Clinical trial results:
A Phase 2, Randomized Study of VELCADE® (Bortezomib), Dexamethasone, and Thalidomide Versus VELCADE® (Bortezomib), Dexamethasone, Thalidomide, and Cyclophosphamide in Subjects With Previously Untreated Multiple Myeloma Who Are Candidates for Autologous Transplantation

Summary

EudraCT number	2006-006050-10
Trial protocol	FR AT HU PT CZ IT
Global end of trial date	16 October 2013

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	26866138MMY2043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00531453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
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	16 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the overall combined complete response rate (CR rate) (defined in this protocol as the combination of complete response [CR, including sCR and nCR]) following induction treatment with VDT or VDTC in subjects with newly diagnosed symptomatic multiple myeloma who are candidates for HDT/SCT.

Protection of trial subjects:

All participating subjects received full supportive care and were followed closely for safety throughout the study. Safety assessments occur through regular clinic visits including laboratory analyses. Special attention was given to the early detection of neurotoxicity (through the FACT/GOG -Ntx questionnaire checklist, investigator assessment, and possibly assessments by a neurologist).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 16
Worldwide total number of subjects	98
EEA total number of subjects	91

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)	90
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

98 patients were enrolled between October 2007 and September 2008

Pre-assignment

Screening details:

All enrolled patients received at least one dose of study drug.

Period 1

Period 1 title	Induction Cycles 1-4 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Four Drug Regimen (VDTC)

Arm description:

Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m2 IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.

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

Dosage and administration details:

Participants will receive velcade 1.3 milligram per meter square [mg/m2] as an intravenous (i.v.) bolus injection on Days 1,4,8, and 11, followed by a 10 day rest period (Days 12 to 21).

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dexamethasone 40 milligram per day (mg/day) was given orally by mouth (p.o.) on Days 1-4 and Days 9-12 in each of 4 cycles.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Thalidomide 100 milligram (mg) orally Every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of Velcade) and continuing until Day 21 of Cycle 4.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

400 milligram per meter square [mg/m2] on Day 1 and Day 8 of each 3-week cycle, for a total of 4 cycles.

Arm title	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali

Arm description:

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m^2 as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime).

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

Dosage and administration details:

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects received VELCADE 1.3 mg/m^2 as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21).

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dexamethasone 40 milligram per day (mg/day) was given orally by mouth (p.o.) on Days 1-4 and Days 9-12 in each of 4 cycles.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Thalidomide 100 milligram (mg) orally Every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of Velcade) and continuing until Day 21 of Cycle 4.

Number of subjects in period 1	Four Drug Regimen (VDTC)	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali
Started	49	49
Completed	45	46
Not completed	4	3
Adverse event, serious fatal	1	-

Adverse event, non-fatal	-	1
Adverse event, serious non-fatal	2	2
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Four Drug Regimen (VDTC)
Reporting group description:	
Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m2 IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.	
Reporting group title	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali
Reporting group description:	
VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m^2 as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime).	

Reporting group values	Four Drug Regimen (VDTC)	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali	Total
Number of subjects	49	49	98
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	44	46	90
From 65 to 84 years	5	3	8
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	55.8	55.1	
standard deviation	± 8.27	± 7.04	-
Title for Gender			
Units: subjects			
Female	24	23	47
Male	25	26	51

End points

End points reporting groups

Reporting group title	Four Drug Regimen (VDTC)

Reporting group description:

Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m2 IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.

Reporting group title	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali

Reporting group description:

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m^2 as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime).

Primary: Percentage of Particpants Achieving Overall Combined Complete Response (CR) Following Induction

End point title	Percentage of Particpants Achieving Overall Combined Complete Response (CR) Following Induction

End point description:

Percent of Particpants Achieving Overall combined complete response (CR w/normalized serum kappa: lambda ratio + CR + near complete response [nCR]) following induction therapy: CR criteria: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and less tha <5 percent (%) plasma cells in bone marrow; kappa: lambda ratio: normal free light chain (FLC) ratio; nCR criteria: positive immunofixation analysis of serum or urine as the only evidence of disease; disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.

End point type	Primary

End point timeframe:

Cycle 1 up to Cycle 4/8 up to End-of-Induction Treatment Visit/ End-of–Extension Treatment Visit (30 days after the last dose of study drugs)

End point values	Four Drug Regimen (VDTC)	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: percentage of participants				
number (confidence interval 95%)	43.75 (29.5 to 58.8)	51.02 (36.3 to 65.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Four Drug Regimen (VDTC) v Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5056
Method	Stratified Log rank test

Secondary: Percentage of Participants Achieving Overall Combined Complete Response (CR) Following High-dose Chemotherapy (HDT)/Stem Cell Transplantation (SCT)

End point title	Percentage of Participants Achieving Overall Combined Complete Response (CR) Following High-dose Chemotherapy (HDT)/Stem Cell Transplantation (SCT)

End point description:

Percent of Participants Achieving Overall Combined Complete Response (CR) (CR w/normalized serum kappa: lambda ratio + CR + Near Complete Response [nCR]) following stem cell transplantation. CR criteria: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow. kappa:lambda ratio: normal free light chain (FLC) ratio. nCR criteria: positive immunofixation analysis of serum or urine as the only evidence of disease; disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.

End point type	Secondary

End point timeframe:

Cycle 1 up to Cycle 4/8 up to End-of-Induction Treatment Visit/ End-of–Extension Treatment Visit (30 days after the last dose of study drugs)

End point values	Four Drug Regimen (VDTC)	Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	27		
Units: Percentage of Participants				
number (confidence interval 95%)	77.78 (57.7 to 91.4)	76.32 (59.8 to 88.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose to 30 days post last dose	
Adverse event reporting additional description:	
Treatment emergent	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	VDTC (Treatment Group B)
Reporting group description:	
Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m2 IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.	
Reporting group title	VDT (Treatment Group A)
Reporting group description:	
Treatment Group A (VDT) - VELCADE 1.3 mg/m2 intravenously (IV) on Days 1, 4, 8, and 11, Dexamethasone 40 mg orally on Days 1 to 4 and Days 9 to 12, and Thalidomide 100 mg orally every day beginning on Day 1 of Cycle 1 until Day 21 of Cycle 4.	

Serious adverse events	VDTC (Treatment Group B)	VDT (Treatment Group A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 49 (40.82%)	11 / 49 (22.45%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Acute Phase Reaction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			

subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Oedema			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	1 / 49 (2.04%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 49 (2.04%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			

subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic Attack			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral Neck Fracture			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubic Rami Fracture			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Autonomic Neuropathy			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 49 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			

subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 49 (4.08%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal Vomiting			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic Skin Eruption			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary Incontinence			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal Sepsis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VDTC (Treatment Group B)	VDT (Treatment Group A)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 49 (89.80%)	48 / 49 (97.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 49 (12.24%)	3 / 49 (6.12%)	
occurrences (all)	6	3	
Hypotension			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 49 (14.29%)	10 / 49 (20.41%)	
occurrences (all)	8	15	
Face Oedema			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	10 / 49 (20.41%)	5 / 49 (10.20%)	
occurrences (all)	27	8	
Oedema			
subjects affected / exposed	6 / 49 (12.24%)	4 / 49 (8.16%)	
occurrences (all)	7	5	
Oedema Peripheral			
subjects affected / exposed	17 / 49 (34.69%)	16 / 49 (32.65%)	
occurrences (all)	25	20	
Pyrexia			
subjects affected / exposed	12 / 49 (24.49%)	6 / 49 (12.24%)	
occurrences (all)	15	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 49 (6.12%)	4 / 49 (8.16%)	
occurrences (all)	3	4	

Dyspnoea			
subjects affected / exposed	2 / 49 (4.08%)	3 / 49 (6.12%)	
occurrences (all)	2	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 49 (6.12%)	5 / 49 (10.20%)	
occurrences (all)	3	8	
Anxiety			
subjects affected / exposed	0 / 49 (0.00%)	5 / 49 (10.20%)	
occurrences (all)	0	5	
Investigations			
Weight Increased			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences (all)	4	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Paraesthesia			
subjects affected / exposed	11 / 49 (22.45%)	11 / 49 (22.45%)	
occurrences (all)	15	16	
Neuropathy Peripheral			
subjects affected / exposed	0 / 49 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	5	
Peripheral Motor Neuropathy			
subjects affected / exposed	3 / 49 (6.12%)	3 / 49 (6.12%)	
occurrences (all)	10	4	
Somnolence			
subjects affected / exposed	0 / 49 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	4	
Peripheral Sensory Neuropathy			
subjects affected / exposed	12 / 49 (24.49%)	11 / 49 (22.45%)	
occurrences (all)	16	19	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 49 (34.69%)	7 / 49 (14.29%)	
occurrences (all)	37	16	

Leukopenia			
subjects affected / exposed	4 / 49 (8.16%)	0 / 49 (0.00%)	
occurrences (all)	11	0	
Lymphopenia			
subjects affected / exposed	5 / 49 (10.20%)	7 / 49 (14.29%)	
occurrences (all)	25	16	
Neutropenia			
subjects affected / exposed	8 / 49 (16.33%)	7 / 49 (14.29%)	
occurrences (all)	17	8	
Thrombocytopenia			
subjects affected / exposed	7 / 49 (14.29%)	4 / 49 (8.16%)	
occurrences (all)	14	8	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences (all)	4	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences (all)	4	2	
Vision Blurred			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	5	
Constipation			
subjects affected / exposed	24 / 49 (48.98%)	27 / 49 (55.10%)	
occurrences (all)	30	34	
Abdominal Pain Upper			
subjects affected / exposed	2 / 49 (4.08%)	4 / 49 (8.16%)	
occurrences (all)	2	4	
Diarrhoea			
subjects affected / exposed	8 / 49 (16.33%)	4 / 49 (8.16%)	
occurrences (all)	12	5	
Nausea			

subjects affected / exposed	9 / 49 (18.37%)	5 / 49 (10.20%)	
occurrences (all)	16	8	
Dyspepsia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 49 (6.12%)	
occurrences (all)	3	4	
Stomatitis			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	4 / 49 (8.16%)	2 / 49 (4.08%)	
occurrences (all)	6	2	
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	2 / 49 (4.08%)	5 / 49 (10.20%)	
occurrences (all)	2	9	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 49 (6.12%)	9 / 49 (18.37%)	
occurrences (all)	5	12	
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	6 / 49 (12.24%)	4 / 49 (8.16%)	
occurrences (all)	7	4	
Back Pain			
subjects affected / exposed	2 / 49 (4.08%)	4 / 49 (8.16%)	
occurrences (all)	2	4	
Pain in Extremity			
subjects affected / exposed	5 / 49 (10.20%)	4 / 49 (8.16%)	
occurrences (all)	5	4	
Muscle Spasms			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	
occurrences (all)	1	5	
Infections and infestations			
Oral Candidiasis			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	

Nasopharyngitis			
subjects affected / exposed	3 / 49 (6.12%)	3 / 49 (6.12%)	
occurrences (all)	5	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 49 (12.24%)	3 / 49 (6.12%)	
occurrences (all)	8	3	
Enzyme Abnormality			
subjects affected / exposed	3 / 49 (6.12%)	5 / 49 (10.20%)	
occurrences (all)	9	15	
Hyperglycaemia			
subjects affected / exposed	2 / 49 (4.08%)	5 / 49 (10.20%)	
occurrences (all)	18	27	
Hyperuricaemia			
subjects affected / exposed	0 / 49 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	4	
Hypoalbuminaemia			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	
occurrences (all)	6	1	
Hypocalcaemia			
subjects affected / exposed	6 / 49 (12.24%)	1 / 49 (2.04%)	
occurrences (all)	13	1	
Hyponatraemia			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences (all)	7	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2010	The overall reason for the amendment was : Tto stop central testing of efficacy assessments, but continue to collect data related to time to progression and other efficacy parameters as routinely done by the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported