Clinical trial results:
A phase 3, prospective, randomized clinical study with Velcade-Thalidomide- Dexamethasone versus Thalidomide-Dexamethasone for previously untreated patients with symptomatic multiple myeloma who are candidates to receive double autologous transplantation. 26866138-MMY-3006

Summary

EudraCT number	2005-003723-39
Trial protocol	IT
Global end of trial date	02 March 2016

Results information

Result version number	v1 (current)
This version publication date	08 May 2022
First version publication date	08 May 2022

Trial information

Trial identification

Sponsor protocol code	123/2005/U/Sper-26866138-MMY-3006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IRCCS Azienda Ospedaliero-Universitaria di Bologna
Sponsor organisation address	Via Albertoni, 15, Bologna, Italy, 40138
Public contact	Prof. Michele Cavo, IRCCS Azienda Ospedaliero-Universitaria di Bologna, +39 051 214 3680, michele.cavo@unibo.it
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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	31 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2016
Global end of trial reached?	Yes
Global end of trial date	02 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the probability of answer to VELCADE-thalidomide-dexamethasone (the group of A treatment) or thalidomide-dexamethasone (group of B treatment) like primary therapy of induction of the answer.

Protection of trial subjects:

Written informed consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 April 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 480
Worldwide total number of subjects	480
EEA total number of subjects	480

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)	480
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May 10, 2006, and April 30, 2008, 480 patients, aged 18–65 years with previously untreated symptomatic multiple myeloma and a Karnofsky Performance Status of 60% or higher were enrolled at 73 centres in Italy.

Pre-assignment

Screening details:

Key inclusion criteria were aged 18–65 years, previously untreated symptomatic and measurable multiple myeloma, Karnofsky Performance Status of 60% or higher, and adequate haematological, renal, cardiac, and hepatic functions.

Pre-assignment period milestones

Number of subjects started	480
Number of subjects completed	474

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 6

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment with VTD

Arm description:

1) VELCADE-THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
2) mobilization with CYCLOPHOSPHAMIDE;
3) double autologous HSCT;
4) VELCADE-THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
5) DEXAMETHASONE maintenance until disease progression or intolerance.

Arm type	Experimental
Investigational medicinal product name	BORTEZOMIB
Investigational medicinal product code	ATC CODE: L01XG01
Other name	VELCADE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.3mg/m2 on days 1-4-8-11 (induction phase, 3 21-day cyles)
1.3mg/m2 on days 1-8-15-22 (consolidation phase, 2 35-day cyles, 3 months after second autologous HSCT)

Investigational medicinal product name	THALIDOMIDE
Investigational medicinal product code	ATC CODE: L04AX02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100mg/die (first 14 days), then 200mg/die thereafter (induction phase, 3 21-day cyles)

100-200mg/die (bridging therapy from induction to second autologous HSCT)
100mg/die (consolidation phase, 2 35-day cyles, 3 months after second autologous HSCT)

Investigational medicinal product name	DEXAMETHASONE
Investigational medicinal product code	ATC CODE: S01BA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/die on days 1-2, 4-5, 8-9 and 11-12 (total dose 320mg/cycle, induction phase, 3 21-day cycles)
40mg/die on days 1-4 (total dose 320mg/cycle, maintenance phase, 2 35-day cycles)
40mg/die on days 1-4 (total dose 320mg/cycle, maintenance phase, 28-day cycles until disease progression or intolerance)

Arm title	Treatment with TD

Arm description:

- THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
- mobilization with CYCLOPHOSPHAMIDE; double autologous HSCT;
- THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
- DEXAMETHASONE maintenance until disease progression or intolerance.

Arm type	Experimental
Investigational medicinal product name	THALIDOMIDE
Investigational medicinal product code	ATC CODE: L04AX02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100mg/die (first 14 days), then 200mg/die thereafter (induction phase, 3 21-day cyles)
100-200mg/die (bridging therapy from induction to second autologous HSCT)
100mg/die (consolidation phase, 2 35-day cyles, 3 months after second autologous HSCT)

Investigational medicinal product name	DEXAMETHASONE
Investigational medicinal product code	ATC CODE: S01BA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/die on days 1-2, 4-5, 8-9 and 11-12 (total dose 320mg/cycle, induction phase, 3 21-day cycles)
40mg/die on days 1-4 (total dose 320mg/cycle, maintenance phase, 2 35-day cycles)
40mg/die on days 1-4 (total dose 320mg/cycle, maintenance phase, 28-day cycles until disease progression or intolerance)

Number of subjects in period 1[1]	Treatment with VTD	Treatment with TD
Started	236	238
Completed	163	168
Not completed	73	70
Adverse event, serious fatal	4	5
Melanoma	1	-
Consent withdrawn by subject	11	8

Physician decision	2	4
Adverse event, non-fatal	34	22
Allogeneic stem-cell transplantation	8	7
Lost to follow-up	3	1
Lack of efficacy	10	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Between May 10, 2006, and April 30, 2008, 480 patients were enrolled and randomly assigned to receive VTD (241 patients) or TD (239 patients). Six patients withdrew consent before start of treatment. 236 patients in the VTD group and 238 patients in the TD group were included in the intention-to-treat analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment with VTD
Reporting group description:	
1) VELCADE-THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles); 2) mobilization with CYCLOPHOSPHAMIDE; 3) double autologous HSCT; 4) VELCADE-THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles); 5) DEXAMETHASONE maintenance until disease progression or intolerance.	
Reporting group title	Treatment with TD
Reporting group description:	
- THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles); - mobilization with CYCLOPHOSPHAMIDE; double autologous HSCT; - THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles); - DEXAMETHASONE maintenance until disease progression or intolerance.	

Reporting group values	Treatment with VTD	Treatment with TD	Total
Number of subjects	236	238	474
Age categorical Units: Subjects			
Adults (18-64 years)	236	238	474
Age continuous Units: years			
arithmetic mean	56.3	55.9	
standard deviation	± 6.9	± 7.4	-
Gender categorical Units: Subjects			
Female	99	102	201
Male	137	136	273
Myeloma subtype			
Secernent/non secernent MM			
Units: Subjects			
IgA	41	54	95
IgG	154	147	301
Light chain	40	34	74
Other	1	3	4
ISS stage (International Staging System)			
ISS 1-2-3			
Units: Subjects			
Category title 1	107	107	214
Category title 2	91	92	183
Category title 3	38	39	77
Cytogenetic abnormalities at baseline			
FISH analysis for Cytogenetic abnormalities			
Units: Subjects			
del(13), del(17) and t(4;14) NEGATIVE	101	108	209
del(13) POSITIVE; del(17) and t(4;14) NEGATIVE	66	59	125

del(13) and t(4;14) POSITIVE; del (17) NEGATIVE	26	30	56
del(13) and del(17) NEGATIVE; t(4; 14) POSITIVE	14	10	24
del(13) and del(17) POSITIVE; t(4; 14) NEGATIVE	11	10	21
del(13), del(17) and t(4;14) POSITIVE	3	5	8
del(17) POSITIVE; del(13) and t(4; 14) NEGATIVE	2	1	3
del(17) and t(4;14) POSITIVE; del (13) NEGATIVE	0	1	1
Not evaluable	13	14	27

Subject analysis sets

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

Subject analysis set description:

Randomly assigned patients who effectively started therapy.

Reporting group values	Final analysis		
Number of subjects	474		
Age categorical Units: Subjects			
Adults (18-64 years)	474		
Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female	201		
Male	273		
Myeloma subtype			
Secernent/non secernent MM			
Units: Subjects			
IgA	95		
IgG	301		
Light chain	74		
Other	1		
ISS stage (International Staging System)			
ISS 1-2-3			
Units: Subjects			
Category title 1	214		
Category title 2	183		
Category title 3	77		
Cytogenetic abnormalities at baseline			
FISH analysis for Cytogenetic abnormalities			
Units: Subjects			
del(13), del(17) and t(4;14) NEGATIVE	209		

del(13) POSITIVE; del(17) and t(4; 14) NEGATIVE	125		
del(13) and t(4;14) POSITIVE; del (17) NEGATIVE	56		
del(13) and del(17) NEGATIVE; t(4; 14) POSITIVE	24		
del(13) and del(17) POSITIVE; t(4; 14) NEGATIVE	21		
del(13), del(17) and t(4;14) POSITIVE	8		
del(17) POSITIVE; del(13) and t(4; 14) NEGATIVE	3		
del(17) and t(4;14) POSITIVE; del (13) NEGATIVE	1		
Not evaluable	27		

End points

End points reporting groups

Reporting group title	Treatment with VTD

Reporting group description:

1) VELCADE-THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
2) mobilization with CYCLOPHOSPHAMIDE;
3) double autologous HSCT;
4) VELCADE-THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
5) DEXAMETHASONE maintenance until disease progression or intolerance.

Reporting group title	Treatment with TD

Reporting group description:

- THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
- mobilization with CYCLOPHOSPHAMIDE; double autologous HSCT;
- THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
- DEXAMETHASONE maintenance until disease progression or intolerance.

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

Subject analysis set description:

Randomly assigned patients who effectively started therapy.

Primary: Rate of CR/nCR to induction therapy

End point title	Rate of CR/nCR to induction therapy

End point description:

Rate of ≥ nCR to primary remission induction therapy with either Vel-Thal-Dex or Thal-Dex, as determined by EBMT/IBMTR criteria (with the addition of a nCR category) and calculated on an intent-to-treat basis.

End point type	Primary

End point timeframe:

Evaluated 28 days after end of induction therapy.

End point values	Treatment with VTD	Treatment with TD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	238		
Units: Number				
number (not applicable)				
CR	44	11		
>=nCR	73	27		

Statistical analyses

Statistical analysis title	Rate of CR/nCR to induction therapy

Statistical analysis description:

The trial was designed to detect a significant increase in the complete response and near complete response rate from 15% to 27% upon an induction therapy with TD or VTD (with a statistical power of 80% and an α error of 0.05)

Comparison groups	Treatment with VTD v Treatment with TD

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Chi-squared

Secondary: Rate of CR/nCR after consolidation therapy

End point title	Rate of CR/nCR after consolidation therapy

End point description:

Rate of nCR after consolidation therapy with either Vel-Thal-Dex or Thal-Dex, as determined by EBMT/IBMTR criteria (with the addition of a nCR category) and calculated on an intent-to-treat basis.

End point type	Secondary

End point timeframe:

Evaluated 28 days after end of consolidation therapy.

End point values	Treatment with VTD	Treatment with TD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	238		
Units: Number				
number (not applicable)				
CR	116	82		
>=nCR	147	108		

Statistical analyses

Statistical analysis title	CR/nCR after consolidation therapy analysis

Statistical analysis description:

The trial was designed to detect a significant increase in the complete response and near complete response rate from 15% to 27% upon an induction therapy with TD or VTD (with a statistical power of 80% and an α error of 0.05)

Comparison groups	Treatment with VTD v Treatment with TD
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Chi-squared

Secondary: Safety and toxicity

End point title	Safety and toxicity

End point description:

End point type	Secondary

End point timeframe:

Up to 30 days after the last dose of treatment

End point values	Treatment with VTD	Treatment with TD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	238		
Units: Number of patients				
Peripheral neuropathy grade >=2	83	24		
Peripheral neuropathy grade >=3	35	6		
any grade 3 or 4 adverse event	132	79		
any grade 3 or 4 adverse event (non-hematological)	120	73		

Statistical analyses

Statistical analysis title	Safety and toxicity analysis

Statistical analysis description:

The trial was designed to detect a significant increase in the complete response and near complete response rate from 15% to 27% upon an induction therapy with TD or VTD (with a statistical power of 80% and an α error of 0.05)

Comparison groups	Treatment with VTD v Treatment with TD
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Chi-squared

Secondary: Safety and toxicity

End point title	Safety and toxicity

End point description:

End point type	Secondary

End point timeframe:

Up to 30 days after the last dose of treatment

End point values	Treatment with VTD	Treatment with TD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	238		
Units: Days				
median (full range (min-max))				
Time of onset of Peripheral neuropathy grade >=2	83 (41 to 133)	37.5 (24 to 142.5)		
Time of onset of Peripheral neuropathy grade >=3	72 (28 to 109)	37.5 (30 to 72)		

Statistical analyses

Statistical analysis title	Safety and toxicity analysis

Statistical analysis description:

The trial was designed to detect a significant increase in the complete response and near complete response rate from 15% to 27% upon an induction therapy with TD or VTD (with a statistical power of 80% and an α error of 0.05)

Comparison groups	Treatment with VTD v Treatment with TD
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of induction therapy to 30 days after last dose treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	8.0

Reporting groups	
Reporting group title	Treatment with VTD

Reporting group description:

1) VELCADE-THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
2) mobilization with CYCLOPHOSPHAMIDE;
3) double autologous HSCT;
4) VELCADE-THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
5) DEXAMETHASONE maintenance until disease progression or intolerance.

Reporting group title	Treatment with TD

Reporting group description:

- THALIDOMIDE-DEXAMETHASONE induction (3 21-day cycles);
- mobilization with CYCLOPHOSPHAMIDE; double autologous HSCT;
- THALIDOMIDE-DEXAMETHASONE consolidation (2 35-day cycles);
- DEXAMETHASONE maintenance until disease progression or intolerance.

Serious adverse events	Treatment with VTD	Treatment with TD	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 236 (14.41%)	22 / 238 (9.24%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	2	3	
Cardiac disorders			
Cardiac toxicity	Additional description: Grade ≥3		
subjects affected / exposed	5 / 236 (2.12%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	1 / 7	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Peripheral neuropathy	Additional description: Grade ≥3		
subjects affected / exposed	23 / 236 (9.75%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	48 / 48	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Deep vein thrombosis	Additional description: Grade ≥3		

subjects affected / exposed	8 / 236 (3.39%)	12 / 238 (5.04%)	
occurrences causally related to treatment / all	6 / 8	12 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation	Additional description: Grade ≥3		
subjects affected / exposed	10 / 236 (4.24%)	7 / 238 (2.94%)	
occurrences causally related to treatment / all	14 / 14	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal events (excluding constipation)			
subjects affected / exposed	5 / 236 (2.12%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver toxicity	Additional description: Grade ≥3		
subjects affected / exposed	4 / 236 (1.69%)	7 / 238 (2.94%)	
occurrences causally related to treatment / all	4 / 5	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin rash	Additional description: Grade ≥3		
subjects affected / exposed	24 / 236 (10.17%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	19 / 24	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections (excluding Herpe Zoster)	Additional description: Grade ≥3		
subjects affected / exposed	7 / 236 (2.97%)	11 / 238 (4.62%)	
occurrences causally related to treatment / all	3 / 8	9 / 13	
deaths causally related to treatment / all	0 / 1	0 / 2	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Treatment with VTD	Treatment with TD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 236 (55.93%)	79 / 238 (33.19%)	
Nervous system disorders			

Peripheral neuropathy			
subjects affected / exposed	57 / 236 (24.15%)	29 / 238 (12.18%)	
occurrences (all)	62	43	
Blood and lymphatic system disorders			
Oedema			
subjects affected / exposed	23 / 236 (9.75%)	11 / 238 (4.62%)	
occurrences (all)	48	31	
Immune system disorders			
Fever	Additional description: Grade 1-2		
subjects affected / exposed	25 / 236 (10.59%)	21 / 238 (8.82%)	
occurrences (all)	87	85	
Gastrointestinal disorders			
Constipation	Additional description: Grade 1-2		
subjects affected / exposed	89 / 236 (37.71%)	60 / 238 (25.21%)	
occurrences (all)	169	103	
Gastrointestinal events (excluding constipation)			
subjects affected / exposed	41 / 236 (17.37%)	18 / 238 (7.56%)	
occurrences (all)	46	26	
Skin and subcutaneous tissue disorders			
Skin rash	Additional description: Grade 1-2		
subjects affected / exposed	43 / 236 (18.22%)	13 / 238 (5.46%)	
occurrences (all)	46	21	
Infections and infestations			
Infections			
subjects affected / exposed	17 / 236 (7.20%)	24 / 238 (10.08%)	
occurrences (all)	41	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2005	• A more detailed description of the substudy on prevention of thromboembolic complications. • Modification of some inclusion/exclusion criteria in the substudy. • Inclusion of Thalidomide in the chapter on information on investigational drugs. • Revision of bibliography.
18 April 2006	• Update of the VELCADE safety section, according to the most recent data provided by the manufacturer (protocol, patient and doctor information form). • Study synopsis: revised and expanded in many sections to allow easier and more correct application of study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported