



Clinical trial results:

A randomized phase III study on the effect of Bortezomib combined with Adriamycin, Dexamethasone (AD) for induction treatment, followed by High Dose Melphalan and Bortezomib alone during maintenance in patients with multiple myeloma

Summary

EudraCT number	2004-000944-26
Trial protocol	BE
Global end of trial date	30 April 2019

Results information

Result version number	v1 (current)
This version publication date	12 April 2023
First version publication date	12 April 2023

Trial information

Trial identification

Sponsor protocol code	HOVON 65 MM / GMMG-HD4
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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	13 April 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2011
Global end of trial reached?	Yes
Global end of trial date	30 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Bortezomib combined with intensive chemotherapy and in maintenance therapy in comparison with intensive therapy with Vincristine followed by thalidomide maintenance in patients with previously untreated multiple myeloma, as measured by the progression free survival as defined in chapter 14

Protection of trial subjects:

Monitoring and Insurance.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Germany: 399
Country: Number of subjects enrolled	Netherlands: 428
Worldwide total number of subjects	833
EEA total number of subjects	833

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)	803
From 65 to 84 years	30

85 years and over	0
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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
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Arm title	Arm1
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg, al cycles, day 1-4

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg at day 1,2,3,4,9,10,11,12,17,18,19,20 all cycles.

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

Dosage and administration details:

9mg/m2, al cycles, day 1-4.

Investigational medicinal product name	Filgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 µg/kg (divided in 2 gifts daily, according to local rules), s.c., day 5 until last pheresis.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 50mg per day.	
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100mg/m2 cycle 1 (day -3,-2), 200mg/m2 cycle 2 (day -3,-2).	
Arm title	Arm2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 40mg at day 1,2,3,4,9,10,11,12,17,18,19,20 all cycles.	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 9mg/m2, all cycles, day 1-4.	
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100mg/m2 cycle 1 (day -3,-2), 200mg/m2 cycle 2 (day -3,-2).	
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1,3mg/m2 for 3 cycles, days 1,4, 8, 11. Maintenance is 1,3 mg/m2 every 2 weeks.	

Number of subjects in period 1	Arm1	Arm2
Started	416	417
Completed	77	115
Not completed	339	302
Adverse reactions	111	104
Other	110	102
Lack of efficacy	118	96

Baseline characteristics

Reporting groups

Reporting group title	Overall period
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Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	833	833	
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)	803	803	
From 65-84 years	30	30	
85 years and over	0	0	
Age continuous			
Units: years			
median	57		
full range (min-max)	25 to 65	-	
Gender categorical			
Units: Subjects			
Female	328	328	
Male	505	505	

End points

End points reporting groups

Reporting group title	Arm1
Reporting group description: -	
Reporting group title	Arm2
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	Arm1	Arm2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	414	413		
Units: Whole	414	413		

Attachments (see zip file)	Statistical data section from publication/HO65 statistical data List of reported non-SAE's/nonsaedata65-21Mar2023.pdf List of reported SAE's/saedata65-27Mar2023.pdf
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, with the exception of progression of multiple myeloma, will be reported from the first study-related procedure until 30 days following the last dose of study drug or until the start of subsequent systemic antineoplastic therapy, if earlier.

Adverse event reporting additional description:

Adverse events occurring after 30 days should also be reported if considered related to study drug. All Grade 3 or 4 adverse events considered related to study drug must be followed until recovery to Grade 0 or 1. Neuropathic and cardiac adverse events of Grade 2 or higher will be followed until improvement to Grade 0 or 1.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Arm1
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Reporting group description: -

Reporting group title	Arm2
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Reporting group description: -

Serious adverse events	Arm1	Arm2	
Total subjects affected by serious adverse events			
subjects affected / exposed	242 / 413 (58.60%)	290 / 412 (70.39%)	
number of deaths (all causes)	263	246	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecified. (inc. cysts/polyp)	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	9 / 413 (2.18%)	5 / 412 (1.21%)	
occurrences causally related to treatment / all	4 / 10	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Vascular disorders			
Vasa praeviacular disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	34 / 413 (8.23%)	36 / 412 (8.74%)	
occurrences causally related to treatment / all	17 / 37	21 / 38	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined, see SAE chart for details.		

subjects affected / exposed	6 / 413 (1.45%)	4 / 412 (0.97%)	
occurrences causally related to treatment / all	1 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	39 / 413 (9.44%)	56 / 412 (13.59%)	
occurrences causally related to treatment / all	35 / 48	53 / 68	
deaths causally related to treatment / all	0 / 0	2 / 3	
Unknown	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	20 / 413 (4.84%)	26 / 412 (6.31%)	
occurrences causally related to treatment / all	12 / 20	17 / 27	
deaths causally related to treatment / all	0 / 1	4 / 4	
Immune system disorders			
Immune system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 413 (0.24%)	3 / 412 (0.73%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 413 (0.24%)	0 / 412 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	25 / 413 (6.05%)	29 / 412 (7.04%)	
occurrences causally related to treatment / all	13 / 25	18 / 34	
deaths causally related to treatment / all	1 / 2	1 / 3	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	6 / 413 (1.45%)	6 / 412 (1.46%)	
occurrences causally related to treatment / all	5 / 6	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Investigations	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	6 / 413 (1.45%)	1 / 412 (0.24%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
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	10 / 413 (2.42%)	17 / 412 (4.13%)	
occurrences causally related to treatment / all	0 / 10	2 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	22 / 413 (5.33%)	21 / 412 (5.10%)	
occurrences causally related to treatment / all	11 / 25	14 / 22	
deaths causally related to treatment / all	1 / 1	4 / 5	
Nervous system disorders			
Nervous system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	23 / 413 (5.57%)	74 / 412 (17.96%)	
occurrences causally related to treatment / all	13 / 25	90 / 98	
deaths causally related to treatment / all	1 / 3	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	13 / 413 (3.15%)	16 / 412 (3.88%)	
occurrences causally related to treatment / all	10 / 13	14 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Eye disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	1 / 413 (0.24%)	0 / 412 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	28 / 413 (6.78%)	57 / 412 (13.83%)	
occurrences causally related to treatment / all	21 / 34	48 / 68	
deaths causally related to treatment / all	3 / 3	3 / 3	

Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	4 / 413 (0.97%)	5 / 412 (1.21%)	
occurrences causally related to treatment / all	3 / 4	2 / 5	
deaths causally related to treatment / all	1 / 2	0 / 1	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	3 / 413 (0.73%)	3 / 412 (0.73%)	
occurrences causally related to treatment / all	3 / 3	2 / 4	
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	19 / 413 (4.60%)	8 / 412 (1.94%)	
occurrences causally related to treatment / all	5 / 20	4 / 9	
deaths causally related to treatment / all	1 / 1	0 / 1	
Endocrine disorders			
Endocrine disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	3 / 413 (0.73%)	0 / 412 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	20 / 413 (4.84%)	16 / 412 (3.88%)	
occurrences causally related to treatment / all	1 / 22	6 / 17	
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	117 / 413 (28.33%)	120 / 412 (29.13%)	
occurrences causally related to treatment / all	99 / 149	112 / 142	
deaths causally related to treatment / all	9 / 12	9 / 13	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All combined, see SAE chart for details.		
subjects affected / exposed	15 / 413 (3.63%)	11 / 412 (2.67%)	
occurrences causally related to treatment / all	11 / 17	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm1	Arm2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	408 / 413 (98.79%)	408 / 412 (99.03%)	
Vascular disorders			
Vascular	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	51 / 413 (12.35%)	58 / 412 (14.08%)	
occurrences (all)	62	66	
Surgical and medical procedures			
Surgery/intra-operative injury	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	11 / 413 (2.66%)	6 / 412 (1.46%)	
occurrences (all)	12	8	
General disorders and administration site conditions			
Coagulation	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	81 / 413 (19.61%)	73 / 412 (17.72%)	
occurrences (all)	245	220	
Constitutional symptoms	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	326 / 413 (78.93%)	315 / 412 (76.46%)	
occurrences (all)	1137	1168	
Growth/development	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	1 / 413 (0.24%)	2 / 412 (0.49%)	
occurrences (all)	1	2	
Other	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	45 / 413 (10.90%)	36 / 412 (8.74%)	
occurrences (all)	49	46	
Pain	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	271 / 413 (65.62%)	274 / 412 (66.50%)	
occurrences (all)	800	781	
Secondary malignancy	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	1 / 413 (0.24%)	1 / 412 (0.24%)	
occurrences (all)	1	1	
Syndromes	Additional description: All combined, see non-SAE chart for details.		

subjects affected / exposed occurrences (all)	21 / 413 (5.08%) 26	31 / 412 (7.52%) 47	
Immune system disorders			
Allergy/immunology	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	67 / 413 (16.22%) 88	51 / 412 (12.38%) 60	
Reproductive system and breast disorders			
Sexual/reproductive	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	16 / 413 (3.87%) 18	20 / 412 (4.85%) 22	
Respiratory, thoracic and mediastinal disorders			
Pulmonary/upper respiratory	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	176 / 413 (42.62%) 304	182 / 412 (44.17%) 327	
Cardiac disorders			
Cardiac arrhythmia	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	91 / 413 (22.03%) 119	79 / 412 (19.17%) 134	
Cardiac general	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	139 / 413 (33.66%) 276	157 / 412 (38.11%) 276	
Nervous system disorders			
Neurology	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	314 / 413 (76.03%) 972	314 / 412 (76.21%) 917	
Blood and lymphatic system disorders			
Blood/bone marrow	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	319 / 413 (77.24%) 2599	325 / 412 (78.88%) 3204	
Hemorrhage/bleeding	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	89 / 413 (21.55%) 125	72 / 412 (17.48%) 99	
Lymphatics	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed occurrences (all)	110 / 413 (26.63%) 181	127 / 412 (30.83%) 194	
Ear and labyrinth disorders			

Auditory/ear subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	30 / 413 (7.26%)	27 / 412 (6.55%)	
	33	30	
Eye disorders Ocular/visual subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	61 / 413 (14.77%)	73 / 412 (17.72%)	
	83	100	
Gastrointestinal disorders GI subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	377 / 413 (91.28%)	379 / 412 (91.99%)	
	2403	2557	
Hepatobiliary disorders Hepatobiliary/pancreas subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	18 / 413 (4.36%)	19 / 412 (4.61%)	
	24	23	
Skin and subcutaneous tissue disorders Dermatology/skin subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	256 / 413 (61.99%)	265 / 412 (64.32%)	
	567	554	
Renal and urinary disorders Renal/genitourinary subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	76 / 413 (18.40%)	61 / 412 (14.81%)	
	98	75	
Endocrine disorders Endocrine subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	49 / 413 (11.86%)	51 / 412 (12.38%)	
	64	69	
Musculoskeletal and connective tissue disorders Musculoskeletal/soft tissue subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	149 / 413 (36.08%)	127 / 412 (30.83%)	
	258	226	
Metabolism and nutrition disorders Metabolic/laboratory subjects affected / exposed occurrences (all)	Additional description: All combined, see non-SAE chart for details.		
	307 / 413 (74.33%)	303 / 412 (73.54%)	
	4246	4582	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2005	Overall updates in the protocol.
25 March 2005	Overall updates in the protocol.
15 February 2006	Some errors in the protocol and patient information have been corrected.
16 November 2007	Overall updates in the protocol.
29 August 2008	Safety information for Bortezomib updated according to updated Investigator Drug Brochure (version 11). Administrative correction (new phone + fax numbers ErasmusMC and new contact address GMMG). Addition of mandatory serum M- and urine M-protein value at registration (to comply with already updated and implemented CRF of 9 July 2007).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported