Clinical trial results:
A multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab in adult patients with minimal residual disease (MRD) of B-precursor acute lympho-blastic leukemia (Blast Successor Trial)

Summary

EudraCT number	2015-000733-76
Trial protocol	DE
Global end of trial date	31 July 2023

Results information

Result version number	v1 (current)
This version publication date	02 August 2024
First version publication date	02 August 2024

Trial information

Trial identification

Sponsor protocol code	GMALL-MOLACT1-BLINA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03109093
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Goethe University
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt , Germany, 60590
Public contact	GMALL-Studienzentrale, Universitätsklinik Frankfurt, Med. Klinik II, +49 (0)6963016365, gmall@em.uni-frankfurt.de
Scientific contact	GMALL-Studienzentrale, Universitätsklinik Frankfurt, Med. Klinik II, +49 (0)6963016365, gmall@em.uni-frankfurt.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	20 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2023
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of blinatumomab to induce complete MRD response in patients regardless of prior SCT

Protection of trial subjects:

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records were identified by a coded number, sex and year of birth only. Medical information about individual patients obtained in the course of this trial is confidential and was not disclosed to third parties, except authorized monitors, auditors or inspectors. Confidentiality was ensured by the use of patient numbers for the identification of each patient; these patient numbers were also used for patient data in the patient files and eCRFs.
Clinical information was not released without written permission given by the subject/legal representative within the informed consent, except as necessary for monitoring by regulatory authorities or the Sponsor of the clinical study. The principal investigator also complied with all applicable national privacy regulations.

Background therapy:

No pre-phase chemotherapy was planned as patients had only minimal residual disease.

Evidence for comparator:

N.A.

Actual start date of recruitment	16 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 83
Worldwide total number of subjects	83
EEA total number of subjects	83

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)	75
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

04-04-2017 First Patient In, 11-10-2019 last Patient out.

Pre-assignment

Screening details:

Screening was conducted to verify that the inclusion criteria for the study were met, with particular attention to the presence of minimal residual disease(MRD).

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. (open-label single-arm phase II study)

Arms

Arm title	Blinatumomab

Arm description:

Patients received one to four consecutive cycles of blinatumomab. A cycle consists of a continuous intravenous infusion at a dose of 28 µg/d over four weeks followed by an infusion free interval of two weeks.

Arm type	open-label single-arm study
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	
Other name	BLINCYTO®, BiTE®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Infusion

Dosage and administration details:

Patients received one to four consecutive cycles of blinatumomab. A cycle consists of a con-tinuous intravenous infusion at a dose of 28 µg/d over four weeks followed by an infusion free interval of two weeks. Blinatumomab were administered as a continuous intravenous (CIV) infusion at a constant flow rate over four weeks followed by a two-week infusion free interval.

Number of subjects in period 1	Blinatumomab
Started	83
Completed	83

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

This study incorporated multiple interim analyses for futility, efficacy, and unblinded sample-size reestimation.

Reporting group values	Overall trial	Total	
Number of subjects	83	83	
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)	75	75	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	38	38	
Male	45	45	

Subject analysis sets	
Subject analysis set title	Evaluable patients
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received any infusion of the investigation durg and for whom at least one evaluable response assessment is available after start of treatment or patients who died before the first evaluation time-point. Patients for whom no sufficient MRD assessment by PCR is established due to technical reasons will be excluded from the analysis of the primary endpoint.

Reporting group values	Evaluable patients		
Number of subjects	83		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	75		

From 65-84 years	8		
85 years and over	0		

Gender categorical Units: Subjects			
Female	38		
Male	45		

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Patients received one to four consecutive cycles of blinatumomab. A cycle consists of a continuous intravenous infusion at a dose of 28 µg/d over four weeks followed by an infusion free interval of two weeks.

Subject analysis set title	Evaluable patients
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received any infusion of the investigation durg and for whom at least one evaluable response assessment is available after start of treatment or patients who died before the first evaluation time-point. Patients for whom no sufficient MRD assessment by PCR is established due to technical reasons will be excluded from the analysis of the primary endpoint.

Primary: Complete MRD response after one cycle of treatmet

End point title	Complete MRD response after one cycle of treatmet[1]

End point description:

End point type	Primary

End point timeframe:

After one cycle of blinatumomab

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: Only descriptive analysis

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	83			
Units: Percent	71			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment phase + follow up	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	All patients with study treatment
Reporting group description:	
All patients who received any infusion of the investigational drug.	

Serious adverse events	All patients with study treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 83 (32.53%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	0		
Investigations			
CRP			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell decreased			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications				
Injury, poisoning and procedural complications - Other, specify				
subjects affected / exposed	3 / 83 (3.61%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cognitive disturbance				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphasia				
subjects affected / exposed	4 / 83 (4.82%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders - Other, specify				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	3 / 83 (3.61%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fever				

subjects affected / exposed	2 / 83 (2.41%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter related infection			
subjects affected / exposed	2 / 83 (2.41%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations - Other, specify			
subjects affected / exposed	3 / 83 (3.61%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumor lysis syndrome			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients with study treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 83 (96.39%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 83 (18.07%)		
occurrences (all)	19		
AST, GOT increased			
subjects affected / exposed	11 / 83 (13.25%)		
occurrences (all)	13		
Immunoglobulin deficiency			
subjects affected / exposed	7 / 83 (8.43%)		
occurrences (all)	14		
Investigations - Other, specify			
subjects affected / exposed	8 / 83 (9.64%)		
occurrences (all)	8		
Lipase increased			
subjects affected / exposed	9 / 83 (10.84%)		
occurrences (all)	11		
Lymphocyte count decreased			
subjects affected / exposed	38 / 83 (45.78%)		
occurrences (all)	64		
Neutrophil count decreased			
subjects affected / exposed	32 / 83 (38.55%)		
occurrences (all)	41		
Platelet count decreased			
subjects affected / exposed	24 / 83 (28.92%)		
occurrences (all)	35		
White blood cell count decreased			
subjects affected / exposed	37 / 83 (44.58%)		
occurrences (all)	60		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications - Other, specify			
subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		

Nervous system disorders			
Dysphasia (Aphasia)			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	21 / 83 (25.30%)		
occurrences (all)	21		
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	16 / 83 (19.28%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia/Hemoglobin			
subjects affected / exposed	25 / 83 (30.12%)		
occurrences (all)	39		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	8 / 83 (9.64%)		
occurrences (all)	12		
Fever/Pyrexia			
subjects affected / exposed	52 / 83 (62.65%)		
occurrences (all)	66		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	9 / 83 (10.84%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		
Mucositis oral			

subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	10 / 83 (12.05%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	6 / 83 (7.23%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	7 / 83 (8.43%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 83 (7.23%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	8 / 83 (9.64%)		
occurrences (all)	8		
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	18 / 83 (21.69%)		
occurrences (all)	28		
Hypokalaemia			
subjects affected / exposed	10 / 83 (12.05%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2016	Protocol Version 1.1(Approval Date: 21.04.2016) The aim of this amendment was to clarify specific protocol sections, for example the Rationale for Dose Selection and Hospitalisation, to correct typing errors and to facilitate the study management in the participating centers.
17 May 2016	Protocol Version 1.2(Approval Date 30.09.2016): The purpose of this amendment was to correct typing errors and clarify specific sections of the protocol. Additional a clarification regarding study drug treatment in pregnant persons was added, indicating that treatment should be discontinued in such patients.
08 November 2016	Protocol Version 1.3(Approval Date 28.12.2016): The purpose of this amendment was to correct typing errors and clarify specific sections of the protocol.Furthermore, additional precautions were specified regarding adverse events related to pancreatitis. Details regarding the new patient groups and inclusion criteria have been added. With regard to the approval of Blinatumomab in MRD positive ALL with MRD levels above 10-3 by the EMA, this patient group will no longer be included in the trial, as patients may receive Blinatumomab within marketing authorization. Of course, patients with MRD between 10-4 and 10-3 will still be included. The study aims to expand experience with Blinatumomab in patients with presence of MRD below 10-4 (non quantifiable or quantifiable) as well as with positive MRD non quantifiable, as data have shown an inferior outcome for these patients groups.
23 August 2018	Protocol Version 1.4(Approval Date 19.09.2018):The purpose of this amendment was to correct typing errors and clarify specific sections of the protocol. The section "2.4.2 Phase II Trial in MRD positive B-Precursor ALL" was clarified, and the adverse neurolocial events, and the "Handling of toxicities" as well. Contact number and adress of Protocol Comission members was actualized.
23 July 2019	Protocol Version 2.0(Approval Date 06.09.2019): The purpose of this amendment was to correct typing errors and clarify specific sections of the protocol. Treatment Interruption/Dose Modification due to Adverse Events Headline Neurologic events of CTCAE grade 2 were added. The duration of study was extended to 36 months recruitment period; evaluation of primary end point to 42 months, estimated End of Study after 60 months.
04 March 2020	Protocol Version 2.1(Approval Date 27.03.2020)Duration of the study adopted to prolonged recruitment phase, recruitment period to 48 Months and 72 Months to final analysis. Clarifications at the sections: treatment assignment, treatment interruption/dose modification due to adverse events, bone marrow aspiration / biopsy, D43/D1 of Subsequent Cycle.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported