Clinical trial results:
Obinutuzumab containing conditioning regimen for CLL patients and patients with Richter`s transformation requiring an allogeneic stem cell transplantation

Summary

EudraCT number	2015-000568-32
Trial protocol	DE
Global end of trial date	30 September 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	CLLTX1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03153514
WHO universal trial number (UTN)	-
Other trial identifiers	Paul-Ehrlich-Institut: 2918/01

Notes:

Sponsors

Sponsor organisation name	German CLL Study Group, University Hospital Cologne
Sponsor organisation address	Gleuelerstr. 176-178, Cologne, Germany, 50935
Public contact	CLLTX1 , German CLL Study Group, 0049 0221478 88220, cllstudie@uk-koeln.de
Scientific contact	CLLTX1 , German CLL Study Group, 0049 0221478 88220, cllstudie@uk-koeln.de

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	07 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the feasibility, efficacy and safety of an Obinutuzumab containing conditioning regimen for CLL patients and patients with Richter`s transformation requiring an allogeneic stem cell transplantation.

Protection of trial subjects:

A premedication with oral acetaminophen/paracetamol (1.000mg) and antihistamines including a H1- (e.g. dimentindene 4mg i.v.) and a H2-antagonist (e.g. ranitidine 50mg i.v.) has to be administered (unless contraindicated) approximately 30 minutes prior to the start of the first infusion of obinutuzumab to avoid infusion related reactions (IRRs). Additionally, prednisolone or prednisone (100mg given i.v. at least one hour before the obinutuzumab infusion) has to be administered. An equivalent dose of dexamethasone (16mg) or methylprednisolone (80mg) is permitted, but hydrocortisone should not be used.
In Addition detailed guidance on the Management on graft versus host disease were provided in the study protocol

Background therapy:

The number of patients who received allogeneic stem cell transplantion has substantially decreased over time; mostly due to the availability of less toxic and novel agents with proven efficacy even after failure to chemoimmunotherapy or to chemofree first-line regimen. However, allogeneic stem cell transplantation continue to have a role for patients who fail, are intolerant, or do not have access to these novel agents
Instead of Obinutuzumab, which was explored in this trial to collect data on the influence of obinutuzumab on the development of graft versus host disease, Antithymocyte globulin is used as graft versus host disease (GvHD) prophylaxis in most unrelated donor transplants. Another alternative is the use of Alemtuzumab in addition to calcineurin inhibitors and mycophenolate mofetil. The use of these T-cell depleting agents are associated with an increase rate of relapse. The protective role of Rituximab in the peri-transplant conditioning as well as its role in the treatment of GvHD highlights the potential for a B-cell depleting agent in the peri-transplant setting.
Allo-SCT is not only a therapeutic option for patients with poor risk CLL and RT but also offers the possibility of potential cure. As myeloblative conditioning regimens are associated with a high transplant related morbidity and mortality (up to 40%) 8, reduced intensity conditioning regimens are currently preferred for these patients. Graft versus leukaemia (GvL) effect has been demonstrated post allo-SCT by many factors such as reduced relapse in the presence of chronic Graft versus host disease (GvHD), ability to eradicate minimal residual disease with the taper of immunsuppression or donor lymphocyte infusions (DLI) and increased relapse following T-cell depletion Encouragingly a recent follow-up by Dreger et al. on the CLL3X trial highlighted that the long term (6 years post SCT) survival on 90 allografted patients as 58% with an event free survival (EFS) of 38%. They also conclu

Evidence for comparator:

n/a

Actual start date of recruitment	06 April 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	Germany: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	2
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

3 patients were enrolled between 11/2017 and 04/2018.

Pre-assignment

Screening details:

4 pre-treated patients with high risk CLL or Richters transformation were registered for central screening. The central screening was performed by the GCLLSG study office in Cologne Germany and included immunophenotyping, transplant requirement, suitable stem cell donor, comorbidity and renal function. 1 patient was not eligible for participation.

Pre-assignment period milestones

Number of subjects started	3
Number of subjects completed	3

Period 1

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

Blinding implementation details:

n/a

Arms

Arm title	Obinutuzumab

Arm description:

Patients received cycle 1 at the time of the stem cell transplantation. Cycle 2 was administered in case of active disease and/or MRD positivity after cycle 1.
Patients were staged at day +60 post-transplant and MRD was determined per central laboratory assessment. Patients found to have active disease or identified as MRD positive, defined as those who have a MRD ≥ 10-4, were offered 4 additional doses of obinutuzumab along with immunetaper ± DLI. Patients who did not receive cycle 2 because staging at day +60 post-transplant showed no active disease and/or MRD positivity received cycle 2 after staging day +90/ 180/ 270 post-transplant if found to have active disease/MRD positivity at this time point.

Arm type	single-arm
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Obinutuzumab will be administered as depicted in Table 2 of the protocol. Regarding the administration of a premedication before the start of obinutuzumab, for adjustments in case of an IRR as well as further guidelines regarding obinutuzumab administration please refer to chapter 5.2.2 Premedication before obinutuzumab therapy and chapter 5.2.3 Infusion-related reactions and anaphylaxis. For obinutuzumab storage and preparation please refer to chaper 8.5 Drug storage and preparation. If the first infusion of obinutuzumab was well tolerated (defined by an absence of IRRs during a final infusion rate of ≥ 100mg/h), subsequent infusions will be administered at an initial rate of 100mg/h.
The infusion rate is increased by 100mg/h increments at 30 minute intervals, as tolerated, to a maximum rate of 400mg/h. At the investigator’s discretion the subsequent obinutuzumab infusions may be split and administered over two days with infusion rates as described in the protocol

Number of subjects in period 1	Obinutuzumab
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	3	3	
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)	2	2	
From 65-84 years	1	1	
85 years and over	0	0	
18-64	0	0	
Age continuous Units: years			
median	57		
inter-quartile range (Q1-Q3)	56.5 to 61	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	3	3	

End points

End points reporting groups

Reporting group title	Obinutuzumab

Reporting group description:

Patients received cycle 1 at the time of the stem cell transplantation. Cycle 2 was administered in case of active disease and/or MRD positivity after cycle 1.
Patients were staged at day +60 post-transplant and MRD was determined per central laboratory assessment. Patients found to have active disease or identified as MRD positive, defined as those who have a MRD ≥ 10-4, were offered 4 additional doses of obinutuzumab along with immunetaper ± DLI.
Patients who did not receive cycle 2 because staging at day +60 post-transplant showed no active disease and/or MRD positivity received cycle 2 after staging day +90/ 180/ 270 post-transplant if found to have active disease/MRD positivity at this time point.

Primary: Rate of patients free from disease progression (PD-free rate) at 12 months post-transplant

End point title	Rate of patients free from disease progression (PD-free rate) at 12 months post-transplant[1]

End point description:

Patients will be followed for Progression. Patients free of disease Progression will be counted .

End point type	Primary

End point timeframe:

12 months post 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: Because of the low number of patients no statistical analyses were done.

End point values	Obinutuzumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: numbers	3			

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	CLLTX1

Reporting group description: -

Serious adverse events	CLLTX1		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cytomegalovirus gastritis	Additional description: Cytomegalovirus gastritis		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection	Additional description: Cytomegalovirus infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis	Additional description: Escherichia sepsis		

subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes simplex	Additional description: Herpes simplex		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection	Additional description: Parainfluenzae virus infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia cytomegaloviral	Additional description: Pneumonia cytomegaloviral		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral	Additional description: Pneumonia respiratory syncytial viral		
subjects affected / exposed	1 / 3 (33.33%)		
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	CLLTX1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Investigations			
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Blood folate decreased	Additional description: Blood folate decreased		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Renal function test abnormal	Additional description: Renal function test abnormal		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Vascular disorders			
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Tremor	Additional description: Tremor		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Haemolysis	Additional description: Haemolysis		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema	Additional description: Oedema		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Immune system disorders			
Acute graft versus host disease in intestine	Additional description: Acute graft versus host disease in intestine		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Autoimmune disorder	Additional description: Autoimmune disorder		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Graft versus host disease	Additional description: Graft versus host disease		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Graft versus host disease in eye	Additional description: Graft versus host disease in eye		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Graft versus host disease in gastrointestinal tract	Additional description: Graft versus host disease in gastrointestinal tract		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	5		
Graft versus host disease in liver	Additional description: Graft versus host disease in liver		
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	6		

Graft versus host disease in lung	Additional description: Graft versus host disease in lung		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Graft versus host disease in skin	Additional description: Graft versus host disease in skin		
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Obstructive airways disorder	Additional description: Obstructive airways disorder		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Clostridium difficile infection	Additional description: Clostridium difficile infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Cytomegalovirus infection	Additional description: Cytomegalovirus infection		

subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infection	Additional description: Infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nail bed infection	Additional description: Nail bed infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Rhinovirus infection	Additional description: Rhinovirus infection		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Folate deficiency	Additional description: Folate deficiency		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Vitamin d deficiency	Additional description: Vitamin d deficiency		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

In this study, the recruitment was stopped after 3 of the 40 planned patients have been enrolled. As a consequence of the low number of of patients enrolled, it was decided that any statistical analysis cannot be performed.

Notes: