny nose, hypotension, hypertension. Premedication with methylprednisolone, paracetamol and piriton will be given to minimise the risk of reactions. ACTH injections will be self administered subcutaneously every other day for the first 12 weeks, going to twice a week during week 12-16 and once weekly weeks 16-20.
There is frequently itchiness and discomfort over the injection site that lasts for 48-72hrs. Bruising and swelling may also occur. Two education sessions about the best technique for avoiding pain and bruising at the injection sites will be given.

Background therapy: -

Evidence for comparator:

No comparator was used in this trial.

Actual start date of recruitment	02 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: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Clinicians from general hospitals/main centres identified patients with newly diagnosed Addison's disease and invited them to contact the centres if they were interested, or to access the information direct from the Addison's disease self help group website. Potential participants could request the PIS from Principal Investigators.

Pre-assignment

Screening details:

The screening visit included; confirmation of eligibility and written consent, and blood tests including SST, urine test, chest X-ray, CT scan adrenals, ACTH injection education.

Period 1

Period 1 title	Baseline (Day 0)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 1	Treatment
Started	17
Completed	13
Not completed	4
Ineligible	4

Period 2	
Period 2 title	Treatment (Day 0 to Day 15)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 2	Treatment
Started	13
Completed	13

Period 3	
Period 3 title	Follow up 6 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 3	Treatment
Started	13
Completed	13

Period 4	
Period 4 title	Follow up 12 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 4	Treatment
Started	13
Completed	13

Period 5	
Period 5 title	Follow up 24 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 5	Treatment
Started	13
Completed	13

Period 6

Period 6 title	Follow up 48 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 6	Treatment
Started	13
Completed	13

Period 7	
Period 7 title	Follow up 72 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g on days 1 and 15, by slow intravenous infusion under cover from methylprednisolone 125mg IV, piriton 10mg IV and paracetamol 1g PO.

Investigational medicinal product name	Synacthen Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Parenteral use

Dosage and administration details:

Depot synacthen 1mg self-administered on alternate days (week 1-12, followed by an 8 week tail)

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	Solu-Medrone
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Day 0 and Day 15, 125mg IV methylprednisolone

Number of subjects in period 7	Treatment
Started	13
Completed	13

Baseline characteristics

Reporting groups	
Reporting group title	Baseline (Day 0)

Reporting group description: -

Reporting group values	Baseline (Day 0)	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
Gender categorical Units: Subjects			
Female	11	11	
Male	6	6	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Treatment

Reporting group description: -

Primary: Proportion achieving restoration of normal glucocorticoid secretion (peak cortisol >550nmol/l) after repeat synacthen testing at 48 weeks

End point title	Proportion achieving restoration of normal glucocorticoid secretion (peak cortisol >550nmol/l) after repeat synacthen testing at 48 weeks[1]

End point description:

End point type	Primary

End point timeframe:

Serum cortisol levels will be measured at 6, 12, 24, 48 or 72 weeks

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: No statistically significant results at 6, 12, 24, 48 or 72 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: nmol/l				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 12 weeks

End point title	Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at

	12 weeks

End point description:

End point type	Secondary

End point timeframe:

Synacthen testing at 12 weeks
Non significant for this secondary endpoint at all time points

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13[2]			
Units: nmol/l				
number (not applicable)	8			

Notes:

[2] - 1/13 (8%)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 24 weeks

End point title	Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 24 weeks

End point description:

Basal and peak cortisol response >100nmol/l over baseline

End point type	Secondary

End point timeframe:

Synacthen testing at 24 weeks
Non significant for this secondary endpoint at all time points

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Number of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 48 weeks

End point title	Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 48 weeks

End point description:

>100nmol/l over baseline

End point type	Secondary

End point timeframe:

Response to synacthen testing at 48 weeks
Non significant for this secondary endpoint at all time points

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Number				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 72 weeks

End point title	Proportion achieving improvement of basal and peak cortisol response (>100nmol/l over baseline) to synacthen testing at 72 weeks

End point description:

End point type	Secondary

End point timeframe:

Response to synacthen testing at 72 weeks
Non significant for this secondary endpoint at all time points

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: nmol/l				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Urine GCMS/MS steroid profile

End point title	Urine GCMS/MS steroid profile

End point description:

See attached document

End point type	Secondary

End point timeframe:

Measured at baseline, week 12 and week 48

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13[3]			
Units: Participants	8			

Notes:

[3] - Steroid Metabolite Response in 8/13 Patients with an Increase in Urinary Steroid Excretion

Attachments (see zip file)	Urine steroids/RADS2_EudraCT_urinesteroids.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at baseline

End point title	Change in peripheral B lymphocyte count at baseline

End point description:

Change in peripheral B lymphocyte count at baseline. CD19* population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19* <0.1% of lymphocytes.

Change in peripheral T lymphocyte count at baseline, 6, 12, 24, 36, 48 and 72 weeks was not measured.

End point type	Secondary

End point timeframe:

Baseline

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage				
number (not applicable)				
NCL01	9.8			
NCL04	22.4			
NCL05	10.7			
NCL06	27.2			
NCL08	9.4			
NCL09	16.6			

NCL10	15.8			
EXE01	11.2			
EXE02	15.5			
EXE04	2.8			
EXE05	24.6			
CAMB01	10.4			
CARD01	12.3			

Attachments (see zip file)	B-lymphocyte depletion/B Lymphocyte CD19+ Populations in

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported quality of life (EQ5D)

End point title	Patient reported quality of life (EQ5D)

End point description:

Number of patients scoring 1, 2 or 3 for each domain. 1 = 'no problems'; 2 = 'some problems'; 3 = 'extreme problems'

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 48

End point values	Treatment	Treatment	Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13[4]	13[5]	13[6]	
Units: Scale Score				
number (not applicable)				
Mobility (1)	1	11	11	
Mobility (2)	10	2	2	
Mobility (3)	2	0	0	
Self-care (1)	1	12	10	
Self-care (2)	12	1	3	
Self-care (3)	0	0	0	
Usual activities (1)	0	9	8	
Usual activities (2)	7	4	5	
Usual activities (3)	6	0	0	
Pain/Discomfort (1)	0	9	6	
Pain/Discomfort (2)	9	4	7	
Pain/Discomfort (3)	4	0	0	
Anxiety/Depression (1)	1	11	8	
Anxiety/Depression (2)	7	1	5	
Anxiety/Depression (3)	5	1	0	

Notes:

[4] - Baseline

[5] - Week 12

[6] - Week 48

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported quality of life (AddiQoL)

End point title	Patient reported quality of life (AddiQoL)

End point description:

AddiQoL scores at Week 12 and Week 48 vs. Baseline.
Total score 120, higher score is better subjective QoL.
Non-significant change in QoL at all time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 48

End point values	Treatment	Treatment	Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13[7]	13[8]	13[9]	
Units: Scale Score				
arithmetic mean (standard deviation)	84.62 (± 15.9)	88.15 (± 14.9)	87.69 (± 14.24)	

Notes:

[7] - Baseline

[8] - Baseline vs Week 12, p = 0.41

[9] - Baseline vs Week 48, p = 0.41

Statistical analyses

No statistical analyses for this end point

Secondary: VAS wellbeing score

End point title	VAS wellbeing score

End point description:

Visual Analogue Scale Scores. Highest score is 100 (= best health state you can imagine).
Non-significant change in QoL as measured by VAS at all time points.

End point type	Secondary

End point timeframe:

Week 12 and Week 48 vs. Baseline

End point values	Treatment	Treatment	Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13[10]	13[11]	13[12]	
Units: Scale Score				
arithmetic mean (standard deviation)	74.77 (± 19.19)	75.31 (± 24.51)	77.5 (± 17.74)	

Notes:

[10] - Baseline

[11] - Baseline vs Week 12, p = 0.94

[12] - Baseline vs Week 48, p = 0.39

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at 6 weeks

End point title	Change in peripheral B lymphocyte count at 6 weeks

End point description:

Change in peripheral B lymphocyte count at 6 weeks. CD19* population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19* <0.1% of lymphocytes.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent				
number (not applicable)				
NCL01	0.2			
NCL04	0.3			
NCL05	0.1			
NCL06	0.1			
NCL08	0.1			
NCL09	0.2			
NCL10	0.1			
EXE01	0.2			
EXE04	0.2			
EXE05	0.1			
CARD01	0.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at 12 weeks.

End point title	Change in peripheral B lymphocyte count at 12 weeks.

End point description:

Change in peripheral B lymphocyte count at 12 weeks. CD19* population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19* <0.1% of lymphocytes.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent				
number (not applicable)				
NCL01	0.9			
NCL04	0.2			
NCL05	0.2			
NCL06	0.1			
NCL08	0.1			
NCL09	0.1			
NCL10	0.0			
EXE01	0.4			
EXE02	0.1			
EXE04	0.2			
EXE05	0.1			
CAMB01	0.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at 24 weeks

End point title	Change in peripheral B lymphocyte count at 24 weeks

End point description:

Change in peripheral B lymphocyte count at 24 weeks. CD19* population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19* <0.1% of lymphocytes.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent				
number (not applicable)				
NCL01	0.1			
NCL04	0.1			
NCL05	0.1			
NCL06	0.2			
NCL08	0.1			
NCL09	0.0			
NCL10	0.6			
EXE01	2.1			
EXE04	0.1			
EXE05	0.1			
CAMB01	0.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at 48 weeks

End point title	Change in peripheral B lymphocyte count at 48 weeks

End point description:

Change in peripheral B lymphocyte count at 48 weeks. CD19* population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19* <0.1% of lymphocytes.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent				
number (not applicable)				
NCL01	2.1			
NCL04	0.0			
NCL05	2.6			
NCL06	9.7			
NCL08	2.5			
NCL09	3.9			
NCL10	3.3			
EXE01	18.8			
EXE02	8.2			
EXE04	5.9			

EXE05	5.9			
CAMB01	3.7			
CARD01	0.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in peripheral B lymphocyte count at 72 weeks.

End point title	Change in peripheral B lymphocyte count at 72 weeks.

End point description:

Change in peripheral B lymphocyte count at 72 weeks. CD19+ population expressed as a percentage of parent lymphocyte population. 10,000 lymphocyte events counted twice for each measurement. Complete depletion was judged as CD19+ <0.1% of lymphocytes.
12/13 patients achieved CD19+ lymphocyte counts measured as 0.0 or 0.1% of the parent population following treatment with rituximab. These included NCL06 who achieved the highest peak cortisol post-intervention and NCL08 who achieved the secondary outcome measure of a rise in cortisol of 100nmol/L post-intervention. In most patients, counts remained low for several months (minimum 12 - maximum 48 depleted weeks), with CD19+ population counts measured as 0.0 - 0.2% of parent population across several major outcome visits. Resurgence (>0.05%) of parent population) was detectable in all patients by the end of study and occurred after a mean period of 48 week (SEM 3.84).

End point type	Secondary

End point timeframe:

72 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent				
number (not applicable)				
NCL01	7.7			
NCL04	0.6			
NCL05	9.6			
NCL06	16.2			
NCL08	3.3			
NCL09	8.5			
EXE01	15.2			
EXE02	13.8			
EXE04	7.0			
EXE05	6.9			
CAMB01	14.9			
CARD01	2.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation of DHEAS levels at 48 weeks

End point title	Normalisation of DHEAS levels at 48 weeks

End point description:

End point type	Secondary

End point timeframe:

48 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13[13]			
Units: percent				
number (not applicable)	0			

Notes:

[13] - 0% of patients achieved normalisation at 48 weeks. Non-significant (p=0.13)

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation of 17αOH progesterone levels

End point title	Normalisation of 17αOH progesterone levels

End point description:

46% (6/13) patients had results in the normal lab reference range at 48 weeks, non significant p=0.52 (BUT, all 6/13 also had results in normal range at the point of trial entry/first biochemical screening)

End point type	Secondary

End point timeframe:

48 weeks

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	13[14]			
Units: percent				
number (not applicable)	46			

Notes:

[14] - 6/13 (46%) also had results in normal range at the point of trial entry/first biochemical screening)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Treatment group

Reporting group description: -

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Laceration	Additional description: Laceration to face after fall		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Gastroenteritis including dehydration		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting and watery diarrhoea	Additional description: High temperature		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Diarrhoea and vomiting		
subjects affected / exposed	1 / 17 (5.88%)		
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	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)		
Injury, poisoning and procedural complications			
Black eye			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fall	Additional description: Fall from bike		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	5		
Sore throat			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Viral illness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Flu symptoms			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
'Cold'			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Insomnia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Paraesthesia	Additional description: In both hands		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Swelling/bruising to abdomen			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
'Cold'/URTI			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Short of breath/fatigue			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Weight loss and dizziness	Additional description: Later diagnosed with Grave's disease		
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	6		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Stomach bloating subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3 3 / 17 (17.65%) 3 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) dyspnoea subjects affected / exposed occurrences (all)	 5 / 17 (29.41%) 15 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 3		
Endocrine disorders Hypothyroidism (subclinical) subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		

Infections and infestations			
Sinusitis			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2013	Update to information in the Participant Information Sheet to reflect the radiation risks in the study.
24 March 2014	Amendment to inclusion criteria, to increase the time allowed from diagnosis of autoimmune Addison's disease from 28 days (4 weeks) to 56 days (8 weeks). Increase the number of sites from 3 to 5 centres across the UK. Addition of a 'Study Patient ID Card' for Rituximab, as specified in the Rituximab (Mabthera) SmPC. Addition of GP letter and Study Withdrawal Form. Amendments to the protocol in accordance with current SPIRIT guidelines for protocol format.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported