Clinical trial results:
Phase I/II Study combining humanised anti-CD20 (veltuzumab), anti-CD22 (epratuzumab) and both monoclonal antibodies with chemotherapy in adults with recurrent B precursor acute lymphoblastic leukaemia (ALL)- MARALL

Summary

EudraCT number	2008-002286-32
Trial protocol	GB
Global end of trial date	10 October 2014

Results information

Result version number	v1 (current)
This version publication date	08 September 2017
First version publication date	08 September 2017

Trial information

Trial identification

Sponsor protocol code	6125

Additional study identifiers

ISRCTN number	ISRCTN15257573
ClinicalTrials.gov id (NCT number)	NCT01279707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	CECM Trials Team, Queen Mary University of London, 0044 02078828197, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, Queen Mary University of London, 0044 02078828197, bci-cecmmonitoring@qmul.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	12 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the safety and tolerability of the combination of veltuzumab and /or epratuzumab with chemotherappy for recurrent adult B-precursor acute lymphoblastic leukaemia

Protection of trial subjects:

Patients will be pre-medicated with chlorphenamine and paracetamol as per local policy, before the start of each antibody infusion, in order to minimise infusional toxicity (hypersensitivity).

Patients will be pre-medicated with chlorphenamine (10mg IV) and paracetamol (1g PO), 30-60 minutes prior to the start of each antibody infusion in order to minimise hypersensitivity (if two antibodies are given only one dose of chlorphenamine and paracetamol is needed).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2010
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	27

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)	21
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Starting in December 2010, 29 patients were recruited in total to the study, of which 26 met the criteria for evaluable.
The study followed a parallel 3+3 design in phase 1 of the study (Cohort A and B). Subsequently, a third cohort (Cohort C) received the combination of antibodies with induction chemotherapy.

Pre-assignment

Screening details:

Inclusion criteria included patients with confirmed diagnosis of recurrent or refractory B-precursor ALL. 29 patients were screened, however only 26 completed study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A - Veltuzumab and Re-induction chemotherapy

Arm description: -

Arm type	Experimental
Investigational medicinal product name	veltuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Veltuzumab with induction chemotherapy. Veltuzumab will be administered at 200mg/m2 IV on Day 8 and subsequently, (if tolerated on Day 8), on Days 15, 22, 29.

Arm title	Cohort B - Epratuzumab + re-induction chemotherapy

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Epratuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Epratuzumab with induction chemotherapy. Epratuzumab will be administered at 360mg/m2 IV on Days 8, 15, 22 and 29.

Arm title	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy

Arm description: -

Arm type	Experimental
Investigational medicinal product name	veltuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Epratuzumab + Veltuzumab with induction chemotherapy. Epratuzumab will be administered at 360mg/m2 IV on Days 8, 15, 22 and 29. Veltuzumab will be administered at 200mg/m2 IV on Day 8, 15, 22 and 29. Veltuzumab will be infused immediately after the infusion of epratuzumab.

Investigational medicinal product name	Epratuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Epratuzumab + Veltuzumab with induction chemotherapy. Epratuzumab will be administered at 360mg/m2 IV on Days 8, 15, 22 and 29. Veltuzumab will be administered at 200mg/m2 IV on Day 8, 15, 22 and 29. Veltuzumab will be infused immediately after the infusion of epratuzumab.

Number of subjects in period 1	Cohort A - Veltuzumab and Re-induction chemotherapy	Cohort B - Epratuzumab + re-induction chemotherapy	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy
Started	3	3	21
Completed	3	3	20
Not completed	0	0	1
Patient died before assessment	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A - Veltuzumab and Re-induction chemotherapy
Reporting group description: -	
Reporting group title	Cohort B - Epratuzumab + re-induction chemotherapy
Reporting group description: -	
Reporting group title	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy
Reporting group description: -	

Reporting group values	Cohort A - Veltuzumab and Re-induction chemotherapy	Cohort B - Epratuzumab + re-induction chemotherapy	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy
Number of subjects	3	3	21
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	15
From 65-84 years	0	0	6
Age continuous Units: years			
median	23	31	51
full range (min-max)	21 to 49	21 to 57	22 to 76
Gender categorical Units: Subjects			
Female	0	0	11
Male	3	3	7
Unknown	0	0	3
ECOG Performance Status Units: Subjects			
ECOG 2	1	0	3
ECOG 0 or 1	2	3	16
ECOG Unknown	0	0	2

Reporting group values	Total		
Number of subjects	27		
Age categorical Units: Subjects			
Adults (18-64 years)	21		
From 65-84 years	6		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	11		
Male	13		

Unknown	3		

ECOG Performance Status Units: Subjects			
ECOG 2	4		
ECOG 0 or 1	21		
ECOG Unknown	2		

End points

End points reporting groups

Reporting group title	Cohort A - Veltuzumab and Re-induction chemotherapy
Reporting group description: -	
Reporting group title	Cohort B - Epratuzumab + re-induction chemotherapy
Reporting group description: -	
Reporting group title	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy
Reporting group description: -	

Primary: Dose Limiting Toxicity

End point title	Dose Limiting Toxicity[1]

End point description:

The primary endpoint of the study is safety, measured by the number of dose-limiting toxicities (DLTs) and tolerability of both veltuzumab and epratuzumab given in combination with ALL reinduction chemotherapy

End point type	Primary

End point timeframe:

Assessment at day 29

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: Dose Limiting Toxicity is a count data and hence no statistics are needed

End point values	Cohort A - Veltuzumab and Re-induction chemotherapy	Cohort B - Epratuzumab + re-induction chemotherapy	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	20	
Units: number/percentage	0	0	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (CR) Rate

End point title	Complete Remission (CR) Rate[2]

End point description:

The complete remission (CR) rate – assessed by morphological CR on a bone marrow taken at Day 29 of therapy or at the commencement of count recovery.

End point type	Secondary

End point timeframe:

Measured at Day 29 of therapy or at the commencement of count recovery.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint is based on cohort C (combination arm) and hence complete remission rate is reported only for cohort C.

End point values	Cohort C - Veltuzumab and Epratuzumab + induction chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage				
number (confidence interval 95%)	40 (19 to 61)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From consent to 30 days post last dose of IMP	
Adverse event reporting additional description:	
Only Grade treatment-related 3/4 AE are reported here	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4

Reporting groups	
Reporting group title	Cohort C
Reporting group description: -	

Serious adverse events	Cohort C		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 21 (66.67%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Investigations			
Liver Toxicity			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rise in GGT levels			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Raised CRP hypophataemia, hypokalemia, anemia and phrombolytopenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Raised LFTs- Liver failure			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fractured Rib			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vasovagal Episode			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PICC Line Thrombus			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic subcapsular infarct			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Asymptotic bradycardia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death due to relapse of ALL				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Rigors and increased temperature 39.3C				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile post epratuzumab and veltuzumab infusion				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea and Vomitting				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation, Dehydration, Nausea and vomiting				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Neutropenic sepsis				

subjects affected / exposed	2 / 21 (9.52%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Chest infection with fever			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort C		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 21 (76.19%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Hyper-glycaemia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2010	• Exclude patients with Philadelphia positive (Ph +ve) ALL • Native E. coli asparaginase replaced by Oncaspar, a peglated form of L-asparaginase with fewer side effects.
08 September 2010	• Inclusion of patients who have had more than one relapse of their leukaemia • Inclusion of patients who are philadelphia positive (Ph+ve) who have failed previous treatment with TK1 • Inclusion of patients who have had prior mediastinal radiotherapy • Changes to Principal Investigators and sites
08 September 2010	change from intensive to less intensive chemotherapy removal of daunorubicin; removal of cardiac MRI and ECG; removal of upper age limit; inclusion of patients who have had more than one relapse; inclusion of patients who have had prior radiotherapy Change of CI: Prof. Andrew Lister to Prof. Matthew Smith
01 February 2011	• Changes to Principal Investigators and sites
01 February 2011	-Amended timeframe of lumbar puncture and bone marrow samples during screening and addition of collection of bone marrow for research at screening, -Extended study duration, Inclusion of refractory patients, reduce time limit since previous antibody therapy, -Addition of new sites

22 September 2011	• Changes to inclusion criteria Include refractory patients. Amend the current definition of refractory patients. Requirement that patients should have greater than or equal to 5% blasts in the marrow. • Changes to exclusion criteria Allowing patients to have received corticosteroids for the current relapse episode for a maximum of 10 days rather than 5. Positive antinuclear antibody (ANA) test. Change of exclusion of patient receiving antibody therapy in the last 9 months to last 3 months in line with recommendations from Immunomedics. • Addition of ANA testing to study schedule and medical examinations and laboratory assessments at screening and Day 29 • Removal of option to provide peripheral blood rather than bone marrow for the MRD test in this protocol to make bone marrow an absolute requirement. • Changes to preparation and administration of Veltuzumab and epratuzumab in line with new administration guidelines from Manufacturer (Immunomedics). • Removal of IMP status of Vincristine, PEG-Asparaginase (OncasparR), Dexamethasone, Methotrexate and Erwinia Asparaginase (ErwinaseR) (now NIMPs) which are standard chemotherapy for ALL patients. • Change to timing of administration of pre-medication from 15-30mins to 30-60mins before administration of epratuzumab or veltuzumab to reduce risk of hypersensitivity in line with Immunomedics guidelines. • Change of Route of administration of PEG-Aspariginase from IV to IV or IM to ensure consistency in protocol document and in line with SmPC.
22 September 2011	Changes to inclusion and exclusion criteria, and addition of ANA testing.
18 July 2012	NB: Urgent Safety Measure In light of signals of liver toxicity being experienced by some patients, the DMC was convened. This toxicity was attributed to the PEG-Asparaginase (nIMP) component of the chemotherapy back bone. Committee recommended an USM be implemented which prescribes changes to the dose of PEG-Asparaginase (nIMP) based on patient disease status, age and any conmeds/comorbidity. These are summarised below: 2 doses of asparaginase – Day 4 and Day 18 • Patients who are being treated with curative intent - this will typically be younger, fitter patients in first relapse heading for an allograft procedure in CR2 • If patients in this group suffer >grade 2 liver toxicity after the first dose of asparaginase, the second dose, on Day 18, should be omitted. 1 dose of asparaginase – Day 18 • Those patients who do not fit into either above or below category, at physician's discretion. 0 doses of asparaginase • Over 60 years of age. • Philadelphia positive on TKIs. • On third line therapy. • Have chronic/underlying liver co-morbidities, including but not limited to liver GVHD or a history of liver disease. • Grade 2 Baseline LFTs. To ensure that these safety measures are effective, mandated expedited reporting of all liver toxicity of grade 3 and grade 4 with a further review of safety data after 10 patients have been recruited to Cohort C of the trial.
18 July 2012	Urgent safety measure - changes to the dose of PEG-Asparaginase (NIMP) based on patient disease status, age and any concomitant medications/ co morbidity. The expedited reporting of all liver toxicity of grade 3 and grade 4 was additionally mandated in this amendment.

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.

The MARALL Trial was terminated prematurely in October 2014 due to lack of veltuzumab supply from the manufacturer (Immunomedics) - it should be noted that the decision to stop supply was not related to drug safety or efficacy.

Notes: