EU Clinical Trials Register

Clinical trial results:
Elimination of the preleukemic clone in children with Down syndrome and transient myeloproliferative disorder (TMD) to prevent AML - Model of leukemia prevention

Summary

EudraCT number	2006-002962-20
Trial protocol	DE NL
Global end of trial date	08 February 2015

Results information

Result version number	v1 (current)
This version publication date	19 January 2025
First version publication date	19 January 2025
Summary attachment (see zip file)	Summary (2017_12_03_TMD_synopsis_final Vs 1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	TMD01/2007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hannover Medical School
Sponsor organisation address	Carl-Neuberg-Str. 1, Hannover, Germany, 30625
Public contact	Zentrum für Klinische Studien, MHH, Hannover Medical School, EudraCT@mh-hannover.de
Scientific contact	Zentrum für Klinische Studien, MHH, Hannover Medical School, EudraCT@mh-hannover.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	03 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2015
Global end of trial reached?	Yes
Global end of trial date	08 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that monitoring of the GATA1s positive preleukemic clone in TMD and elimination of the clone with cytarabine can reduce the risk of DS-AMKL

Protection of trial subjects:

The clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the standards of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). A continuous risk assessment was performed during the study.

Background therapy:

Monitoring of GATA1s positive preleukemic clones and low-dose cytaribine treatment in children with persisiting GATA1s clone according to a defined treatment algorithm.
43 patients were treated with Cytarabine, 27 received one cozrse, 10 two courses and six three courses of chemotheapy.

Evidence for comparator: -

Actual start date of recruitment	01 June 2007
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: 224
Country: Number of subjects enrolled	Netherlands: 26
Worldwide total number of subjects	250
EEA total number of subjects	250

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	97
Infants and toddlers (28 days-23 months)	153
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment to the study based on the diagnosis of transient leukemia within the first 4 weeks after birth, in-time initiation of the study site and the informed consent of the parents/guardians. Potentially in all 69 children's hospitals with a department of pediatric
hematology/oncology participating in the AML-BMF Studies (GER/NL).

Pre-assignment

Screening details:

Eligibility will be determined based upon the inclusion and exclusion criteria

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TMD study population

Arm description:

All children with trisomy 21 in Germany and the Netherlands that showed > 5% myeloid blasts or with detection of a GATA1-mutation (exon 1, 2, or 3) in the peripheral blood and/or bone
marrow within the first 3 months of life were eligible for inclusion in the study.

Arm type	Experimental
Investigational medicinal product name	cytarabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Cytarabin 1,5mg/kgKG i.v./s.c. on day 1,2,3,4,5,6,7 (=one course) maximum treatment of three courses with blood count controls on day 0 or 1, day 4 and day 10 (including blood count,GOT and GST, creatinine)
cytostatic therapy indicated in following patients:
a)clinical symptoms due to TMD or "hepatopathy)
b) MRD $\leq 10^{-3}$MRD after 8 weeks
c) MRD: IP$\leq 10^{-2}$ or qPCR$\leq 10^{-3}$ after treatment

Arm title	Control Group

Arm description:

The historical control group is a previously reported cohort of patients that were reported to the Acute Myeloid Leukemia Berlin-Frankfurt-Münster (AML-BFM) study group between 01 January 1993 and 31 December 2006 using similar criteria for in- and exclusion.

Arm type	historical control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	TMD study population	Control Group
Started	104	146
Completed	101	146
Not completed	3	0
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	TMD study population

Reporting group description:

All children with trisomy 21 in Germany and the Netherlands that showed > 5% myeloid blasts or with detection of a GATA1-mutation (exon 1, 2, or 3) in the peripheral blood and/or bone
marrow within the first 3 months of life were eligible for inclusion in the study.

Reporting group title	Control Group

Reporting group description:

The historical control group is a previously reported cohort of patients that were reported to the Acute Myeloid Leukemia Berlin-Frankfurt-Münster (AML-BFM) study group between 01 January 1993 and 31 December 2006 using similar criteria for in- and exclusion.

Reporting group values	TMD study population	Control Group	Total
Number of subjects	104	146	250
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	104	146	250
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: weeks			
median	37	37	
full range (min-max)	28 to 43	30 to 41	-
Gender categorical			
Units: Subjects			
Female	44	66	110
Male	60	80	140

End points

End points reporting groups

Reporting group title	TMD study population

Reporting group description:

All children with trisomy 21 in Germany and the Netherlands that showed > 5% myeloid blasts or with detection of a GATA1-mutation (exon 1, 2, or 3) in the peripheral blood and/or bone marrow within the first 3 months of life were eligible for inclusion in the study.

Reporting group title	Control Group

Reporting group description:

The historical control group is a previously reported cohort of patients that were reported to the Acute Myeloid Leukemia Berlin-Frankfurt-Münster (AML-BFM) study group between 01 January 1993 and 31 December 2006 using similar criteria for in- and exclusion.

Primary: Incidence of acute megakaryoblastic leukemia

End point title	Incidence of acute megakaryoblastic leukemia

End point description:

The primary end point of the study was the cumulative incidence (CI) of ML-DS (constructed by the method of Kalbfleisch and Prentice) 3 years after diagnosis of TMD (3y-CI ML-DS). The null hypothesis (no difference from the historical control or higher rate in the study cohort) was tested using the 1-sided 95% confidence interval of the difference. In addition, Gray's test was used for comparisons.16 The secondary end point of the study was the MRD level (independent of prior treatment) at week 12.

End point type	Primary

End point timeframe:

Outcome was assessed at 10 different time points: week 0, 4 to 8, 8, and 12, as well as month 6, 9, 12, 18, 24 and 36 after diagnosis.

End point values	TMD study population	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	146		
Units: percent				
arithmetic mean (confidence interval 95%)	19.9 (16.4 to 23.4)	19.7 (15.4 to 24.0)		

Statistical analyses

Statistical analysis title	Control versus TMD

Statistical analysis description:

Historical Control versus TMD, three-years cumulative incidence of AMKL

Comparison groups	TMD study population v Control Group

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.62
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	1-sided
lower limit	-8.9
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[1] - Efficacy: Main target criterion is the proportion of patients who survive the TMD and develop AMKL within 3 years after diagnosis. The null hypothesis (no difference to the historical control group, AMKL-rate 22%) has been tested with a one-sided 95% confidence interval for the difference of the 3-years cumulative incidence of AMKL.

Secondary: MRD level at week 12

End point title	MRD level at week 12[2]

End point description:

The secondary end point of the study was the MRD level at week 12 irrespective of prior intervention. (GATA1s negativity (sensitivity 10-4) at week 12)

End point type	Secondary

End point timeframe:

12 week

Notes:

[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: The endpoint MRD level at week 12 was evaluated exclusively in the TMD study population in the current trial.

End point values	TMD study population			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: GATA1s negativity				
number (not applicable)				
MRD negative	50			
MRD positive	13			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival

End point title	Overall survival

End point description:

End point type	Other pre-specified

End point timeframe:

three years period

End point values	TMD study population	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	146		
Units: percent				
number (confidence interval 95%)	90 (87 to 93)	85 (82 to 88)		

Statistical analyses

Statistical analysis title	Control versus TMD, overall survival
Comparison groups	TMD study population v Control Group
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.16
Method	Logrank

Notes:

[3] - The Kaplan-Meier method was used to estimate survival rates.17 The 2-sided logrank test was used to compare differences between different groups. Standard errors were obtained using Greenwoods formula.

Other pre-specified: Eventfree survival

End point title	Eventfree survival

End point description:

End point type	Other pre-specified

End point timeframe:

three years

End point values	TMD study population	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	146		
Units: percent				
number (confidence interval 95%)	72 (68 to 76)	63 (59 to 67)		

Statistical analyses

Statistical analysis title	Control versus TMD, eventfree survival

Statistical analysis description:

The Kaplan-Meier method was used to estimate survival rates. The 2-sided logrank test was used to compare differences between different groups.

Comparison groups	TMD study population v Control Group
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Throughout the entire study period	
Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTC
Dictionary version	2.0

Reporting groups

Reporting group title	TMD study population

Reporting group description: -

Serious adverse events	TMD study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 104 (0.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	TMD study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 104 (45.19%)		
Vascular disorders			
Thrombosis			
subjects affected / exposed	44 / 104 (42.31%)		
occurrences (all)	44		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	44 / 104 (42.31%)		
occurrences (all)	44		
Cardiac function			
subjects affected / exposed	27 / 104 (25.96%)		
occurrences (all)	27		
Echokardio: LV-SF			

subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Nervous system disorders			
Central Neurotoxicity			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Peripheral Neurotoxicity			
subjects affected / exposed	39 / 104 (37.50%)		
occurrences (all)	39		
General disorders and administration site conditions			
General condition			
subjects affected / exposed	45 / 104 (43.27%)		
occurrences (all)	45		
Blood and lymphatic system disorders			
Bilirubin			
subjects affected / exposed	46 / 104 (44.23%)		
occurrences (all)	46		
Immune system disorders			
Fever			
subjects affected / exposed	45 / 104 (43.27%)		
occurrences (all)	45		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	41 / 104 (39.42%)		
occurrences (all)	41		
Vomiting			
subjects affected / exposed	46 / 104 (44.23%)		
occurrences (all)	46		
Stomatitis			
subjects affected / exposed	46 / 104 (44.23%)		
occurrences (all)	46		
Diarrhae			
subjects affected / exposed	46 / 104 (44.23%)		
occurrences (all)	46		
Hepatobiliary disorders			

SGOT/SPOT			
subjects affected / exposed	46 / 104 (44.23%)		
occurrences (all)	46		
Respiratory, thoracic and mediastinal disorders			
Lung problems			
subjects affected / exposed	42 / 104 (40.38%)		
occurrences (all)	42		
Skin and subcutaneous tissue disorders			
Skin changes			
subjects affected / exposed	45 / 104 (43.27%)		
occurrences (all)	45		
Renal and urinary disorders			
Creatinine			
subjects affected / exposed	47 / 104 (45.19%)		
occurrences (all)	47		
Infections and infestations			
Infection			
subjects affected / exposed	45 / 104 (43.27%)		
occurrences (all)	45		

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

 None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29959152

http://www.ncbi.nlm.nih.gov/pubmed/18182574