Clinical trial results:
A PHASE II MULTI-CENTRE, RANDOMIZED, OPEN LABEL STUDY OF PROLONGED THERAPY WITH SUBCUTANEOUS BORTEZOMIB TWICE MONTHLY ASSOCIATED WITH DEXAMETHASONE, IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA PATIENTS AFTER SALVAGE WITH BORTEZOMIB-BASED THERAPY.

Summary

EudraCT number	2013-000432-10
Trial protocol	IT
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	04 November 2023
First version publication date	04 November 2023

Trial information

Trial identification

Sponsor protocol code	26866138MMY2084

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, +39 0110243236, clinicaltrialoffice@emnitaly.org
Scientific contact	Clinical Trial Office, Fondazione EMN Italy Onlus, +39 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	11 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of a prolonged treatment with bortezomib twice monthly s.c. in association with dexamethasone, after a salvage treatment containing bortezomib i.v. in relapsed and refractory multiple myeloma patients.
- To assess the safety of prolonged treatment with bortezomib s.c.

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	01 April 2013
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: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	11

From 65 to 84 years	49
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This is a multicenter, randomized, non-comparative open label study designed to evaluate the efficacy and safety of treatment with bortezomib and dexamethasone after a salvage treatment containing bortezomib for relapsed or refractory multiple myeloma patients.

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	Phase II (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm B

Arm description:

Observation every 28 days

Arm type	Observation

No investigational medicinal product assigned in this arm

Arm title	Arm C

Arm description:

Treatment at biochemical relapse. Patients randomized in this group will be observed. At the occurrence of biochemical relapse, 6 VD cycles will be administered. Biochemical relapse is defined as an increase of 25% from the lowest response value in any of the following: serum M-component (absolute increase must be 0.5 g/dL), and/or urine M-component (absolute increase must be 200 mg/24 h).

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

Dosage and administration details:

At the occurrence of biochemical relapse 6 VD cycles will be administered:
1. Bortezomib (VELCADE) will be given as subcutaneous (s.c.) injection at the dose of 1.3 mg/m2 on days 1, 8, 15, 22. Each cycle will be repeated every 28 days.

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

Dosage and administration details:

At the occurrence of biochemical relapse 6 VD cycles will be administered:
2. Dexamethasone will be given orally at the dose of 40 mg weekly. Each cycle will be repeated every 28 days.

Arm title	Arm A

Arm description:

VD Prolonged therapy
1. Bortezomib (VELCADE) will be given as subcutaneous (SC) injection at the dose of 1.3 mg/m2 on days 1, 15. Each cycle will be repeated every 28 days, until development of PD.
2. Dexamethasone will be given orally at the dose of 20 mg on days 1, 2, and 15, 16 of each cycle. Each cycle will be repeated every 28 days, until development of PD.

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

Dosage and administration details:

At the occurrence of biochemical relapse 6 VD cycles will be administered:
1. Bortezomib (VELCADE) will be given as subcutaneous (s.c.) injection at the dose of 1.3 mg/m2 on days 1, 8, 15, 22. Each cycle will be repeated every 28 days.

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

Dosage and administration details:

At the occurrence of biochemical relapse 6 VD cycles will be administered:
2. Dexamethasone will be given orally at the dose of 40 mg weekly. Each cycle will be repeated every 28 days.

Number of subjects in period 1	Arm B	Arm C	Arm A
Started	23	24	16
Completed	0	0	0
Not completed	23	24	16
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	2	3	3
Physician decision	-	1	-
Adverse event, non-fatal	-	2	3
screening failure	-	1	-
Lack of efficacy	21	16	10

Baseline characteristics

Reporting groups	
Reporting group title	Arm B
Reporting group description:	
Observation every 28 days	
Reporting group title	Arm C
Reporting group description:	
Treatment at biochemical relapse. Patients randomized in this group will be observed. At the occurrence of biochemical relapse, 6 VD cycles will be administered. Biochemical relapse is defined as an increase of 25% from the lowest response value in any of the following: serum M-component (absolute increase must be 0.5 g/dL), and/or urine M-component (absolute increase must be 200 mg/24 h).	
Reporting group title	Arm A
Reporting group description:	
VD Prolonged therapy 1. Bortezomib (VELCADE) will be given as subcutaneous (SC) injection at the dose of 1.3 mg/m2 on days 1, 15. Each cycle will be repeated every 28 days, until development of PD. 2. Dexamethasone will be given orally at the dose of 20 mg on days 1, 2, and 15, 16 of each cycle. Each cycle will be repeated every 28 days, until development of PD.	

Reporting group values	Arm B	Arm C	Arm A
Number of subjects	23	24	16
Age categorical Units: Subjects			
Adults (18-64 years)	6	1	3
From 65-84 years	15	23	12
85 years and over	2	0	1
Age continuous Units: years			
arithmetic mean	68	73	72
full range (min-max)	48 to 85	63 to 83	50 to 89
Gender categorical Units: Subjects			
Female	13	11	7
Male	10	13	9
ISS Stage Units: Subjects			
ISS Stage I	17	15	11
ISS Stage II	3	7	3
ISS Stage III	3	2	2

Reporting group values	Total		
Number of subjects	63		
Age categorical Units: Subjects			
Adults (18-64 years)	10		
From 65-84 years	50		
85 years and over	3		

Age continuous Units: years arithmetic mean full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	31		
Male	32		
ISS Stage Units: Subjects			
ISS Stage I	43		
ISS Stage II	13		
ISS Stage III	7		

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	63		
Age categorical Units: Subjects			
Adults (18-64 years)	10		
From 65-84 years	50		
85 years and over	3		
Age continuous Units: years			
arithmetic mean	71		
full range (min-max)	48 to 89		
Gender categorical Units: Subjects			
Female	31		
Male	32		
ISS Stage Units: Subjects			
ISS Stage I	43		
ISS Stage II	13		
ISS Stage III	7		

End points

End points reporting groups

Reporting group title	Arm B
Reporting group description:	
Observation every 28 days	
Reporting group title	Arm C
Reporting group description:	
Treatment at biochemical relapse. Patients randomized in this group will be observed. At the occurrence of biochemical relapse, 6 VD cycles will be administered. Biochemical relapse is defined as an increase of 25% from the lowest response value in any of the following: serum M-component (absolute increase must be 0.5 g/dL), and/or urine M-component (absolute increase must be 200 mg/24 h).	
Reporting group title	Arm A
Reporting group description:	
VD Prolonged therapy 1. Bortezomib (VELCADE) will be given as subcutaneous (SC) injection at the dose of 1.3 mg/m2 on days 1, 15. Each cycle will be repeated every 28 days, until development of PD. 2. Dexamethasone will be given orally at the dose of 20 mg on days 1, 2, and 15, 16 of each cycle. Each cycle will be repeated every 28 days, until development of PD.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT	

Primary: 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 deaths related to disease progression	
End point type	Primary
End point timeframe:	
24 months	

End point values	Arm B	Arm C	Arm A	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	16	63
Units: month				
median (confidence interval 95%)	5.6 (3.7 to 15.4)	8.1 (4.8 to 19.4)	18.2 (12.8 to 31.1)	8.4 (6.1 to 17.2)

Statistical analyses

Statistical analysis title	No statistical analysis
Statistical analysis description:	
No statistical analysis	
Comparison groups	Arm B v Arm C v Arm A v ITT

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0 [2]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - No statistical analysis

[2] - No statistical analysis

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 death, will be censored as an event

End point type	Secondary

End point timeframe:

24 months

End point values	Arm B	Arm C	Arm A	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	16	63
Units: month				
median (confidence interval 95%)	29.6 (24.03 to 62.7)	31.7 (27.4 to 62.7)	45.1 (39.3 to 62.7)	39.3 (29.1 to 62.7)

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:

No statistical analysis

Comparison groups	Arm B v Arm C v Arm A v ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0 [4]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	0

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

Notes:

[3] - No statistical analysis

[4] - 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 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

End point type	Secondary

End point timeframe:

24 monhts

End point values	Arm B	Arm C	Arm A	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	16	63
Units: month				
median (confidence interval 95%)	5.6 (3.7 to 15.4)	8.2 (4.8 to 19.4)	18.2 (12.8 to 31.1)	8.4 (6 to 17.2)

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:

No statistical analysis

Comparison groups	Arm B v Arm C v Arm A v ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0 [6]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Variability estimate	Standard deviation
Dispersion value	0

Notes:

[5] - No statistical analysis

[6] - No statistical analysis

Secondary: TNT

End point title	TNT

End point description:

TTP will be measured in months from the date of the beginning of the salvage treatment to the date of first observation of disease progression, or deaths related to disease progression

End point type	Secondary

End point timeframe:

24 monts

End point values	Arm B	Arm C	Arm A	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	16	63
Units: month				
median (confidence interval 95%)	11 (6.9 to 26.7)	21.5 (18.6 to 70.4)	42.8 (22.7 to 50)	21.5 (15.5 to 28)

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:

No statistical analysis

Comparison groups	Arm B v Arm C v Arm A v ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0 [8]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[7] - No statistical analysis

[8] - No statistical analysis

Secondary: ORR Rate

End point title	ORR Rate

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Arm B	Arm C	Arm A	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	16	63
Units: Patients				
PR/VGPR/CR/sCR	7	14	9	30
SD/PD/NE	16	10	7	33

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:

No statistical analysis

Comparison groups	Arm B v Arm C v Arm A v ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0 [10]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[9] - No statistical analysis

[10] - No statistical analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Per protocol

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

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	6 / 62 (9.68%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal adhesions			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
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	42 / 62 (67.74%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Nervous system disorders			

Paraesthesia subjects affected / exposed occurrences (all)	10 / 62 (16.13%) 10		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 15 / 62 (24.19%) 15 5 / 62 (8.06%) 5 5 / 62 (8.06%) 5		
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all)	 4 / 62 (6.45%) 4 3 / 62 (4.84%) 3 3 / 62 (4.84%) 3		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 4 / 62 (6.45%) 4 4 / 62 (6.45%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2013	Substantial Amendment n.1: With this amendment a third maintenance arm was added, with subcutaneous Velcade and dexamethasone upon the occurrence of biochemical relapse (Arm C). It should be noted that a comparison will be made between the control arm Arm B (no maintenance) and the two experimental arms Arm A (prolonged VD) and Arm C to demonstrate the superiority of the experimental arms. This means that the control arm will be the same for both experimental arms, and the two experimental arms will not be compared to each other. This change led to an increase in the sample, therefore 216 patients will have to be enrolled.
18 March 2014	Substantial Amendment n.2: With this amendment, a change was made to the study design. More precisely, patients randomized to Arm C, upon the occurrence of biochemical relapse, will be treated with 6 cycles of treatment (Velcade and Dexamethasone). Velcade and Dexamethasone will be administered on days 1, 8, 15, 22. This treatment will be repeated at each biochemical relapse until the clinical relapse of the disease.
10 November 2015	Substantial Amendment n.3: Considering the experimental nature of the maintenance treatment, it was deemed appropriate to reduce the sample of patients to be subjected to the treatment in order to obtain a preliminary evaluation on a small number of patients. Furthermore, this preventive measure will allow us not to expose an excessive number of patients to a treatment that may be too toxic or ineffective. With this amendment, one of the primary objectives is to evaluate the efficacy and feasibility of maintenance treatment with bortezomib administered in combination with dexamethasone at biochemical relapse, after salvage treatment containing bortezomib. Therefore a comparison will be made between Arm B and Arm C. With this sample reduction, 46 patients will need to be enrolled (23 per arm).
04 April 2017	Substantial Amendment n.4: This amendment was necessary to update the contacts of the Sponsor and the Principal Investigator from the study, as well as update the criteria for evaluating the disease response. This amendment also transmits the instructions relating to monitoring the temperature of the drug bortezomib, provided by the company supplying the drug B&C, under the instructions of Janssen International. The participating centers will have to communicate any temperature excursion, verified during transport until delivery to each individual center. The side effects of the drug Velcade were also updated on the informed consent and those of Dexamethasone were added.
20 April 2021	Substantial Amendment n.5: The request for a substantial amendment concerns the change of the promoter of the study from HOVON Foundation to STICHTING EUROPEAN MYELOMA NETWORK (EMN) and the updating of the side effects of the drug bortezomib, reported on the information sheet and informed consent form. Following this change of promoter, all study documents have been modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported