Clinical trial results:
Randomised induction and post induction therapy in older patients (>=61 years of age) with acute myeloid leukaemia (AML) and refractory anaemia with excess blasts (RAEB, RAEB-t)

Summary

EudraCT number	2004-001918-13
Trial protocol	GB
Global end of trial date	23 November 2015

Results information

Result version number	v1 (current)
This version publication date	11 June 2023
First version publication date	11 June 2023

Trial information

Trial identification

Sponsor protocol code	Hovon 43

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl

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	30 April 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2008
Global end of trial reached?	Yes
Global end of trial date	23 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objectives:
-Evaluation of the effect of an escalated dose of Daunorubincin in induction treatment
-Evaluation of the effect of maintenance treatment with GO for patients in CR

Protection of trial subjects:

Monitoring and Insurance.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2000
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	United Kingdom: 17
Country: Number of subjects enrolled	Belgium: 159
Country: Number of subjects enrolled	Germany: 193
Country: Number of subjects enrolled	Switzerland: 109
Country: Number of subjects enrolled	Netherlands: 388
Worldwide total number of subjects	866
EEA total number of subjects	740

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)	249

From 65 to 84 years	617
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects gave written informed consent and were screened according to the inclusion- and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Dauromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

45 mg/m2, 3hr infusion on days 1,2,3

Investigational medicinal product name	Cytarabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m2 CI (24 hrs), days 1 thru 7 cycle 1
1000 mg/m2 q 12 hrs, 6 hr infusion, days 1 thru 4 cycle 2

Arm title	Arm B

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Dauromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m2, 3hr infusion on days 1,2,3

Investigational medicinal product name	Cytarabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: 200 mg/m2 CI (24 hrs), days 1 thru 7 cycle 1 1000 mg/m2 q 12 hrs, 6 hr infusion, days 1 thru 4 cycle 2

Investigational medicinal product name	Gemtuzumab ozogamicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/m2, 2hrs infusion, days 1, 29, 57 post induction

Number of subjects in period 1	Arm A	Arm B
Started	433	433
Completed	93	101
Not completed	340	332
Adverse reactions	46	57
Other	130	121
Lack of efficacy	164	154

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	866	866	
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)	249	249	
From 65-84 years	617	617	
85 years and over	0	0	
Age continuous Units: years			
median	67		
full range (min-max)	60 to 83	-	
Gender categorical Units: Subjects			
Female	383	383	
Male	483	483	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Primary: Primary endpoint

End point title	Primary endpoint[1]
End point description:	
End point type	Primary
End point timeframe:	
See publication.	

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: See attached chart/documents for results.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	402		
Units: Whole	411	402		

Attachments (see zip file)	List of reported non-SAE's/nonsaedata43-19May2023.pdf List of reported SAE's/saedata43-19May2023.pdf Statistical data section from publication/Statistical data section

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During protocol treatment all deaths, all SAE's that are life-threatening and any unexpected SAE must be reported within 48 hours of the initial observation of the event. All details should be documented on the Serious Adverse Event and Death Report.

Adverse event reporting additional description:

Initial reports must be followed-up by a complete report within a further 14 calendar days.

Assessment type	Systematic

Dictionary used

Dictionary name	CTC
Dictionary version	2

Reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	239 / 420 (56.90%)	228 / 419 (54.42%)	
number of deaths (all causes)	373	365	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecif. (inc. cysts/polyp)	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	34 / 420 (8.10%)	33 / 419 (7.88%)	
occurrences causally related to treatment / all	2 / 34	2 / 34	
deaths causally related to treatment / all	2 / 34	0 / 31	
Vascular disorders			
Vascular disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	6 / 420 (1.43%)	3 / 419 (0.72%)	
occurrences causally related to treatment / all	4 / 7	1 / 3	
deaths causally related to treatment / all	1 / 4	0 / 1	
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 420 (0.24%)	1 / 419 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	28 / 420 (6.67%)	25 / 419 (5.97%)	
occurrences causally related to treatment / all	9 / 28	11 / 25	
deaths causally related to treatment / all	6 / 25	8 / 22	
Unknown	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	54 / 420 (12.86%)	49 / 419 (11.69%)	
occurrences causally related to treatment / all	25 / 55	22 / 51	
deaths causally related to treatment / all	19 / 48	15 / 42	
Immune system disorders			
Immune system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	0 / 420 (0.00%)	1 / 419 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social circumstances	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 420 (0.24%)	0 / 419 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	12 / 420 (2.86%)	13 / 419 (3.10%)	
occurrences causally related to treatment / all	9 / 12	10 / 13	
deaths causally related to treatment / all	8 / 10	6 / 8	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 420 (0.24%)	0 / 419 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 420 (0.24%)	0 / 419 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	4 / 420 (0.95%)	4 / 419 (0.95%)	
occurrences causally related to treatment / all	3 / 4	3 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	2 / 420 (0.48%)	1 / 419 (0.24%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	11 / 420 (2.62%)	7 / 419 (1.67%)	
occurrences causally related to treatment / all	5 / 11	2 / 7	
deaths causally related to treatment / all	3 / 7	0 / 5	
Nervous system disorders			
Nervous system disorder	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	23 / 420 (5.48%)	18 / 419 (4.30%)	
occurrences causally related to treatment / all	15 / 23	8 / 18	
deaths causally related to treatment / all	11 / 19	6 / 16	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	15 / 420 (3.57%)	6 / 419 (1.43%)	
occurrences causally related to treatment / all	12 / 16	6 / 7	
deaths causally related to treatment / all	5 / 8	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	7 / 420 (1.67%)	9 / 419 (2.15%)	
occurrences causally related to treatment / all	4 / 7	5 / 9	
deaths causally related to treatment / all	2 / 3	3 / 6	
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see SAE chart for details.		

subjects affected / exposed	6 / 420 (1.43%)	5 / 419 (1.19%)	
occurrences causally related to treatment / all	6 / 6	4 / 5	
deaths causally related to treatment / all	2 / 2	1 / 1	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	0 / 420 (0.00%)	1 / 419 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	5 / 420 (1.19%)	0 / 419 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	0 / 420 (0.00%)	1 / 419 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	57 / 420 (13.57%)	71 / 419 (16.95%)	
occurrences causally related to treatment / all	40 / 61	52 / 72	
deaths causally related to treatment / all	22 / 41	35 / 50	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	401 / 420 (95.48%)	407 / 419 (97.14%)	
General disorders and administration site conditions			
(prolonged) hospitalisation	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	44 / 420 (10.48%)	43 / 419 (10.26%)	
occurrences (all)	51	48	
Death	Additional description: All combined, see non-SAE chart for details.		

subjects affected / exposed	50 / 420 (11.90%)	52 / 419 (12.41%)	
occurrences (all)	55	63	
Life threatening	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	5 / 420 (1.19%)	4 / 419 (0.95%)	
occurrences (all)	5	4	
Other	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	86 / 420 (20.48%)	95 / 419 (22.67%)	
occurrences (all)	125	122	
Pain	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	51 / 420 (12.14%)	42 / 419 (10.02%)	
occurrences (all)	63	53	
Severe/permanent disability	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	91 / 420 (21.67%)	109 / 419 (26.01%)	
occurrences (all)	114	145	
Syndromes	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 420 (0.71%)	6 / 419 (1.43%)	
occurrences (all)	3	7	
Respiratory, thoracic and mediastinal disorders			
Pulmonary	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	83 / 420 (19.76%)	88 / 419 (21.00%)	
occurrences (all)	103	110	
Congenital, familial and genetic disorders			
Congenital anomaly	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	12 / 420 (2.86%)	21 / 419 (5.01%)	
occurrences (all)	12	23	
Nervous system disorders			
Neurology	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	77 / 420 (18.33%)	65 / 419 (15.51%)	
occurrences (all)	96	87	
Blood and lymphatic system disorders			
Hemorrhage	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	55 / 420 (13.10%)	54 / 419 (12.89%)	
occurrences (all)	66	65	
Lymphatic	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	3 / 420 (0.71%)	1 / 419 (0.24%)	
occurrences (all)	3	1	

Eye disorders			
Ocular	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	12 / 420 (2.86%)	23 / 419 (5.49%)	
occurrences (all)	13	24	
Gastrointestinal disorders			
GI	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	222 / 420 (52.86%)	244 / 419 (58.23%)	
occurrences (all)	383	441	
Hepatobiliary disorders			
Hepatic	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	100 / 420 (23.81%)	111 / 419 (26.49%)	
occurrences (all)	170	184	
Skin and subcutaneous tissue disorders			
Dermatology/skin	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	185 / 420 (44.05%)	202 / 419 (48.21%)	
occurrences (all)	252	299	
Renal and urinary disorders			
GU and renal	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	61 / 420 (14.52%)	64 / 419 (15.27%)	
occurrences (all)	65	73	
Endocrine disorders			
Endocrine	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	6 / 420 (1.43%)	8 / 419 (1.91%)	
occurrences (all)	6	8	
Musculoskeletal and connective tissue disorders			
Musculoskeletal	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	7 / 420 (1.67%)	14 / 419 (3.34%)	
occurrences (all)	8	15	
Infections and infestations			
Infections	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	384 / 420 (91.43%)	389 / 419 (92.84%)	
occurrences (all)	1336	1397	
Metabolism and nutrition disorders			
Metabolic	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	78 / 420 (18.57%)	86 / 419 (20.53%)	
occurrences (all)	123	149	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2000	The requirement of a confirmation of a complete remission after an interval of at least 28 days has been removed from the definition of CR (Appendix C). This has led to some minor changes in the protocol. These and a few other minor changes and corrections.
30 January 2001	The antibody testing against gemtuzumab has been removed, since it is no longer required.
15 June 2001	The participation of the German AML study group has been added to the title page and the list of study coordinators, the forwarding of SAE reports to Wyeth has been added and the definition of complex cytogenetic abnormalities has been modified. These and a few other minor changes and corrections.
10 June 2004	The percentage of patients, randomized for post induction treatment (second randomization), turned out to be lower than expected (30% instead of 40%). With the recruitment of 600 patients for the first randomization, it is now expected that only 180 patients will have a second randomization instead of the 240, which is stated in the protocol. Therefore the power, necessary for answering the research question whether GO has an additional value in patients with CR on induction, will be too low. We propose to raise the target number of patients to 800 in order to gain the necessary power for this research question. The power for answering the induction question will also benefit from this.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported