



## Clinical trial results:

### Multizentrische Therapieoptimierungsstudie AML-BFM 2004 zur Behandlung der akuten myeloischen Leukämien bei Kindern und Jugendlichen

### Multicentric therapy optimizing study AML-BFM 2004 for the treatment of acute myeloic leukaemias for children and juveniles

#### Summary

EudraCT number	2006-004710-41
Trial protocol	AT
Global end of trial date	25 October 2015

#### Results information

Result version number	v1 (current)
This version publication date	10 November 2016
First version publication date	10 November 2016
Summary attachment (see zip file)	Synopsis AML-BFM 2004 (Synopsis AML-BFM 2004 referring to ANNEX 1 ICH E3 sign.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	AMLBFM0401
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	St. Anna Kinderkrebsforschung
Sponsor organisation address	Zimmermannplatz 10, Vienna, Austria, 1090
Public contact	Univ.Prof. Dr. Ruth Ladenstein, St. Anna Kinderkrebsforschung, +43 140470,
Scientific contact	Univ.Prof. Dr. Ruth Ladenstein, St. Anna Kinderkrebsforschung, +43 140470,

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	25 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2015
Global end of trial reached?	Yes
Global end of trial date	25 October 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

1. improvement of prognosis of children and adolescents by intensification of cytostatic therapy by randomized implementation of liposomal daunorubicine in first induction
2. randomized implementation of 2-CDA as intensification in consolidation therapy for patients in high risk group with the aim of improvement of prognosis
3. randomized examination of efficacy of prophylactic CNS radiation 18 Gy vs. 12 Gy

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic Trial because the study was started on the national level in the month after a national legislative revision of the Austrian Medicinal Products Act in line with EU-Directive 2001/20/EC, whereas the trial was conducted in the main other countries under rules not yet falling under this Revision.

Protection of trial subjects:

detailed supportive care measures were specified within the Trial protocol

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2004
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	Austria: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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	12

months)	
Children (2-11 years)	27
Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

recruitment in 8 Austrian participating hospitals from 01.03.2004 until 01.03.2011

### Pre-assignment

Screening details:

Principal inclusion criteria:

\* age 0-18y

\* de novo AML, including Down Syndrome, primary myelosarcoma of acute mixed lineage leukemia

\* treatment in participating center

### Period 1

Period 1 title	whole study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	ADxE

Arm description:

liposomal daunorubicin in first induction course

Arm type	Experimental
Investigational medicinal product name	Daunoxome
Investigational medicinal product code	L01DB02
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 mg/m<sup>2</sup>

<b>Arm title</b>	AIE induction
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Arm description:

standard induction therapy with cytarabine, idarubicin and etoposide

Arm type	standard chemotherapy arm
No investigational medicinal product assigned in this arm	

<b>Arm title</b>	AI/2-CDA
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Arm description:

addition of 2-CDA to consolidation course

Arm type	Experimental
Investigational medicinal product name	Cladribine
Investigational medicinal product code	L01BB04
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/m<sup>2</sup>

<b>Arm title</b>	AI consolidation
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Arm description:

standard consolidation course with cytarabine and idarubicine

Arm type	standard chemotherapy arm
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No investigational medicinal product assigned in this arm	
<b>Arm title</b>	12 Gy
Arm description:	
CNS irradiation reduced to 12 Gray	
Arm type	experimental arm: reduced irradiation
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	18 Gy
Arm description:	
standard arm with CNS irradiation with 18 Gy	
Arm type	standard irradiation arm
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	ADxE	AIE induction	AI/2-CDA
Started	28	30	17
Completed	26	30	15
Not completed	2	0	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	1
organisational reasons	2	-	-
Lack of efficacy	-	-	1

<b>Number of subjects in period 1</b>	AI consolidation	12 Gy	18 Gy
Started	17	13	11
Completed	17	12	11
Not completed	0	1	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
organisational reasons	-	-	-
Lack of efficacy	-	-	-

## Baseline characteristics

### Reporting groups

Reporting group title	whole study period
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Reporting group description: -

Reporting group values	whole study period	Total	
Number of subjects	74	74	
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)	12	12	
Children (2-11 years)	27	27	
Adolescents (12-17 years)	35	35	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	36	36	
Male	38	38	

## End points

### End points reporting groups

Reporting group title	ADxE
Reporting group description: liposomal daunorubicin in first induction course	
Reporting group title	AIE induction
Reporting group description: standard induction therapy with cytarabine, idarubicin and etoposide	
Reporting group title	AI/2-CDA
Reporting group description: addition of 2-CDA to consolidation course	
Reporting group title	AI consolidation
Reporting group description: standard consolidation course with cytarabine and idarubicine	
Reporting group title	12 Gy
Reporting group description: CNS irradiation reduced to 12 Gray	
Reporting group title	18 Gy
Reporting group description: standard arm with CNS irradiation with 18 Gy	

### Primary: survival

End point title	survival <sup>[1][2]</sup>
End point description:	
End point type	Primary
End point timeframe: from diagnosis	

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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

[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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

End point values	ADxE	AIE induction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: years				
event-free survival	5	5		
overall survival	5	5		

## Statistical analyses

No statistical analyses for this end point

### Primary: survival

End point title	survival <sup>[3]</sup> <sup>[4]</sup>
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End point description:

End point type	Primary
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End point timeframe:

from 2nd randomisation

Notes:

[3] - 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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

[4] - 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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

End point values	AI/2-CDA	AI consolidation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: years				
event-free survival	5	5		
overall survival	5	5		

## Statistical analyses

No statistical analyses for this end point

### Primary: survival

End point title	survival <sup>[5]</sup> <sup>[6]</sup>
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End point description:

End point type	Primary
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End point timeframe:

from 3rd randomisation



Notes:

[5] - 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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

[6] - 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: Statistics is not meaningful for the small Austrian cohort - the full international data set is not available!

Notably, EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this much larger international academic trial whereas the trial was conducted in the main other countries under rules not yet falling under EU-Directive 2001/20/EC.

End point values	12 Gy	18 Gy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: years				
disease-free survival	5	5		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:  
from start of treatment up to 5 years after treatment

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	2.0

### Reporting groups

Reporting group title	ADxE
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Reporting group description:

liposomal daunorubicin in first induction course

Reporting group title	AIE induction
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Reporting group description:

standard induction therapy with cytarabine, idarubicin and etoposide

Reporting group title	AI/2-CDA
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Reporting group description:

addition of 2-CDA to consolidation course

Reporting group title	AI consolidation
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Reporting group description:

standard consolidation course with cytarabine and idarubicine

Reporting group title	12 Gy
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Reporting group description:

CNS irradiation reduced to 12 Gray

Reporting group title	18 Gy
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Reporting group description:

standard arm with CNS irradiation with 18 Gy

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: Non-serious events have not been reported in detail

Serious adverse events	ADxE	AIE induction	AI/2-CDA
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 26 (19.23%)	11 / 30 (36.67%)	6 / 15 (40.00%)
number of deaths (all causes)	8	8	7
number of deaths resulting from adverse events	2	2	2
Vascular disorders			
major bleeding or DIC			
subjects affected / exposed	0 / 26 (0.00%)	2 / 30 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 8	0 / 8	0 / 7
Cardiac disorders			
Cardiomyopathy			

subjects affected / exposed	0 / 26 (0.00%)	1 / 30 (3.33%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 8	0 / 8	0 / 7
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 26 (3.85%)	1 / 30 (3.33%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 8	0 / 8	1 / 7
Blood and lymphatic system disorders			
Aplasia			
Additional description: non-regeneration			
subjects affected / exposed	0 / 26 (0.00%)	1 / 30 (3.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 8	0 / 8	0 / 7
Immune system disorders			
HLH			
subjects affected / exposed	2 / 26 (7.69%)	0 / 30 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 8	1 / 8	0 / 7
Infections and infestations			
severe bacterial infections			
subjects affected / exposed	1 / 26 (3.85%)	6 / 30 (20.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	1 / 1	6 / 6	1 / 1
deaths causally related to treatment / all	0 / 8	1 / 8	0 / 7
invasive fungal infection			
subjects affected / exposed	2 / 26 (7.69%)	2 / 30 (6.67%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	1 / 8	1 / 8	2 / 7
<b>Serious adverse events</b>			
AI consolidation			
12 Gy			
18 Gy			
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	0 / 12 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	7	3	2
number of deaths resulting from adverse events	1	0	0
Vascular disorders			
major bleeding or DIC			

subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
Blood and lymphatic system disorders			
Aplasia	Additional description: non-regeneration		
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
Immune system disorders			
HLH			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
Infections and infestations			
severe bacterial infections			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2
invasive fungal infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 7	0 / 3	0 / 2

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

<b>Non-serious adverse events</b>	ADxE	AIE induction	AI/2-CDA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 30 (0.00%)	0 / 15 (0.00%)

<b>Non-serious adverse events</b>	AI consolidation	12 Gy	18 Gy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2010	<p>Amendment 05-2010 for Austria study AML-BFM 2004:</p> <ul style="list-style-type: none"><li>- all randomisations closed</li><li>- continuation with best therapy, i.e.:</li><li>- 1st induction with liposomal daunorubicine 80 mg/m<sup>2</sup>/d/3x (ADxE)</li><li>- consolidation for high risk patients: 2-CDA 2x6mg/m<sup>2</sup> as intensification in AI</li><li>- extension of study duration</li><li>- prophylactic CNS irradiation with 12 Gy</li><li>- re-introduction of HAM for AML with t(8;21)</li></ul> <p>ML-DS (Down Syndrom) amendment for Austria in AML-BFM 2004:</p> <ul style="list-style-type: none"><li>- all ML-DS-Patienten receive AIE induction (idarubicine 8 mg/m<sup>2</sup>)</li><li>- reduction of number of prophylactic intrathecal cytarabine injections from 7 to 4</li><li>- dosage of cytostatic therapy according to kg body weight until body weight of 12 kg (up to date 10 kg)</li><li>- no more etoposide in intensification ==&gt; high dose cytarabine; HA)</li><li>- maintenance therapy is dispensed</li></ul>

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.

Statistics is not meaningful for the small Austrian cohort - the full international data set is not available because the trial was in the main other countries not conducted under rules depending on EU-Directive 2001/20/EC.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21480469>

<http://www.ncbi.nlm.nih.gov/pubmed/23700063>

<http://www.ncbi.nlm.nih.gov/pubmed/23704089>

<http://www.ncbi.nlm.nih.gov/pubmed/25985446>

<http://www.ncbi.nlm.nih.gov/pubmed/25869725>

<http://www.ncbi.nlm.nih.gov/pubmed/26771808>

<http://www.ncbi.nlm.nih.gov/pubmed/26814618>