Clinical trial results:
A Phase 2, Multicentre, Randomised, Open-Label, Parallel Group Study to Evaluate the Effect of VELCADE® on Myeloma related Bone Disease.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2008-004264-39
Trial protocol	CZ DK AT GB SE DE GR
Global end of trial date	30 April 2014

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	26866138-MMY-2060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01286077
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, 2340, Beerse,, Belgium,
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com

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	30 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of bortezomib on myeloma related bone disease by analyzing bone mineral density (BMD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Turkey: 48
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	104
EEA total number of subjects	56

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)	91
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to enroll about 120 participants in order to obtain at least 100 participants eligible for evaluation (i.e, about 50 in each group). Overall, 115 participants were enrolled of which 106 were randomized with 52 participants allocated to the bortezomib and 54 participants to the observational arm.

Pre-assignment

Screening details:

At Screening, demographic parameters comprised gender, age, body height and weight, body surface area (BSA), body mass index (BMI), and Karnofsky performance status (KPS). Medical history was recorded including prior cardiac and neurological details with a special focus on multiple myeloma (MM).

Period 1

Period 1 title	Treatment/Observation Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bortezomib

Arm description:

Bortezomib (Velcade) Arm

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each cycle will consist of 5 weeks treatment. participants in the treatment group will receive: Velcade® 1.6 milligram per square meter mg/m2 as an intravenous bolus injection on Days 1, 8, 15, and 22 of each cycle followed by a 13-day rest period (Days 23 to 35) Cycle will be repeated on Day 36. Participants in the treatment group will receive up to 4 treatment cycles, unless they experience either unacceptable toxicity or if the participants requests to withdraw from the study.

Arm title	Observation

Arm description:

Observation Arm

Arm type	other

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Bortezomib	Observation
Started	51	53
Completed	41	46
Not completed	10	7
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	2

refill medication not received in time	1	-
The subject starts with alternative MMY	-	3
Death	1	-
Intercurrent illness	1	-
Non-compliance	1	-
Progression of disease	-	1
Patient's decision to stop treatment	3	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Bortezomib
Reporting group description: Bortezomib (Velcade) Arm	
Reporting group title	Observation
Reporting group description: Observation Arm	

Reporting group values	Bortezomib	Observation	Total
Number of subjects	51	53	104
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	45	46	91
From 65 to 84 years	6	7	13
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	56.7	54.7	
standard deviation	± 8.3	± 9.13	-
Title for Gender Units: subjects			
Female	18	22	40
Male	33	31	64

End points

End points reporting groups

Reporting group title	Bortezomib
Reporting group description: Bortezomib (Velcade) Arm	
Reporting group title	Observation
Reporting group description: Observation Arm	
Subject analysis set title	Intent-to-treat Set (ITTS)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITTS included all participants who were randomized and received at least one dose of study medication (bortezomib group) or had at least one post-baseline assessment in the observation arm.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS included all participants of the ITTS who have a baseline value and at least one post-baseline assessment for BMD.	

Primary: Change From Baseline in Bone Mineral Density (BMD) in the Spine at End of treatment (EOT)

End point title	Change From Baseline in Bone Mineral Density (BMD) in the Spine at End of treatment (EOT)
End point description: Change from baseline in bone mineral density (BMD) will be assessed by dual energy x-ray absorptiometry scans at baseline and the EOT visit	
End point type	Primary
End point timeframe: At screening (i.e. between 14 and 1 days prior to start of treatment) and at end of treatment (EOT), i.e. 24 weeks after randomization or until start of alternative MMY therapy, if earlier.	

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[1]	39[2]		
Units: Gram per milli meter square ([g/mm2)				
arithmetic mean (standard deviation)	0.0214 (± 0.0306)	0.0167 (± 0.0301)		

Notes:

[1] - Intension- to-treat.

[2] - Intension- to-treat.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bortezomib v Observation

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5287
Method	ANCOVA

Primary: Change From Baseline in Bone Mineral Density (BMD) in the Femur at End of Treatment

End point title	Change From Baseline in Bone Mineral Density (BMD) in the Femur at End of Treatment

End point description:

Change from baseline in bone mineral density (BMD) will be assessed by dual energy x-ray absorptiometry scans at baseline and the end of treatment EOT visit

End point type	Primary

End point timeframe:

At screening (i.e. between 14 and 1 days prior to start of treatment) and at end of treatment (EOT), i.e. 24 weeks after randomization or until start of alternative MMY therapy, if earlier

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[3]	45[4]		
Units: Gram per millimeter square [g/mm2]				
arithmetic mean (standard deviation)				
Femur neck	0.0053 (± 0.0221)	0.0044 (± 0.0299)		
Femur total	0.0071 (± 0.0151)	0.0138 (± 0.0288)		

Notes:

[3] - Intension to treat.

[4] - Intension to treat.

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Bortezomib v Observation
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9019
Method	ANCOVA

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

The PFS time is defined as the duration from randomization to either first observation of progressive

disease (PD) or occurrence of death due to any cause within 60 days of the last tumor assessment or randomization. Participants without event are censored on the date of last tumor assessment.

End point type	Secondary

End point timeframe:

Until 18 months after end of treatment (approximately 24 months after randomization.

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[5]	47[6]		
Units: Months				
arithmetic mean (standard error)				
PFS from start of first MM treatment	39.56 (± 2.02)	31.66 (± 1.81)		
PFS from randomization	31.35 (± 2.41)	16.72 (± 1.2)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change From Baseline in Biochemical Bone Markers

End point title	Percent change From Baseline in Biochemical Bone Markers

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 1 of cycle 3, EOT visit (24 weeks after randomization or until start of alternative MMY therapy, if earlier) and 4, 6, 12 and 18 months after EOT

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[7]	47[8]		
Units: Percent Change				
arithmetic mean (standard deviation)				
LOCF EOT(n=43,44)	-3.1 (± 38.8)	-10.52 (± 27.45)		
LOCF FU(n =42,40)	3.44 (± 47.35)	-15.25 (± 31.86)		

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Skeletal related Events

End point title	Number of Participants with Skeletal related Events

End point description:

Skeletal events are defined as radiation to bone, clinical fracture, surgery to bone and spinal cord compression and death due to prostate cancer.

End point type	Secondary

End point timeframe:

At each visit from screening to 18 months after EOT (approximately 24 months after randomization)

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[9]	47[10]		
Units: Participants				
number (not applicable)	0	0		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in BMD Over Time

End point title	Percent Change From Baseline in BMD Over Time

End point description:

End point type	Secondary

End point timeframe:

Screening EOT and Follow up

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[11]	47		
Units: percent change				
arithmetic mean (standard deviation)				
Screening (n= 38)	0.9898 (± 0.173)	1.0181 (± 0.208)		
Percent Change at LOCF EOT (n=38)	1.0111 (± 0.178)	1.0347 (± 0.2053)		
Percent Change at LOCF FU (n=38)	1.0407 (± 0.1927)	1.0697 (± 0.1964)		

Notes:

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Karnofsky Performance Status

End point title	Karnofsky Performance Status

End point description:

End point type	Secondary

End point timeframe:

At screening, Day 1 of Cycle 2, 3, and 4 or Day 36, 71 and 106 for observation arm, at EOT Visit, and and 4, 6, 12 and 18 months after EOT or start of alternative MMY therapy

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[12]	47[13]		
Units: percent change				
arithmetic mean (standard deviation)				
Screening	92.4 (± 9.2)	91.9 (± 9.7)		
LOCF EOT	91.7 (± 9)	91.7 (± 7.3)		
LOCF FU	92.4 (± 10.2)	92.3 (± 7)		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the time from the date of randomization to the date of death due to any cause. Participants were censored at the last date of tumor measurement, the last date in the study drug log, or the date of last follow-up.

End point type	Secondary

End point timeframe:

until 18 months after EOT (approximately 24 months after randomization)

End point values	Bortezomib	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[14]	47[15]		
Units: Months				
arithmetic mean (standard error)	49.9 (± 1.48)	47.26 (± 1.26)		

Notes:

[14] - FAS

[15] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0
Reporting groups	
Reporting group title	Observation
Reporting group description:	
Observation Arm	
Reporting group title	Bortezomib
Reporting group description:	
Bortezomib (Velcade) Arm	

Serious adverse events	Observation	Bortezomib	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 53 (5.66%)	6 / 51 (11.76%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Neoplasm			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute Hepatic Failure			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Device Related Infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Observation	Bortezomib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 53 (66.04%)	47 / 51 (92.16%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 53 (1.89%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Neuropathy Peripheral			
subjects affected / exposed	1 / 53 (1.89%)	4 / 51 (7.84%)	
occurrences (all)	1	5	
Neuralgia			

subjects affected / exposed	0 / 53 (0.00%)	5 / 51 (9.80%)	
occurrences (all)	0	7	
Peripheral Sensory Neuropathy			
subjects affected / exposed	2 / 53 (3.77%)	10 / 51 (19.61%)	
occurrences (all)	3	21	
Paraesthesia			
subjects affected / exposed	3 / 53 (5.66%)	4 / 51 (7.84%)	
occurrences (all)	3	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Leukopenia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	5	
Neutropenia			
subjects affected / exposed	1 / 53 (1.89%)	6 / 51 (11.76%)	
occurrences (all)	1	11	
Thrombocytopenia			
subjects affected / exposed	0 / 53 (0.00%)	5 / 51 (9.80%)	
occurrences (all)	0	9	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 53 (3.77%)	8 / 51 (15.69%)	
occurrences (all)	2	9	
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	7 / 51 (13.73%)	
occurrences (all)	1	7	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	10	
Abdominal Pain Upper			
subjects affected / exposed	1 / 53 (1.89%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Dry Mouth			

subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	0 / 53 (0.00%)	19 / 51 (37.25%)	
occurrences (all)	0	58	
Dyspepsia			
subjects affected / exposed	1 / 53 (1.89%)	4 / 51 (7.84%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	0 / 53 (0.00%)	9 / 51 (17.65%)	
occurrences (all)	0	17	
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	8 / 51 (15.69%)	
occurrences (all)	0	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 53 (9.43%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 53 (0.00%)	4 / 51 (7.84%)	
occurrences (all)	0	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 53 (9.43%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Bone Pain			
subjects affected / exposed	4 / 53 (7.55%)	3 / 51 (5.88%)	
occurrences (all)	4	4	
Back Pain			
subjects affected / exposed	5 / 53 (9.43%)	5 / 51 (9.80%)	
occurrences (all)	5	6	

Musculoskeletal Pain			
subjects affected / exposed	3 / 53 (5.66%)	2 / 51 (3.92%)	
occurrences (all)	3	2	
Pain in Extremity			
subjects affected / exposed	1 / 53 (1.89%)	4 / 51 (7.84%)	
occurrences (all)	1	5	
Infections and infestations			
Herpes Zoster			
subjects affected / exposed	3 / 53 (5.66%)	4 / 51 (7.84%)	
occurrences (all)	3	4	
Influenza			
subjects affected / exposed	4 / 53 (7.55%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Nasopharyngitis			
subjects affected / exposed	4 / 53 (7.55%)	6 / 51 (11.76%)	
occurrences (all)	4	8	
Upper Respiratory Tract Infection			
subjects affected / exposed	9 / 53 (16.98%)	9 / 51 (17.65%)	
occurrences (all)	10	16	
Metabolism and nutrition disorders			
Vitamin B12 Deficiency			
subjects affected / exposed	3 / 53 (5.66%)	2 / 51 (3.92%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2010	Amendment EU-3) was considered substantial and included the following changes: deletion of exclusion criterion referring to participants with oligosecretory or non-secretory MM and minor editorial changes. Rationale for deletion of the exclusion criterion was the consideration that participants enrolled had already achieved PR following first-line therapy. In addition, BMD can be monitored in participants with oligosecretory or non-secretory MM. Disease progression in such participants was to be monitored using a free light chains assay.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported