Clinical trial results:
A multicenter phase II study of subcutaneous Velcade plus oral Melphalna and Prednisone or plus Oral cyclophosphamide and Prednisone or plus Prednisone in newly diagnosed elderly multiple myeloma patients.

Summary

EudraCT number	2010-018873-39
Trial protocol	IT
Global end of trial date	18 January 2024

Results information

Result version number	v1 (current)
This version publication date	12 May 2024
First version publication date	12 May 2024

Trial information

Trial identification

Sponsor protocol code	26866138MMY2069

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01913730
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	STICHTING EUROPEAN MYELOMA NETWORK
Sponsor organisation address	Dr. Molewaterplein 40, ROTTERDAM, Netherlands, 3015 GD
Public contact	Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236, clinicaltrialoffice@emnitaly.org
Scientific contact	Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236, clinicaltrialoffice@emnitaly.org

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	04 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Determine wheter VMP and VCP and VP induce a significant Very Good partial response`` rate in patients wwith newly diagnosed MM 2. determine the Complete Response (CR) rate 3. Determine the Partial response rate

Protection of trial subjects:

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2010
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	Italy: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	2
From 65 to 84 years	139

85 years and over	11

Subject disposition

Recruitment

Recruitment details:

This protocol is a single-arm, three-cohort, phase II multicenter study designed to assess the safety and the efficacy of VMP and VCP and VP as up-front treatment in elderly MM patients.
Patients will be evaluated at scheduled visits in up to 3 study periods: pre-treatment, treatment and long-term follow-up (LTFU).

Pre-assignment

Screening details:

The pre-treatment period includes screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the availability of inclusion criteria.

Period 1

Period 1 title	Induction therapy
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	VMP cohort

Arm description:

•Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Melphalan will be given orally at the dose of 2 mg every other day for 28 days for a total dose 28 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Arm type	Experimental
Investigational medicinal product name	Velcade
Investigational medicinal product code	26866138
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.

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

Dosage and administration details:

Melphalan will be given orally at the dose of 2 mg every other day for 28 days for a total dose 28 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

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

Dosage and administration details:

Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Arm title	VCP cohort

Arm description:

• Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
• Cyclophosphamide will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.
• Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Arm type	Experimental
Investigational medicinal product name	Velcade
Investigational medicinal product code	26866138
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.

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

Dosage and administration details:

Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

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

Dosage and administration details:

Cyclophosphamide will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Arm title	VP cohort

Arm description:

•Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Prednisone will be given orally at the dose of 50 mg every other day for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Arm type	Experimental
Investigational medicinal product name	Velcade
Investigational medicinal product code	26866138
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.

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

Dosage and administration details:

Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700

mg/28days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Number of subjects in period 1	VMP cohort	VCP cohort	VP cohort
Started	50	51	51
Completed	29	25	25
Not completed	21	26	26
Adverse event, serious fatal	2	5	6
Consent withdrawn by subject	1	-	2
Physician decision	-	2	-
Adverse event, non-fatal	9	7	5
Lost to follow-up	1	1	3
Lack of efficacy	8	11	10

Period 2	
Period 2 title	Maintenance therapy
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Velcade

Arm description:

Velcade will be given at the dose of 1.3 mg/m2 as SC injection every 2 weeks. Each cycle will be repeated every 28 days, until PD.

Arm type	Experimental
Investigational medicinal product name	Velcade
Investigational medicinal product code	26866138
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Velcade will be given at the dose of 1.3 mg/m2 as SC injection every 2 weeks. Each cycle will be repeated every 28 days, until PD.

Number of subjects in period 2	Velcade
Started	79
Completed	0
Not completed	79
Adverse event, serious fatal	3
Consent withdrawn by subject	4
Adverse event, non-fatal	20
Lost to follow-up	5
Lack of efficacy	46
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Induction therapy

Reporting group description: -

Reporting group values	Induction therapy	Total	
Number of subjects	152	152	
Age categorical Units: Subjects			
<= 75	39	39	
> 75	113	113	
Age continuous Units: years			
median	78		
full range (min-max)	59 to 88	-	
Gender categorical Units: Subjects			
Female	74	74	
Male	78	78	
ISS Stage Units: Subjects			
ISS Stage I	41	41	
ISS Stage II	44	44	
ISS Stage III	67	67	

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:
ITT

Reporting group values	ITT		
Number of subjects	152		
Age categorical Units: Subjects			
<= 75	39		
> 75	113		
Age continuous Units: years			
median	78		
full range (min-max)	59 to 88		
Gender categorical Units: Subjects			
Female	74		
Male	78		

ISS Stage Units: Subjects			
ISS Stage I	41		
ISS Stage II	44		
ISS Stage III	67		

End points

End points reporting groups

Reporting group title	VMP cohort

Reporting group description:

•Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Melphalan will be given orally at the dose of 2 mg every other day for 28 days for a total dose 28 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Reporting group title	VCP cohort

Reporting group description:

• Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
• Cyclophosphamide will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.
• Prednisone will be given orally at the dose of 50 mg every other day for 28 days for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Reporting group title	VP cohort

Reporting group description:

•Velcade will be given at the dose of 1.3 mg/m2 as subcutaneous (SC) injection on days 1, 8, 15, 22. Each cycle will be repeated every 28 days, for a total of 9 cycles.
•Prednisone will be given orally at the dose of 50 mg every other day for a total dose 700 mg/28 days. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Reporting group title	Velcade

Reporting group description:

Velcade will be given at the dose of 1.3 mg/m2 as SC injection every 2 weeks. Each cycle will be repeated every 28 days, until PD.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT

Primary: The primary endpoints of the study is the VGPR, CR, PR rates.

End point title	The primary endpoints of the study is the VGPR, CR, PR rates.

End point description:

Objective overall Response rate (including CR and PR using the International Response Criteria reported by Durie et al.). Categories of response will include stringent Complete Response (sCR), CR, VGPR, PR and PD. If, during the course of the study, other relevant categories are identified in the literature, then these categories may be added. Responders are defined as subjects with at least a PR.

End point type	Primary

End point timeframe:

24 monhts

End point values	VMP cohort	VCP cohort	VP cohort	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	50	51	51	152
Units: Patients				
at least PR	43	36	32	111
< PR	7	15	19	41

Statistical analyses

Statistical analysis title	No statistical analysis
Comparison groups	VP cohort v VCP cohort v VMP cohort
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0 [2]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	111
Confidence interval	
level	95 %
sides	2-sided
lower limit	111
upper limit	111
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - No statistical analysis

[2] - No statistical analysis

Secondary: PFS

End point title	PFS

End point description:

PFS will be measured in months from the date of enrolment to the date of first observation of disease progression, or relapse from CR or death to any cause as an event. Subjects who withdraw from the study will be considered censored at the time of the last complete disease assessment. Subject who complete the study, have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study will also be censored at the time of last contact.

End point type	Secondary

End point timeframe:

monhts

End point values	VMP cohort	VCP cohort	VP cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	51	51	
Units: month				
median (confidence interval 95%)	18.7 (14.4 to 40.6)	15.8 (12.8 to 19.6)	14.4 (10.5 to 20.9)	

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	VMP cohort v VCP cohort v VP cohort
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.36
Method	Logrank
Parameter estimate	Log rank test
Confidence interval	
level	95 %

Notes:

[3] - Log rank test

Secondary: TTP

End point title	TTP

End point description:

TTP will be measured in months from the date of enrolment to the date of first observation of disease progression, or relapse from CR or deaths related to disease progression. Subjects who withdraw from the study or die of causes other than disease progression will be considered censored at the time of the last complete disease assessment. Subject who complete the study, have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study will also be censored at the time of last contact.

End point type	Secondary

End point timeframe:

months

End point values	VMP cohort	VCP cohort	VP cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	51	51	
Units: month				
median (confidence interval 95%)	25 (16.1 to 95.5)	18.1 (14.2 to 34.6)	15.7 (12.6 to 30.6)	

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	VMP cohort v VCP cohort v VP cohort

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.23 [5]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.23
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[4] - Log rank test

[5] - Log rank test

Secondary: OS

End point title	OS

End point description:

OS is defined as the time between enrolment and death. Subject who die, regardless the cause of the death, will be censored as an event. Subjects who withdraw consent for study will be censored at the time of withdrawal. Subject who complete the study and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study will also be censored at the time of last contact.

End point type	Secondary

End point timeframe:

5 years

End point values	VMP cohort	VCP cohort	VP cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	51	51	
Units: percent				
number (confidence interval 95%)	0.52 (0.39 to 0.7)	0.48 (0.35 to 0.65)	0.58 (0.46 to 0.75)	

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	VMP cohort v VCP cohort v VP cohort
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.97 [7]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	0.97
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[6] - Log rank test

[7] - Log rank test

Secondary: TTNT

End point title	TTNT

End point description:

TTNT will be measured in months from the date of enrolment to the date of next anti-myeloma therapy. Death due to disease progression before starting therapy will be considered an event. Subjects who withdraw from the study or die of causes other than disease progression will be considered censored at the time of the last complete disease assessment. Subject who complete the study, have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study will also be censored at the time of last contact.

End point type	Secondary

End point timeframe:

onths

End point values	VMP cohort	VCP cohort	VP cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	51	51	
Units: month				
median (confidence interval 95%)	24.8 (14.9 to 42.9)	16.5 (13 to 20.3)	14.4 (11.8 to 21.2)	

Statistical analyses

Statistical analysis title	Log rank test

Statistical analysis description:

Log rank test

Comparison groups	VMP cohort v VCP cohort v VP cohort
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.27 [9]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.27
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[8] - Log rank test

[9] - Log rank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Per protocol

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Per Protocol

Reporting group description: -

Serious adverse events	Per Protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 148 (50.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	11		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic neuroendocrine tumour			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	8 / 148 (5.41%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 2		
Surgical and medical procedures			
Haemorrhoid operation			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 148 (1.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Death			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Fatigue			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Mucosal inflammation			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	3 / 148 (2.03%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	9 / 148 (6.08%)		
occurrences causally related to treatment / all	4 / 12		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 148 (2.03%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	2 / 148 (1.35%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 148 (3.38%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Pleural effusion				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	3 / 148 (2.03%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Bradyphrenia				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Insomnia				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Epiphyseal fracture				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	2 / 148 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation			
subjects affected / exposed	3 / 148 (2.03%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	6 / 148 (4.05%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 1		
Cardiogenic shock			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary failure			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial ischaemia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carotid sinus syndrome			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			

subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	12 / 148 (8.11%)			
occurrences causally related to treatment / all	5 / 16			
deaths causally related to treatment / all	0 / 4			
Neutropenia				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 148 (1.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 148 (1.35%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				

subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parotid gland enlargement			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Renal failure				
subjects affected / exposed	3 / 148 (2.03%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	3 / 148 (2.03%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	10 / 148 (6.76%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	1 / 2			
Postoperative wound infection				
subjects affected / exposed	1 / 148 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pulmonary sepsis			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 148 (1.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 148 (1.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hyperglycaemia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 148 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 148 (1.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Per Protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 148 (93.92%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 148 (5.41%)		
occurrences (all)	8		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 148 (6.08%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	85 / 148 (57.43%)		
occurrences (all)	85		
Neutropenia			
subjects affected / exposed	21 / 148 (14.19%)		
occurrences (all)	21		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	35 / 148 (23.65%)		
occurrences (all)	35		
Fatigue			
subjects affected / exposed	22 / 148 (14.86%)		
occurrences (all)	22		
Gastrointestinal disorders			
Pyrexia			
subjects affected / exposed	24 / 148 (16.22%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	17 / 148 (11.49%)		
occurrences (all)	17		
Constipation			
subjects affected / exposed	10 / 148 (6.76%)		
occurrences (all)	10		
Nausea			

subjects affected / exposed occurrences (all)	8 / 148 (5.41%) 8		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 15 / 148 (10.14%) 15 9 / 148 (6.08%) 9		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	 14 / 148 (9.46%) 14		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 11 / 148 (7.43%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	Amendment 1: The substantive amendment request concerns updating the criteria for disease response assessment. With this Amendment, side effects of the drug Velcade, risks to fetus and fertility (male and female) and the appendix on confidentiality protection were also updated on the Information Sheet and Informed Consent Form. Instructions on temperature monitoring of the drug bortezomib, provided by the drug supplier B&C, are also forwarded, following instructions from Janssen International. Participating centers will be required to report any temperature excursions, verified during transport until delivery to each individual center. The expiration of the insurance certificate has been extended.
08 June 2021	Amendment 2: The substantive amendment request concerns the change of the study Promoter with change from HOVON Foundation to STICHTING EUROPEAN MYELOMA NETWORK (EMN), the change of name of the requesting entity and Italian co-promoter from FONESA Onlus to Fondazione EMN Italy Onlus, and the update of the side effects of the drug bortezomib, reported on the information sheet and informed consent form. As a result of this Promoter change, all study documents, including the bortezomib drug labels, were modified. In addition, the bortezomib drug release sites have been updated: - FISHER Clinical Services GmbH (FCS) Germany - FISHER Clinical Services GmbH (FCS) Switzerland FCS Germany will assume all responsibilities that Fisher Horsham has had until now. FCS Switzerland may be involved for the relabeling activities of the drug bortezomib, so both sites are identified as importers and manufacturers for the final release of the drug.
10 November 2023	Amendment 3: The substantive amendment request concerns the study duration per patient, which was reduced to 10 years from enrollment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported