Clinical trial results:
A multicenter Phase I/II trial investigating the safety and efficacy (CR rate and OS) of low dose AraC with Clofarabine in patients 60 years with AML not eligible for conventional Chemotherapy

Summary

EudraCT number	2009-017347-33
Trial protocol	DE
Global end of trial date	13 December 2013
Results information	
Result version number	v1 (current)
This version publication date	15 August 2020
First version publication date	15 August 2020
Summary attachment (see zip file)	Final report 2014-02-20 (Abschlussbericht_2014-02-20_geschwärzt.pdf)

Trial information

Trial identification	
Sponsor protocol code	Clofarabine
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University of Leipzig
Sponsor organisation address	Ritterstrasse 26, Leipzig, Germany, D 04109
Public contact	University of Leipzig Indep. Department for Haematology, Internistic Oncology and Haemostastogy, University of Leipzig Indep. Department for Haematology, Internistic Oncology and Haemostastogy, +49 341 97-13050, haematologie@medizin.uni-leipzig.de
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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	28 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2013
Global end of trial reached?	Yes
Global end of trial date	13 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I – Dose evaluation
To investigate feasibility of induction therapy with low dose Ara-C (20 mg/m2 sc injection d1-d14) and clofarabine at three different dose levels for the first induction cycle (Clofarabine 10, 15 or 20 mg/m2 1h iv infusion d1-d5).

Phase II – Safety
To assess safety (in terms of AEs/ARs, SAEs/SARs and Adverse reactions CTC grade 4 (AR4)) of induction therapy with low dose AraC in combination with Clofarabine (at the dose level resulting from the dose evaluation phase of the trial).

Protection of trial subjects:

A DMC was installed. However, the trial ended prematurely before the first meeting of the DMC.
Toxicities and adverse events were captured at the end of every treatment period.
Patients who experience ≥ grade 3 drug-related non-hematologic toxicity or asymptomatic grade 2 serum creatinine or serum total bilirubin elevation during any clofarabine administration period should have the drug held until recovery to baseline or grade <2 before resuming treatment. If the patient suffers subsequently a grade 3 drug related non-hematologic toxicity, he will be excluded from the study. There will be no dose modifications.

Background therapy:

Application of filgrastim /pegfilgrastim was documented for 3 patients.

Prophylactic steroid administration to minimize the occurrence and/or severity of the following potential clofarabine-related toxicities: nausea, vomiting, skin rash/desquamation, and capillary leak syndrome was suggested.

Evidence for comparator:

In comparison to the “golden standard” of low dose AraC, Clofarabine monotherapy increases response rates in a historical control analysis (Burnett et al). For patients with secondary AML the response rate was only 4% with low dose AraC compared to 31 % with clofarabine. The combination of clofarabine and low-dose AraC increased the CR rate (63 vs. 31%) and event free survival (7.1 vs. 1.7 months; p=0.04) even more (see Faderl et al. 2008)).

Actual start date of recruitment	03 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	0
From 65 to 84 years	12
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

13 patients were recruited in two trial sites from March 3rd, 2011 to January 17, 2012

Pre-assignment

Screening details:

Not available

Period 1

Period 1 title	Phase I: Dose escalation
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Clofarabine

Arm description:

Therapy with Clofarabine / AraC following a dose escalation scheme

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

following the dose-escalation scheme

Investigational medicinal product name	Ara-C
Investigational medicinal product code	
Other name	Cytarabin, AraC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

20 mg/m² from day 1 to day 14 of the cycle

Number of subjects in period 1	Clofarabine
Started	13
Completed	13

Period 2

Period 2 title	Phase II: 2nd Induction / Consolidation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Only one arm

Arms

Arm title	Clofarabine

Arm description:

Therapy with Clofarabine / AraC following a dose escalation scheme

Arm type	Experimental
Investigational medicinal product name	Clofarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

following the dose-escalation scheme

Investigational medicinal product name	Ara-C
Investigational medicinal product code	
Other name	Cytarabin, AraC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

20 mg/m² from day 1 to day 14 of the cycle

Number of subjects in period 2[1]	Clofarabine
Started	12
Completed	12

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One patient withdrew consent.

Baseline characteristics

Reporting groups	
Reporting group title	Clofarabine
Reporting group description:	
Therapy with Clofarabine / AraC following a dose escalation scheme	

Reporting group values	Clofarabine	Total	
Number of subjects	13	13	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age (years)			
Units: years			
arithmetic mean	79.6		
standard deviation	± 3.2	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	7	7	
AML			
AML Type			
Units: Subjects			
Primary AML	7	7	
Secondary AML	5	5	
AML after Myelofibrosis	1	1	
ECOG state Units: Subjects			
Grade 0	2	2	
Grade 1	6	6	
Grade 2	2	2	
Grade 3	1	1	
Not available	2	2	
BMI			
body mass index			
Units: kg/m²			
arithmetic mean	27.1		
standard deviation	± 4.2	-	

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Full Analysis Set = Safety Set

Reporting group values	Safety set		
Number of subjects	13		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age (years)			
Units: years			
arithmetic mean	79.6		
standard deviation	± 3.2		
Gender categorical Units: Subjects			
Female	6		
Male	7		
AML			
AML Type			
Units: Subjects			
Primary AML	7		
Secondary AML	5		
AML after Myelofibrosis	1		
ECOG state Units: Subjects			
Grade 0	2		
Grade 1	6		
Grade 2	2		
Grade 3	1		
Not available	2		
BMI			
body mass index			
Units: kg/m²			
arithmetic mean	27.1		
standard deviation	± 4.2		

End points

End points reporting groups

Reporting group title	Clofarabine
Reporting group description: Therapy with Clofarabine / AraC following a dose escalation scheme	
Reporting group title	Clofarabine
Reporting group description: Therapy with Clofarabine / AraC following a dose escalation scheme	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: Full Analysis Set = Safety Set	

Primary: SAEs during induction therapy

End point title	SAEs during induction therapy[1]
End point description: safety endpoint	
End point type	Primary
End point timeframe: induction therapy	

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 one arm in study,
thus, no confirmative analysis.

End point values	Clofarabine	Safety set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: events				
SAE	7	7		
No SAE	6	6		

Statistical analyses

No statistical analyses for this end point

Primary: Adverse events during induction therapy

End point title	Adverse events during induction therapy[2]
End point description:	
End point type	Primary
End point timeframe: Induction therapy	

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: Only one arm in study.
Thus, no confirmatory analysis was possible.

End point values	Clofarabine	Safety set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: events				
AE present	13	13		
No AE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Induction response

End point title	Induction response

End point description:

End point type	Secondary

End point timeframe:

induction therapy

End point values	Clofarabine	Safety set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: patients				
CR	1	1		
CRi	5	5		
PR	0	0		
SD	3	3		
PD	3	3		
Death	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Death from every cause

End point title	Death from every cause

End point description:

End point type	Secondary
End point timeframe: study duration	

End point values	Clofarabine	Safety set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: months				
median (confidence interval 95%)	2.3 (1.0 to 3.6)	2.3 (1.0 to 3.6)		

Attachments (see zip file)	Clofarabine_OS.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First induction therapy

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Clofarabine

Reporting group description: -

Serious adverse events	Clofarabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	4		
Vascular disorders			
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Disorientation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymph node abscess			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Respiratory failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			

Sepsis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Enterococcal sepsis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Klebsiella sepsis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Clofarabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Vascular disorders			
Ascites			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		
Haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Phlebitis			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	13 / 13 (100.00%)		
occurrences (all)	13		
Fall			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Immune system disorders			
Mucosal inflammation			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Hypersensitivity			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Cystitis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pleural effusion			

subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 13 (76.92%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 13 (100.00%)		
occurrences (all)	13		
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 13 (76.92%)		
occurrences (all)	10		
Blood bilirubin increased			
subjects affected / exposed	13 / 13 (100.00%)		
occurrences (all)	13		
Blood iron			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
excoriation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		

Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Intestinal obstruction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mouth haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		
Vomiting			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	7		
Blood blister			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Decubitus ulcer			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		
Intertrigo			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	7		
Renal failure			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Urethral haemorrhage			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Soft tissue infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperproteinaemia			
subjects affected / exposed	9 / 13 (69.23%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2011	Changes for patients with renal insufficiency, Permission of concomitant medication with Litalir, Events related to tumour progression are not more documented as SAE.

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 trial was finished prematurely after 13 patients had been enrolled.

Notes: