Clinical trial results:
Alemtuzumab and rheumatoid arthritis - an immunisation study

Summary

EudraCT number	2010-021146-22
Trial protocol	GB
Global end of trial date	20 November 2014

Results information

Result version number	v1
This version publication date	29 July 2016
First version publication date	29 July 2016
Summary attachment (see zip file)	Alemtuzumab EudraCT 2010-021146-22 - secondary outcome data (Alemtuzumab EudraCT 2010-021146-22 - secondary outcome data.pdf)

Trial information

Trial identification

Sponsor protocol code	5339

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Newcastle upon Tyne Hospitals NHS Foundation Trust, Joint Research Office
Sponsor organisation address	Regent Point (Level 1), Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Professor John Isaacs, Institute of Cellular Medicine, Musculoskeletal Research Group, Newcastle University, 0191 222 5337, j.d.isaacs@ncl.ac.uk
Scientific contact	Professor John Isaacs, Institute of Cellular Medicine, Musculoskeletal Research Group, Newcastle University, 0191 222 5337, j.d.isaacs@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	16 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2014
Global end of trial reached?	Yes
Global end of trial date	20 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the ability to mount immune responses (to measure the function of the immune system) in patients who received alemtuzumab for rheumatoid arthritis between 1991 and 1994 and a matched control group with long-standing rheumatoid arthritis. The control group will be matched for disease duration (within 5 years of matched case), age (within 10 years of matched case) and gender.

Protection of trial subjects:

Potential participants will have the study explained to them and be given ample time to ask questions and consider participation prior to obtaining written informed consent.

All study procedures performed by qualified and trained study staff

All AEs/SAEs recorded by site staff during study participation.

Trial Management Group to meet at regular intervals to discuss any study issues, especially information relevant to participant safety or welfare

Background therapy: -

Evidence for comparator:

Patients receiving alemtuzumab for RA between 1991 and 1994 have remained lymphopenic during long-term follow-up but do not appear otherwise to be immunosuppressed. An observational study is performed approximately every 5 years on these patients, documenting mortality against a closely matched cohort of patients with RA who have never received alemtuzumab. This has confirmed no excess in mortality over 12 years follow-up to date. There were no specific control subjects in the original alemtuzumab studies but mortality has been compared with a closely matched control group of patients from the EULAR database. However, the latter database does not provide morbidity outcomes for comparison.

A recent immunization study looked at serological responses to vaccines in alemtuzumab recipients but, due to restrictions within the study, it was not possible to compare responses with matched controls. The current study seeks to rectify that evidence gap.

Actual start date of recruitment	01 October 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)	8
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients that were treated with alemtuzumab between 1991 and 1994 were identified by the Chief Investigator from the previous study database. Matched-control patients who had not received alemtuzumab, were identified locally in Addenbrookes Hospital, Cambridge, UK. All participants were recruited between October 2013 and October 2014.

Pre-assignment

Screening details:

Inclusion criteriafor for the study were as follows

Alemtuzumab recipients -Received alemtuzumab in original Cambridge studies (1991-94)

Matched controls - Rheumatoid arthritis according to 1987 ACR criteria, Disease duration within 5 years of matched case, Age within 10 years of matched case, Gender profile to match alemtuzumab recipients

Period 1

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

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Alemtuzumab cohort

Arm description:

Patients that were treated with alemtuzumab (CAMPATH-1H) for RA between 1991 and 1994

Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous drip use

Dosage and administration details:

Alemtuzumab administered previously to the Alemtuzumab cohort during 1991-1994 study, not administered in the current study

Arm title	Control

Arm description:

Age and sex matched RA patients with a similar disease duration, who had not received alemtuzumab

Arm type	Experimental matched control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Alemtuzumab cohort	Control
Started	9	8
Completed	9	8

Baseline characteristics

Reporting groups	
Reporting group title	Alemtuzumab cohort
Reporting group description:	
Patients that were treated with alemtuzumab (CAMPATH-1H) for RA between 1991 and 1994	
Reporting group title	Control
Reporting group description:	
Age and sex matched RA patients with a similar disease duration, who had not received alemtuzumab	

Reporting group values	Alemtuzumab cohort	Control	Total
Number of subjects	9	8	17
Age categorical Units: Subjects			
Adults (18-64 years)	4	4	8
From 65-84 years	5	4	9
Gender categorical Units: Subjects			
Female	7	7	14
Male	2	1	3
Disease duration Units: Years			
median	31	24.5	
full range (min-max)	23 to 40	20 to 41	-
DAS-28 Units: DAS score			
median	3.44	3.9	
full range (min-max)	1.38 to 5.33	2.03 to 5.75	-
CRP Units: mg/L			
median	7	1.5	
full range (min-max)	2 to 134	1 to 2	-
ESR Units: mm/hr			
median	34	11.5	
full range (min-max)	4 to 104	2 to 38	-
HAQ Units: HAQ score			
median	2.25	1.69	
full range (min-max)	2 to 3	0.25 to 2.125	-
VAS Units: VAS score			
median	25	23	
full range (min-max)	2 to 56	4 to 75	-
IgG Units: g/ml			
median	9.5	9.95	
full range (min-max)	6.2 to 16.6	4.4 to 16.3	-
IgA			

Units: g/ml			
median	2.6	1.9	
full range (min-max)	1.1 to 4.2	0.4 to 3.9	-
IgM			
Units: g/ml			
median	0.85	0.85	
full range (min-max)	0.006 to 3.2	0.3 to 2.5	-
RF			
Units: IU			
median	0	39	
full range (min-max)	0 to 67	0 to 275	-
CCP			
Units: U/ml			
median	0.55	215	
full range (min-max)	0 to 340	1.2 to 340	-
Total lymphocytes			
Units: x109/L			
median	0.93	1.125	
full range (min-max)	0.41 to 3.1	0.34 to 2.38	-
CD4+ T cells			
Units: x109/L			
median	0.37	0.48	
full range (min-max)	0.13 to 0.94	0.13 to 0.65	-
CD4+ naive T cells			
Units: x109/L			
median	0.23	0.21	
full range (min-max)	0.01 to 0.61	0.07 to 0.29	-
CD4+ total memory T cells			
Units: x109/L			
median	0.13	0.26	
full range (min-max)	0.11 to 0.34	0.06 to 0.56	-
CD4+ central memory T cells			
Units: x109/L			
median	0.08	0.2	
full range (min-max)	0.05 to 0.16	0.03 to 0.42	-
CD4+ effector memory T cells			
Units: x109/L			
median	0.05	0.06	
full range (min-max)	0.02 to 0.17	0.02 to 0.14	-
CD8+ T cells			
Units: x109/L			
median	0.1	0.11	
full range (min-max)	0.04 to 0.72	0.05 to 0.42	-
CD8+ naive T cells			
Units: x109/L			
median	0.05	0.02	
full range (min-max)	0.01 to 0.14	0.01 to 0.08	-
CD8+ total memory T cells			
Units: x109/L			
median	0.07	0.06	
full range (min-max)	0.02 to 0.13	0.01 to 0.19	-
CD8+ central memory T cells			

Units: x109/L			
median	0.01	0.02	
full range (min-max)	0.003 to 0.01	0.005 to 0.11	-
CD8+ effector memory T cells			
Units: x109/L			
median	0.01	0.03	
full range (min-max)	0.007 to 0.07	0.007 to 0.1	-
B cells			
Units: x109/L			
median	0.01	0.09	
full range (min-max)	0.01 to 0.05	0.02 to 0.2	-
Naive B cells			
Units: x109/L			
median	0.01	0.08	
full range (min-max)	0.001 to 0.02	0.07 to 0.14	-
Memory B cells			
Units: x109/L			
median	0.006	0.01	
full range (min-max)	0.002 to 0.02	0.008 to 0.03	-
CD5+ B cells			
Units: x109/L			
median	0.001	0.03	
full range (min-max)	0.001 to 0.005	0.001 to 0.08	-
CD19+ CD24hi CD38hi B cells			
Units: x109/L			
median	0.001	0.009	
full range (min-max)	0.00005 to 0.002	0.0008 to 0.038	-
NK cells			
Units: x109/L			
median	0.1	0.07	
full range (min-max)	0.02 to 0.17	0.02 to 0.1	-
NK T cells			
Units: x109/L			
median	0.01	0.009	
full range (min-max)	0.0006 to 0.13	0.002 to 0.02	-

End points

End points reporting groups

Reporting group title	Alemtuzumab cohort
Reporting group description:	
Patients that were treated with alemtuzumab (CAMPATH-1H) for RA between 1991 and 1994	
Reporting group title	Control
Reporting group description:	
Age and sex matched RA patients with a similar disease duration, who had not received alemtuzumab	

Primary: Seroprotection rate %

End point title	Seroprotection rate %[1]
End point description:	

End point type	Primary
End point timeframe:	
4 weeks after immunisation	

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: End point data are sera analysis results of vaccine responses comparing baseline and 4 weeks post-vaccination. End point data are not result of statistical analysis.

End point values	Alemtuzumab cohort	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: percent				
number (not applicable)				
Diptheria toxoid	66	100		
Tetanus toxoid	100	100		
Poliovirus P1	100	100		
Poliovirus P2	83.3	100		
Poliovirus P3	83.3	100		

Statistical analyses

No statistical analyses for this end point

Primary: Seroconversion rate %

End point title	Seroconversion rate %[2]
End point description:	

End point type	Primary
End point timeframe:	
4 weeks after immunisation	

Notes:

[2] - 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: End point data are sera analysis results of vaccine responses comparing baseline and 4 weeks post-vaccination. End point data are not result of statistical analysis.

End point values	Alemtuzumab cohort	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: percent				
number (not applicable)				
Diptheria toxoid	33	25		
Tetanus toxoid	66.7	50		
Poliovirus P1	50	100		
Poliovirus P2	16.6	100		
Poliovirus P3	83.3	100		

Statistical analyses

No statistical analyses for this end point

Primary: % satisfactory response

End point title	% satisfactory response[3]

End point description:

End point type	Primary

End point timeframe:

4 weeks after immunisation

Notes:

[3] - 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: End point data are sera analysis results of vaccine responses comparing baseline and 4 weeks post-vaccination. End point data are not result of statistical analysis.

End point values	Alemtuzumab cohort	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: percent				
number (not applicable)				
Pneumococcus antigen	66	0		

Statistical analyses

No statistical analyses for this end point

Primary: Influenza vaccine Seroprotection rate %

End point title	Influenza vaccine Seroprotection rate %[4]

End point description:

End point type	Primary

End point timeframe:

4 weeks after immunisation

Notes:

[4] - 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: End point data are sera analysis results of vaccine responses comparing baseline and 4 weeks post-vaccination. End point data are not result of statistical analysis.

End point values	Alemtuzumab cohort	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: percent				
number (not applicable)				
A/Cal/7/09	22	87.5		
A/Texas/50/12	56	87.5		
B/Mass/02/12	11	37.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study participation	
Assessment type	Systematic

Dictionary used	
Dictionary name	As reported
Dictionary version	0

Reporting groups	
Reporting group title	Alemtuzumab cohort
Reporting group description:	
Patients that were treated with alemtuzumab (CAMPATH-1H) for RA between 1991 and 1994	
Reporting group title	Control
Reporting group description:	
Age and sex matched RA patients with a similar disease duration, who had not received alemtuzumab	

Serious adverse events	Alemtuzumab cohort	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Alemtuzumab cohort	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	5 / 8 (62.50%)	
General disorders and administration site conditions			
injection site reaction			
subjects affected / exposed	2 / 9 (22.22%)	3 / 8 (37.50%)	
occurrences (all)	3	4	
Feeling unwell			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Loss of appetite			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 0	0 / 8 (0.00%) 0	
Immune system disorders common cold subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 8 (37.50%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2012	• Re-classification of IMP by MHRA. MHRA now define the alemtuzumab (administered to the alemtuzumab recipients at Cambridge between 1991 and 1994) as the IMP for this study. The seasonal flu, pneumonia and diptheria, polio and tetanus booster vaccines to be administered within the context of this study are now NIMPs (physiological probes). • The Pharmacovigilance section of the protocol is substantially altered to reflect the IMP & NIMP definitions. The time elapsed since last administration of IMP is also referenced (stipulating that adverse reactions to the IMP, or SUSARs linked to an interaction between the IMP and NIMP are NOT anticipated) . Pregnancy information for female partners of male participants will also now be collected only for the alemtuzumab group (who were originally administered the IMP). • Streamline participant follow-up and the time points I assessments as per the primary and secondary outcome measures; also amended are the time points stipulated in the definition of end of study and the time points for collecting AEs/SAEs. • Reduction in the total volume of blood required at the screening and follow- up visit. • SmPC documentation is updated to incorporate the re-classification of the IMP, change of flu vaccine brand routinely available at Addenbrooke's Hospital in 2012- 2013 and an update to Pneumovax II SmPC. • Logistics to now allow the screening and baseline visit to be combined into one single clinic visit (with the exception of female participants of child bearing potential, where results from the study-specific serum pregnancy test are required prior to vaccination) . • Protocol section 11 is substantially reworded, primarily to reflect that the ONS data (for alemtuzumab recipients) as received by the Chief Investigator does not contain patient contact details (as was previously perceived). • Amendments to study documentation in line with the changes outlined in protocol
18 July 2013	SmPC documentation updated The process outlined for identification, screening and recruitment of alemtuzumab participants (protocol section 11.1) has been amended/further clarification provided. Exclusion criteria amended for control patients to exclude patients who received rituximab within the past 6 months (extended from 3 months, as per previous study protocol) Exclusion criteria amended for control patients to exclude females who are known to be pregnant or breast feeding Reduction in total volume of blood required for analysis, following latest confirmation from labs. Following Sponsor confirmation, statistical input to the Trial Oversight Committee is not deemed necessary. The Independent Chair and Independent Assessor for safety/adverse events are now appointed. The format/layout of the DAS28 (incorporated as protocol Appendix E) has been amended. Minor changes to study documentation, including change to contact details/name of central labs, blood volume inconsistency within protocol, etc.

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.

We acknowledge that due to the small numbers in both groups robust statistical comparison was not possible. Additionally, the timing of vaccination outwith this study was unknown potentially making meaningful comparison difficult

Notes: