



## Clinical trial results:

### Alemtuzumab for ANCA-Associated Refractory Vasculitis - A study of safety and efficacy (ALEVIATE).

#### Summary

EudraCT number	2009-017087-17
Trial protocol	GB
Global end of trial date	29 May 2018

#### Results information

Result version number	v1 (current)
This version publication date	14 June 2019
First version publication date	14 June 2019

#### Trial information

##### Trial identification

Sponsor protocol code	AL7.0
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Prof David Jayne, Cambridge University Hospitals NHS Trust & University of Cambridge, 01223 748062,
Scientific contact	Prof David Jayne, Cambridge University Hospitals NHS Trust & University of Cambridge, 01223 748062,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2018
Global end of trial reached?	Yes
Global end of trial date	29 May 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The trial objectives are to assess the efficacy (vasculitis response at 6 months) and safety (proportion of patients with severe adverse events) of alemtuzumab in refractory or relapsing primary systemic vasculitis.

Protection of trial subjects:

Alemtuzumab is a monoclonal antibody that depletes lymphocytes. It is known to be associated with increased risk of infections and new onset autoimmunity (especially thyroid). All patients that received alemtuzumab in this trial are followed up closely at Addenbrookes hospital for the development of new-onset autoimmunity. Patients, as well as GPs have been appraised of these risks. We are in the process of obtaining ethical approval to follow these patients long-term.

Background therapy:

All other immunosuppressive & immunomodulator therapies are stopped before entering the trial and receiving alemtuzumab. Oral glucocorticoids are allowed.

Evidence for comparator:

In this phase II trial, two dosing regimens of alemtuzumab were compared to establish if lower dose is as efficacious as higher dose and if it is associated with better safety. There is no prior randomised control trial literature to support one dose over the other.

Actual start date of recruitment	07 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

24 patients were recruited from a single center (Addenbrookes hospital, Cambridge, UK) over a period of 7 years (11/4/2011 to 29/5/2018). Recruitment was delayed due to small patient pool from which to recruit from, unavailability of the drug for a period as the company withdrew the license for rebranding purposes.

### Pre-assignment

Screening details:

Patients were evaluated by trial investigators to ensure they met all the inclusion criteria and none of the exclusion criteria as detailed in the trial protocol. A total of XX patients were screened for inclusion into the trial.

### Period 1

Period 1 title	Consent
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Low dose arm

Arm description: -

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

Dosage and administration details:

15mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 30mg.

<b>Arm title</b>	High dose arm
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Arm description: -

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

Dosage and administration details:

30mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 60mg.

Number of subjects in period 1	Low dose arm	High dose arm
Started	13	11
Completed	13	10
Not completed	0	1
Physician decision	-	1

## Period 2

Period 2 title	Baseline
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Randomised - controlled
Blinding used	Not blinded
Blinding implementation details:	
Not applicable	

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Low dose arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

### Dosage and administration details:

15mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 30mg.

<b>Arm title</b>	High dose arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

### Dosage and administration details:

30mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 60mg.

### Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: A new period called consent has been created as one of the patients in the high dose group after consenting was withdrawn straight away even before receiving IMP due to the physician's decision. This patient is not included in further analysis.

Number of subjects in period 2 <sup>[2]</sup>	Low dose arm	High dose arm
Started	13	10
Completed	13	10

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As above

### Period 3

Period 3 title	Post-treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Low dose arm

Arm description: -

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

Dosage and administration details:

15mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 30mg.

<b>Arm title</b>	High dose arm
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Arm description: -

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

Dosage and administration details:

30mg of alemtuzumab administered intravenously over a period of 4 to 8 hours. The dose is repeated next day. Total alemtuzumab dose 60mg.

<b>Number of subjects in period 3</b>	Low dose arm	High dose arm
Started	13	10
Completed	10	7
Not completed	3	3
Lack of efficacy	3	3

## Baseline characteristics

### Reporting groups

Reporting group title	Low dose arm
Reporting group description: -	
Reporting group title	High dose arm
Reporting group description: -	

Reporting group values	Low dose arm	High dose arm	Total
Number of subjects	13	10	23
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			
Age in years			
Units: years			
median	35	41	
inter-quartile range (Q1-Q3)	25 to 46.1	33 to 44	-
Gender categorical			
Units: Subjects			
Female	7	8	15
Male	6	2	8
Disease			
Disease category			
Units: Subjects			
ANCA associated vasculitis	6	6	12
Behcet's disease	7	4	11
ANCA specificity			
ANCA subtype			
Units: Subjects			
PR3	4	3	7
MPO	1	0	1
ANCA negative	8	7	15
BVAS/WG score			
Disease activity score at entry			
Units: score			
median	4	4.5	
inter-quartile range (Q1-Q3)	4 to 6	4 to 5	-
Prior disease duration			



Disease duration prior to enrolment into trial			
Units: months			
median	76	51	
inter-quartile range (Q1-Q3)	52 to 115	40 to 68.5	-

## End points

### End points reporting groups

Reporting group title	Low dose arm
Reporting group description: -	
Reporting group title	High dose arm
Reporting group description: -	
Reporting group title	Low dose arm
Reporting group description: -	
Reporting group title	High dose arm
Reporting group description: -	
Reporting group title	Low dose arm
Reporting group description: -	
Reporting group title	High dose arm
Reporting group description: -	
Subject analysis set title	Full analysis population
Subject analysis set type	Full analysis
Subject analysis set description: All subjects that were recruited into the trial and received at least one course of alemtuzumab therapy will constitute Full Analysis Population.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least one course of alemtuzumab therapy within the trial will constitute safety population.	

### Primary: Proportion of patients in remission at 6 months

End point title	Proportion of patients in remission at 6 months
End point description: Proportion of patients in remission at six months	
End point type	Primary
End point timeframe: Remission at 6 months	

End point values	Low dose arm	High dose arm	Full analysis population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	10	23	
Units: Number				
Remission	9	7	16	
Not in remission	4	3	7	

### Statistical analyses

Statistical analysis title	Logistic regression
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**Statistical analysis description:**

The odds ratio of achieving complete or partial remission at six months with high dose (low dose reference group) adjusted for age, ANCA subtype and disease duration.

Comparison groups	Low dose arm v High dose arm
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.91 <sup>[1]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	10.4

**Notes:**

[1] - Age: 0.73

PR3: 0.99

ANCA neg: 0.65

Disease duration: 0.82

**Primary: Proportion of patients with Serious adverse events related to IMP**

End point title	Proportion of patients with Serious adverse events related to IMP <sup>[2]</sup>
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**End point description:**

Number of patients that developed serious adverse events (as defined in protocol)

End point type	Primary
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**End point timeframe:**

Over the course of 12 months trial duration

**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: This is primarily a descriptive analysis

End point values	Low dose arm	High dose arm	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	10	23	
Units: Number				
SAE	4	3	7	
No SAE	9	7	16	

<b>Attachments (see zip file)</b>	Serious adverse events/SAE_chart.docx
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**Statistical analyses**

No statistical analyses for this end point

**Secondary: Proportion of patients with treatment failure**

End point title	Proportion of patients with treatment failure
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End point description:

Treatment failure was defined as failure to achieve a vasculitis response by 6 months or vasculitis relapse between 6 and 12 months.

End point type	Secondary
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End point timeframe:

Over a period of 12 months

End point values	Low dose arm	High dose arm	Full analysis population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	10		
Units: Number				
Yes	7	6	13	
No	6	4	10	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of patients with one or more relapses

End point title	Proportion of patients with one or more relapses
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End point description:

A vasculitis relapse is defined as the appearance or re-appearance of severe disease (major BVAS/WG item) or appearance or re-appearance of at least two minor BVAS/WG items. Patients who did not achieve remission and are withdrawn (thus technically not possible to satisfy relapse definition) are censored.

End point type	Secondary
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End point timeframe:

Over a period of 12 months.

End point values	Low dose arm	High dose arm	Full analysis population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12 <sup>[3]</sup>	9 <sup>[4]</sup>	21 <sup>[5]</sup>	
Units: Number				
Yes	9	5	14	
No	3	4	7	

Notes:

[3] - 1 patient withdrawn due to progressive disease & not satisfying the relapse criteria is removed

[4] - 1 patient withdrawn due to progressive disease & not satisfying the relapse criteria is removed

[5] - 2 patients withdrawn due to progressive disease & not satisfying the relapse criteria are removed

Attachments (see zip file)	survival_analysis.docx
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## Statistical analyses

<b>Statistical analysis title</b>	Kaplan Meier
Statistical analysis description: Kaplan Meier survival for risk of relapse	
Comparison groups	Low dose arm v High dose arm
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	= 0.67
Method	Logrank

Notes:

[6] - Kaplan Meier Survival analysis. Log-rank test performed to test the hypothesis that there is no difference in the time to relapse between the two arms.

<b>Statistical analysis title</b>	Cox regression analysis
Statistical analysis description: Cox regression analysis adjusting for age, ANCA subtype and disease duration.	
Comparison groups	Low dose arm v High dose arm
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	= 0.76 <sup>[8]</sup>
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	3.6

Notes:

[7] - Cox regression analysis

[8] - Age: 0.81

PR3 ANCA: 0.99

ANCA neg: 0.38

Disease duration: 0.59

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Low Dose
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Reporting group description: -

Reporting group title	High Dose
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Reporting group description: -

Serious adverse events	Low Dose	High Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 13 (30.77%)	3 / 10 (30.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Elevated troponin	Additional description: Elevated troponin		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine storm	Additional description: Cytokine storm		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease flare	Additional description: Disease flare		

subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
C Diff diarrhoea	Additional description: C Diff diarrhoea		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CMV colitis			
Additional description: CMV colitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
Additional description: Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
Additional description: Skin infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (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	Low Dose	High Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	10 / 10 (100.00%)	
Injury, poisoning and procedural complications			
Injury	Additional description: Injury		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
IRR			
Additional description: IRR			
subjects affected / exposed	12 / 13 (92.31%)	10 / 10 (100.00%)	
occurrences (all)	22	15	
Vascular disorders			

PE subjects affected / exposed occurrences (all)	Additional description: PE		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	
Thrombophlebitis subjects affected / exposed occurrences (all)	Additional description: Thrombophlebitis		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all)  Tachycardia subjects affected / exposed occurrences (all)			
	Additional description: Arrhythmia		
	0 / 13 (0.00%) 0	1 / 10 (10.00%) 1	
	Additional description: Tachycardia		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	
Nervous system disorders Benign intracranial HTN subjects affected / exposed occurrences (all)  Headaches subjects affected / exposed occurrences (all)  Vasovagal subjects affected / exposed occurrences (all)			
	Additional description: Benign intracranial HTN		
	1 / 13 (7.69%) 2	0 / 10 (0.00%) 0	
	Additional description: Headaches		
	0 / 13 (0.00%) 0	1 / 10 (10.00%) 1	
	Additional description: Vasovagal		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	
Eye disorders Meibomian gland dysfunction subjects affected / exposed occurrences (all)			
	Additional description: Meibomian gland dysfunction		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	
Gastrointestinal disorders Abdo pain subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)			
	Additional description: Abdo pain		
	1 / 13 (7.69%) 1	1 / 10 (10.00%) 1	
	Additional description: Constipation		
	0 / 13 (0.00%) 0	1 / 10 (10.00%) 1	
	Additional description: Diarrhoea		
	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0	



Periodontitis subjects affected / exposed occurrences (all)	Additional description: Periodontitis		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	
Skin and subcutaneous tissue disorders IgA dermatosis subjects affected / exposed occurrences (all)	Additional description: IgA dermatosis		
	0 / 13 (0.00%)	1 / 10 (10.00%)	
	0	1	
Intertrigo subjects affected / exposed occurrences (all)	Additional description: Intertrigo		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	
Psychiatric disorders Hallucinations: drug induced subjects affected / exposed occurrences (all)	Additional description: Hallucinations: drug induced		
	0 / 13 (0.00%)	1 / 10 (10.00%)	
	0	1	
Endocrine disorders Hypothyroid subjects affected / exposed occurrences (all)	Additional description: Hypothyroid		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	
Infections and infestations CMV subjects affected / exposed occurrences (all)	Additional description: CMV		
	0 / 13 (0.00%)	1 / 10 (10.00%)	
	0	1	
CMV viraemia subjects affected / exposed occurrences (all)	Additional description: CMV viraemia		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	
LRTI subjects affected / exposed occurrences (all)	Additional description: LRTI		
	5 / 13 (38.46%)	6 / 10 (60.00%)	
	9	6	
Ocular infection subjects affected / exposed occurrences (all)	Additional description: Ocular infection		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	
PR bleed subjects affected / exposed occurrences (all)	Additional description: PR bleed		
	0 / 13 (0.00%)	1 / 10 (10.00%)	
	0	1	
Root canal infection subjects affected / exposed occurrences (all)	Additional description: Root canal infection		
	1 / 13 (7.69%)	0 / 10 (0.00%)	
	1	0	

Thrush	Additional description: Thrush		
	subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	1
URTI	Additional description: URTI		
	subjects affected / exposed	4 / 13 (30.77%)	5 / 10 (50.00%)
	occurrences (all)	4	5
Uterine infection	Additional description: Uterine infection		
	subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	1
UTI	Additional description: UTI		
	subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)
	occurrences (all)	3	2
Vaginal candidiasis	Additional description: Vaginal candidiasis		
	subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)
	occurrences (all)	0	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2015	Changes to PIS with updated SmPC (PML)
30 September 2016	Changes to PIS with new safety information as per updated SmPC
30 October 2016	Updated patient information sheet to bring it in line with the updated SmPC safety information
06 July 2017	Amendment submitted to update the trial protocol to align with MHRA process for reference safety information (RSI) management, with added reference to the latest approved RSI for alemtuzumab

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 August 2013	In August 2012, Genzyme temporarily withdrew alemtuzumab. This was a commercial decision made prior to them submitting alemtuzumab for approval as a treatment of relapsing-remitting multiple sclerosis. The trial was temporarily interrupted between Aug 2012 and September 2013	01 September 2013

Notes:

### Limitations and caveats

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

The recruitment was rather long due to a small pool of patients that are eligible to enter the trial.

Notes: