Clinical trial results:
Randomised Trial of Anti-CD20 in C4d+ Chronic Allograft Nephropathy

Summary

EudraCT number	2006-002330-38
Trial protocol	GB
Global end of trial date	09 March 2017

Results information

Result version number	v1 (current)
This version publication date	23 June 2019
First version publication date	23 June 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (FINAL STUDY REPORT.pdf)

Trial information

Trial identification

Sponsor protocol code	RituxiCAN-C4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00476164
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Anthony Dorling, Kings College London, 44 020 7188 8711, anthony.dorling@kcl.ac.uk
Scientific contact	Professor Anthony Dorling, Kings College London, 44 020 7188 8711, anthony.dorling@kcl.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	09 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2017
Global end of trial reached?	Yes
Global end of trial date	09 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether anti-CD20 therapy can stabilise or improve renal function and/or proteinuria in patients with C4d+, chronic (humoral) rejection in whom standard therapeutic approaches have failed.

Protection of trial subjects:

During the initial phase of the run-in period, the following standard clinical therapies will be introduced and/or optimised according to the following guidelines;

• Mycophenolate mofetil bd, or enteric coated mycophenolic acid bd, with dose determined according to local unit guidelines. In those centres monitoring MPA levels, dose will be titrated to achieve plasma 12-hour post-dose levels of 1.6-2.75. In these centres, the starting dose will be 500mg bd in patients not already on MMF
• Tacrolimus bd titrated to achieve 12-hour post-dose levels of 4-8. Starting dose 0.05mg/kg bd in patients not already on Tacrolimus
• Statin therapy to achieve total non-fasting cholesterol to ≤ 4.5
• ACE-I and ARB combination therapy to achieve a target bp of ≤140/≤80

Background therapy:

Optimised Tacrolimus, MMF, ACE-I/ARB, statins

Evidence for comparator:

n/a

Actual start date of recruitment	12 April 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	22
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 16 sites across the UK

Pre-assignment

Screening details:

All eligible patients will be undergo a run-in period during which time standard therapy will be optimised (0-2 months) followed by 3 months on fully optimised therapy. At the end of the run-in, graft function and degree of proteinuria will be re-assessed and patients who still meet the criteria for entrance into the study.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

Control group were randomised to stay on standard therapy with the formal 3-month analysis period will begin on the day of randomisation.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Rituximab Arm

Arm description:

Participants in the Rituximab arm received two 1g infusions 14 days apart, administered with paracetamol and chlorphenamine +/- hydrocortisone followed by co-trimoxazole (or alternative) for 6 months.

Arm type	Experimental
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:

Participants received Rituximab 1g infusions on two occaisions 14 days apart.

Number of subjects in period 1	Control Arm	Rituximab Arm
Started	11	12
Completed	11	9
Not completed	0	3
Consent withdrawn by subject	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Control Arm
Reporting group description:	
Control group were randomised to stay on standard therapy with the formal 3-month analysis period will begin on the day of randomisation.	
Reporting group title	Rituximab Arm
Reporting group description:	
Participants in the Rituximab arm received two 1g infusions 14 days apart, administered with paracetamol and chlorphenamine +/- hydrocortisone followed by co-trimoxazole (or alternative) for 6 months.	

Reporting group values	Control Arm	Rituximab Arm	Total
Number of subjects	11	12	23
Age categorical Units: Subjects			
Adults (18-64 years)	11	12	23
From 65-84 years	0	0	0
Gender categorical Units: Subjects			
Female	3	4	7
Male	8	8	16

End points

End points reporting groups

Reporting group title	Control Arm

Reporting group description:

Control group were randomised to stay on standard therapy with the formal 3-month analysis period will begin on the day of randomisation.

Reporting group title	Rituximab Arm

Reporting group description:

Participants in the Rituximab arm received two 1g infusions 14 days apart, administered with paracetamol and chlorphenamine +/- hydrocortisone followed by co-trimoxazole (or alternative) for 6 months.

Primary: Rate of deterioration of renal function

End point title	Rate of deterioration of renal function[1]

End point description:

End point type	Primary

End point timeframe:

At least 6 data points over three months

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: Please see final study report for details of analysis.

End point values	Control Arm	Rituximab Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: estimated mean differences in slope	11	12		

Attachments (see zip file)	FINAL STUDY REPORT/FINAL STUDY REPORT.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be recorded from consent up to the primary end-point.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Control Arm

Reporting group description:

Control group were randomised to stay on standard therapy with the formal 3-month analysis period will begin on the day of randomisation.

Reporting group title	Rituximab Arm

Reporting group description:

Participants in the Rituximab arm received two 1g infusions 14 days apart, administered with paracetamol and chlorphenamine +/- hydrocortisone followed by co-trimoxazole (or alternative) for 6 months.

Serious adverse events	Control Arm	Rituximab Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	9 / 12 (75.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastric cancer			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post peritoneal catheter insertion complication			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated incisional hernia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Abscess			

subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Complication post biopsy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control Arm	Rituximab Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	9 / 12 (75.00%)	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	3 / 11 (27.27%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Nervous system disorders			
Other			
subjects affected / exposed	2 / 11 (18.18%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 11 (36.36%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Other			

subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Drug related			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Other			
subjects affected / exposed	3 / 11 (27.27%)	5 / 12 (41.67%)	
occurrences (all)	3	5	
Respiratory, thoracic and mediastinal disorders			
Infection			
subjects affected / exposed	3 / 11 (27.27%)	6 / 12 (50.00%)	
occurrences (all)	3	6	
Other			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Infection			
subjects affected / exposed	2 / 11 (18.18%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Neoplasm			
subjects affected / exposed	3 / 11 (27.27%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Other			
subjects affected / exposed	1 / 11 (9.09%)	3 / 12 (25.00%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Infection			
subjects affected / exposed	4 / 11 (36.36%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Other			
subjects affected / exposed	1 / 11 (9.09%)	5 / 12 (41.67%)	
occurrences (all)	1	5	
Infections and infestations			

Systemic infection			
subjects affected / exposed	3 / 11 (27.27%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Other			
subjects affected / exposed	0 / 11 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2009	Change of Sponsor from Imperial College London to King's College London
14 February 2010	a) Addition of "administration of lymphocyte depleting antibody within 3 months of enrolment" to the exclusion criteria. b) Requirement for units to give 6 months of prophylactic co-trimoxazole to all patients receiving rituximab. The dose will be that used by each unit for prophtlaxis.
20 December 2010	Allow use enteric coated mycophenolic acid instead of MMF. Allow use imaging techniques other than MRA. Amended IMP labels
07 February 2012	Two changes have been made to the exclusion criteria, the first to reflect a difficulty the trial team have had in obtaining timely imaging to exclude renal artery stenosis (which after 40 recruits has not excluded anybody), and the second to reflect a minor change in the SmPC for rituximab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported