Clinical trial results:
A phase IIa study of Rituximab and Varlilumab in relapsed or refractory B-cell malignancies

Summary

EudraCT number	2017-000302-37
Trial protocol	GB
Global end of trial date	29 March 2023

Results information

Result version number	v1 (current)
This version publication date	09 December 2023
First version publication date	09 December 2023

Trial information

Trial identification

Sponsor protocol code	RHMCAN1278

Additional study identifiers

ISRCTN number	ISRCTN15025004
ClinicalTrials.gov id (NCT number)	NCT03307746
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2017-000302-37

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	Clinical Trials Unit, Southampton, United Kingdom, SO16 6YD
Public contact	Ailsa Duckworth, University Hospital Southampton NHS Foundation Trust, 44 023 8120 5131, ailsa.duckworth@uhs.nhs.uk
Scientific contact	Ailsa Duckworth, University Hospital Southampton NHS Foundation Trust, 44 023 8120 5131, ailsa.duckworth@uhs.nhs.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	29 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary endpoint
Phase I
• The causality of each adverse event and grading of severity according to NCI CTCAE Version 4.03.
• Response (stable disease, partial response or complete response) in each case according to the Lugano Revised Response Criteria for Malignant Lymphoma.

Secondary endpoints
• Progression-free survival and overall survival at 1 year for all participants.

Tertiary endpoints
• B-cell depletion and/or intratumoural B cell levels using flow cytometry, in pre- and post-treatment samples.
• Measurement of peripheral blood and/or intratumoural immune cell subset levels (CD4 and CD8 T-cell subsets, NK cells, neutrophil, monocyte and macrophage levels) by flow cytometry, in pre- and post-treatment samples.
• Measurement of CD27 expression level on CD8 T-cells, effector CD4 T-cells, regulatory CD4 T-cells, NK cells and B-cells in pre-treatment peripheral blood and/or intratumoural material by flow cytometry.
• Measurement of PK levels from peripheral blood fro

Protection of trial subjects:

Yearly independent data monitoring committee meeting

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2017
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	0

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)	9
From 65 to 84 years	17
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The RiVa trial recruited and randomised 27 of 40 planned patients from Jan 2018 to Dec 2020 when recruitment ended due to recruitment challenges, in part due to the COVID-19 pandemic.

Pre-assignment

Screening details:

Patients were randomised 1:1; stratified by grade (low or high)
First patient enrolled 29-Jan-2018

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Low grade lymphoma

Arm description:

e.g. follicular lymphoma grade 1, 2 or 3a, marginal zone lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma

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

Dosage and administration details:

Cycle 1, 2, 3, 4, 5 day 1- 375 mg/m2;
Cycle 6 - 375 mg/m2;

Investigational medicinal product name	Varlilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cycle 1 day 2 - 3 mg/kg;
Cycle 3 and day 2 3 mg/kg;

Arm title	High grade lymphoma

Arm description:

Diffuse large B-cell lymphoma, FL grade 3b, transformed FL

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

Dosage and administration details:

Cycle 1, 2, 3, 4, 5 day 1- 375 mg/m2;
Cycle 6 - 375 mg/m2;

Investigational medicinal product name	Varlilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cycle 1 day 8 - 3 mg/kg;
Cycle 3 and day 2 3 mg/kg;

Number of subjects in period 1	Low grade lymphoma	High grade lymphoma
Started	16	11
Completed	10	6
Not completed	6	5
Death	5	4
withdrew after cycle 1 due to ineligibility	-	1
Subject withdrawal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Low grade lymphoma
Reporting group description:	
e.g. follicular lymphoma grade 1, 2 or 3a, marginal zone lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma	
Reporting group title	High grade lymphoma
Reporting group description:	
Diffuse large B-cell lymphoma, FL grade 3b, transformed FL	

Reporting group values	Low grade lymphoma	High grade lymphoma	Total
Number of subjects	16	11	27
Age categorical Units: Subjects			
Adults (18-64 years)	7	2	9
From 65-84 years	9	8	17
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	68.1	70.9	
standard deviation	± 8.45	± 12.13	-
Gender categorical Units: Subjects			
Female	7	4	11
Male	9	7	16
Lymphoma sub-type Units: Subjects			
Follicular lymphoma (grade 1, 2 or 3a)	15	0	15
Mantle cell lymphoma	1	0	1
DLBCL	0	8	8
Follicular lymphoma (grade 3b)	0	2	2
Transformed follicular lymphoma	0	1	1
Stage at study entry Units: Subjects			
I stage	0	0	0
II stage	1	0	1
III stage	3	3	6
IV stage	12	8	20
BMI Units: kg/m2			
arithmetic mean	26	26.9	
standard deviation	± 4.77	± 5.32	-

End points

End points reporting groups

Reporting group title	Low grade lymphoma
Reporting group description:	
e.g. follicular lymphoma grade 1, 2 or 3a, marginal zone lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma	
Reporting group title	High grade lymphoma
Reporting group description:	
Diffuse large B-cell lymphoma, FL grade 3b, transformed FL	

Primary: The causality of each adverse event

End point title	The causality of each adverse event[1]
End point description:	
The causality of each adverse event according to NCI CTCAE Version 4.03.	

End point type	Primary
End point timeframe:	
1 year	

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 formal analyses to compare the number of AEs because the study was not powered to detect differences here & the analyses were exploratory.

End point values	Low grade lymphoma	High grade lymphoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: Number of participants				
Blood and lymphatic system disorders	3	2		
Cardiac disorders	1	0		
Ear and labyrinth disorders	1	0		
Eye disorders	1	0		
Gastrointestinal disorders	11	4		
General disorders and administration site conditio	15	8		
Infections and infestations	8	4		
Injury, poisoning and procedural complications	5	1		
Investigations	2	1		
Metabolism and nutrition disorders	2	2		
Musculoskeletal and connective tissue disorders	6	4		
Neoplasms benign, malignant and unspecified (incl	0	1		
Nervous system disorders	3	3		
Product issues	1	0		
Psychiatric disorders	2	1		
Renal and urinary disorders	1	0		
Reproductive system and breast disorders	0	1		

Respiratory, thoracic and mediastinal disorders	9	3		
Skin and subcutaneous tissue disorders	6	5		
Vascular disorders	4	0		

Statistical analyses

No statistical analyses for this end point

Primary: Overall toxicity by CTCAE Grade

End point title	Overall toxicity by CTCAE Grade[2]

End point description:

End point type	Primary

End point timeframe:

1 year

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: No formal analyses to compare the number of AEs because the study was not powered to detect differences here & the analyses were exploratory.

End point values	Low grade lymphoma	High grade lymphoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: Number of participants				
CTCAE 4.0 Grade 1	2	1		
CTCAE 4.0 Grade 2	3	4		
CTCAE 4.0 Grade 3	8	3		
CTCAE 4.0 Grade 4	2	0		
CTCAE 4.0 Grade 5	1	2		
no AE	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Primary endpoint - Overall response rate/disease control rate (CR or PR or SD) at EOT

End point title	Primary endpoint - Overall response rate/disease control rate (CR or PR or SD) at EOT[3]

End point description:

End point type	Primary

End point timeframe:

1 year

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: This endpoints all have CIs.

End point values	Low grade lymphoma	High grade lymphoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: percent				
number (confidence interval 90%)	37.5 (17.8 to 60.9)	20 (3.7 to 50.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS at 12 months

End point title	PFS at 12 months

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Low grade lymphoma	High grade lymphoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: percent				
number (confidence interval 90%)	8.9 (1 to 27.8)	20 (4.6 to 43)		

Statistical analyses

No statistical analyses for this end point

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Low-grade

Reporting group description: -

Reporting group title	High-grade

Reporting group description: -

Serious adverse events	Low-grade	High-grade	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)	4 / 11 (36.36%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events	1	1	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism	Additional description: Embolism		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Radiculopathy	Additional description: Radiculopathy		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression	Additional description: Disease progression		
subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis	Additional description: Colitis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (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			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome	Additional description: Stevens-Johnson syndrome		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Infection	Additional description: Infection		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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-grade	High-grade	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	11 / 11 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma	Additional description: Diffuse large B-cell lymphoma		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Peripheral coldness	Additional description: Peripheral coldness		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Disease progression	Additional description: Disease progression		
subjects affected / exposed	7 / 16 (43.75%)	5 / 11 (45.45%)	
occurrences (all)	7	5	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Catheter site pain	Additional description: Catheter site pain		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Axillary pain	Additional description: Axillary pain		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Adverse drug reaction	Additional description: Adverse drug reaction		
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Oedema peripheral	Additional description: Oedema peripheral		

subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Oedema	Additional description: Oedema		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Face oedema	Additional description: Face oedema		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	5 / 16 (31.25%)	2 / 11 (18.18%)	
occurrences (all)	6	2	
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: Vaginal haemorrhage		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	4 / 16 (25.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pleural effusion	Additional description: Pleural effusion		

subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Psychiatric disorders			
Confusional state	Additional description: Confusional state		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device leakage	Additional description: Device leakage		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Investigations			
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Neutrophil count increased	Additional description: Neutrophil count increased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Mean cell volume decreased	Additional description: Mean cell volume decreased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lymphocyte count increased	Additional description: Lymphocyte count increased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
C-reactive protein increased	Additional description: C-reactive protein increased		

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
White blood cell count increased	Additional description: White blood cell count increased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Platelet count increased	Additional description: Platelet count increased		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lethargy	Additional description: Lethargy		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Headache	Additional description: Headache		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			

Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain	Additional description: Eye pain		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lip swelling	Additional description: Lip swelling		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration	Additional description: Mouth ulceration		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dyspepsia	Additional description: Dyspepsia		

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	5 / 16 (31.25%)	1 / 11 (9.09%)	
occurrences (all)	7	1	
Ascites	Additional description: Ascites		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Nausea	Additional description: Nausea		
subjects affected / exposed	3 / 16 (18.75%)	3 / 11 (27.27%)	
occurrences (all)	4	3	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	3 / 16 (18.75%)	2 / 11 (18.18%)	
occurrences (all)	4	2	
Retching	Additional description: Retching		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash	Additional description: Rash		
subjects affected / exposed	3 / 16 (18.75%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	

Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Erythema	Additional description: Erythema		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dermatitis contact	Additional description: Dermatitis contact		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eczema	Additional description: Eczema		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Seborrhoeic dermatitis	Additional description: Seborrhoeic dermatitis		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	2 / 16 (12.50%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Groin pain	Additional description: Groin pain		

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Medical device site infection	Additional description: Medical device site infection		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Neutropenic sepsis	Additional description: Neutropenic sepsis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tinea pedis	Additional description: Tinea pedis		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2018	Addition of Biopsy Information Sheet and Biopsy Consent Form
25 June 2018	Addition of Freeman Hospital as a new site.
27 July 2018	Addition of Beatson West of Scotland Cancer Centre as a site.
18 January 2019	Introduction of central monitoring of signed consent forms, addition of a GI toxicity management appendix, introduced permitted time windows for visit dates and PK samples, updated randomisation procedures, updated RSI for varlilumab and rituximab in line with updated IB and SmPC, addition of liver enzymes as a AE of special interest, addition of treatment delay as dose limiting toxicity, update to statistics section, clarifications and typographical corrections throughout.
19 March 2019	Removal of the SAE reporting exception for grade 4 neutropenia from the protocol (MHRA grounds for non-acceptance of SA4). Updated varlilumab IB and rituximab SmPC also submitted.
06 April 2020	Change of PI at Derriford Hospital
27 November 2020	Addition of end date of recruitment of 31st Dec 2020. Protocol updated with most recent IB for varlilumab and SmPC for rituximab. Permitted window added for physical exams. Changed vital signs at 30 and 60 mins post infusion to 30 min post infusion only. Clarification of the 72 hour window for haematology and biochemistry bloods. Deauville score added to PET. Added bidimensional reporting wording for CT for clarity. Added requirement for rituximab infusion stop time to match database data. Clarification around AE reporting. Amended PK sample wording to allow for 6 patients with at least 50% of expected PK samples. Addition of a section for data sharing policy. Updated wording of statistics section for clarity.
15 January 2021	Updated IMPD for varlilumab to extend shelf life of varlilumab. This was to allow for a recruitment extension to compensate for time lost due to COVID-19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30413184