Clinical trial results:
Phase II Study of Fractionated 90Y Ibritumomab tiuxetan (ZevalinTM) as initial therapy of Follicular Lymphoma

Summary

EudraCT number	2006-000598-31
Trial protocol	GB
Global end of trial date	06 November 2015

Results information

Result version number	v1 (current)
This version publication date	07 March 2020
First version publication date	07 March 2020

Trial information

Trial identification

Sponsor protocol code	06_DOG05_33

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01493479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	The Christie NHS Foundation Trust, The Christie NHS Foundation Trust, christiesponsoredresearch@christie.nhs.uk
Scientific contact	The Christie NHS Foundation Trust, The Christie NHS Foundation Trust, christiesponsoredresearch@christie.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	23 January 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2011
Global end of trial reached?	Yes
Global end of trial date	06 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this project is to test the safety and efficacy of two fractions of 90Y ibritumomab tiuxetan in patients with previously untreated follicular lymphoma in a Phase II study.

Protection of trial subjects:

Rituximab is given by intravenous infusion on day 1 and day 8, which can take up to a few hours to complete. 90-Y-ibritumomab tiuxetan (ZevalinTM) is also given by intravenous infusion which takes approximately 10 minutes on day 8.
Both these drugs may cause flu-like symptoms and other side effects as listed in the patient information sheet. Patients are advised

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	France: 31
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	45
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening and baseline evaluations performed within 3 weeks of study entry included - ECG, US echo or left VEF , CT scan, PET scan if patients are eligible for treatment with Zevalin, HAMA and HACA reactivity analysis, Bone marrow biopsy for cytology, pathology, immuno-phenotyping (CD20 staining) and percentage of involvement (must be ≤20%)

Period 1

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

Arms

Arm title	Single arm

Arm description:

The FIZZ trial investigated the use of 90Y Ibritumomab tiuxetan (Zevalin), as an initial treatment for previously untreated follicular lymphoma. This is a single arm, open-label trial; patients receive 2 infusions of 90Y Ibritumomab tiuxetan (ZevalinTM), (11.1 MBq/kg) given 8-12 weeks apart. Each treatment is preceded by 2 infusions of rituximab 7-8 days apart. Patients with >20% bone marrow involvement also receive 4 x weekly rituximab infusions prior to entering the main trial.

Arm type	Experimental
Investigational medicinal product name	Zevalin
Investigational medicinal product code	
Other name	90Y Ibritumomab tiuxetan
Pharmaceutical forms	Kit for radiopharmaceutical preparation
Routes of administration	Intravenous use

Dosage and administration details:

90Y-ibritumomab tiuxetan (Zevalin) is composed of a murine IgG1 monoclonal antibody (ibritumomab) covalently bound to the chelating agent tiuxetan. The antibody is chelated with the ß-emitter yttrium-90 chloride immediately before intravenous administration to prepare [90Y] Zevalin, the active therapeutic agent.
90Y-ibritumomab tiuxetan (11.1 MBq/kg) treatment is preceded by two infusions of 250 mg/m2 Rituximab given 7-8 days apart with the second infusion given immediately prior to [90Y] Zevalin. Rituximab is a chimeric human/murine IgG1 monoclonal antibody. Two treatments of 90Y-ibritumomab tiuxetan (11.1 MBq/kg) are given 8-12 weeks apart.
In patients with greater than 20% bone marrow involvement with lymphoma, Rituximab (375 mg/m2) is administered as 4 weekly infusions. Following a repeat bone marrow biopsy, patients with less than or equal to 20% involvement will follow the protocol in the previous paragraph.

Number of subjects in period 1	Single arm
Started	72
Completed	72

Baseline characteristics

Reporting groups	
Reporting group title	Single arm

Reporting group description:

The FIZZ trial investigated the use of 90Y Ibritumomab tiuxetan (Zevalin), as an initial treatment for previously untreated follicular lymphoma. This is a single arm, open-label trial; patients receive 2 infusions of 90Y Ibritumomab tiuxetan (ZevalinTM), (11.1 MBq/kg) given 8-12 weeks apart. Each treatment is preceded by 2 infusions of rituximab 7-8 days apart. Patients with >20% bone marrow involvement also receive 4 x weekly rituximab infusions prior to entering the main trial.

Reporting group values	Single arm	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	45	45	
From 65-84 years	27	27	
85 years and over	0	0	
Age continuous Units: years			
median	61		
full range (min-max)	28 to 80	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	33	33	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

The FIZZ trial investigated the use of 90Y Ibritumomab tiuxetan (Zevalin), as an initial treatment for previously untreated follicular lymphoma. This is a single arm, open-label trial; patients receive 2 infusions of 90Y Ibritumomab tiuxetan (ZevalinTM), (11.1 MBq/kg) given 8-12 weeks apart. Each treatment is preceded by 2 infusions of rituximab 7-8 days apart. Patients with >20% bone marrow involvement also receive 4 x weekly rituximab infusions prior to entering the main trial.

Subject analysis set title	Zevalin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All 72 subjects receiving at least one dose of Zevalin

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[1]

End point description:

End point type	Primary

End point timeframe:

initial primary end point evaluation. From baseline to 3 months post treatment.

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: Single arm study. ORR: 68 out of 72; 94.4% with 95% CI (86.4%, 98.5%)

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Number of patients	68			

Statistical analyses

No statistical analyses for this end point

Primary: Combined Complete Response (CR/CRu)

End point title	Combined Complete Response (CR/CRu)[2]

End point description:

End point type	Primary

End point timeframe:

initial primary end point evaluation. From baseline to 3 months post treatment.

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: Single arm study. CR/CRu: 42 out of 72; 58.3% with 95% CI (46.1%, 69.8%)

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Number of patients	42			

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	Zevalin

Reporting group description: -

Serious adverse events	Zevalin		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 72 (23.61%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA	Additional description: BASAL CELL CARCINOMA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PLEURAL CARCINOMA	Additional description: PLEURAL CARCINOMA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
SIGMOID COLON CANCER	Additional description: SIGMOID COLON CANCER		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
NEUTROPENIA	Additional description: NEUTROPENIA		

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
FRACTURE	Additional description: FRACTURE		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ACUTE MYELOBLASTIC LEUKEMIA	Additional description: ACUTE MYELOBLASTIC LEUKEMIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
FEBRILE NEUTROPENIA	Additional description: FEBRILE NEUTROPENIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
MYELODYSPLASIA	Additional description: MYELODYSPLASIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
MYELODYSPLASIA (RCMD)	Additional description: MYELODYSPLASIA (RCMD)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
FEVER	Additional description: FEVER		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
PAIN	Additional description: PAIN		

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
BREAST CANCER	Additional description: BREAST CANCER		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA	Additional description: DYSPNOEA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMOPTYSIS	Additional description: HAEMOPTYSIS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
CELLULITIS	Additional description: CELLULITIS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
PSYCHOSIS	Additional description: PSYCHOSIS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
INFECTION	Additional description: INFECTION		

subjects affected / exposed	1 / 72 (1.39%)		
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	Zevalin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 72 (84.72%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CYST (EPIDIDYMIS)	Additional description: CYST (EPIDIDYMIS)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
NODULE (LEFT AXILLA)	Additional description: NODULE (LEFT AXILLA)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
SMALL SKIN LESION ON LEFT SIDE - POSSIBLE BCC	Additional description: SMALL SKIN LESION ON LEFT SIDE - POSSIBLE BCC		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Surgical and medical procedures			
RIGHT INGUINAL HERNIA REPAIR	Additional description: RIGHT INGUINAL HERNIA REPAIR		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
General disorders and administration site conditions			
FEELING SHAKEN (RTA)	Additional description: FEELING SHAKEN (RTA)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
FEELING SHAKY	Additional description: FEELING SHAKY		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
FEELING UNWELL	Additional description: FEELING UNWELL		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
FEVER	Additional description: FEVER		

subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	13		
HEADACHE	Additional description: HEADACHE		
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	12		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	17		
INFUSION REACTION (RITUXIMAB)	Additional description: INFUSION REACTION (RITUXIMAB)		
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
LETHARGY	Additional description: LETHARGY		
subjects affected / exposed	28 / 72 (38.89%)		
occurrences (all)	39		
OEDEMA	Additional description: OEDEMA		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
PAIN	Additional description: PAIN		
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	10		
Reproductive system and breast disorders			
AMENORRHEA	Additional description: AMENORRHEA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
IRREGULAR MENSES	Additional description: IRREGULAR MENSES		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
AIRWAY OBSTRUCTION	Additional description: AIRWAY OBSTRUCTION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
ALLERGIC REACTION	Additional description: ALLERGIC REACTION		
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
CATARRH	Additional description: CATARRH		

subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
CORYZAL SYMPTOMS	Additional description: CORYZAL SYMPTOMS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
COUGH	Additional description: COUGH		
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	12		
DRY THROAT	Additional description: DRY THROAT		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
DYSPNOEA	Additional description: DYSPNOEA		
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	7		
EPISTAXIS (NOSE)	Additional description: EPISTAXIS (NOSE)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	15 / 72 (20.83%)		
occurrences (all)	19		
REDUCED CHEST EXPANSION	Additional description: REDUCED CHEST EXPANSION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
SORE THROAT	Additional description: SORE THROAT		
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	11		
TIGHTNESS CHEST	Additional description: TIGHTNESS CHEST		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Psychiatric disorders			
ANXIETY	Additional description: ANXIETY		
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
DEPRESSION	Additional description: DEPRESSION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		

INSOMNIA	Additional description: INSOMNIA		
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	6		
Investigations			
HYPERCHOLESTEROLAEMIA	Additional description: HYPERCHOLESTEROLAEMIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
HYPOKALAEMIA	Additional description: HYPOKALAEMIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
LYMPHOPENIA	Additional description: LYMPHOPENIA		
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	10		
NEUTROPENIA	Additional description: NEUTROPENIA		
subjects affected / exposed	22 / 72 (30.56%)		
occurrences (all)	54		
RAISED ALANINE TRANSAMINASE	Additional description: RAISED ALANINE TRANSAMINASE		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
THROMBOCYTOPAENIA	Additional description: THROMBOCYTOPAENIA		
subjects affected / exposed	37 / 72 (51.39%)		
occurrences (all)	83		
Injury, poisoning and procedural complications			
ANKLE FRACTURE	Additional description: ANKLE FRACTURE		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
BRUISING	Additional description: BRUISING		
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	7		
Cardiac disorders			
BRADYCARDIA SINUS	Additional description: BRADYCARDIA SINUS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
CARDIAC ARRHYTHMIAS (PREMATURE ECTOPIES)	Additional description: CARDIAC ARRHYTHMIAS (PREMATURE ECTOPIES)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		

HYPERTENSION	Additional description: HYPERTENSION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
HYPOTENSION	Additional description: HYPOTENSION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
LIGHTHEADEDNESS	Additional description: LIGHTHEADEDNESS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
TACHYCARDIA	Additional description: TACHYCARDIA		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Nervous system disorders			
DIZZINESS	Additional description: DIZZINESS		
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
DYSGEUSIA	Additional description: DYSGEUSIA		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
LETHARGY	Additional description: LETHARGY		
subjects affected / exposed	7 / 72 (9.72%)		
occurrences (all)	8		
MOTOR SENSORY IMPAIRMENT (LEFT TEMPORAL + PERINEAL)	Additional description: MOTOR SENSORY IMPAIRMENT (LEFT TEMPORAL + PERINEAL)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
PINS AND NEEDLES (LEFT LOWER ARM)	Additional description: PINS AND NEEDLES (LEFT LOWER ARM)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
PTOSIS (LEFT EYE)	Additional description: PTOSIS (LEFT EYE)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
TREMOR (HANDS)	Additional description: TREMOR (HANDS)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

ANAEMIA	Additional description: ANAEMIA		
subjects affected / exposed	20 / 72 (27.78%)		
occurrences (all)	36		
DERANGED BLOOD COUNTS	Additional description: DERANGED BLOOD COUNTS		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
HAEMORRHAGE (GUMS)	Additional description: HAEMORRHAGE (GUMS)		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
JUGULAR VEIN THROMBOSIS	Additional description: JUGULAR VEIN THROMBOSIS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
LEUCOPENIA	Additional description: LEUCOPENIA		
subjects affected / exposed	23 / 72 (31.94%)		
occurrences (all)	50		
MYELOSUPPRESSION	Additional description: MYELOSUPPRESSION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
PETECHIA (LOWER LIMBS)	Additional description: PETECHIA (LOWER LIMBS)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
VERTIGO DUE TO ANAEMIA SYNDROME	Additional description: VERTIGO DUE TO ANAEMIA SYNDROME		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Ear and labyrinth disorders			
INFECTION	Additional description: INFECTION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
OTORRHAGIA	Additional description: OTORRHAGIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
REDUCED HEARING	Additional description: REDUCED HEARING		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Eye disorders			

CATARACT (LEFT EYE)	Additional description: CATARACT (LEFT EYE)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
DIPLOPIA (LEFT EYE)	Additional description: DIPLOPIA (LEFT EYE)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
DRY EYES	Additional description: DRY EYES		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
DRYNESS	Additional description: DRYNESS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Gastrointestinal disorders			
ANOREXIA	Additional description: ANOREXIA		
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
BLOATING	Additional description: BLOATING		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
CONSTIPATION	Additional description: CONSTIPATION		
subjects affected / exposed	8 / 72 (11.11%)		
occurrences (all)	9		
DIARRHOEA	Additional description: DIARRHOEA		
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	10		
DRY MOUTH	Additional description: DRY MOUTH		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
DYSPEPSIA	Additional description: DYSPEPSIA		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
DYSPHAGIA	Additional description: DYSPHAGIA		

subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	2		
FLATULENCE	Additional description: FLATULENCE		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
FLEXIBLE AND DEPRESSIBLE ABDOMINAL	Additional description: FLEXIBLE AND DEPRESSIBLE ABDOMINAL		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
FULLNESS (LEFT GROIN)	Additional description: FULLNESS (LEFT GROIN)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
INDIGESTION	Additional description: INDIGESTION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
MUCOSITIS	Additional description: MUCOSITIS		
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
NAUSEA	Additional description: NAUSEA		
subjects affected / exposed	18 / 72 (25.00%)		
occurrences (all)	21		
PYROSIS	Additional description: PYROSIS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
RECTAL BLEEDING	Additional description: RECTAL BLEEDING		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
TOOTH PAIN	Additional description: TOOTH PAIN		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
VOMITING	Additional description: VOMITING		
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	4		

Skin and subcutaneous tissue disorders			
BALANTIS XEROTICA OBLITERANS	Additional description: BALANTIS XEROTICA OBLITERANS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
BLISTERED HAND	Additional description: BLISTERED HAND		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
COLD SORES	Additional description: COLD SORES		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	3		
DESQUAMATION	Additional description: DESQUAMATION		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
DRY SKIN	Additional description: DRY SKIN		
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	5		
ECZEMA	Additional description: ECZEMA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
INFECTION	Additional description: INFECTION		
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
PALLID	Additional description: PALLID		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
PRURITIS	Additional description: PRURITIS		
subjects affected / exposed	11 / 72 (15.28%)		
occurrences (all)	13		
RASH	Additional description: RASH		
subjects affected / exposed	15 / 72 (20.83%)		
occurrences (all)	17		
RESIDUAL BRUSIE + ULCERATED SKIN (RIGHT FOOT)	Additional description: RESIDUAL BRUSIE + ULCERATED SKIN (RIGHT FOOT)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
SENSITIVE SKIN	Additional description: SENSITIVE SKIN		

subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	Additional description: ARTHRALGIA		
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
DISCOMFORT (LEFT CALF)	Additional description: DISCOMFORT (LEFT CALF)		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
GOUT	Additional description: GOUT		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
MUSCLE WEAKNESS	Additional description: MUSCLE WEAKNESS		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
MYALGIA	Additional description: MYALGIA		
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	13		
PAIN	Additional description: PAIN		
subjects affected / exposed	17 / 72 (23.61%)		
occurrences (all)	27		
SCIATICA	Additional description: SCIATICA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
SWELLING	Additional description: SWELLING		
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Infections and infestations			
INFECTION	Additional description: INFECTION		
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
HYPOCALCEMIA	Additional description: HYPOCALCEMIA		
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2007	Addition to exclusion criteria: Presence of human anti-mouse antibody (HAMA) reactivity and Known hypersensitivity to murine antibodies or proteins. Typographical error in the protocol: The study outline should state that Zevalin is given weeks 9-13 and not weeks 9-12.
14 December 2007	Amendment made in light of new information that has been published or secondary to new investigations that may provide new scientific insights into how treatment modality works.
24 June 2008	A further substudy was added to the trial. Previously the trial included a single substudy, including both dosimetry procedures and analysis of biomarkers. Upon further discussion of the biomarker analysis, and after performing the initial dosimetry analyses, the timepoints at which samples for biomarker analysis will be obtained are updated, and dosimetry and biomarker analysis divided into two separate substudies, giving patients the option to consent to one, or to neither.
17 February 2009	Amendment to the biomarker study to update the timepoints at which samples for biomarker analysis will be obtained. An additional blood sample at a different timepoint has been added at Day -7, 1 week prior to treatment with Zevalin.
06 November 2009	Additional guidance added to the protocol regarding situations where the second infusion of 90Y Ibritumomab tiuxetan should be reduced/ omitted, in order to reduce the occurrence of serious haematological toxicities.
22 November 2011	To reduce the reporting time period for adverse events. Events occurring more than 30 days after completion of treatment are only now reported if they are considered related to treatment, during the 5 year follow up period.

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.

Primary completion date is a best guest estimate based on the date the last participant was enrolled, when their last IMP administration occurred and when they had their 3 month scan.

Notes: