Clinical trial results:
Phase I/II trial of Lenalidomide plus Bortezomib combined with Dexamethasone in elderly patients in 1st relapse or primary refractory after first line therapy for Multiple Myeloma

Summary

EudraCT number	2007-002533-37
Trial protocol	NL BE
Global end of trial date	04 March 2020

Results information

Result version number	v1 (current)
This version publication date	06 January 2023
First version publication date	06 January 2023

Trial information

Trial identification

Sponsor protocol code	HOVON 86 MM

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	12 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2014
Global end of trial reached?	Yes
Global end of trial date	04 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1
To determine the maximum tolerated dose (MTD) and recommended phase II dose level (RDL) of Bortezomib administered once weekly, and of Lenalidomide administered for 3 weeks when combined with Dexamethasone in a 28-days schedule.

Phase 2
To investigate the efficacy of a maximum of 8 cycles of Bortezomib plus Lenalidomide with Dexamethasone at the RDL, as determined by the (s)CR+VGPR rate

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2008
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	Netherlands: 80
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	33

From 65 to 84 years	48
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 trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental Group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: 1,3mg/m2 or 1,6mg/m2 on day 1, 8, 15 per cycle.	
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimib
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 10mg, 15mg or 20mg on day 1-21 per cycle.	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 20mg on day 1,2,8,9,15,16 per cycle.	

Number of subjects in period 1	Experimental Group
Started	81
Completed	0
Not completed	81
Adverse reactions	17
Other	19

Lack of efficacy	45

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	81	81	
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)	33	33	
From 65-84 years	48	48	
85 years and over	0	0	
Age continuous Units: years			
median	66		
full range (min-max)	46 to 84	-	
Gender categorical Units: Subjects			
Female	30	30	
Male	51	51	

End points

End points reporting groups

Reporting group title	Experimental Group

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 Group			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: Whole	77			

Attachments (see zip file)	Statistical data section from publication/Broijl-2016- List of reported non-SAE's/nonsaedata86-15Dec2022.pdf List of reported SAE's/saedata86-15Dec2022.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be reported from the first study-related procedure until 30 days following the last protocol treatment or until the start of subsequent systemic therapy for the disease under study, if earlier.

Adverse event reporting additional description:

Adverse events occurring after 30 days should also be reported if considered related to study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

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	35 / 81 (43.21%)		
number of deaths (all causes)	52		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	8 / 81 (9.88%)		
occurrences causally related to treatment / all	6 / 9		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vascular disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 81 (6.17%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	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	5 / 81 (6.17%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 81 (6.17%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 81 (6.17%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic disorders	Additional description: All combined, see SAE chart for details		

subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	12 / 81 (14.81%)		
occurrences causally related to treatment / all	8 / 12		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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	77 / 81 (95.06%)		
Vascular disorders			
Vascular	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Surgical and medical procedures			
Surgery/intra-operative injury	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	5		
General disorders and administration site conditions			
Constitutional symptoms	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	23		
Pain	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	26		
Secondary malignancy	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	5		
Immune system disorders			
Allergy/immunology	Additional description: All combined, see non-SAE chart for details.		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Sexual/reproductive function	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary/upper respiratory	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	12 / 81 (14.81%)		
occurrences (all)	12		
Cardiac disorders			

Cardiac arrythmia	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Cardiac general	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	8		
Nervous system disorders			
Neurology	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	48 / 81 (59.26%)		
occurrences (all)	85		
Blood and lymphatic system disorders			
Blood/bone marrow	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	41 / 81 (50.62%)		
occurrences (all)	192		
Lymphatics	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Auditory/ear	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Eye disorders			
Ocular/visual	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Gastrointestinal disorders			
Gastrointestinal	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	29 / 81 (35.80%)		
occurrences (all)	50		
Skin and subcutaneous tissue disorders			
Dermatology/skin	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	16 / 81 (19.75%)		
occurrences (all)	22		
Renal and urinary disorders			
Renal/genitourinary	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Endocrine disorders			

Endocrine	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal/soft tissue	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	24		
Infections and infestations			
Infection	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	32 / 81 (39.51%)		
occurrences (all)	58		
Metabolism and nutrition disorders			
Metabolic/laboratory	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	43		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2009	Change of CKTO number and addition of 'amendment 1' with version date on first page Change of planned date end of recruitment into III 2010 (was IV 2008) Change of MR into PR under § 7.2 (Study design, phase II) Deletion of FLC references in definition of Measurable Disease under § 8.1.1 (Inclusion criteria) Addition of History of active malignancy during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma under § 8.1.2 (Exclusion criteria) Change of skeletal radiography every 12 months (was every 6 months) during maintenance and follow up and adjustment of footnote 3 (skeletal survey) in § 11.2.3 (Required investigations) Adjustment of required skeletal survey (footnote 3) in § 11.2 (Required investigations) Rephrasing of § 11.2.5 and § 11.2.6 (Required investigations), concerning Micro-array analysis and SNP analysis Addition of clinically significant in a clinically significant abnormal laboratory finding under § 13.1 (Definitions of (serious) adverse events) Addition of polyneuropathy grade 1 under § 13.2 (Reporting of (serious) adverse events) Addition of section concerning foetal exposure to Lenalidomide under § 13.2 (Reporting of (serious) adverse events) Addition of the product manufacturers under § 13.3 (Processing of (serious) adverse events) Adjustments concerning the Serum free light chain values in the Response Criteria for MM and the definition of measurable disease in appendix B. Replacement appendix H version 11 January 2008 into version 30 January 2009 Adjustments in de Required bone marrow and peripheral blood and logistics in appendix I and J
13 December 2010	Removal of "elderly" in study title Addition of final level (level 2; 1,6 mg/m2 Bortezomib, and 10 mg Lenalidomide, 20 mg Dexamethasone) to Scheme of study Patient population: removed the restriction of age 60-85 from description, added inclusion criteria: Age ≥18 years Adjusted the planned end of recruitment to IV 2012 Removed "Age 60-86 years inclusive" from inclusion criteria, added inclusion criteria: Age ≥18 years Added exclusion criterium: "Patient is unable or unwilling to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan." Changed treatment table to reflect the final dose level in phase II Added information on Lenalidomide (paragraph 9.3) Added information on SAE and SUSAR reporting to authorities, according to addendum which was previously brought in place Added information on pregnancies (paragraph 13.4) Changed information requested at registering patient from "patient initials" into "local patient code (optional)" + removed request of "Patient's hospital record number (not obligatory)
24 December 2012	Sections regarding SPM added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported