Clinical trial results:
A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma

Summary

EudraCT number	2009-017903-28
Trial protocol	NL IS BE DK AT SE IT CZ SK GR PT FI HU LU
Global end of trial date	18 October 2024

Results information

Result version number	v1 (current)
This version publication date	11 May 2025
First version publication date	11 May 2025

Trial information

Trial identification

Sponsor protocol code	HO95

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	Dr. Molewaterplein 40, Rotterdam, Netherlands,
Public contact	HOVON, HOVON, hovon@erasmusmc.nl
Scientific contact	HOVON, HOVON, hovon@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	02 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2020
Global end of trial reached?	Yes
Global end of trial date	18 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the efficacy of VMP versus high-dose therapy and stem cell transplantation (HDT) in patients with previously untreated multiple myeloma, as measured by the progression free survival.
- To evaluate the effect of consolidation with VRD followed by Lenalidomide maintenance with no consolidation but Lenalidomide maintenance alone on progression free survival.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2011
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	Netherlands: 356
Country: Number of subjects enrolled	Norway: 29
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Sweden: 53
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Czechia: 80
Country: Number of subjects enrolled	Denmark: 54
Country: Number of subjects enrolled	Greece: 37
Country: Number of subjects enrolled	Iceland: 2
Country: Number of subjects enrolled	Italy: 718
Country: Number of subjects enrolled	Luxembourg: 1
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Türkiye: 60
Country: Number of subjects enrolled	Switzerland: 42
Worldwide total number of subjects	1503
EEA total number of subjects	1384

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)	1417
From 65 to 84 years	86
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

Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	lenalidomide
Investigational medicinal product code	
Other name	REVLIMID®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The recommendations for initial starting doses of REVLIMID® for patients with MM are as follows while maintaining a 21 out of 28 day treatment cycle:

Renal Function (CrCL) | Multiple Myeloma Dose
Mild Renal Impairment (90 > CrCL ≥ 60 mL/min) | 25 mg (Normal Dose) Every 24 hours
Moderate Renal Impairment (30 ≤ CrCL < 60 mL/min) | 10 mga Every 24 hours
Severe Renal Impairment (CrCL < 30 mL/min, not requiring dialysis) |15 mg Every 48 hours
End Stage Renal Disease (CrCL < 30 mL/min, requiring dialysis) | 5 mg Once daily. On dialysis days the dose should be administered following dialysis

The dose may be escalated to 15 mg every 24 hours after 2 cycles if patient is not responding to treatment and is tolerating the drug.

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

Dosage and administration details:

The recommended starting dose of bortezomib is 1.3 mg/m2 body surface area twice a week for two weeks (administration on days 1, 4, 8 and 11), followed by a 10-day rest period (days 12-21). This three-week period is considered one treatment cycle. There must be at least 72 hours between successive doses of VELCADE. It is recommended that patients with proven complete remission be treated with 2 additional VELCADE cycles after establishing complete remission. It is also recommended that responding patients who do not achieve complete remission be treated with a total of 8 VELCADE cycles. Few data are currently available on re-treatment with VELCADE.

Number of subjects in period 1	Experimental
Started	1503
Completed	0
Not completed	1503
Consent withdrawn by subject	68
Adverse event, non-fatal	309
Other	424
Unknown (Early consent withdrawal)	3
Lack of efficacy	699

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	1503	1503	
Age categorical Units: Subjects			
Adults (18-64 years)	1417	1417	
Adults (65 years)	86	86	
Age continuous Units: years			
median	58		
full range (min-max)	28 to 66	-	
Gender categorical Units: Subjects			
Female	634	634	
Male	869	869	

End points

End points reporting groups

Reporting group title	Experimental

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	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	1503			
Units: Whole	1503			

Attachments (see zip file)	Statistical data section from publication/Methods+results.pdf List of reported SAEs/saedata95-25Nov2024.pdf List of reported non-SAEs/nonsaedata95-25Nov2024.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	v4

Reporting groups

Reporting group title	Experimental group

Reporting group description: -

Serious adverse events	Experimental group		
Total subjects affected by serious adverse events			
subjects affected / exposed	714 / 1493 (47.82%)		
number of deaths (all causes)	686		
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: combined		
subjects affected / exposed	101 / 1493 (6.76%)		
occurrences causally related to treatment / all	75 / 113		
deaths causally related to treatment / all	6 / 12		
Vascular disorders			
Vascular disorders	Additional description: combined		
subjects affected / exposed	39 / 1493 (2.61%)		
occurrences causally related to treatment / all	23 / 41		
deaths causally related to treatment / all	1 / 3		
Surgical and medical procedures			
Surgical and medical procedures	Additional description: combined		
subjects affected / exposed	12 / 1493 (0.80%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			

General disorders and administration site conditions	Additional description: combined		
subjects affected / exposed	164 / 1493 (10.98%)		
occurrences causally related to treatment / all	90 / 218		
deaths causally related to treatment / all	5 / 26		
Immune system disorders			
Immune system disorders	Additional description: Combined		
subjects affected / exposed	7 / 1493 (0.47%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: combined		
subjects affected / exposed	4 / 1493 (0.27%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: combined		
subjects affected / exposed	75 / 1493 (5.02%)		
occurrences causally related to treatment / all	50 / 85		
deaths causally related to treatment / all	3 / 16		
Psychiatric disorders			
Psychiatric disorders	Additional description: combined		
subjects affected / exposed	12 / 1493 (0.80%)		
occurrences causally related to treatment / all	7 / 12		
deaths causally related to treatment / all	0 / 2		
Investigations			
Investigations	Additional description: combined		
subjects affected / exposed	17 / 1493 (1.14%)		
occurrences causally related to treatment / all	22 / 24		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: combined		

subjects affected / exposed	32 / 1493 (2.14%)		
occurrences causally related to treatment / all	3 / 32		
deaths causally related to treatment / all	0 / 1		
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders	Additional description: Combined		
subjects affected / exposed	2 / 1493 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders	Additional description: Combined		
subjects affected / exposed	33 / 1493 (2.21%)		
occurrences causally related to treatment / all	17 / 33		
deaths causally related to treatment / all	1 / 5		
Nervous system disorders			
Nervous system disorder	Additional description: combined		
subjects affected / exposed	67 / 1493 (4.49%)		
occurrences causally related to treatment / all	29 / 79		
deaths causally related to treatment / all	0 / 4		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: Combined		
subjects affected / exposed	52 / 1493 (3.48%)		
occurrences causally related to treatment / all	38 / 53		
deaths causally related to treatment / all	2 / 7		
Eye disorders			
Eye disorders	Additional description: Combined		
subjects affected / exposed	5 / 1493 (0.33%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: combined		
subjects affected / exposed	97 / 1493 (6.50%)		
occurrences causally related to treatment / all	59 / 107		
deaths causally related to treatment / all	2 / 7		
Hepatobiliary disorders			

Hepatobiliary disorders	Additional description: Combined		
subjects affected / exposed	14 / 1493 (0.94%)		
occurrences causally related to treatment / all	3 / 14		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: combined		
subjects affected / exposed	16 / 1493 (1.07%)		
occurrences causally related to treatment / all	9 / 16		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: combined		
subjects affected / exposed	25 / 1493 (1.67%)		
occurrences causally related to treatment / all	12 / 25		
deaths causally related to treatment / all	2 / 5		
Endocrine disorders			
Endocrine disorders	Additional description: Combined		
subjects affected / exposed	2 / 1493 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: combined		
subjects affected / exposed	45 / 1493 (3.01%)		
occurrences causally related to treatment / all	7 / 48		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations	Additional description: combined		
subjects affected / exposed	240 / 1493 (16.08%)		
occurrences causally related to treatment / all	186 / 329		
deaths causally related to treatment / all	5 / 13		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: combined		
subjects affected / exposed	32 / 1493 (2.14%)		
occurrences causally related to treatment / all	14 / 32		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Experimental group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1436 / 1493 (96.18%)		
Injury, poisoning and procedural complications			
Other toxicity	Additional description: Combined		
subjects affected / exposed	678 / 1493 (45.41%)		
occurrences (all)	1335		
Vascular disorders			
Vascular disorders	Additional description: Combined		
subjects affected / exposed	193 / 1493 (12.93%)		
occurrences (all)	279		
Cardiac disorders			
Cardiac disorders	Additional description: Combined		
subjects affected / exposed	111 / 1493 (7.43%)		
occurrences (all)	143		
Blood and lymphatic system disorders			
Anaemia	Additional description: Combined		
subjects affected / exposed	941 / 1493 (63.03%)		
occurrences (all)	2563		
Neutropenia	Additional description: Combined		
subjects affected / exposed	978 / 1493 (65.51%)		
occurrences (all)	2290		
Thrombocytopenia	Additional description: Combined		
subjects affected / exposed	913 / 1493 (61.15%)		
occurrences (all)	2053		
Gastrointestinal disorders			
GI & Hepatic disorders	Additional description: Combined		
subjects affected / exposed	891 / 1493 (59.68%)		
occurrences (all)	1727		

Respiratory, thoracic and mediastinal disorders			
Respir, thor, medias disorders	Additional description: Combined		
subjects affected / exposed	299 / 1493 (20.03%)		
occurrences (all)	353		

Skin and subcutaneous tissue disorders			
Skin & subcutaneous disorders	Additional description: Combined		
subjects affected / exposed	482 / 1493 (32.28%)		
occurrences (all)	716		

Renal and urinary disorders			
Renal & urin. disorders	Additional description: Combined		
subjects affected / exposed	102 / 1493 (6.83%)		
occurrences (all)	121		

Infections and infestations			
Infection & Febrile neut	Additional description: Combined		
subjects affected / exposed	666 / 1493 (44.61%)		
occurrences (all)	998		

Metabolism and nutrition disorders			
Invest. & metab. disorders	Additional description: Combined		
subjects affected / exposed	452 / 1493 (30.27%)		
occurrences (all)	869		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2011	AM 1 Italy
03 January 2012	AM 2 The change(s) in this amendment relates to the addition of ROD2 JIT label Lenalidomide.
26 March 2012	AM 1 nordic
30 November 2012	AM 3 addition Quality of life substudy - addition Iron deficiency substudy - addition substudy Evaluation PET scan in young MM patients - duration of follow-up period - criteria measurable disease - modification schedule VCD induction - addition dose adjustments during VCD, VMP and VRD treatment - change in information molecular substudies - addition reporting of Second Primary Malignancies
13 May 2013	AM 4 (protocol v5) The changes in this amendment relate to - removing the 7.5mg and 2.5mg doses of Lenalidomide for dose reduction during the VRD course in case of toxicities - changing the dose reduction schedule of Cyclophosphamide during VCD (removal day 15).

12 March 2014	AM5 (= protocol v 6) change in the duration of a course of Lenalidomide maintenance treatment from 28 days to 21 days change in eligibility criteria of stem cell mobilization clarification of the timelines of randomization relative to the start of VRD/maintenance treatment addition of FISH analysis at progression correction response evaluation clarification of precautions during Bortezomib treatment and Lenalidomide maintenance treatment clarification of dose adjustments of Bortezomib addition of the possibility of crossover from the VMP arm to the HDM arm in case of Bortezomib toxicity during VMP clarification of timelines of bone marrow punctures and response evaluations addition of additional information about the MRD substudy addition of side effects of Bortezomib correction dose of cyclophosphamide and CRAB criteria change local investigator in specified sites
28 November 2014	AM06 Switzerland
06 May 2019	AM07 (Brexit preparations) Change in marketing authorization holder Addition of EU IMP release site
12 February 2020	AM08 (= protocol v 7) -Lenalidomide maintenance treatment is given until progression of disease (previously until relapse/progression) -All patients are followed up to 10 years after registration instead of 7 years - Administrative changes
02 July 2021	AM09 (= protocol v 8) Lenalidomide maintenance treatment is given as an investigational treatment for 10 years. Patients who continue to benefit from this treatment after 10 years continue their maintenance regimens outside of study settings. - - - - Additional patient information letter Change of local investigator or independent physician Merger/renaming of hospitals

Notes:

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/34774221