Clinical trial results:
90-Yttrium-labelled anti-CD66 monoclonal antibody as part of a reduced intensity conditioning regimen prior to allogeneic haematopoietic stem cell transplantation: an open label, dose escalating phase I study in children with relapsed/refractory leukaemia

Summary

EudraCT number	2013-000015-24
Trial protocol	GB
Global end of trial date	14 May 2020

Results information

Result version number	v1 (current)
This version publication date	17 April 2021
First version publication date	17 April 2021

Trial information

Trial identification

Sponsor protocol code	07MI05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04082286
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Great Ormond Street Hospital for Children NHS Foundation Trust
Sponsor organisation address	30 Guilford Street, London, United Kingdom,
Public contact	Dr. Robert Chiesa, Dr. Robert Chiesa, 44 2079052863, CTIMP.Safety@gosh.nhs.uk
Scientific contact	Dr. Robert Chiesa, Great Ormond Street Hospital for Children NHS Foundation Trust, robert.chiesa@gosh.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	11 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether a radiolabelled antibody that tergets the bone marrow (the anti-CD66) can be administered safely to children as part of the preparative treatment prior to haematopoietic stem cell transplantation.

To evaluate the safety (and maximum tolerated dose) and feasibility of targeted radiotherapy delivered by 90-Yttrium-labelled anti-CD66 monoclonal antibody within a reduced intensity conditioning regimen in children with relapsed/refractory leukaemia undergoing allogeneic haematopoietic stem cell transplantation.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements. Prior to initiation at each study center, the study protocol was reviewed by an Independent Ethics Committee (IEC). All subjects were to provide written informed consent prior to entering the study and before initiation of any study-related procedure (including administration of investigational product). The investigator was responsible for explaining the benefits and risks of participation in the study to each subject or the subject’s legally acceptable representative and for obtaining written informed consent.

Background therapy:

Patients would receive a reduced intensity conditioning regimen consisting on Fludarabine (150 mg/sqm), Treosulfan (30-42 g/sqm), Thiotepa (10 mg/kg) +/- Alemtuzumab or ATG will be administered after the infusion of 90Y-labelled anti-CD66 monoclonal antibody, starting from day – 8 prior to transplant.

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 May 2016
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: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

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)	5
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 2 sites in the UK (GOSH and UCLH) between 26-May-2016 (First Patient enrolment) and 15-Aug-2019 (Last Patient enrolment).

Pre-assignment

Screening details:

14 subjects were screened and consented for this study, but 5 patients failed the screeneing phase. Nine patients were eventually recruited and treated with radio-immunotherapy

Period 1

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

Blinding implementation details:

not applicable

Arms

Arm title	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody

Arm description:

Patients enrolled into this study received a single dose of Yttrium-90 labelled anti-CD66 antibody as part of a reduced toxicity conditioning regimen, prior to allogeneic haematopoietic stem cell transplant

Arm type	Experimental
Investigational medicinal product name	Indium-111-labelled anti CD66 monoclonal antibody
Investigational medicinal product code	In111i
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

100 MBq/sqm, given as a single dose iv over 15-30 minutes

Investigational medicinal product name	Yttrium-90 labelled anti CD66 monoclonal antibody
Investigational medicinal product code	Y90
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.5-3 mg of antibody protein (with increasing doses of Yttrium90, according to protocol) infused iv as a single dose

Number of subjects in period 1	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody
Started	9
Completed	9

Baseline characteristics

Reporting groups	
Reporting group title	Baseline & Overall Study Period
Reporting group description:	
Children with relapsed/refractory leukaemia	

Reporting group values	Baseline & Overall Study Period	Total	
Number of subjects	9	9	
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)	5	5	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
We treated 5 femaled and 4 males			
Units: Subjects			
Female	5	5	
Male	4	4	

End points

End points reporting groups

Reporting group title	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody

Reporting group description:

Patients enrolled into this study received a single dose of Yttrium-90 labelled anti-CD66 antibody as part of a reduced toxicity conditioning regimen, prior to allogeneic haematopoietic stem cell transplant

Primary: Safety endpoint: assessment of dose limiting toxicity

End point title	Safety endpoint: assessment of dose limiting toxicity[1]

End point description:

Dose-limiting toxicity (DLT) was defined as follows, using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 4.0) :
a) graft failure: neutrophils < 0.5 x 109/L by day + 45 post transplant (unless clearly due to concomitant infections, other medications or poor stem cell dose/viability);
b) Hepatic/gastrointestinal toxicity (excluding oral mucositis) by day +30 post transplant: ≥ grade 3, excluding causes such as concomitant drugs, infections or GvHD;
c) Gastrointestinal toxicity (oral mucositis) by day +30 post transplant: > grade 3, excluding causes such as concomitant drugs, infections or GvHD;
d) Neurological toxicity by day +30 post transplant: ≥ grade 3, excluding causes such asconcomitant drugs or infections;
e) Pulmonary toxicity by day +30 post transplant: ≥ grade 3, excluding infectious causes, peri-engraftment syndrome or concomitant drugs;
f) Cutaneous toxicity by day +30 post transplant: ≥ grade 3, excluding concomitant drug reactions, infe

End point type	Primary

End point timeframe:

Assessment of dose limiting toxicity (DLT) within 30 days post-stem cell transplant

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: Children received increasing doses of targeted radio-immunotherapy, with a max infused activity of 47 MBq/kg and a max absorbed dose to the bone marrow= 45 Gy. As the antibody used in this trial expired, the study ended prematurely and we couldn't escalate the dose up to 55 MBq/kg. Nevertheless children in the last cohort received a high dose of radiation to the bone marrow and RIT was extremely well tolerated by 9/9 children. None experienced a Dose Limiting Toxicity.

End point values	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: 0-10				
Number of patients experiencing DLT	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease response after 90Yttrium-labelled anti-CD66 monoclonal

antibody

End point title	Disease response after 90Yttrium-labelled anti-CD66 monoclonal antibody

End point description:

To assess disease response after RIT and stem cell transplant.

End point type	Secondary

End point timeframe:

Disease response at 1 year post-stem cell transplant

End point values	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: 0-9				
Patients in complete remisison 1 year after RIT	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Timing of myeloid and platelet recovery after allogeneic haematopoietic stem cell transplantation

End point title	Timing of myeloid and platelet recovery after allogeneic haematopoietic stem cell transplantation

End point description:

Timing of myeloid and platelet recovery after allogeneic haematopoietic stem cell transplantation

End point type	Secondary

End point timeframe:

Timing of myeloid and platelet recovery within 2 months post-stem cell transplantation

End point values	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: median				
median (full range (min-max))				
Median time to neutrophil recovery	17 (11 to 31)			
Median time to platelet recovery	28 (14 to 43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Donor engraftment rate and quality of chimerism after allogeneic haematopoietic stem cell transplant

End point title	Donor engraftment rate and quality of chimerism after allogeneic haematopoietic stem cell transplant
End point description:	
Analysis of donor engrfatment after BMT.	
End point type	Secondary
End point timeframe:	
Chimerism d+30 post transplant	

End point values	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (not applicable)				
Percentage of children with full donor engraftment	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Biodistribution of Indium-111, after imaging with gamma camera / SPECT-CT scans and blood samples

End point title	Biodistribution of Indium-111, after imaging with gamma camera / SPECT-CT scans and blood samples
End point description:	
Biodistribution of In111-labelled anti-CD66 ab after infusion (dosimetry)	
End point type	Secondary
End point timeframe:	
Biodistribution of In111-labelled anti-CD66 ab within 7 days post infusion	

End point values	Infusion of Yttrium-90 labelled monoclonal anti-CD66 antibody			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (not applicable)				
% children with good In-111 biodistribution	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were recorded from Study enrolment to 1 year post-stem cell transplant

Adverse event reporting additional description:

Adverse events were described and graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 4.0).

Assessment type	Systematic

Dictionary used

Dictionary name	NCI
Dictionary version	4

Reporting groups

Reporting group title	Adverse events RIT phase 1 study

Reporting group description:

Children with relapsed/refractory leukaemia undergoing allogeneic haematopoietic stem cell transplant after receiving a infusion of Yttrium-90 labelled anti-CD66 monoclonal antibody, as part of a reduced toxicity conditioning regimen.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As the Radio Immuno Therapy (RIT) was followed by chemotherapy and an allogeneic haematopoietic stem cell transplant, all children experienced multiple non-serious AEs, as expected. It would be difficult to include them all in this report owing to huge number and as most of these AEs were related to the transplant, rather than the radio-immunotherapy.

Serious adverse events	Adverse events RIT phase 1 study		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Seizure	Additional description: Seizures resolved with medications.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukaemia	Additional description: Relapse of leukaemia, switched to palliative care.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dehydration	Additional description: Vomiting, weakness, decreased renal function. Resolved		

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Increased ALT	Additional description: Self-resolved NCI grade III increased ALT, not related to IMP.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venoocclusive disease	Additional description: VOD post BMT, unrelated to IMP, but due to other risk factors (second BMT, conditioning regimen, azole toxicity). Resolved.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Oxygen saturation decreased	Additional description: Respiratory failure post leukaemia relapse, unrelated to IMP. Switched to palliative care.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Febrile neutropenia	Additional description: Febrile neutropenia, resolved with antibiotics		
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sphingomonas paucimobilis infection	Additional description: Infection due to Sphingomonas Paucimobilis, resolved with antibiotics		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Graft versus host disease	Additional description: 3 GvHD events of GI system (Diarrhoea and vomiting after BMT, due to graft versus host disease. Resolved with use of steroids)		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Viraemia	Additional description: 3 events of CMV viraemia requiring iv anti-viral therapy, which resolved. 1 event of Adenoviraemia.		

subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fever	Additional description: 3 events of fevers needing admission and antibiotics.		
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Raised CRP	Additional description: Self resolved raised inflammatory markers, treated with antibiotics.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: Admitted for sepsis and treated with antibiotics. Unrelated to IMP. Resolved.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal infection	Additional description: 1 event of fungal chest infection pre-IMP infusion requiring lobectomy. 1 event of aspergillosis post BMT (risk factor: pre-BMT aspergilloma), which progressed leading to patient's death. Unrelated to IMP, but immunodeficiency following transplant.		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Adverse events RIT phase 1 study		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 9 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2015	Notification of updated IMPD (IMPD v2, dated 01/02/2015)
14 December 2016	•Update the list of co-investigators and collaborators •Facilitate the enrolment process •Clarify the assessment of the dose limiting toxicity •Reduce the number of bloods to be taken after the transplant (HAMA bloods) •Facilitate the infusion of IMP1 and IMP2
22 February 2018	Notification of trial halt due to unavailability of staff to perform scans at UCLH
09 April 2018	Notification of trial restart following staffing issues at UCLH for scans being resolved
04 November 2018	•Amendment seeks approval to change the exclusion criteria from "isolated bone marrow relapse" to just "relapse" in order to allow patients who present with relapses of ALL and AML in other organs to be included in the study. •Changes to scheduled radiation procedures, i.e. skipping dose level 3 of 50MBq/kg and move to dose level 4 of 55MBq/kg for next cohort. •Submission of updated protocol/IB/IMPD: Protocol v5 (26/10/2018), IB v8 (31/03/2018), IMPD v4.1 (30/04/2018)
09 September 2019	The changes relate to a short extension of the storage of the drug substance, CHX A"-DTPA-anti-CD66 monoclonal antibody.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 February 2018	The trial was halted btween February and April 2018, due to unavailability of staff to perform scans (dosimetry) in UCLH. A substantial amendment was submitted as well.	09 April 2018

Notes:

Limitations and caveats

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

The antibody used in this trial expired before the conclusion of the study, so pateints could not be treated at the highest level of radiation foreseen by the protocol. Neverheless suffieient data was collected to demonstrate lack of toxicity.

Notes: